American Heart Association | American Stroke Association

Seeking Culprit Lesions in Cryptogenic Stroke: The Utility of Vessel Wall Imaging

Jie Sun, MD; Chun Yuan, PhD

Although clinical diagnosis of ischemic stroke is usually straightforward, with objective evidence of ischemic brain injuries that can be obtained from neurologic examination and brain imaging, our ability to determine the underlying etiology and thus classify stroke subtypes is quite limited. The widely applied TOAST classification scheme[1] specifies "stroke of undetermined origin" as describing those ischemic events that cannot be conclusively attributed to large-artery atherosclerosis, cardioembolism, small-artery disease, or other uncommon etiologies. This group represents a large (20% to 40% of all ischemic strokes in published data) and heterogeneous clinical population for which further insights on pathophysiological mechanisms are needed for effective primary and secondary prevention.

It is conceivable that multiple factors may contribute to the high prevalence of cryptogenic stroke in current clinical practice. Blood flow to the brain, which uses ≈15% of cardiac output, is delivered through a lengthy circulatory system in which many pathologies of the heart or arterial system, including those less recognized (eg, fibromuscular dysplasia), may become sources for distal embolization. Furthermore, the timing of clinical workup is imperfect for capturing "smoking gun" evidence. Luminal thrombus from a disrupted atherosclerotic plaque may have largely fallen off (or lysed) by the time of vascular imaging. Paroxysmal atrial fibrillation may have ebbed away. Importantly, the lack of definitive clues from standard of care imaging is at least partly accountable for the ambiguous classification of stroke subtypes in certain patients. In a preliminary study, Freilinger et al[2] used a multisequence carotid magnetic resonance imaging protocol to investigate vessel wall pathologies in 32 consecutive cryptogenic stroke patients with unilateral anterior circulation infarcts and nonstenotic (<50%) carotid artery plaques. They found that 12 patients (37.5%) had complex carotid plaques (featuring hemorrhage, thrombus, or fibrous cap rupture on carotid magnetic resonance imaging) located exclusively on the ipsilateral side of stroke. This finding highlights the limitation of angiography in clinical workups of cryptogenic stroke. As a means to diagnose vessel wall pathologies such as atherosclerosis and dissection, angiography gives useful information on luminal narrowing but does not directly visualize vessel wall pathologies.

In this issue of the *Journal of the American Heart Association* (*JAHA*), the report by Gupta et al[3] provides additional confirmatory evidence on this topic. Similar to the previous report,[2] cryptogenic stroke patients with unilateral anterior circulation infarcts and <50% carotid stenosis were recruited. Intraplaque hemorrhage, as shown on a 3-dimensional time-of-flight sequence, was found in 6 patients (22.2%). Again, all high-risk plaques identified are on the ipsilateral side of stroke. Because findings in the contralateral carotid arteries can be viewed as coincidental and can serve as controls, the fact that plaques with intraplaque hemorrhage are exclusively found ipsilateral to ischemic stroke in this population suggests that these findings are likely not coincidental but rather culprit lesions. Collectively, the 2 studies suggest that nonstenotic carotid plaques—previously thought to be at low risk for atherothrombosis and thus an uncertain finding in patients with cryptogenic stroke—may well be the culprit lesions if high-risk plaque features such as intraplaque hemorrhage are present.

Can nonstenotic carotid plaques lead to ischemic strokes? Mechanistically, patients with carotid plaques could suffer ischemic brain injuries if plaque rupture and subsequent thrombosis cause acute carotid artery obstruction or distal branch embolization. Although in situ thrombotic obstruction of a previously nonstenotic carotid artery may be difficult, given the large diameter and high flow velocity in the carotid artery, artery-to-artery embolization could happen in the absence of substantial stenosis. Saam et al[4] reported that magnetic resonance imaging–detected complex plaques (eg, fibrous cap rupture, intraplaque hemorrhage) were observed

From the Department of Radiology, University of Washington, Seattle, WA.

Correspondence to: Chun Yuan, PhD, 850 Republican St Rm 124, Seattle, WA 98109. E-mail: cyuan@uw.edu

J Am Heart Assoc. 2015; 4:e002207 doi: 10.1161/JAHA.115.002207.

in 8.1% of arteries with 1% to 15% stenosis by duplex ultrasound. Associations between these high-risk plaque features and ipsilateral ischemic stroke or acute brain infarct have been demonstrated, even in nonstenotic carotid arteries.[5–7] Furthermore, in prospective studies with clinical follow-up, high-risk features in the carotid plaque have been shown to predict recurrent events in symptomatic patients with mild or moderate carotid stenosis.[8–10]

A noticeable finding from the studies by Freilinger et al[2] and Gupta et al[3] is that none of the carotid arteries contralateral to ischemic stroke "coincidentally" harbored intraplaque hemorrhage. Although intraplaque hemorrhage indicates increased atherothrombotic risk, it is not equal to luminal thrombus and is known to be present in never-symptomatic patients. In a previous study with serial images, it was shown that carotid plaques could develop intraplaque hemorrhage without coincident clinical symptoms.[11] Nonetheless, it is conceivable that the diagnostic value of high-risk plaque features such as intraplaque hemorrhage may be higher in stroke patients with less-stenotic carotid plaques. In a study of patients with suspected ischemic stroke symptoms, McNally et al[7] reported that carotid intraplaque hemorrhage was associated with an overall relative risk of 6.4 for acute brain infarct, with the highest relative risk seen in the lowest stenosis category (10.3, 2.9, and 2.2 in 0% to 29%, 30% to 69%, and 70% to 99% carotid stenosis, respectively). To date, there is little knowledge on the different types of intraplaque hemorrhage, such as those in asymptomatic plaques versus those in culprit lesions. Further studies are warranted to understand the mediating steps from the occurrence of intraplaque hemorrhage to clinical events.

In conclusion, a large proportion of patients presenting with ischemic strokes remain diagnosed as cryptogenic after a standard workup in current clinical practice. The study by Gupta et al[3] provides evidence that intraplaque hemorrhage is present in ≈20% to 30% of those patients; that appears unlikely to be coincidental and indicates culprit lesions for the clinical events. This is further backed by the strong associations of intraplaque hemorrhage with ischemic stroke and with recurrent events, as shown in previous studies. Vessel wall imaging overcomes the limitations of angiography by providing direct information on vessel wall pathologies and is likely to find its position in clinical stroke protocols in the future.

Disclosures

Dr Yuan receives research grants from the NIH and Philips Healthcare, and serves as a Member of Radiology Advisory Network, Philips. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

References

1. Adams HJ, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE III. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24:35–41.
2. Freilinger TM, Schindler A, Schmidt C, Grimm J, Cyran C, Schwarz F, Bamberg F, Linn J, Reiser M, Yuan C, Nikolaou K, Dichgans M, Saam T. Prevalence of nonstenosing, complicated atherosclerotic plaques in cryptogenic stroke. *JACC Cardiovasc Imaging*. 2012;5:397–405.
3. Gupta A, Gialdini G, Lerario M, Baradaran H, Giambrone A, Navi BB, Marshall RS, Iadecola C, Kamel H. Magnetic resonance angiography detection of abnormal carotid artery plaque in patients with cryptogenic stroke. *J Am Heart Assoc*. 2015;4:e002012 doi: 10.1161/JAHA.115.002012.
4. Saam T, Underhill HR, Chu B, Takaya N, Cai J, Polissar NL, Yuan C, Hatsukami TS. Prevalence of American Heart Association type VI carotid atherosclerotic lesions identified by magnetic resonance imaging for different levels of stenosis as measured by duplex ultrasound. *J Am Coll Cardiol*. 2008;51:1014–1021.
5. Yamada N, Higashi M, Otsubo R, Sakuma T, Oyama N, Tanaka R, Iihara K, Naritomi H, Minematsu K, Naito H. Association between signal hyperintensity on T1-weighted MR imaging of carotid plaques and ipsilateral ischemic events. *AJNR Am J Neuroradiol*. 2007;28:287–292.
6. Parmar JP, Rogers WJ, Mugler JR, Baskurt E, Altes TA, Nandalur KR, Stukenborg GJ, Phillips CD, Hagspiel KD, Matsumoto AH, Dake MD, Kramer CM. Magnetic resonance imaging of carotid atherosclerotic plaque in clinically suspected acute transient ischemic attack and acute ischemic stroke. *Circulation*. 2010;122:2031–2038.
7. McNally JS, Kim SE, Yoon HC, Findeiss LK, Roberts JA, Nightingale DR, Narra KK, Parker DL, Treiman GS. Carotid magnetization-prepared rapid acquisition with gradient-echo signal is associated with acute territorial cerebral ischemic events detected by diffusion-weighted MRI. *Circ Cardiovasc Imaging*. 2012;5:376–382.
8. Altaf N, Daniels L, Morgan PS, Auer D, MacSweeney ST, Moody AR, Gladman JR. Detection of intraplaque hemorrhage by magnetic resonance imaging in symptomatic patients with mild to moderate carotid stenosis predicts recurrent neurological events. *J Vasc Surg*. 2008;47:337–342.
9. Yoshida K, Sadamasa N, Narumi O, Chin M, Yamagata S, Miyamoto S. Symptomatic low-grade carotid stenosis with intraplaque hemorrhage and expansive arterial remodeling is associated with a high relapse rate refractory to medical treatment. *Neurosurgery*. 2012;70:1143–1150.
10. Kwee RM, van Oostenbrugge RJ, Mess WH, Prins MH, van der Geest RJ, ter Berg JW, Franke CL, Korten AG, Meems BJ, van Engelshoven JM, Wildberger JE, Kooi ME. MRI of carotid atherosclerosis to identify TIA and stroke patients who are at risk of a recurrence. *J Magn Reson Imaging*. 2013;37:1189–1194.
11. Sun J, Underhill HR, Hippe DS, Xue Y, Yuan C, Hatsukami TS. Sustained acceleration in carotid atherosclerotic plaque progression with intraplaque hemorrhage: a long-term time course study. *JACC Cardiovasc Imaging*. 2012;5:798–804.

Key Words: Editorials • atherothrombotic stroke • ischemic stroke • magnetic resonance imaging • vascular imaging