Stroke Mimics: An Important Source of Bias in Acute Ischemic Stroke Research

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Study Objective: Stroke mimics may be difficult distinguish from acute ischemic strokes and are often treated with alteplase though not by intent. We report the characteristics, frequency, and outcomes of stroke mimics treated at our institution. Using our data, we then explore how the inclusion of stroke mimics in stroke outcomes research may be an important source of bias. *Methods:* We retrospectively identified all patients treated with alteplase in our emergency department from August 2013 to December 2017 for suspected acute ischemic stroke. We collected the following variables: gender, age, risk factors (hypertension, diabetes, and atrial fibrillation), admission glucose, admission National Institute of Health Stroke Scale, admission mean arterial pressure, onset-to-treatment time, adverse events, discharge diagnosis, length of stay, discharge NIHSS, discharge destination, and 3 month modified Rankin score. *Results:* One hundred and eighteen patients were treated with alteplase for suspected acute ischemic stroke of which 33 (27.9%) were stroke mimics. Compared to ischemic strokes, stroke mimics were younger (median age 53 versus 69; $P < .0003$); were less likely to have vascular risk factors (hypertension [51.5% versus 78.8%; $P < .005$] diabetes (9.1% versus 32.9%; $P < .007$), and atrial fibrillation (3.0% versus 23.5%; $P < .006$). The most common stroke mimic was transient ischemic attack (33.3%). Stroke mimics were significantly more likely to be discharged home (75.8% versus 41.2%; $P < .002$). Outcomes unadjusted for stroke mimics led to artificial inflation of a favorable discharge destination. *Conclusions:* Inclusion of stroke mimics led to an artificial inflation of a favorable discharge destination for our entire cohort. Our study highlights the potential for bias in reporting favorable outcomes if appropriate adjustment accounting for stroke mimics does not occur.

Key Words: Acute ischemic stroke—stroke mimic—bias—randomized controlled trial—averted infarction—false negative diffusion weighted image.

Introduction

Conditions such as seizures, migraines, and conversion disorders may present as acute neurological deficits that mimic an ischemic stroke. A significant number of stroke mimics are treated with alteplase in both retrospective studies[1-11] and randomized controlled trials[12,13] (RCT). Importantly, stroke mimics treated with alteplase have a markedly different natural history than ischemic strokes treated with alteplase.[1-10] Therefore, outcome analyses unadjusted for stroke mimics may be subject to biased conclusions.

In prior studies, patients with normal post-thrombolysis diffusion-weighted magnetic resonance imaging (DWI) may have been categorized as ischemic strokes. The rationale was a clinical cerebrovascular event with rapid recanalization due to thrombolysis may cause false-negative DWI findings. These patients were excluded from the stroke mimic cohort[1,2,4,5,7] or classified as having "neuroimaging negative cerebral ischemia"[8]; or "neuroimaging

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negative ischemic stroke".[10] This designation, however, is not supported by evidence regarding averted infarction following thrombolysis[14] or DWI sensitivity in acute ischemic stroke.[15]

Herein, we report a retrospective analysis of acute ischemic stroke patients treated with thrombolytic therapy from our institution using a DWI-based definition of ischemic stroke. The purpose of this study is to compare stroke mimic patients to ischemic stroke patients who received thrombolytic therapy. We illustrate how using a non-imaging-based definition of ischemic stroke may artificially inflate favorable outcomes in outcomes research.

Materials and Methods

Study Design

We conducted a retrospective cohort study of all acute ischemic stroke patients treated with alteplase from our prospective stroke registry for the time period of August 2013 to December 2017. Our hospital is a 547-bed academic center and regional comprehensive stroke center. Patients more than or equal to 18 years of age who were treated with alteplase within 4.5 hours of symptom onset were included. Patients treated via our telestroke network, outside hospital transfers, patients undergoing mechanical thrombectomy without alteplase, and patients with missing data were excluded. Institutional review board approval was obtained for this review. One chart abstractor was blinded to the study hypothesis and collected data. The chart abstractor underwent institutional training regarding ethical research practice and was given a 30-minute training session; and written instructions on how to systematically obtain data from patient charts. A sample of charts was reviewed independently by the primary author to ensure accuracy.

Our institution follows the American Heart Association guidelines for the management of acute ischemic stroke.[16] All patients who present to the Emergency Department are evaluated by an emergency medicine attending, a member of our dedicated stroke service, and an emergency medicine or critical care pharmacist (between 07:00 and 21:30). Nonenhanced cranial computed tomography and, in select cases, computed tomography angiography of the head and neck were obtained prior to treatment with alteplase. The final decision for treatment with alteplase is made by the stroke service attending physician. Following the completion of the alteplase infusion, patients are monitored for at least 24 hours in a dedicated neurointensive care unit.

The following variables were collected from our institutional database: gender, age, risk factors (hypertension, diabetes, and atrial fibrillation), admission glucose, admission National Institute of Health Stroke Scale (NIHSS), admission mean arterial pressure, onset-to-treatment time, adverse events, length of stay (LOS), discharge NIHSS, discharge destination, and 3-month modified Rankin score (mRS). All neuroimaging for the hospitalization associated with thrombolytic treatment was reviewed. Final diagnoses were determined retrospectively. Diagnosis of acute ischemic stroke was assigned only to patients with infarction present on post-thrombolysis DWI. Diagnosis of stroke mimic was determined by the absence of infarction on post-thrombolysis DWI obtained within 24-72 hours from treatment. In patients with a negative post-thrombolysis DWI, the etiology of the stroke mimic was determined by all 3 authors after reviewing documentation for the hospitalization, including notes by the treating attending physician. Symptomatic intracranial hemorrhage (ICH) was defined as a new hemorrhage not previously seen on nonenhanced cranial computed tomography associated with decline in neurological status (4 points in the NIHSS or death); and hemorrhage was the identified as the cause of neurologic deterioration.[17]

Outcomes and Analysis

We compared the baseline characteristics of ischemic strokes and stroke mimics including the frequency, vascular risk factors (age, hypertension, diabetes, and atrial fibrillation), admission predictors of outcome (NIHSS, glucose, mean arterial pressure, and onset-to-treatment time). Stroke mimics were categorized by etiology. Outcomes selected a priori for comparison included LOS; discharge NIHSS less than 2; discharge destination; in-hospital mortality; symptomatic intracranial hemorrhage; and 3-month mRS. Frequency of discharge destination home from the entire cohort was evaluated before and after exclusion of stroke mimics. The odds of discharge destination home comparing transient ischemic attacks (TIA) to other stroke mimics were also evaluated. Discharge destination home was chosen due to its strong correlation with 3-month mRS[18] and also because of its use as an endpoint in national registries.[19]

Baseline characteristics were described as means with standard deviations or medians with interquartile ranges, and percentages. Continuous parametric variables were compared using a *t* test. Continuous nonparametric data were analyzed utilizing the Mann-Whitney *U* test. A Shapiro-Wilk test was used to determine normality. Chi-square test or Fischer's exact test were used to compare categorical variables. A P value $< .05$ was considered significant in the univariate analysis.

Results

Baseline Characteristics and Stroke Mimic Etiologies

Overall, 163 charts were identified in our ischemic stroke database during the study period. Of these15 were excluded due to alteplase treatment via our telestroke network; 3 were excluded due to no post-thrombolysis DWI due to pacemaker placement; 7 were excluded due to no

treatment with alteplase (mislabeled as treated patients in the registry); and 20 were excluded due to treatment with IV alteplase and mechanical thrombectomy; or mechanical thrombectomy alone. Hundred and eighteen charts were left for inclusion in the primary analysis.

The baseline characteristics of the stroke mimics are detailed in Table 1. Over the study period, we treated 118 patients with alteplase for suspected acute ischemic stroke of which 33 (27.9%) were assigned a diagnosis of stroke mimic. Stroke mimics were younger; had fewer vascular risk factors (hypertension, diabetes, and atrial fibrillation); and had lower glucose on presentation. The etiologies of our stroke mimics are detailed in Table 2. TIA was the most common stroke mimic, followed by conversion disorder. There were no cases of disagreement between the attending physician documentation and our retrospective determination of stroke mimic etiology; however, this is limited by 4 stroke mimic cases in which documentation was deemed to be ambiguous. Two of these cases were ultimately assigned a diagnosis of recrudescence of stroke symptoms; and 2 were diagnosed with TIA. The final diagnoses for these cases were made by consensus of all 3 authors.

Patient Outcomes and Reduction in Favorable Outcomes

Table 3 details the patient-centered outcomes. Stroke mimics had a shorter LOS; were more often discharged home; and were more likely to have favorable 3-month mRS (100% versus 29.7%). Of note, the 3-month mRS was only available for 37 ischemic stroke patients and 6 stroke mimic patients. One patient in the stroke mimic group had a symptomatic intracranial hemorrhage. This patient's final diagnosis was sepsis with septic cerebral emboli.

Table 4 details the reduction in a favorable discharge destination of alteplase treated patients after stroke mimics are excluded. Both TIA and other stroke mimics had greater odds of discharge destination home compared to ischemic strokes. The odd's ratio for discharge destination home for TIA was 6.42 (95% confidence interval [CI] 1.31-31.6) and for other stroke mimics was 3.81 (95% CI 1.36-10.7).

Table 2. *Stroke mimic etiologies*

Stroke mimics (n = 33)	Frequency, No. (%)
Transient ischemic attack	11 (33.3)
Conversion disorder	10 (30.3)
Migraine	3 (9)
Recrudescence of stroke symptoms	2 (6)
Seizure	2 (6)
Sepsis	2 (6)
Peripheral neuropathy	1 (3)
Subdural hematoma	1 (3)
Parkinson's disease	1 (3)

Discussion

Several similarities exist between our retrospective cohort and prior studies. Our study supports the favorable outcomes of stroke mimics treated with thrombolysis.[1-10] Only one stroke mimic had a symptomatic intracranial hemorrhage. This patient was diagnosed with infective endocarditis; and had multiple, hemorrhagic, contrast-enhancing cerebral lesions. The differences in outcomes between studies may be in part due to differences in the definitions of favorable outcomes and the timing at which outcomes were assessed. The etiologies of stroke mimics also vary between studies.[3] We suspect this range is most likely a reflection of sample bias due to relatively small sample size among stroke mimic studies, including ours.

The prevalence of stroke mimics varies widely in the literature and is overall higher in our cohort.[3] A major difference in our study is a strict DWI-based definition of ischemic stroke. In 2 studies[6,8] the prevalence of negative post-thrombolysis DWI was 21% and 26%, comparable to our prevalence of 27.9%. Therefore, it is likely that

Table 1. *Baseline characteristics of alteplase treated patients*

	Ischemic Stroke (N = 85)	Stroke Mimic (N = 33)
Gender, male, n (%)	47 (74.6)	16 (25.4)
*Age, y, median (IQR, 25-75)	69 (60-76)	53 (35-69)
*Hypertension, n (%)	67 (78.8)	17 (51.5)
*Diabetes, n (%)	28 (32.9)	3 (9.09)
*Atrial Fibrillation, n (%)	20 (23.5)	1 (3.03)
*Admission Glucose, Median (IQR, 25-75)	128 (105-168)	104 (95-124)
Admission NIHSS, Median (IQR, 25-75)	7 (4-12)	5 (3-8)
Admission MAP Median (IQR, 25-75)	105 (95-121)	105 (92.67-112)
OTT 0-90 minutes, n (%)	31 (36.5)	9 (27.7)
OTT 91-180 minutes n (%)	40 (47.1)	18 (54.6)
OTT 180-270 minutes n (%)	13 (15.3)	6 (18.8)

Abbreviations: NIHSS, National Institute of Health Stroke Scale; MAP, mean arterial pressure; OTT, Onset-To-Treatment;.
*$P < .05$.

Table 3. *Alteplase treated patient outcomes*

	Ischemic stroke (N = 85)	Stroke mimic (N = 33)
*Length of stay, median (IQR, 25-75)	4 (2-8)	2 (2-3)
Discharge NIHSS <2, No. (%)	34 (40.0)	18 (54.6)
*Discharge home	35 (41.2)	25 (75.8)
Discharge NIHSS, median (IQR, 25-75)	3 (1-10)	1 (0-3)
In-hospital mortality, No. (%)	5 (5.88)	0 (0.00)
Symptomatic ICH, No. (%)	7 (8.23)	1 (3.03)

Abbreviations: ICH, intracerebral hemorrhage; NIHSS, National Institute of Health Stroke Scale; mRS, Modified Rankin Score.
*$P < .05$.

differences in definitions of stroke mimics explain this discrepancy.

In prior studies, patients without neuroimaging evidence of acute ischemic infarction may have been excluded from the stroke mimic group if the clinical diagnosis was suspected to be a cerebrovascular etiology.[1,2,4,5,7,8,10] For example, if the clinician suspected a cerebral infarction had been averted by thrombolysis by rapid recanalization or the DWI was falsely negative, these patients may have been assigned to the ischemic stroke group; or other groups called "neuroimaging negative cerebral ischemia"[8]; or "neuroimaging negative ischemic stroke."[10] This group makes up a significant number of patients excluded from the stroke mimic group. For example, in the largest stroke mimic study[10] the reported prevalence of "neuroimaging negative ischemic stroke" was 27.9%.

These retrospectives studies were published prior to prospective study by Freeman et al[14] which was the first study to address the issue of infarction averted by thrombolysis.[14] In this study, 267 patients had a pretreatment DWI and only those with a positive lesion were treated with alteplase. Following treatment, only 2 patients (<1%) had complete DWI lesion reversal. The authors convincingly showed that averted infarction after intravenous rt-PA is rare. Given that current evidence suggests the "aborted stroke" is extremely rare, we suspect that cases of "neuroimaging negative cerebral ischemia"/"neuroimaging negative ischemic stroke" mostly represent TIAs. Indeed, in the study by Chernyshev[8] which included DWI in their evaluation of ischemic stroke, they noted presumptive diagnoses of either TIA or "aborted stoke" in the "neuroimaging negative cerebral ischemia" group.

Table 4. *Reduction in discharge destination home without stroke mimics*

Discharge destination home of all patients treated with alteplase	50.1%
Outcomes excluding stroke mimics	41.7%
Reduction in favorable outcomes	8.4%

Abbreviations: NIHSS, National Institute of Health Stroke Scale; mRs, Modified Rankin Scale.

A major difference between our single-center study and prior retrospective studies is the inclusion of TIAs in the stroke mimic group. In one single center retrospective study, similar to our study, TIA was the most common etiology of negative post-thrombolysis DWI. Most studies[1-3,5,7,10] do not clarify if TIAs treated with alteplase are included in ischemic stroke outcomes as part of an "acute neurovascular syndrome[20]" or the "neuroimaging negative ischemic stroke"/"neuroimaging negative cerebral ischemia" group due to presumed "aborted stroke" similar to the study by Chernyshev.[8]

Although both TIAs and ischemic strokes are acute neurovascular syndromes, there may be ambiguity in the final diagnosis based on adherence to definitions and whether or not DWI is included in the evaluation.[20] The accuracy of a clinical only diagnosis of cases of negative post-thrombolysis DWI and TIA should be considered. In a study that surveyed 65 neurology physicians on 10 case-vignettes of patients treated with thrombolysis with subsequent clinical improvement who lacked radiographic evidence of acute infarction, interobserver agreement was fair in four case-vignettes (Kappa .21 [95% CI .06-.54]) and slight in 6 case-vignettes (Kappa .04 [95% CI 0-.44]).[21] Another study found poor agreement among 3 fellowship trained vascular neurologists on the diagnosis of TIA in 55 patients when relying on history and examination only.[22] Furthermore, if the final diagnoses is determined solely by the physician that was responsible for making the decision regarding thrombolytic therapy in the acute phase, this may be a source of bias. To our knowledge, this has not been systematically assessed in stroke outcomes research.

Most importantly, in addition to limitations of a clinical-only diagnosis, patients with TIAs have outcomes closely related to other stroke mimics. For example, in the studies by Chernyshev et al[8] and Artto et al,[10] patients categorized as having "neuroimaging negative cerebral ischemia" or "neuroimaging negative ischemic stroke" closely mimicked the clinical outcomes of other stroke mimics when compared to neuroimaging positive ischemic strokes. In fact, patients in the "neuroimaging negative cerebral ischemia" group had slightly better outcomes than other stroke mimics in the study by Chernyshev et al.[8] This is also consistent with our single center experience. Patients with TIAs had a greater odds of favorable discharge destination compared to other stroke mimics. Therefore, in addition to the radiographic evidence, the epidemiology of these patients would suggest they are a different patient population compared to ischemic strokes.

False-negative DWI in patients with a clinical diagnosis of ischemic stroke has also been described. Many factors may be related to the prevalence of DWI negative ischemic stroke, especially if symptoms are referable to the posterior circulation.[15] Despite these limitations, a meta-analysis of 3236 patients yielded a pooled prevalence of 6.8% false negative DWI.[15] Of note, there were no patients in our cohort in which the clinician suspected a false-negative DWI due to symptoms referable to the posterior circulation. Therefore, even a generous estimation of averted infarction and false-negative DWI would not explain the reported 27.9% prevalence of "neuroimaging negative ischemic stroke."

A definition of stroke mimic that does include DWI may be an important source of bias in stroke outcomes research. For example, in a large registry of acute ischemic stroke patients treated with thrombolysis, information on post-thrombolysis DWI is not collected.[23] Additionally, the methodology does not specify how stroke mimics are defined or excluded from the registry, if at all. In another large national registry reporting discharge destination home, stroke mimics, but not "aborted strokes," are excluded[24]; and information on post-thrombolysis DWI is not provided. In our dataset, exclusion of all stroke mimics led to an 8.4% reduction in patients discharged home (Table 4). TIAs in our cohort had greater odds of discharge destination home compared to other stroke mimics; and therefore, we suspect that residual bias exists in these registries if post-thrombolysis DWI is not accounted for and TIAs are not excluded.

Bias introduced into randomized controlled trials is less problematic due to post-hoc adjustments. For example, in the "Tenecteplase versus alteplase for management of acute ischemic stroke (NOR-TEST)" study,[13] 99 patients (18%) in the tenecteplase arm and 91 (17%) patients in the alteplase arm had a final discharge diagnosis of stroke mimic. Enrollment of stroke mimics between arms was similar in this study by chance and had little effect on the per-protocol analysis. Given the power of the NOR-TEST trial, it is likely that randomization guarded against imbalances in the enrollment of stroke mimics. Nevertheless, an adjusted analysis was reported. In the "Effect of Alteplase versus Aspirin on Functional Outcome for Patients with Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits" (PRISMS) RCT, there was no difference in post-hoc adjusted analysis for stroke mimics.[12] The median baseline NIHSS scores were 2.3 in the alteplase arm and 2.0 in the placebo arm. Given the comparable good outcomes of minor strokes and stroke mimics, it is unsurprising that outcomes in the intention to treat and per-protocol groups were similar. Unlike modern thrombolytic trials, the "Tissue Plasminogen Activator for Acute Ischemic Stroke" (NINDS rt-PA)[25] and "Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke" (ECASS-III)[17] studies did not report the enrollment of stroke mimic. It is possible that enrollment of stroke mimics diluted or inflated the efficacy of thrombolysis; further conclusions, however, remain speculative in the absence of neuroimaging.

The study by Burton et al mimics our concerns regarding artificial inflation of reported favorable outcomes due to stroke mimics.[9] In their retrospective cohort, they noted that the rate of alteplase treated stroke mimics has increased at spoke hospitals without pretreatment DWI due to multiple factors. These include a focus on reducing door to needle times and generalized acceptance of the safety profile for the treatment of stroke mimics. They noted that alteplase treated patients at spoke hospitals had significantly more favorable outcomes than patients treated at hub hospitals. After excluding stroke mimics, patients treated at spoke and hub hospitals had similar outcomes. These results are congruent with our conclusion regarding artificial inflation of favorable outcomes in stroke outcomes research.

The study by Burton et al and our data support the importance of adherence to an DWI-based definition of stroke mimic for future studies given the lack of evidence for infarction averted by thrombolysis[14]; the low prevalence of false negative DWI[15]; the poor inter-rater agreement of a clinical only diagnoses[21]; and similar epidemiological outcomes between "neuroimaging negative ischemic strokes" and stroke mimics.[8,10]

This study has the notable limitations of retrospective design, single enter experience, and modest power. Although aborted stroke is a rare event, this does not preclude true aborted ischemic strokes being reclassified as stroke mimics in our classification. Furthermore, in the study by Freeman et al,[14] only patients with a positive DWI at baseline were included. There may be a select group of patients with evolving ischemia or robust collateralization with a normal early DWI excluded from this study; and this may be a source of selection bias. Our cohort had also incomplete 90-day mRS outcome data which is the gold standard outcome measure for acute ischemic stroke research. This study should be considered hypothesis generating and future studies would benefit from prospective design; multicenter experience; increased sample size; and 90-day mRS reporting.

A future area of research is how different definitions bias outcomes reporting in select populations such as minor stroke. Given that stroke mimics often have a lower NIHSS, we suspect that this effect may be more profound if DWI is not considered.

In conclusion, stroke mimics had fewer stroke risk factors and more favorable discharge destination outcomes compared to ischemic strokes treated with alteplase. Outcomes unadjusted for stroke mimics led to an artificial inflation of discharge destination home.

Conflicts of Interest

The authors have no conflicts of interest to diclose.

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