Migraine History: A Predictor of Negative Diffusion-Weighted Imaging in IV-tPA-Treated Stroke Mimics

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Background: Migraine, seizures, and psychiatric disorders are frequently reported as "stroke mimics" in patients with negative diffusion-weighted imaging (DWI) after IV-tPA. We sought to determine predictors of negative DWI in suspected stroke patients treated with IV-tPA. *Method:* A retrospective case-control study encompassing all acute stroke patients treated with IV-tPA (at our hospital or "dripped and shipped") from January 2013 to December 2014 was con- ducted. A total of 275 patients were identified with 47 negative DWI cases and 228 positive DWI controls. Variables including demographic factors, stroke characteristics, and clinical comorbidities were analyzed for statistical significance. A multivariate logistic regression was performed (SPSS-24) to identify predictors of negative DWI. *Results:* Approximately 17% of patients had negative DWI after IV-tPA. Compared to controls, migraine history independently predicted negative DWI (odds ratio [OR] 5.0 95% confidence interval [CI] 1.03-24.6, $P = .046$). Increasing age (OR .97 95% CI .94-.99, $P = .02$) and atrial fibrillation (OR .25 95% CI .08-.77, $P = .01$) predicted lower probability of negative DWI. Gender, admission NIHSS, treatment location, preadmission modified Rankin scale, diabetes mellitus, hypertension, hyperlipidemia, symptom side, seizure history, and psychiatric history did not predict negative DWI status. *Conclusions:* In our study, roughly 1 in 6 patients treated with IV-tPA were later found to be stroke mimics with negative DWI. Despite a high proportion of suspected stroke mimics in our study, only preexisting migraine history independently predicted negative DWI status after IV-tPA treatment in suspected stroke patients.

Key Words: Stroke mimics—diffusion-weighted imaging—thrombolytic—acute ischemic stroke—MRI

Introduction

Migraine is a common neurological condition accounting for over 800,000 emergency room visits annually[1] with a reported prevalence of 14%-17% among females and 5%-6% in males.[2] Most commonly, migraine headaches present without any neurologic dysfunction. However, in approximately 10% of migraineurs, neurologic deficits are the main presenting symptom (commonly referred to as acephaligic migraine) despite no or minimal associated headache.[3] The acute onset of neurologic symptoms among migraine patients (particularly first-time events), or newly experienced complex aura can be erroneously diagnosed as acute stroke symptoms.

Acute neurologic symptoms of nonvascular etiologies simulating strokes have been typically named "stroke

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mimics."[4] The frequency of stroke mimics in the emergency room has been reported to represent up to 30% of all suspected stroke diagnosis.[5] Beyond migraine, several other nonvascular disorders presenting with acute neurological deficits such as seizure, conversion disorders, metabolic or infectious encephalopathies, neurodegenerative disorders, peripheral neuropathies, and syncope represent the remainder of stroke mimics.[6] Due to the urgent nature of acute ischemic stroke and known consequences associated with treatment delays, a significant proportion of stroke mimics receive intravenous tissue plasminogen activator (IV-tPA)[7] with up to 20% of IV-tPA recipients with negative diffusion-weighted imaging (DWI).[8] Investigating the subset of patients with negative DWI-MRI after IV-tPA administration would allow us to better understand predictors of stroke mimics.

Methods

After institutional IRB approval, we evaluated all consecutive patients 18 years old with suspected diagnosis of acute ischemic stroke that received IV-tPA at our institution or presented to our emergency department from a transferring hospital under the "drip and ship" paradigm between January 2013 and December 2014. Our institution is a large tertiary care hospital and comprehensive stroke center serving as the hub among several affiliated hospitals in a hub and spoke model for our stroke system of care. Patients with suspect stroke at the spoke facilities that are treated with IV-tPA and require a higher level of care are transferred to the hub and have been included in the study. We then conducted a retrospective case-control study comparing post-IV-tPA patients with negative MRI to post-IV-tPA patients with positive DWI restriction, (ie, evidence of acute ischemic stroke on MRI). Data collected included patient demographics, clinical presentation, and medical history, National Institutes of Health Stroke Scale (NIHSS) on admission and discharge, discharge modified Rankin Scale score, MRI findings, symptomatic intracerebral hemorrhage, as defined as worsening of NIHSS by greater than or equal to 4 points, dominant side versus on dominant side of deficits (right versus left, respectively) and final discharge diagnosis. Initial and follow-up imaging with CT and/or MRI was performed as a part of our routine stroke care.

The study group consisted of post-IV-tPA patients with "negative MRI DWI." The control group consisted of IV-tPA patients with evidence of ischemic stroke on MRI or "positive MRI DWI." Patients who received IV-tPA with abnormal MRI suggestive of an etiology other than acute ischemic stroke such as brain tumor or brain infection were excluded. Within the study period, a total of 275 patients met study criteria with 47 patients within the negative DWI group and 228 patients within the positive DWI group after IV-tPA.

For both groups, past medical history, previous stroke or transient ischemic attack, suspected risk factors for a stroke mimic (migraine, epilepsy, and psychological disturbance) history of the present event, including nature of the neurological symptoms, symptom onset, and neurological examination including the NIHSS were compared for statistical significance. For univariate categorical variables, chi-square test and continuous variable independent sample t test was performed. A multivariate logistic regression analysis was performed to identify the independent predictors of DWI negative MRI.

Results

The mean age was 62.3 years in the negative MRI group and 72 years in the positive MRI group. There was no difference in prevalence of hypertension or diabetes, though atrial fibrillation was more prevalent in the DWI positive group as compared to the DWI negative (37.3% versus 8.5%) (odds ratio [OR]: .250, 95% confidence interval [CI]: .080-.777, $p = 0.017$). Migraine history was 5 times more prevalent in the DWI negative group (10%) as compared to DWI positive (2%) (OR: 5, 95% CI 1.026-24.582, $p = 0.04$, $p = 0.017$). Additional baseline characteristics of both groups are listed in Table 1. Although the mean NIHSS in the DWI negative group was higher than the DWI positive group, this was not statistically significant (12.8 versus 9.5, $P = .298$). There was no significant difference of dominant side of deficits (defined as patient with right sided or left side motor and/or sensory deficit),

Table 1. *Patient characteristics*

	DWI −ve	DWI +ve	*P* value
Total N	47	228	
Mean age (years)	62.34 (15.25)	72.00 (15.30)	<.001
Female gender (%),	42.6	47.4	.547
Mean admit NIHSS	9.55 (7.49)	12.85 (8.14)	.298
Tx from OSH (%)	42.6	44.3	.263
Preadmit MRS (%)			.344
1	70.0	66.0	
2	7.5	8.5	
3	9.3	6.4	
4	4.4	4.3	
5	2.6	0	
Diabetes (%)	21.3	25.4	.547
Hypertension (%)	78.7	81.1	.702
Psychiatric Dx (%)	14.6	15.8	.878
Seizure history (%)	6.4	3.5	.360
Migraine history (%)	10.6	1.3	.001
Dominant (right) sided deficit (%)	40.4	36.8	.213
Atrial fibrillation (%)	8.5	37.3	<.001
Hyperlipidemia (%)	48.9	57.0	.310
Symptomatic ICH (%)	2	8	.135

DWI, diffusion-weighted imaging; Dx, diagnosis; MRS, modified Rankin scale; Tx from OSH (transferred from outside hospital after thrombolytic treatment); .

Table 2. *Multivariate logistic regression model for negative diffusion-weighted imaging in patients treated with IV thrombolytic*

Covariate	OR	95% CI	*P* (sig)
Age	.969	.944-.995	.020
Sex	.615	.299-1.268	.188
Admission NIHSS	.974	.927-1.023	.298
Location of treatment (inhouse versus outside hospital treatment)	.659	.318-1.365	.261
Preadmission mRS	1.116	.835-1.491	.458
Diabetes	.912	.383-2.169	.835
Hypertension	1.403	.559-3.522	.471
Psychiatric diagnosis	.838	.311-2.256	.726
History of seizures	1.663	.348-7.945	.524
History of migraine	5.021	1.026-24.582	.046
Dominant (right) sided deficit	.601	.357-1.015	.057
Atrial fibrillation	.250	.080-.777	.017
Hyperlipidemia	.780	.377-1.614	.503

presence of psychiatric history, seizure history or treatment at our institution versus transferred ("drip and ship") (Table 2). In addition, 13 patients in the negative DWI group had a final discharge diagnosis of "aborted stroke," constituting a potential false negative rate of 27.6%. Only 1 patient in the negative DWI patient cohort had a symptomatic ICH versus 19 in the DWI positive group (2% versus 8.3%).

Discussion

Stroke mimics are numerous and distinguishing between mimics and true strokes acutely can be challenging.[9] In our study, the proportion of patients that received IV-tPA and had negative DWI represented 17% of all patients, similar to previous reports.[10-15] Although the focality of neurologic signs has been suggested to indicate true stroke over mimics, the presentation of stroke is at times unpredictable.[14] Given the "time is brain dogma" and the known functional detriment associated with every 15-minute delay without treatment, every minute in decision-making is critical.[16]

Tools to help predict stroke mimics in the emergency department setting have been previously proposed. The FABS score, a scale with 6 variables with 1 point for each variable present (absence of Facial droop, negative history of atrial fibrillation, age less than 50 years, systolic Blood pressure less than 150 mm Hg at presentation, history of seizures, and isolated sensory symptoms without weakness at presentation) has been reported to identify stroke mimics in patients with a score greater than or equal to 3 with 90% sensitivity (95% CI, 86%-93%) and 91% specificity (95% CI, 88%-93%).[17] Other scales, such as the Recognition of Stroke in the Emergency Room scale that help distinguish true strokes have a high reported sensitivity of (92%) and specificity (86%);[18] however, neither score take into account history of migraine headaches.

Migraine is a common neurologic disorder especially in young population and accounts for roughly 12% (95% CI 6.34%-22.31%) of stroke mimics.[18,19] In this scenario, the decision-making for administration of the IV thrombolytic is challenging as a minority of patients with acute stroke present with headache.[19] As expected, the prevalence of migraine headaches among stroke mimics is higher. Our study showed that patients with migraine are 5 times higher in the group with negative DWI than in the group with true stroke. Terrin et al published a systematic review that showed migraine with aura alone being responsible for up to 18% of "improper thrombolytic treatments."[19] The safety of IV thrombolytic in eligible patients is high, which support the administration of this drug in patients with stroke symptoms as per current guidelines.[20] The higher NIHSS in patients with stroke mimics was a chance finding due to sample size and was not statistically significant.

Some limitations should be considered in this study. The main limitations are a single center and retrospective design study. Other limitation was not included the subgroup of migraine with aura that could relevant in the setting of stroke mimic and not clearly documented in the chart.

Conclusions

Stroke mimics continue to be treated in the emergency department setting due to concern of missing an opportunity for treatment. In our study, we found that migraine headache is the only factor that predicted stroke mimic status. Although helpful in acute evaluation, this should not preclude treatment with IV-tPA considering the outcomes of missed strokes and low complication risk of IV-tpa in these patients. In younger patients with known migraine history and no traditional risk factors, acute MRI of the brain can be considered to make the final decision regarding IV-tPA. This may also help reduce the misdiagnoses a patient with an "aborted stroke" and the consequences a diagnosis as such may bear.

Declaration of Competing Interest

None.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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