Detection of Vulnerable Plaque in Patients with Cryptogenic Stroke

Anna Bayer-Karpinska, MD[a,*], Andreas Schindler, MD[b], Tobias Saam, MD[b]

KEYWORDS

• Cryptogenic stroke • Carotid artery plaque • Carotid MR angiography • Intraplaque hemorrhage • Lipid-rich necrotic core • Fibrous cap rupture • Echogenicity • Plaque inflammation

KEY POINTS

- Cryptogenic stroke accounts for up to 40% of ischemic stroke cases with a recurrence rate of 3% to 6%.
- Mild and nonstenosing carotid artery plaques represent a possible but underestimated embolic source in patients with cryptogenic stroke.
- Ultrasonography, computed angiography, high-resolution carotid magnetic resonance angiography, and PET with fluorodeoxyglucose allow noninvasive imaging of carotid artery plaques and characteristic features of plaque vulnerability.
- In patients with mild and nonstenosing plaques, high-resolution carotid MR imaging might be the most promising tool to assess the correlation of vulnerable plaques and cryptogenic stroke, stroke recurrence, and plaque progression.

INTRODUCTION

Stroke is still one of the leading causes of death and disability in industrialized countries.[1] Currently used stroke classification systems consider atherosclerotic lesions of the carotid bifurcation only as causative, if they are associated with substantial luminal narrowing of at least 50%.[2] Patients with mild or nonstenosing carotid artery plaques do not fulfill these criteria and, thus, are often diagnosed as stroke of unknown cause, so-called cryptogenic stroke. It has been shown in the coronary arteries that most myocardial infarctions occur in arteries with 50% or less stenosis.[3] Similarly it is commonly assumed that most macroangiopathic ischemic strokes are caused by arterio-arterial embolism from ruptured atherosclerotic plaques and not from high-grade stenosis. In fact, several studies demonstrated an association of vulnerable plaques in stenosed vessels with previous or subsequent stroke and stroke recurrence, respectively.[4] Data regarding arterio-arterial embolism from nonstenosing plaques in patients with a cryptogenic stroke are rare. Nevertheless, in this article, the authors present several plaque imaging techniques, including ultrasonography with and without contrast medium, microemboli signal (MES) detection, computed tomography angiography (CTA), 18F-fluorodeoxyglucose (FDG)–PET, as well as high-resolution MR imaging, and discuss their role in the diagnostic work-up of patients with cryptogenic stroke.

Disclosure Statement: The authors have nothing to disclose.

[a] Institute for Stroke and Dementia Research, Ludwig-Maximilians-University Hospital Munich, Feodor-Lynen-Str. 17, Munich 81377, Germany; [b] Institute for Clinical Radiology, Ludwig-Maximilians-University Hospital Munich, Pettenkoferstr. 8a, Munich 81377, Germany

* Corresponding author.

E-mail address: anna.bayer@med.uni-muenchen.de

Neuroimag Clin N Am 26 (2016) 97–110

http://dx.doi.org/10.1016/j.nic.2015.09.008

Furthermore, the focus is on studies regarding the progression of plaque burden after stroke, the influence of medical therapy on plaque progression, and the association of vulnerable plaques and stroke recurrence. Finally, the authors highlight ongoing studies in this field.

CRYPTOGENIC STROKE

Current etiologic classification systems try to assign ischemic stroke causes into one of 4 major categories: occlusive large artery atherosclerosis, cardioembolism, small vessel disease, and other rare causes, such as arterial dissection or vasculitis. However, despite intense clinical work-up in 23% to 40% of all ischemic strokes, no definite cause can be established; they are, thus, classified as cryptogenic strokes.[5]

The definition of a cryptogenic stroke is slightly different depending on the classification system used. According to the widely used Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system, which was established in 1993, an ischemic stroke is considered to be cryptogenic if the stroke cause remains unknown, if more than one cause seems causative, or if the diagnostic assessment is incomplete.[6] Newer classification systems, such as the ASCOD classification, which was established in 2009, define cryptogenic stroke as ischemic stroke with unknown cause.[7] Thus, in this newer classification system, strokes with more than one potential source or strokes with incomplete diagnostic assessment are no longer classified as cryptogenic.

Identification of the potential cause of the ischemic stroke is of utmost importance because therapy and the risk of a recurrent event vary across different stroke subtypes.[8] Thus, the diagnosis of cryptogenic stroke is unsatisfying for the clinician as well as for patients given that recurrence rates of ischemic stroke of up to 30% within 1 year have been reported.[9] To date, standardized diagnostic criteria for cryptogenic stroke are still missing and no consensus exists on the appropriate diagnostic work-up. In the authors' opinion, the minimal diagnostic work-up should include imaging of the extracranial and intracranial vessels, brain imaging by MR imaging, and cardiac tests including 24-hour electrocardiogram (ECG) monitoring and transthoracic echocardiography (**Box 1**). In some cases, especially in young patients, further blood and cerebrospinal fluid investigations may be necessary.[10] With the diagnostic approach mentioned earlier, high-risk cardioembolic sources like atrial fibrillation or intraventricular thrombus, occlusive or stenosing atherosclerotic disease, vasculitis, arterial dissection, and lacunar infarcts due to cerebral small vessel disease can be diagnosed or excluded.

Recently a new clinical construct termed embolic stroke of undetermined source (ESUS) was introduced to describe stroke entities with a presumed embolic cause.[11] ESUS comprises a subset of patients with signs of embolic stroke on MR imaging and sufficient diagnostic work-up to exclude the major-risk causes of embolic stroke mentioned earlier. The rationale for this new clinical construct is the hypothesis that oral

Box 1
Minimal diagnostic requirements for cryptogenic stroke

Diagnostic Assessment	Stroke Cause
Imaging of the extracranial and intracranial vessels by ultrasound, CTA, or MRA	Occlusive atherosclerotic disease Artery dissection
Brain imaging by MR imaging	Small vessel disease with lacunar infarct
12-lead ECG and 24-hour or greater ECG monitoring	Major risk cardioembolic source • For example, atrial fibrillation
Transthoracic echocardiography	For example, thrombus from the aortic or mitral valve, the left cardiac chamber
Optional, according to age and medical history:	
Imaging of the aorta by CTA or TEE	Arteriogenic embolism from aortic arch atheroma
Blood tests for prothrombotic factors and inflammatory diseases	Paradoxic embolism (in combination with patent foramen ovale) Vasculitis Endocarditis
Lumbar puncture (CSF)	Vasculitis

Abbreviations: CSF, cerebrospinal fluid; MRA, magnetic resonance angiography; TEE, transesophageal echocardiography.