Cryptogenic Stroke and Nonstenosing Intracranial Calcified Atherosclerosis

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Objective: Because some cryptogenic strokes may result from large-artery atherosclerosis that goes unrecognized as it causes <50% luminal stenosis, we compared the prevalence of nonstenosing intracranial atherosclerotic plaques ipsilateral to cryptogenic cerebral infarcts versus the unaffected side using imaging biomarkers of calcium burden. *Methods:* In a prospective stroke registry, we identified patients with cerebral infarction limited to the territory of one internal carotid artery (ICA). We included patients with stroke of undetermined etiology and, as controls, patients with cardioembolic stroke. We used noncontrast computed tomography to measure calcification in both intracranial ICAs, including qualitative calcium scoring and quantitative scoring utilizing the Agatston–Janowitz (AJ) calcium scoring. Within subjects, the Wilcoxon signed-rank sum test for nonparametric paired data was used to compare the calcium burden in the ICA upstream of the infarction versus the ICA on the unaffected side. *Results:* We obtained 440 calcium measures from 110 ICAs in 55 patients. Among 34 patients with stroke of undetermined etiology, we found greater calcium in the ICA *ipsilateral* to the infarction (mean Modified Woodcock Visual Scale score, 6.7 ± 4.6) compared with the *contralateral* side (5.4 ± 4.1) ($P = .005$). Among 21 patients with cardioembolic stroke, we found no difference in calcium burden ipsilateral to the infarction (6.7 ± 5.9) versus the contralateral side (7.3 ± 6.3) ($P = .13$). The results were similar using quantitative calcium measurements, including the AJ calcium scores. *Conclusion:* In patients with strokes of undetermined etiology, the burden of calcified intracranial large-artery plaque was associated with downstream cerebral infarction. **Key Words:** Cryptogenic stroke—intracranial atherosclerosis—CT scan—calcium—stroke etiology.

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Received August 19, 2016; revision received October 14, 2016; accepted October 26, 2016.

Source of funding: The study is supported by grants K23NS082367 (Kamel), K23NS091395 (Navi), R01NS034179 (Iadecola), and KL2TR000458 (Gupta) from the National Institutes of Health.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.10.035

One third of ischemic strokes are classified as cryptogenic because a definite cause cannot be identified.[1] It is increasingly recognized that many cryptogenic strokes arise from a distant thromboembolic source, not in situ cerebrovascular disease. This has prompted the formulation of an entity called embolic stroke of undetermined source, which likely involves a mixture of occult cardiac embolism and artery-to-artery embolism.[2]

The most common cause of artery-to-artery embolism is atherosclerosis. The current criterion for diagnosing atherosclerotic artery-to-artery embolism requires a plaque to have caused ≥50% stenosis of the arterial lumen.[3] However, recent studies suggest that artery-to-artery embolism can occur from vulnerable plaque elements in the extracranial internal carotid artery (ICA) even in the absence of significant luminal narrowing.[4,5] It is unknown whether nonstenosing atherosclerotic lesions in the *intracranial* ICA are also associated with stroke.

More widespread recognition that large-artery atherosclerosis can cause artery-to-artery embolism without causing luminal narrowing would have several implications. It would suggest that updated diagnostic criteria for large-vessel stroke might reclassify many strokes that are currently classified as cryptogenic and instead allow them to be labeled as being due to large-artery disease. This could extend to a new group of patients the benefits of treatments that appear effective in those with currently recognized large-artery atherosclerosis.[6,7] Therefore, we examined whether nonstenosing atherosclerosis of the intracranial ICA is associated with downstream cerebral infarction.

Methods

Design

If nonstenosing intracranial plaques *cause* some proportion of cryptogenic strokes, these strokes should more often occur downstream of such plaques than downstream of vessels without such plaque. We therefore tested the hypothesis that atherosclerotic plaque is more common upstream of a cryptogenic cerebral infarction than it is upstream of the unaffected hemisphere. In other words, we hypothesized that a patient with a cryptogenic stroke affecting the left cerebral hemisphere would be more likely to harbor a higher burden of atherosclerotic plaque in the *left* intracranial ICA, upstream of the infarct, than in the *right* intracranial ICA. As a further control, we included a cohort of patients with cardioembolic stroke. We hypothesized that there would not be the same left-versus-right asymmetry in large-artery plaque in these patients, as their stroke arose from a central thrombus in the heart. As our marker of vulnerable atherosclerotic plaque, we used measurements of arterial calcification, which has been established as a marker of atherosclerosis, especially in the coronary arteries, and more recently has been shown to be a marker of overall stroke risk.[8] Our study was approved by the Weill Cornell Medical College institutional review board, which waived the requirement for informed consent.

Subjects

All patients with acute ischemic stroke admitted to the New York-Presbyterian Hospital/Weill Cornell Medical Center in 2013 were prospectively included in the American Heart Association's Get With the Guidelines (GWTG)—Stroke registry.[9] Patients were registered after their attending vascular neurologist confirmed the diagnosis of ischemic stroke, defined as an episode of cerebral dysfunction with neuroimaging evidence of infarction or clinical symptoms persisting >24 hours without an obvious nonvascular cause.

Using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification scheme,[3] two neurologists used all available medical records to independently assign a stroke etiology. A third neurologist independently resolved any disagreements regarding the classification. Because we were interested in whether cryptogenic strokes can be caused by undiagnosed atherosclerosis, we included all patients with a stroke of undetermined etiology. As a control group, we included patients with cardioembolic strokes because their pathophysiological basis did not involve arterial disease. Because we were interested in the *occult* atherosclerotic disease, we excluded strokes whose etiology was recognized as large-artery atherosclerosis based on ≥50% luminal stenosis as required by the TOAST classification. We excluded small-vessel occlusion and strokes due to another determined etiology because of the relatively small numbers of cases.

Because we were interested in arterial calcification in the intracranial ICA, from among otherwise eligible patients with stroke of undetermined etiology or cardioembolic stroke, we included only those who underwent noncontrast head computed tomography (CT) with 2.5-mm slice thickness and who had unilateral infarction in one ICA territory.

Clinical Measurements

Trained hospital personnel used standardized methods to prospectively collect data regarding demographics, the National Institutes of Health Stroke Scale score on admission, and vascular risk factors: tobacco use, diabetes, hypertension, dyslipidemia, atrial fibrillation, congestive heart failure, coronary heart disease, peripheral vascular disease, and cardiac valvular disease.

CT Imaging Technique

All head CT studies were performed on one of the General Electric CT scanners at our institution: the Optima 660, LightSpeed Xtra, Discovery HD 750, or the Lightspeed Pro (General Electric, Fairfield, CT, USA). Imaging was performed according to the standard protocol used during this time period for patients referred for a suspected or