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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 relyupon clinical features, imaging studies, and laboratory testing to classify AIS. Magnetic Resonance Imaging (MRI) increases the accuracy of stroke etiology de-

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termination[5], and Diffusion Weighted Imaging (DWI) has emerged as a principle means of predicting stroke classification according to TOAST criteria[6].

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 byother processes that limit blood flow in multiple territories, such as vasculitides, hypercoagulablestates, 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 approaches10%[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 AIShave not been thoroughly studied.

The purpose of this study was to determine the relationship between bilateral AIS findings on DWI sequences and stroke etiologyin our stroke registry as well as to examine risk factors and biomarkers forbilateral 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 noacute 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 vascularterritories of the bilateral infarcts are reported in Table 3. Compared to patients with unilateral MRI findings, patients

	Unilateral 88.50% n=567	Bilateral 11.50% n=74
TOAST		
Cardioembolic (%)	123 (21.8)	22 (30.1)
Large vessel (%)	134 (23.8)	15 (20.6)
Small vessel (%)	141 (25.0)	0 (0.0)
Other etiology		
Vasculitis (%)	8 (1.4)	5 (6.9)
Hypercoagulable state (%)	11 (2.0)	6 (8.2)
Unknown etiology		
Cryptogenic >1 cause (%)	13 (2.3)	5 (6.9)
Cryptogenic no cause (%)	94 (16.7)	12 (16.4)
Cryptogenic incomplete workup (%)	8 (1.4)	3 (4.1)

Table 1: TOAST etiology of patients with restriction on DWI according to unilateral or bilateral MRI findings (n=641).

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 ininvestigatedlaboratory 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,

	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)	12 (16.2)	0.043
Atrial fibrillation	52 (9.2)	4 (5.5)	0.021
Congestive heart failure (%)	40 (7.1)	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 etiology than patients with unilateral AIS findings (42.4% vs. 25.5%, p=0.011).

Etiology	Vessel			Circulation		
	Large	Small	Both	Anterior	Posterior	Both
Cardioembolic	14	0	4	7	3	8
Hypercoagulable state	3	1	2	2	1	3
Vasculitis	1	1	3	2	0	3
Large vessel	11	1	0	4	6	2
Catheter-related	2	0	1	2	0	1
Cryptogenic	17	2	1	3	7	10
Other	1	0	0	0	0	1
Total	49	5	11	20	17	28

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.

	Unilateral 88.5% n=567	Bilateral 11.5% n=74	p value
Imaging and tests			
MRI			
Left acute stroke (%)	185 (28.9)	-	-
Right acute stroke (%)	177 (27.6)	-	-
MRA head (%)	357 (95.5)	69 (93.2)	0.421
Intracranial stenosis (%)	139 (39.4)	22 (32.4)	0.275
MRA neck (%)	161 (28.8)	11 (16.7)	0.034
CTA neck (%)	207 (38.9)	28 (43.1)	0.767
Carotid US (%)	174 (32.4)	27 (40.3)	0.196
Extracranial imaging (CUS, MRA neck, CTA neck)	425 (79.0)	54 (80.6)	0.761
TTE (%)	469 (87.3)	59 (89.4)	0.891
Left atrial enlargement (%)	181 (51.1)	33 (53.2)	0.779
Ejection fraction <30% (%)	18 (3.5)	5 (7.6)	0.113
TEE	137 (25.5)	28 (42.4)	0.011
Factor VIII	128 (23.8)	27 (40.3)	0.143

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 etiolo-

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
Rhematoid 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.

gy. Yet, our results show that TEE was performed significantly more during workup of bilateral AIS etiology (Table 4), suggesting possible overutilization of resources and presenting an opportunity to reduce invasive workup, cost, and hospital length of stay.

Consistent with a previous study showing an association between hypercoagulable states and bilateral hemispheric stroke in the anterior circulation[8], we found that bilateral AIS increased the odds of hypercoagulable TOAST classification. Hypercoagulability is a diffuse hematologic process, either inherited or acquired, by which there is a propensity for clot formation in the venous and arterial circulatory systems. Increased likelihood of clot formation renders multiple vascular territories, including the neurovasculature, susceptible to infarct. We diagnosed patients at our facility suspected of having a genetic thrombophilia or a hypercoagulable state by means of a hypercoagulation laboratory panel (Table 5). Interestingly, baseline factor VIII levels were significantly increased in our bilateral AIS population. However, this may be explained by selection bias due to an increased proportion of factor VIII levels ordered for patients with findings of bilateral AIS (Table 4). Factor VIII levels have previously been implicated in worse stroke outcomes[15], consistent with our finding that bilateral AIS patients had worse NIHSS both at presentation and discharge.

Bilateral AIS also increased the odds of vasculitis as etiology of stroke in this study. Vasculitidesare a collection of diseases characterized by an autoimmune state in which the blood vessels are mistakenly recognized as foreign. Primary CNS angiitis is confined to the brain, meninges, or spinal cord whereas secondary CNS vasculitis occurs in the setting of systemic vasculitis, autoimmune disease, or infectious disease[16]. The autoimmune state affects the CNS by rendering multiple neurovasculature territories restrictive to blood flow either by narrowing of the vessel or formation of clot at sites of inflammatory insult.In this study, we utilized a conjunction of clinical presentation, imaging findings, laboratory data, and history of comorbid conditions to provide evidence for the diagnosis of vasculitis (Table 6). Biopsy was not performed to confirm diagnosis.

Our study is limited by our sample size and low occurrence rate of bilateral infarcts, which may prevent detection of differences between groups. Our retrospective study design permits only hypothesis-supporting results and conclusions cannot be drawn. Further, this study was performed in a single urban tertiary stroke center, which limits the generalizability to similar populations.

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.

Financial Disclosures

The authors have no financial considerations to disclose.

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