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Clinical Short Communication

Embolic stroke of undetermined source: The role of the nonstenotic carotid plaque

Zachary Bulwa[a,*], Ajay Gupta[b,c]

[a] Department of Neurology, University of Chicago, Chicago, IL, United States
[b] Department of Radiology, Weill Cornell Medicine, New York, NY, United States
[c] Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY, United States

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ABSTRACT

Cryptogenic stroke, or stroke of undetermined cause, presents a remarkably challenging dilemma for the treating physician as there are limited therapeutic options to prevent recurrence. Roughly one third of transient ischemic attacks (TIAs) and ischemic strokes are classified as cryptogenic, with an even greater proportion in young patients. While classification systems have been successfully used in trials to refine therapeutic approaches specific to subtype, there has been little progress made in secondary prevention of cryptogenic stroke. The cryptogenic stroke/ESUS International Working Group recently proposed a new entity under the realm of cryptogenic stroke called embolic stroke of undetermined source (ESUS). This clinical construct emerged from data suggesting thromboembolism as the primary etiology of cryptogenic strokes. While current trials are addressing covert atrial fibrillation as a significant source of embolism, more recent population data has called this hypothesis into question and illustrated the heterogeneity, and often multiplicity, of embolic sources. The importance of carotid artery plaques which do not cause significant stenosis as a source of emboli to the brain has generally been ignored given the long-standing focus of using percent stenosis measurements as the primary criterion for defining high-risk carotid atherosclerotic disease. As part of the required diagnostic workup to define ESUS, vascular imaging, and advances therein, provides a unique opportunity to prospectively determine a subset of patients who may benefit from aggressive medical therapy or endovascular interventions in the prevention of recurrent ESUS. Here we review the role of the nonstenotic, and potentially vulnerable, carotid plaque in ESUS.

1. Introduction

Cryptogenic stroke, or stroke of undetermined cause, presents a remarkably challenging dilemma for the treating physician as there are limited therapeutic options to prevent recurrence. Roughly one third of transient ischemic attacks (TIAs) and ischemic strokes are classified as cryptogenic, with an even greater proportion in young patients [1]. While classification systems have been successfully used in trials to refine therapeutic approaches specific to subtype, there has been little progress made in secondary prevention of cryptogenic stroke [2–3]. The Cryptogenic Stroke/ESUS International Working Group recently proposed a new entity under the realm of cryptogenic stroke called embolic stroke of undetermined source (ESUS) [3]. This clinical construct emerged from data suggesting thromboembolism as the primary etiology of cryptogenic strokes [3]. Three ongoing trials are evaluating the use of novel oral anticoagulants in the prevention of recurrent ESUS, whereas others are identifying the burden of covert atrial fibrillation in this population [4–8]. While current trials are addressing covert atrial fibrillation as a significant source of embolism, more recent population data has called this hypothesis into question and illustrated the heterogeneity, and often multiplicity, of embolic sources [3,9–21]. The importance of carotid artery plaques which do not cause significant stenosis as a source of emboli to the brain has generally been ignored given the long-standing focus of using percent stenosis measurements as the primary criterion for defining high-risk carotid atherosclerotic disease. As part of the required diagnostic workup to define ESUS, vascular imaging, and advances therein, provides a unique opportunity to prospectively determine a subset of patients who may benefit from aggressive medical therapy or endovascular interventions in the prevention of recurrent ESUS [3]. Here we review the role of the nonstenotic, and potentially vulnerable, carotid plaque in ESUS.

* Corresponding author at: University of Chicago, 5841 S. Maryland Ave., Chicago, IL 60637, United States.
E-mail addresses: Zachary.Bulwa@uchospitals.edu (Z. Bulwa), ajg9004@med.cornell.edu (A. Gupta).

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2. Embolic stroke of undetermined source

Maybe the greatest benefit of the Cryptogenic Stroke/ESUS International Working Group's proposal of the ESUS entity is the standardization of ischemic stroke workup in order to classify cryptogenic stroke as ESUS [3]. This model transforms cryptogenic stroke from a diagnosis of exclusion, or in some cases incomplete workup, to ESUS, a criteria-based diagnosis [3]. ESUS requires a minimum diagnostic assessment of brain imaging (CT or MRI), 12-lead electrocardiogram and cardiac monitoring ≥ 24 h with automated rhythm detection, transthoracic echocardiography, and imaging of both extracranial and intracranial arteries supplying the area of ischemia [3]. By implementing the required diagnostic workup and criteria for diagnosis [3], retrospective and prospective observational studies have demonstrated the prevalence of ESUS in multiple populations [9–21]. Roughly 1 in 6 ischemic strokes is due to embolic stroke of undetermined source [22]. Relative to other strokes classifications, pooled data depicts an ESUS population that is younger (mean age 65 years old) and with less vascular risk factors.

Limited data reveals an annualized recurrence rate of roughly 4.5% [22]. Age, diabetes, nontraditional lipid ratios, CAM (calcification in the aortic arch, age, multiple infarction) score, and higher $CHADS_2$ and CHA_2DS-$_2$VASc scores were risk factors for recurrence in singular populations [14,23–25]. Emerging data has also identified clinical and radiological predictors of underlying mechanism [14–26]. Yet, there remains an urgent need for trials to determine precision treatment and neurologic prognosis relative to etiology.

3. The role of the nonstenotic carotid plaque

Recent population data in ESUS patients has demonstrated a heterogeneity and multiplicity of risk factors, shedding light on another prominent etiology: arteriogenic embolism.

Arteriogenic emboli considered as minor-risk potential causes of ESUS include aortic arch atherosclerotic plaques and nonstenotic cerebral artery plaques with ulceration [3]. While not the focus of this discussion, aortic arch atheromas (AAA) are an important and often underappreciated source of embolic stroke worthy of brief mention. AAA of increasing size (> 4 mm), mobility and complexity in the elderly carry the greatest stroke risk [27–29]. Ryoo et al. found vulnerable AAA as causative for ESUS in 40 of 321 patients and were able to identify defining clinical and radiological features (elderly patients with hypertension and multiple, small cortical and border zone infarcts) of AAA relative to patent foramen ovale and paroxysmal atrial fibrillation [12].

Like AAA, nonstenotic carotid plaques have been hypothesized to play an independent role in ESUS. Recent studies have founded that the presence of ultrasound-detected nonstenotic carotid plaques is inversely associated with both patent foramen ovale and markers of atrial cardiopathy in patients with ESUS, suggestive of distinctive etiologies of ESUS [30–31]. In the ESUS Global Registry, 35% of patients had one or more minor-risk potential embolic sources, *excluding* carotid artery plaques [11]. Even more striking, 79% of patients had nonstenotic plaques in the cervical carotid arteries [11].

For the better part of three decades, clinical trials and guidelines in vascular neurology have relied on measurements of carotid stenosis to stratify risk in the primary and secondary prevention of stroke [32–36]. Evolving imaging technology has made it possible to risk stratify patients, not solely on the degree of carotid artery stenosis, but also on plaque characteristics including plaque size, composition, and metabolic activity [37–39]. Advances in computed tomography angiography (CTA), magnetic resonance angiography (MRA), ultrasonography with and without contrast medium, microemboli signal detection, and ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) have ushered in a new era of risk stratification based on the presence of high-risk plaque features including intraplaque hemorrhage, plaque ulceration, plaque neovascularization, fibrous cap thickness, the presence of a lipid-rich necrotic core, and evaluation of plaque inflammatory activity [37–39].

Several small studies have investigated the incidence of these imaging findings in the patient with stroke of undetermined cause. A notable early study of this kind was published in 2012. Freilinger et al. used black-blood carotid magnetic resonance imaging (MRI) to assess the prevalence of complicated plaques in cryptogenic stroke. 37.5% of carotid arteries ipsilateral to the ischemic stroke had American Heart Associated (AHA) lesion type VI plaques compared to zero AHA type VI plaques contralateral to the stroke. The most common feature of AHA type VI plaques was intraplaque hemorrhage (75%), followed by fibrous plaque rupture (50%), and luminal thrombus (33%). This study's imaging technique required the use of a dedicated surface carotid coil and an $\sim$18 min multi-sequence protocol, thereby allowing for the detailed detection of various high-risk carotid plaque elements [40].

In 2015, Gupta et al. used non-contrast 3-dimensional time-of-flight MRA to enhance current stroke risk stratification. 22.2% of patients had intraplaque high-intensity signal (IHIS), a marker for intraplaque hemorrhage, in nonstenosing carotid plaques ipsilateral to ischemic stroke compared to zero patients with IHIS-positive carotid plaques contralateral to stroke [41]. Unlike the work of Freilinger et al., this study determined the presence of high-risk plaque from a standard 5 min angiographic sequence already in place to evaluate luminal stenosis for which no extra hardware (such as a surface carotid coil) was needed. Gupta et al. furthered their work by comparing IHIS in patients with a variety of stroke subtypes. A higher proportion of IHIS was found in carotid plaques ipsilateral to stroke in cryptogenic stroke patients, but no significant difference in strokes due to cardioembolism or small vessel occlusion [42].

In 2016, Hyafil et al. combined ^{18}F-FDG PET imaging with MRI to investigate morphological and biological aspects of nonstenotic carotid artery plaques in cryptogenic stroke in small series of 18 patients. Approximately 39% of ipsilateral arteries had complicated atherosclerotic plaques compared to zero complicated plaques in contralateral arteries. The addition of ^{18}F-FDG PET imaging allowed for comparison between patients with and without AHA type VI plaques. In patients with at least one complicated plaque on MRI, ^{18}F-FDG uptake in both carotid arteries was significantly higher than in patients with no lesions, potentially indicating a diffuse inflammatory process associated with a vulnerable plaque [43].

More recently, Coutinho et al. used standard, clinically acquired source images from CTA neck exams to determine whether thick, nonstenotic plaques occur more frequently ipsilateral in ESUS. Plaques with thickness > 5 mm were present ipsilateral to stroke in 11% of patients and contralateral in 1%. Plaques with thickness > 4 mm were present ipsilateral to stroke in 19% of patients and contralateral in 5%. Plaques with thickness > 3 mm were present ipsilateral to stroke in 35% of patients and contralateral in 15% [18].

While these studies were small, accumulating data suggest an association between high-risk nonstenotic carotid plaques and stroke of undetermined cause. However, there remains controversy as to whether such plaques are causative of ipsilateral ischemic stroke [44–46]. For example, an analysis of the population-based Oxfordshire Vascular Study including over 800 cryptogenic ischemic events did not find an association between nonstenosing plaque and stroke, with Li et al. concluding that causal links between nonstenosing plaques and cryptogenic stroke “should be interpreted with caution” [1]. Similarly, recent reports from the Plaque at RISK multicenter study in Europe found that the presence of MRI detected intraplaque hemorrhage in low to moderate carotid stenosis (30–69%) ipsilateral to a recent ischemic infarct was associated not associated with increased microembolic signals on transcranial Doppler or with increased ipsilateral cerebral infarcts on brain MRI [45–46].

The existing uncertainty in the literature about the causative role of nonstenotic carotid plaque in ischemic stroke likely arises from the lack