9-27-2022

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Recommended Citation

Jumah A, Aboul Nour H, Intikhab O, Choudhury O, Gagi K, Fana M, Alhajala H, Alkhoujah M, Alsrouji OK, Eltous L, Schultz L, Latack K, Brady M, Chebl A, Marin H, and Miller D. Non-stenosing carotid artery plaques in embolic stroke of undetermined source: a retrospective analysis. Neurol Sci 2022.

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Neurological Sciences
https://doi.org/10.1007/s10072-022-06425-w

ORIGINAL ARTICLE

Non-stenosing carotid artery plaques in embolic stroke of undetermined source: a retrospective analysis

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Received: 8 August 2022 / Accepted: 21 September 2022

Abstract

Background We aim to identify the association between high-risk carotid plaques and their laterality to stroke in ESUS patient population. We also discuss recurrent stroke events and their laterality to the index stroke.

Methods This was a retrospective study. We reviewed data for patients with ESUS between June 20, 2016, and June 20, 2021. Using computed tomography angiography, we analyzed plaque features that are associated with ESUS, and then, we identified the recurrent stroke events and characterized lateralization to the index stroke.

Results Out of 1779 patients with cryptogenic ischemic stroke, we included 152 patients who met the criteria for ESUS. High-risk plaque features were found more often ipsilateral to the stroke side when compared contralaterally: plaque ulceration (19.08% vs 5.26%, $p < .0001$), plaque thickness > 3 mm (19.08% vs 7.24%, $p = 0.001$), and plaque length > 1 cm (13.16% vs 5.92%, $p = 0.0218$). There was also a significant difference in plaque component in which both components (soft and calcified) and only soft plaques were more prevalent ipsilaterally (42.76% vs 23.68% and 17.76% vs 9.21%, respectively, $p < .0001$). Of the 152 patients, 17 patients were found to have a recurrent stroke event, and 47% ($n = 8$) had an ipsilateral stroke to the index event. Moreover, stroke was bilateral in 41% of the patients ($n = 7$), and contralateral in 12% ($n = 2$).

Conclusion High-risk plaque features studied here were more prevalent ipsilaterally to the stroke side in ESUS than contralaterally. Multicenter studies are needed to form precise prediction models and scoring systems to help guide treatment, i.e., choice of medical therapy and/or revascularization.

Keywords Carotid plaques · Stroke · ESUS

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Abbreviations

ESUS	Embolic stroke of undetermined source
CTA	Computed tomography angiography
TOAST	Trial of Org 10172 in Acute Stroke Treatment
NASCET	The North American Symptomatic Carotid Endarterectomy Trial
ECST	European Carotid Surgery Trial
CEA	Carotid endarterectomy
CAS	Carotid artery stenting
CEA	Carotid endarterectomy
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Introduction

Acute ischemic stroke (AIS) is among the leading causes of disability and death worldwide and a major cause is cervical internal carotid artery stenosis. The North American

Published online: 27 September 2022

Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ECST) trials both investigated the utility of medical versus carotid endarterectomy (CEA) of acute stroke and included patients with < 50% carotid artery stenosis [1–3]. A pooled analysis of the data from these studies suggested that CEA in these patients provided no appreciable benefit for stroke prevention and in patients with < 30% carotid stenosis, it was harmful [4]. Consequently, classifying stroke as due to large artery atherosclerosis necessitated a major vessel arterial stenosis > 50%, now considered as the standardized threshold in clinical practice [5].

Stroke etiology has been characterized by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification which categorizes stroke into five etiologies: large artery atherosclerosis, cardioembolic, small vessel disease, stroke of other determined causes, and stroke of an undetermined cause [5]. ESUS was introduced as a non-lacunar stroke, without any evidence of ≥ 50% narrowing of the ICA or a cardiac source of embolism and is a subset of cryptogenic stroke [5]. Per the TOAST classification system, a significant portion of ischemic strokes are cryptogenic, a subset of which are referred to as ESUS and comprise approximately 9–25% of all ischemic strokes [5]. Studies that have characterized ESUS highlight a concern that despite < 50% stenosis of the internal carotid arteries, the presence of concomitant non-stenosing plaques with high-risk features might serve as individual risks factors for ischemic stroke [6–9]. Therefore, plaques of various morphologies and features are proposed to be associated with ipsilateral ESUS in the setting of a non-stenosing carotid plaque.

Given these deficiencies in the knowledge base for non-stenosing plaques, in this retrospective study we evaluated the plaque features and incidence of ESUS in patients with high-risk plaque features.

Methods

Study setting and population (Fig. 1)

This is a retrospective observational study of selected patients admitted to the stroke unit at Henry Ford Hospital between June 1, 2016, and June 1, 2021. The patients were collected using a database that is part of the Get With the Guidelines Stroke national registry. Stroke etiology was defined by inpatient vascular neurologists. The study was approved by the Institutional Review Board and the need for informed consent was waived due to the retrospective nature of the study.

The following inclusion criteria were applied: (1) evidence of a non-lacunar, anterior circulation and single vascular territory infarct, (2) available computed tomography scan of the head and vascular imaging of the head and neck through computed tomography angiography (CTA) during the inpatient admission. The following were the exclusion criteria: (1) bilateral or posterior circulation acute ischemic strokes, (2) evidence of internal carotid artery (ICA) stenosis > 50% on CTA per NASCET criteria when evaluating both initial and recurrent events, (3) patients treated with CEA/CAS, (4) patients in whom no CTA imaging was performed, (5) patients with intracranial atherosclerotic

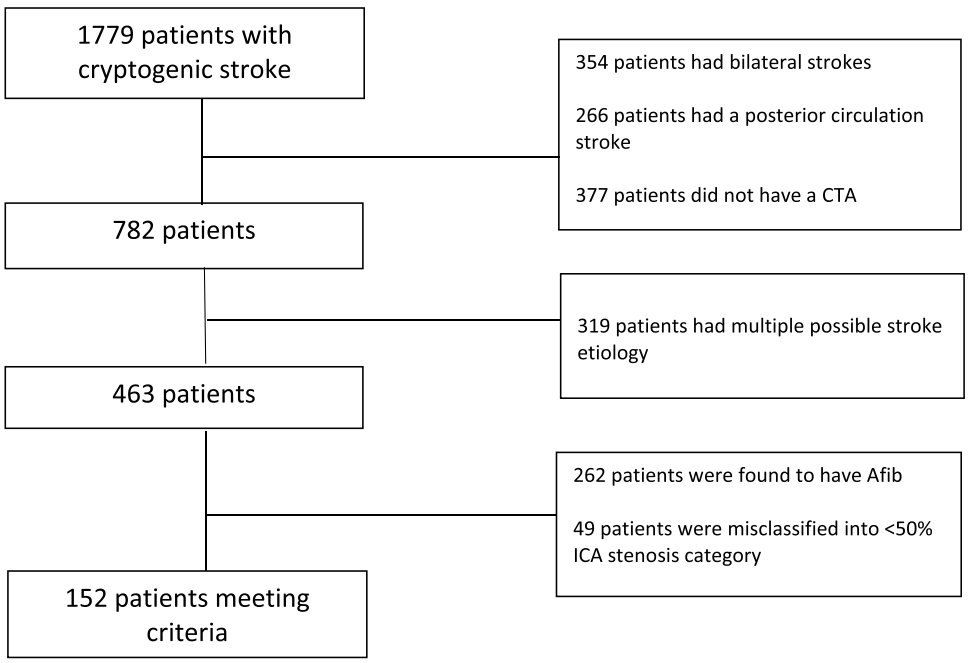

Fig. 1 Flow chart of participants

stenosis > 50% according to WASID criteria [10], and (6) patients with more than 1 potential stroke etiology.

Imaging analysis

Head and neck CTA with coverage from the aortic arch to the vertex was obtained within 10 days of patient presentation to study carotid plaque morphology. The images were interpreted by a neuroradiology fellow, and uncertainties were adjudicated by a senior board-certified neuroradiologist. The readers were blinded to the patients' clinical information. The reader viewed axial CTA source images, generated coronal and sagittal projections, maximum intensity projections (MIPs), and 3-D images. The reader first assessed image quality and determined whether there were any limitations (e.g., poor contrast timing, artifact) that would prevent accurate evaluation of ICA plaques. They initially assessed carotid arteries with < 50% stenosis per NASCET criteria and qualitatively assessed the presence of various plaque features associated with higher risk of stroke. Plaque features identified included the following characteristics: plaque ulceration (> 1 mm depression), the presence of calcifications only, hypodense plaque only, or an intermixed calcified and hypodense component, > 1 cm plaque length, and > 3-mm plaque thickness. The degree of stenosis was divided into three groups using NASCET criteria: < 10%, 10–30%, and 30–49%.

Outcome measures

The primary endpoint was the incidence of index AIS and its relationship with ipsilateral high-risk plaque features. Secondary endpoint was the incidence of ipsilateral recurrent ESUS compared to bilateral and contralateral events.

Covariates

Baseline demographics (age, sex, and race), medical comorbidities (hypertension, diabetes mellitus, smoking, obstructive sleep apnea, prior stroke, myocardial infarction, and peripheral vascular disease), and date of death or last follow-up health care encounter were collected for each patient using an electronic medical record (www.EPIC.com). At a minimum, the diagnostic assessment for both initial and recurrent stroke events had to include a CT or MRI of the brain showing the infarct, imaging of the cervical and intracranial arteries, a 12-lead ECG, a transthoracic and/or transesophageal echocardiogram, ECG telemetry during the admission, and a prolonged cardiac rhythm monitoring. The decision to obtain a hypercoagulability testing was decided upon by the treating vascular neurologist.

Statistical analysis

Demographic data is displayed as count and percentage for categorical variables and median, interquartile range (IQR), mean, and standard deviation for age. Comparisons for plaque morphology between ipsilateral and contralateral stroke are made using McNemar's Test for dichotomous variables and Bowker's Symmetry

Table 1 Descriptive demographics

	Total ($N = 152$)
Age	
N	152
Median (IQR)	67.0 (59.0, 78.0)
Mean (SD)	67.6 (13.38)
NIHSS at admission	
N	152
Median (IQR)	5.0 (2.0, 10.0)
Mean (SD)	7.4 (7.39)
Gender, *n* (%)	
Female	79 (52.0%)
Male	73 (48.0%)
Race	
Asian	1 (0.7%)
Black or African American	104 (68%)
Black or African American: Native Hawaiian/ Pacific Islander	1 (0.7%)
Non-specified	9 (5.9%)
White	37 (24.7%)
Stroke location	
Left	84 (55.3%)
Right	68 (44.7%)
Hypertension, *n* (%)	127 (83.6%)
Obesity/Overweight	104 (68.4%)
Previous TIA	5 (3.3%)
CAD/prior MI	30 (19.7%)
Diabetes mellitus	57 (37.5%)
Dyslipidemia	56 (36.8%)
PVD	10 (6.6%)
Sleep apnea	6 (3.9%)
Smoker	45 (29.6%)
Previous stroke	41 (27.0%)
HF	21 (13.8%)
Drugs/Alcohol abuse	28 (18.4%)
Renal insufficiency—chronic	6 (3.9%)
DVT/PE	4 (2.6%)
Treatment on discharge	
Aspirin only	120 (78.9%)
Plavix only	7 (4.6%)
Aspirin and Plavix	16 (10.5%)
Coumadin (for pulmonary embolism)	1 (0.7%)

Table 2 Plaque morphology in index stroke

		Ipsilateral to stroke side	Contralateral to stroke side	*p* value
Stenosis	< 10%	117 (76.97%)	132 (86.8%)	0.0327
	10–30%	27 (17.76%)	16 (10.5%)	
	31–49%	8 (5.26%)	4 (2.6%)	
Ulceration	> 1 mm depression	29 (19.08%)	8 (5.26%)	< .0001
Plaque length	> 1 cm	20 (13.16%)	9 (5.92%)	0.0218
Plaque thickness	> 0.3 cm	29 (19.08%)	11 (7.24%)	0.001
Calcified plaque/soft component	Calcified	57 (38%)	65 (42.76%)	< .0001
	Soft	29 (19%)	14 (9.21%)	
	Both	66 (43%)	36 (23.68%)	
	None	–	37 (24.34%)	
At risk plaque	Yes	109 (71.71%)	60 (39.47)	< .0001

Test for variables with more than 2 outcomes. All analyses are performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline variables

Of the 1779 patients with cryptogenic stroke, 152 (8.6%) patients met our inclusion criteria for ESUS. The median and interquartile range (IQR) for age was 67.0 (59.0, 78.0), and 79 (52%) were female, 104 (68%) were African American, and 37 (24.7%) were White. Vascular risk factors included hypertension (83.6%), hyperlipidemia (36.8%), diabetes mellitus (37.5%), and smoking (29.6%). Other relevant information, including the stroke side, National Institute of Health Stroke Scale (NIHSS) at the time of presentation, and relevant comorbidities, is reported in Table 1. Median follow-up time in months was 16.57 (IQR = 2.3, 37.43) and 33 patients died.

Plaque features and ipsilateral index stroke

High-risk plaque features were found to be more prevalent ipsilateral to the index stroke side when compared to the contralateral side (Table 2). Features showing significant association included plaque ulceration (19.08% vs 5.26%, $p < 0.0001$), plaque thickness > 3 mm (19.08% vs 7.24%, $p = 0.001$), and plaque length > 1 cm (13.16% vs 5.92%, $p = 0.0218$). There was also a significant difference in plaque component in which both components (soft and calcified) and only soft plaques were more prevalent ipsilaterally (42.76% vs 23.68% and 17.76% vs 9.21%, respectively, $p < 0.0001$). Also, a cumulative analysis was conducted to assess the prevalence of plaques at risk ipsilateral and contralateral to ESUS. Plaque at risk was defined as patients who had plaque ulceration, plaque length of > 1 cm, plaque thickness > 3 mm, and/or soft or soft + calcified plaques. Interestingly, 71.7% of the patients ($n = 109$) had at least one high-risk plaque feature ipsilateral to ESUS side.

Plaque features and subsequent strokes

Of the 152 patients, 17 patients were found to have a recurrent stroke event, and 8 patients (47%) had an ipsilateral stroke to the index event. Bilateral strokes were found in 7 patients (41%), and contralateral strokes in 2 (12%). Median follow-up was 25.3 months (IQR = 7.2, 37.5) and 5 patients were deceased.

Discussion

In our study, we highlight that high-risk plaque features—including plaque ulceration, plaque length of > 1 cm, plaque thickness > 3 mm, as well as soft and mixed plaques—are often seen ipsilateral to ESUS. Indeed, formulating a prediction model for recurrent stroke events or a scoring system to guide further medical management was limited by our small patient sample size.

Most recently, researchers have focused on non-stenosing carotid plaques and the risk of ESUS [11, 12]. Specifically, majority of focus was on plaque vulnerability, laterality of carotid plaque in relation to stroke side, and arterial stiffness indices [13] using different tools such as ultrasound [13], computed tomography angiography [14], magnetic resonance imaging [15], and positron emission tomography [6] scans which were identified to delineate vascular abnormalities. This helped in determining the prevalence of a concurrent ipsilateral ESUS and the risk of stroke. Throughout the literature, different plaque features were studied and analyzed, including plaque inflammation/hypermetabolism [6], intraplaque hemorrhage (IPH) [7, 8], lipid-rich necrotic core[16], echolucency [17], and thin/ruptured fibrous cap [18, 19]. In one meta-analysis by Kamtchum-Tatuene et al., symptomatic carotid stenosis was associated with a three times higher prevalence of finding a high-risk plaque feature [20]. From the authors' perspective, we do believe that the association between high-risk plaque features and ESUS is plausible. Also, a

routine description of these features into radiology reports is warranted, as this can be used in the future as a reference in clinical trials to help guide whether interventions with CEA or CAS to prevent stroke recurrence are justifiable.

Our study has several limitations: mainly its retrospective nature. Moreover, some patients may have moved or switched to different hospital systems, thereby reducing the reported number of recurrent stroke events. However, given the wide utility of EPIC as an EMR in Southeast Michigan, this allowed access to patient data as shared between hospital systems (EPIC—Care Everywhere). Another important limitation is our small sample size which hampered our ability to perform multivariate regression models. This, per se, limits us in constructing a scoring system as well as prediction models that would guide treatment. This will require larger multicenter studies. Finally, measured associations do not prove causation.

Despite these limitations, our findings carry important clinical implications. Most importantly, ipsilateral high-risk plaque features should be looked for when encountering ESUS. Prospective randomized controlled trials implementing CAE or CAS versus optimized medical therapy to prevent recurrent ESUS events are warranted.

Author contribution Dr. Miller created the idea of the project, contributed to methodology and design, and supervised the project. Dr. Marin contributed to methodology, design, statistical planning, and project supervision. Dr. Jumah and Dr. Aboul Nour contributed to methodology and design, statistical planning, data extraction and cleaning, literature review. Dr. Eltous and Dr. Jumah contributed in manuscript writing. Dr. Alhajala contributed to methodology and design. Dr. Choudhury, Dr. Fana, Dr. Alsrouji, and Dr. Gagi contributed to data extraction and cleaning. Dr. Schultz and Dr. Latack contributed to statistical planning and execution. Ms. Brady contributed to data extraction and cleaning. All authors contributed to data interpretation, composition, and revision of the article. Dr. Chebl contributed to critical analysis and drafting of the manuscript.

Data availability All data are available from the corresponding author upon reasonable request.

Declarations

Ethical approval and consent to participate The study was approved by the Institutional Review Board and the need for informed consent was waived due to the retrospective nature of the study.

Conflict of interest The authors declare no competing interests.

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