Bilateral Cerebral Infarcts on Diffusion-Weighted Imaging Predict Etiology of Stroke

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Abstract

**Objective:** To identify significant etiological differences between patients with bilateral and unilateral Acute Ischemic Stroke (AIS).

**Background:** Limited data suggest bilateral AIS is relatively common, accounting for approximately ten percent of AIS. However, stroke etiology as defined by TOAST criteria has not been well defined for patients with evidence of bilateral AIS on MRI.

**Methods:** Consecutive patients with AIS presenting to our stroke center (July 2008 to July 2013) were retrospectively identified. Patients with bilateral strokes were defined by restriction on DWI/ADC sequences. Univariate analyses and multivariate logistic regression were performed with appropriate test statistics.

**Results:** Of the 641 AIS patient who met inclusion criteria, 74 (11.5%) had bilateral AIS findings on MRI. Compared to patients with unilateral AIS findings, patients with bilateral AIS findings had higher rates of cardioembolic disease (30.1% vs. 21.8%, p<0.001), hypercoagulable state (8.2% vs. 2.0%, p<0.001), and vasculitis (6.9% vs. 1.4%, p<0.001) but did not have significantly different rates of atrial fibrillation by telemetry or ECG (1.4% vs. 5.8%, p=0.111) or ejection fraction <30% (7.6% vs. 3.5%, p=0.113). Patients with bilateral AIS findings were over seven times as likely to have vasculitis (OR=7.11, 95% CI=2.1083-23.9786, p=0.002) and four times as likely to have a hypercoagulable state (OR=4.69, 95% CI 1.6737-13.1173, p=0.003) as the etiology relative to patients with unilateral stroke, but bilateral AIS findings did not significantly increase the odds of a cardioembolic stroke (OR=1.40, 95% CI 0.7917-2.4715, p=0.248).

**Conclusions:** Cardioembolic etiology of stroke occurs more often in patients with bilateral acute infarction on imaging, but only the odds of vasculitis and hypercoagulable state as etiologies were significantly increased by bilateral acute infarction. Further studies are warranted to understand imaging characteristics of bilateral strokes in regard to etiology.

Keywords: Acute ischemic stroke; Bilateral stroke; Stroke etiology; Cardioembolic; Hypercoagulable; Vasculitis

Introduction

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classifies subtypes of Acute Ischemic Stroke (AIS) by etiology[1]. Subtypes of stroke include cardioembolic disease, large artery atherosclerosis, small vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology. Other determined etiologies of stroke include such causes as primary or secondary hypercoagulable states, non-atherosclerotic vasculopathies including primary or secondary cerebral vasculitides, and hematologic disorders involving acquired autoantibodies or formed blood elements[2]. Distribution of stroke etiology is generally reported around 25% cardioembolic disease, 20% large artery atherosclerosis, 20% small vessel occlusion, 5% other etiology, and 25% undetermined etiology[3, 4]. The etiology of AIS influences management of AIS and prognosis after AIS. Thus, TOAST classification is a valuable tool for the physician treating stroke. Physicians rely upon clinical features, imaging studies, and laboratory testing to classify AIS. Magnetic Resonance Imaging (MRI) increases the accuracy of stroke etiology de-
Bilateral stroke is seen on MRI as restriction on DWI sequences on both sides of the brain, representing multiple acute infarcts. The pathophysiology of bilateral AIS can involve embolization of a clot from a pathway common to vasculature of both sides of the brain, such as the atrium of the heart, the aortic arch, or, more rarely, bilateral carotid arteries or a single carotid artery in the presence of a common origin of both ACAs. Clot embolization corresponds with a TOAST classification of cardioembolic disease or large artery atherosclerosis in which a clot showers to multiple vascular territories of the brain. Bilateral strokes can also be caused by other processes that limit blood flow in multiple territories, such as vasculitides, hypercoagulable states, and hematologic disorders. Vasculitides are diffuse inflammatory processes that involve the neurovasculature in stroke patients, hypercoagulable states involve all vascular beds, including the neurovasculature, and hematologic disorders restrict blood flow through the neurovasculature. The incidence of bilateral AIS findings on DWI approaches 10% [7], yet the most common etiologies of bilateral AIS are unclear. A study in 2000 found bilateral stroke to be associated with malignancy, elevated fibrinogen levels, and elevated hematocrit levels [8], corresponding to secondary hypercoagulable states and hematologic disorders classified in the TOAST scheme as causes of other determined stroke etiology. In an earlier study, bilateral hemispheric strokes of the anterior circulation were associated with cardioembolic disease or bilateral carotid disease [9]. Further, although risk factor profiling has been performed for subtypes of stroke, yielding such well-known associations as cardioembolic stroke and atrial fibrillation [10], specifically, risk factors for bilateral versus unilateral AIS have not been thoroughly studied.

The purpose of this study was to determine the relationship between bilateral AIS findings on DWI sequences and stroke etiology in our stroke registry as well as to examine risk factors and biomarkers for bilateral stroke.

**Methods**

We conducted a single-center cross-sectional study of patients with AIS admitted to our comprehensive stroke center between July 1, 2008 and July 31, 2013. Patients with AIS were identified retrospectively from a prospectively collected stroke registry [11]. Inclusion criteria were age of at least 18 years and first-time admission for diagnosis of stroke. Patients were excluded if MRI was not performed or if there were no acute stroke findings on MRI. Acute stroke findings were defined as restriction on DWI/ADC sequences of MRI. Restrictions on DWI/ADC sequences were classified as unilateral or bilateral. Stroke risk factors were considered present only if reported or documented within the electronic medical record. Inpatient complications were defined as per our prior work [12, 13]. Stroke subtype was defined according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. Categorical variables were assessed using Pearson Chi-square and continuous variables were assessed with Wilcoxon Rank Sum. Logistic regression was used to assess the odds of dichotomous outcomes for each TOAST classification separately as predicted by bilateral MRI findings. IRB approval was obtained from Tulane University (IRB 447869-2).

**Results**

Of the 641 AIS patient who met inclusion criteria, 74 (11.5%) had bilateral acute AIS findings on MRI (Table 1). These patients had a median age of 62, 52.7% were female, 66.2% were African American, and demographics were overall similar to patients with unilateral infarction (Table 2). Affected vascular territories of the bilateral infarcts are reported in Table 3. Compared to patients with unilateral MRI findings, patients with bilateral findings had significantly higher rates of stated history of Congestive Heart Failure (CHF) (18.9% vs. 7.1%, p<0.001) and diabetes (36.4% vs. 29.6%, p=0.025). The only significant difference between the bilateral compared to unilateral groups investigated laboratory values was factor VIII level (250.9 vs. 178.3, p<0.001). Bilateral MRI patients had worse NIHSS scores at admission (9 vs. 5, p=0.005) and discharge (5 vs. 2, p=0.001). The distribution of discharge mRS scores were significantly different, however, median values were identical (3 vs. 3, p=0.007). Patients with bilateral and unilateral infarcts had similar mRS scores 90 days post-discharge (3 vs. 2, p=0.08). Stroke etiology was classified during the index admission for stroke, and those etiologies diagnosed as hypercoagulable state or vasculitis were supported by specific evidence reported in Tables 5 and 6, respectively. Compared to patients with unilateral AIS findings, patients with bilateral AIS findings had higher rates of cardioembolic disease (30.1% vs. 21.8%, p=0.001), hypercoagulable state (8.2% vs. 2.0%, p<0.001), and vasculitis (6.9% vs. 1.4%, p<0.001). However, patients with bilateral AIS findings did not have significantly different rates of ejection fraction < 30% (7.6% vs. 3.5%, p=0.113) and actually had lower rates of atrial fibrillation by telemetry or ECG (5.4% vs. 9.2%, p=0.021). Patients with bilateral AIS findings were over seven times as likely to have vasculitis (OR=7.11, 95% CI=2.1083-23.9786, p=0.002) and four times as likely to have a hypercoagulable state (OR=4.69, 95% CI=1.3461-16.9303, p=0.013).
Unilateral 88.5% n=567  
Bilateral 11.5% n=74  
p value

Demographics
Age, median (IQR) 63 (3, 103) 62 (19, 98) 0.25
Gender, no. female (%) 260 (46.2) 39 (52.7) 0.291
Race, no. African American (%) 376 (66.8) 49 (66.2) 0.195
BMI, median 27.3 27.6 0.349

Past medical history
Diabetes (%) 166 (29.6) 27 (36.5) 0.025
Hypertension (%) 417 (74.1) 61 (82.4) 0.207
Stroke 214 (38.0) 33 (44.6) 0.678
Coronary artery disease (%) 106 (18.8) 14 (18.9) 0  
Atrial fibrillation on telemetry, history, or ECG (%) 62 (11.5) 2 (3.0) 0.032

Baseline laboratory values
Factor VIII, median (range) 178.3 (67.0, 608.0) 250.9 (90.0, 407.2) <0.001
Serum glucose, median (mg/dl) (range) 116 (10, 625) 118 (66, 447) 0.617
HbA1c, median (range) 5.9 (3.4, 16.0) 5.9 (3.5, 12.8) 0.724
Triglycerides, median (range) 106 (23, 997) 108 (27, 467) 0.873
Total cholesterol, median (range) 162 (53, 329) 161 (69, 406) 0.82
HDL, median (range) 42 (5, 106) 41 (7, 100) 0.363
LDL, median (range) 99 (15, 246) 99 (24, 239) 0.95
Hematocrit, median (range) 39.5 (17.6, 57.6) 38.3 (19.4, 51.7) 0.093
Platelets, median (range) 222 (7, 751) 222 (39, 520) 0.556

NIHSS
Admission, median 5 9 0.006
Discharge, median 2 5 0.011
mRS
Discharge, median (range) 3 (0-6) 3 (0-6) 0.007
90 days post-discharge, median (range) 2 (0-6) 3 (0-6) 0.08

Table 2: Demographics, baseline lab values, and NIHSS characteristics of patients with restriction on DWI according to unilateral or bilateral MRI findings (n=641). 95% CI 1.6737-13.1173, p=0.003 as the defined TOAST etiology relative to patients with unilateral stroke, but bilateral AIS findings did not significantly increase the odds of a cardioembolic stroke (OR=1.40, 95% CI 0.7917-2.4715, p=0.248). Patients with bilateral AIS findings had significantly more TEE procedures performed during workup of stroke than patients with unilateral AIS findings (42.4% vs. 25.5%, p=0.011).

Table 3: Vascular territories involved in patients with bilateral stroke findings on MRI according to vessel size and circulation (n=65). Large vessels include ACA, MCA, PCA, SCA, AICA, PICA, and BA. Small vessels include perforating branches of large vessels. Anterior circulation includes ACA, MCA, and perforating branches of ACA and MCA. Posterior circulation includes PCA, SCA, AICA, PICA, BA, and perforating branches of these large vessels.

Table 4: Imaging and tests performed on patients with restriction on DWI according to unilateral or bilateral MRI findings (n=641).

Discussion
The most common etiology of bilateral AIS in patients in our stroke registry is cardioembolic stroke. Cardioembolic stroke occurs when a formed clot, typically in the left atrium, embolizes and travels into multiple vascular territories of the brain, effectively showering emboli throughout multiple parenchymal regions. We diagnosed etiology as cardioembolic per the Causative Classification of Stroke System[14], using TTE and/or TEE to identify potential cardiac sources of infarction. However, despite a higher rate of cardioembolic classification in patients suffering bilateral AIS than unilateral AIS, bilateral AIS did not increase the odds of cardioembolic stroke etiology.
Arterial panel
- Homocysteine
- MTHFR
- Anti-cardiolipin
- Anti-phosphatidylserine
- Beta-2 glycoprotein
- Factor VIII
- Von Willebrand factor antigen
- HIT antibodies
- Dil Russel viper venom test
- Lipoprotein A

Venous panel
- Anti-thrombin III
- Protein C
- Protein S
- Activated protein C resistance
- Factor V Leiden
- Factor II
- Fibrinogen

Auto-immune panel
- CRP
- ESR
- ANA
- dsDNA
- Rheumatoid factor
- SS-A
- SS-B
- c-ANCA
- p-ANCA
- Complement 3
- Complement 4

Other
- ACE levels
- Hepatitis panel
- HIV
- RPR
- SPEP
- Hemoglobin electrophoresis

Table 5: Hypercoagulation panel ordered for patients suspected of having stroke etiology of hypercoagulable state.

Patient | Imaging | Laboratory tests | CSF analysis | Other conditions
--------|---------|-----------------|--------------|---------------------
1        | angiography | -               | -            | diagnosis of lupus
2        | angiography | -               | -            | -
3        | vascular imaging other than angiography | high ESR, high CRP | - | -
4        | vascular imaging other than angiography | high CRP | supportive | -
5        | - | - | supportive | active encephalitis

Table 6: Data supporting diagnosis of vasculitis as etiology in five patients with bilateral stroke.
In summary, we expected the presence of bilateral acute infarction to predict cardioembolic pathophysiology, we found that the presence of bilateral stroke increased the probability of hypercoagulable state and vasculitis as the determined etiology of stroke. While cardioembolic strokes were more common in the bilateral stroke group of patients, the presence of bilateral stroke did not increase the probability of cardioembolic stroke as the etiology compared with unilateral stroke. Further studies are warranted to correlate bilateral infarcts with their etiology, pathophysiology, and clinical management.

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The authors have no financial considerations to disclose.

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