Progress Review

Evaluation of Cryptogenic Stroke With Advanced Diagnostic Techniques

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The term cryptogenic stroke generally refers to a stroke for which there is no specific attributable cause after a comprehensive evaluation for the most common causes. Cryptogenic stroke accounts for 23% to 40% of patients, more frequent in younger patients.1,2

The issue of cryptogenic stroke is a relevant one for several reasons. First, prognosis—high risks of recurrence have been reported after cryptogenic stroke or transient ischemic attack (TIA). Third, perception—because no distinctive treatment is often recommended in patients with cryptogenic stroke, physicians and patients may otherwise not take adherence to prescribed treatments as seriously as they should given the high risk of recurrence. Third, and perhaps most importantly, advanced diagnostic techniques, including long-term monitoring to document paroxysmal atrial fibrillation (AF), high-resolution MRI technique to visualize wall pathology (ie, plaque, dissection, or vasculitis), and coronary computed tomographic angiography (CCTA) to evaluate aortocardiac embolism/concomitant coronary heart disease, might be useful in reducing the proportion of patients diagnosed with cryptogenic stroke, thereby facilitating the implementation of therapies targeting the underlying cause of the index stroke, especially because recurrent strokes are often of the same subtype as the preceding index stroke.

The purpose of this review article is to present the most recent advances in diagnostic techniques that may be helpful in reducing the proportion of patients diagnosed with cryptogenic strokes.

Challenges in the Diagnosis of Cryptogenic Stroke

First, patients diagnosed with a cryptogenic stroke may have evidence of a mild degree of stenosis in vessels corresponding to the area of symptomatic vascular brain injury. However, even an artery with a mild degree of stenosis can harbor unstable plaque, which can rupture or erupt, resulting in stroke via arteroembolism. Indeed, it has been shown that thrombotic coronary artery occlusion usually follows rupture of an unstable plaque, and the at-risk or vulnerable coronary artery plaque is not necessarily associated with high-grade stenosis. Furthermore, among patients who presented with an acute coronary syndrome, cardiovascular events during follow-up were equally attributable to recurrence at the site of culprit lesions and to nonculprit lesions.6 In addition, atherosclerotic plaque in the intracranial artery can protrude into a perforator’s orifice and occlude the lumen, causing a subcortical infarction (branch occlusive disease).7 Although patients showing small deep infarcts and mild degree of arterial stenosis are often misclassified as lacunar stroke or cryptogenic stroke, the recurrence rate in these patients is high, and similar to the rate seen among patients with atherosclerotic stroke and significant stenosis.8

Another challenge with properly excluding the diagnosis of cryptogenic stroke is that the cause of stroke may be transitory or spontaneously reversible, and so diagnostic workup results may be unrevealing if testing was undertaken during the time of reversion to normalcy. For instance, although paroxysmal AF is more prevalent than persistent AF in patients with stroke/TIA,9 identification of paroxysmal AF is more difficult because of its transitory nature, yet it is also independently associated with increased risk of ischemic stroke or systemic embolism.10 Large clinical trials showed that subjects with paroxysmal AF at high risk had stroke/systemic embolism rates that were not dissimilar to those among subjects with persistent AF.11 Other causes of stroke that can be transitory or reversible include arterial dissection, vasospasm/reversible vasoconstriction syndrome, and migraine-induced stroke. Careful history taking, including trauma, headache, or localized pain, could be informative in these cases, and specific diagnostic tests for the many rare causes of ischemic stroke should be guided by suspected clinical findings in young adults.12

Finally, the actual cause of a stroke may be inadequately investigated or ignored, especially in the clear absence of traditional and common conditions (eg, arterial stenosis or AF). As such, underlying causes of stroke, such as paradoxical or aortogenic embolism and intravascular coagulopathy, may not be addressed. These conditions are often inadequately investigated or ignored because they can also be observed in subjects without stroke: patent foramen ovale (PFO) is prevalent in both general population and patients with stroke, and it was estimated that in patients with otherwise cryptogenic stroke...
approximately one third of discovered PFOs are likely to be incidental and hence not benefit from closure. Therefore, both could be either pathogenic or incidental finding in patients with cryptogenic stroke. The probability of having PFO or AAA as possible causes of stroke in patients with cryptogenic stroke may differ among patients. Among patients with cryptogenic stroke, younger patients without vascular risk factors are much more likely to have PFO than do patients with risk factors. Several morphological features of atheroma (thickness ≥4 mm, ulcerated or mobile, located at proximal or arch of aorta) have been characterized as stroke prone.

Cancer and ischemic stroke are 2 of the most common causes of death among the elderly, and associations between them have been reported. Because of the advances in cancer medicine and the steadily increasing proportion of elderly people, the number of people living with cancer is increasing. As a consequence, the proportion of patients who have cancer is expected to increase among patients with stroke, especially in those without other stroke pathogeneses. Certain cancers, such as lung cancer (especially adenocarcinoma), and gastrointestinal malignancy secret substances, such as cysteine proteases, tissue factor, and sialic acid moieties of mucin, exhibit procoagulant activity, resulting in the activation of factors X and VII. In addition, aggressive antitumor therapy may also increase the risk of thrombosis. Given that appropriate anticoagulation can effectively prevent cancer-related stroke, early identification of this stroke mechanism is important and requires additional studies.

### Advanced Diagnostic Techniques in Cryptogenic Stroke

#### Advanced Vascular Imaging and Additional Sonographic Studies for Arterial Pathology

Plaque vulnerability can be identified by MRI. MRI-based tissue quantification is accurate and reproducible; when compared with carotid endarterectomy specimens, in vivo multi-contrast MRI could distinguish advanced lesions from earlier atherosclerotic plaques. MRI for carotid plaque imaging can identify nonstenotic ruptured unstable plaque in patients with cryptogenic stroke. In addition, carotid Duplex and transcranial Doppler (TCD) monitoring for microembolism can detect high-risk patients with asymptomatic carotid stenosis and also help identification of mild degree of symptomatic carotid stenosis in patients with cryptogenic stroke (Figure 1A). More recently, 3-dimensional ultrasound and contrast-enhanced ultrasound have been introduced as a tool for evaluating the vulnerable plaque at risk for rupture in patients with carotid atherosclerotic disease.

With the recent development of high-resolution-MRI techniques, vessel wall imaging findings in various causes of intracranial stenosis, has been reported, including intracranial atherosclerosis, dissection, and vasculitis. MRI technique to find vulnerable plaque is important because vulnerable plaques often have well-preserved lumen because plaque grows outward initially. Vulnerable plaque components are associated with a high degree of positive remodeling because of which ischemic events often result from a plaque without significant stenosis. Not only the plaque burden but also plaque distribution has clinical relevance. In patients with subcortical infarcts adjacent to the proximal middle cerebral artery, superior wall plaques are more likely to be symptomatic because they are nearer to the orifices of penetrating arteries (Figure 1B). Advanced vascular imaging techniques can be used in monitoring the effect of treatment, such as statins. Resolution of the enhancement and plaque regression in arterial wall imaging might suggest a state of vulnerability of plaque.

### Monitoring and Imaging Techniques for Paroxysmal AF

Current guidelines recommend that cardiac monitoring should be performed for at least the first 24 hours. However, AF-detection rate of 24-hour Holter monitoring seems not to be sufficient, being reportedly inferior even to serial ECG for 3 days. Recent technological advances have made it possible to perform long-term cardiac rhythm monitoring up to months or even years after a stroke. When compared with 24-hour Holter monitoring, higher yield of AF detection with in-hospital and outpatient telemetry, and more recently implantable loop recorder, has been reported. However, the yield varied greatly depending on the study population (age and stroke subtypes), interval of monitoring from stroke onset, duration of monitoring, and the definition of AF, as well as the choice of monitoring devices (Figure 2). Therefore, more studies are needed to establish the yield of AF detection with newer devices controlling these factors.

Cryptogenic Stroke and Underlying AF trial (CRYSTAL-AF; NCT00924638 in ClinicalTrials.gov), a multinational randomized prospective study comparing the time with first documented episode of AF between standard arrhythmia monitoring versus continuous monitoring using an insertable cardiac monitor in patients who had a cryptogenic stroke or TIA, has recently completed enrollment.

Besides monitoring methods, transesophageal echocardiographic (TEE) and CCTA can also visualize left atrial appendage (LAA) thrombus in patients for whom chronic anticoagulation may be warranted. LAA is the most typical origin for intracardiac thrombus formation when associated with AF. Changes in both LAA volume and morphology are associated with cryptogenic stroke, and CCTA findings of either enlarged LAA volume or certain LAA morphologies may guide tools for longer (and more expensive) ECG monitoring in cryptogenic stroke.

### Diagnostic Techniques for Paradoxical and Aortogenic Embolism

Selection of appropriate investigation might be more difficult in patients who had stroke involving multiple vascular territories than patients with stroke within one vascular territory. In this case, the cause of stroke may be underestimated or inadequately investigated. Transthoracic echocardiogram is still the first choice of technique in patients with stroke. However, transthoracic echocardiogram is considered insufficient as a screening tool in patients with stroke. Only 0.7% patients...
Recently, there have been efforts to use CCTA, a noninvasive technique, to visualize potential sources of embolism. CCTA could be useful modality for detecting high-risk cardiac sources of embolism in patients with stroke. This technique can directly visualize the aortogenic and paradoxical embolic sources (Figure 3). A contrast agent jet from left atrium to right atrium toward the inferior vena cava with channel-like appearance of the interatrial septum on CT images confirms the presence of a PFO with high accuracy. CCTA was similar to TEE in detecting AAA, and detected smaller atheromas and was better in defining athromata morphology. A recent study showed that the combined use of CCTA and TEE was more sensitive than CCTA or TEE alone for detecting cardiac or aortogenic embolic sources, suggesting a complementary value of CCTA and TEE for the diagnostics of stroke pathogenesis.

Finally, agitated saline TCD monitoring and transthoracic study can be used to detect paradoxical embolism. Agitated saline TCD monitoring is based on intracranial detection of intravenously injected microemboli. The size and functional relevance of right-to-left shunt can more easily be assessed using TCD, with similar sensitivity and specificity with TEE. Right-to-left shunt can also be detected noninvasively using dye dilution or ear oximetry methods with high sensitivity and specificity when compared with TEE.

Workup for Cancer-Related Coagulopathy

Although coagulation tests are being tested in most centers, such as antiphospholipid antibodies in younger stroke patients, they are often of little value in the evaluation of patients with stroke. Therefore, laboratory tests for coagulopathy may be reserved in selected patients. In clinical practice, a much more important cause of coagulopathy is cancer. In a recent analysis of patients with cryptogenic stroke, patients with active cancer were present (71 of 348 patients; 20%) and had distinctive D-dimer levels (a marker of coagulopathy, >20× higher than those without cancer) and infarct patterns (multiple lesions in multiple vascular territories). Interestingly, in this study, among 10 patients who showed such characteristics but no known cancer, workup for hidden malignancy revealed occult cancer in all patients (Figure 4). Therefore, patients who present with characteristic symptoms and infarct patterns, and no other apparent explanation for their index stroke, D-dimer level and screening for hidden malignancy (serological or radiological tests) should be considered. D-dimer level can also be used in monitoring the effect of anticoagulation therapy. However, treatment of cancer, cancer itself, and stroke itself can all cause elevated D-dimer levels, so it could be difficult to attribute a stroke definitively to hypercoagulability based on D-dimer level only. Further studies are needed, including evaluating the use of novel biomarkers such as tissue factor-bearing microvesicles.

The detection of an embolic signal with TCD may provide clues on the cancer-specific mechanism related to hypercoagulopathy and may be used to monitor the effect of treatment in the acute stroke period. Unlike nonbacterial thrombotic endocarditis, these patients usually had multiple small diffusion-weighted imaging (DWI) lesions with microembolic signals on TCD monitoring, and TEE usually did not reveal vegetations, suggesting intravascular coagulopathy.
Practical Approach to Working Up Cases of Suspected Cryptogenic Stroke

Targeted selection and judicious use of appropriate tests in the workup of cryptogenic stroke are crucial. Although extensive pathogenic workup generally decreases cause-undetermined cases, it may also paradoxically increase the prevalence of cryptogenic stroke: for instance, imprudent use of TEE may inadvertently lead to a rise in cases with ≥2 determined causes. As such, diagnostic investigations of suspected cryptogenic stroke, particularly advanced diagnostic techniques, should be guided and chosen in accordance with patients’ characteristics at the time of clinical presentation. The cost-effectiveness of advanced diagnostic technologies will greatly depend on the appropriate selection of patients for the various diagnostic tests.

Lesion Pattern Analysis

In application of advanced diagnostic techniques, including cardiac telemonitoring, high-resolution wall imaging, and aorto-cardiac workups, topography of lesion could be analyzed in the following order (Figure 5):

1. DWI infarct pattern: embolic versus deep and large versus small scattered.
2. DWI infarct distribution: ≥1 vascular territory involved.
3. Past stroke on history or fluid-attenuated inversion recovery image: the same side versus different territory.

Baseline DWI

The knowledge of the clinical and radiological features of cryptogenic strokes will help physicians understand the pathogenic mechanisms involved in stroke development. This information is essential for focused planning and implementation of secondary prevention programs in patients with cryptogenic stroke. Because comprehensive workup of stroke mechanisms is time-consuming, there have been
efforts to identify mechanisms of stroke using DWI. Single cortico/subcortical lesions and multiple bilateral lesions in the anterior and posterior circulation on DWI have been associated with cardiac embolic sources, whereas multiple unilateral lesions in the anterior circulation have been linked with arterogenic embolism, such as atherosclerosis or dissection. When compared with final diagnoses, pre-MRI Trial of ORG 10172 in Acute Stroke Treatment (TOAST) diagnoses matched final diagnoses in 48%, improving to 83% after DWI, and 94% after both DWI and MR angiography. In addition, embolic stroke has unique clinical features and infarct patterns depending on the embolic sources (ie, cardiogenic versus paradoxical versus aortogenic sources). Moreover, DWI lesion pattern may help in recognition of the likely differences in the early prognostic end points (ie, recurrence and infarct growth) after ischemic stroke. Therefore, DWI is advantageous as a guide to specific diagnostic workups and therapy.

**Past Stroke on History and Fluid-Attenuated Inversion Recovery Imaging**

In addition to DWI, fluid-attenuated inversion recovery imaging can be informative because the stroke subtype and infarct pattern of past stroke greatly influence the index stroke. Specifically, patients with cortical infarcts by atheroembolism often have recurrent stroke with cortical infarcts within the same arterial system, whereas patients with deep infarcts because of branch occlusive disease developed recurrent branch occlusion. The same is true for small arterial occlusion and cardioembolism, regardless of the presence of asymptomatic stenosis on the cerebrovascular system. In patients with first ever stroke, the presence of cardioembolic sources (eg, AF) was associated with unrecognized cerebral infarcts involving multiple territories on fluid-attenuated inversion recovery.

However, about DWI lesion pattern association with hidden pathogeneses, the proposed patterns have been described mostly in series of patients with the underlying disease being the probable cause of stroke (ie, large artery disease or AF).
Therefore, it remains to be determined which patterns are associated with a not overt underlying disease in patients with cryptogenic stroke. More studies are needed in patients with cryptogenic stroke to see if the recommendations of this review on predictive DWI patterns are true.

Selection of Advanced Diagnostic Techniques

Advanced Vascular Imaging

For patients with infarcts within 1 arterial system, advanced vascular imaging, such as high-resolution wall imaging, may help in documentation of unstable plaque, arterial dissection, or vasculitis. This is particularly helpful in patients with (1) past stroke within the same vascular territory, (2) multiple small scattered infarcts within 1 arterial system, and (3) deep infarct that is suspected to have branch occlusive disease (those who have comma-shaped infarcts extending adjacent to parent artery or deep infarcts on brain stem).70

Advanced Monitoring for AF Detection

A longer monitoring may be particularly important in patients with large stroke or strokes involving multiple vascular territories.65 Because the clot from the left atrium or LAA usually large (fibrin-containing) and occlude distal internal carotid artery, proximal middle cerebral artery, or distal basilar artery, AF is associated with more severe ischemic stroke and longer (>60 minutes) TIA than arteroembolic stroke from carotid or intracranial disease. Several clinical (women, diabetes mellitus), genetic, and electrophysiological (premature atrial complex, left atrial dilation, and reduced left ventricular ejection fraction) features have also been reported as predictors of paroxysmal AF, which may guide performing a longer monitoring in patients with cryptogenic stroke.32,38,41,43 In addition, blood biomarkers, such as high pro–brain natriuretic peptide levels, may be predictors for incident AF in patients with cryptogenic stroke.71–73

Aortogenic Embolic Source Evaluation

TCD microembolism study showed that AAA has embolic potential,74 and DWI patterns are characterized by multiple small scattered lesions in multiple vascular territories that are mainly located in cortical and borderzone regions.75 These are in line with an autopsy study of cases with cerebral atheromatous embolism, which showed that atheromatous emboli containing mostly cholesterol crystals are associated with borderzone infarct, whereas large emboli containing fibrin are associated with large territory infarcts.76 Therefore, additional workup to document aortogenic sources are recommended in elderly patients with vascular risk factor and infarct patterns associated with complex AAA; (1) multiple brain infarcts involving multiple vascular territories,77 (2) small-sized infarcts,69 and (3) location of cortical and borderzone region.75

Paradoxical Embolic Source Evaluation

Because PFO could be an incidental finding, it is important to elucidate the specific infarct patterns related to paradoxical embolism. DWI lesion pattern may differ depending on the presence and the degree of right-to-left shunt. Specifically, patients with PFO showed a higher incidence of multiple lesions in the posterior circulation,78 and the majority (80%) of patients with a large amount of right-to-left shunt have small infarcts.79 Therefore, additional workup to identify paradoxical embolism may have to be considered in young (<55 years old) patients without conventional risk factors, history of migraine, and infarct pattern of small, multiple infarcts involving posterior circulation.65,78,79 A recent analysis of data from 12 studies showed that among patients who were <30 years and had none of the conventional risk factors, and a superficially located lesion, the likelihood of detecting a PFO was nearly three fourths (a fourth in general population), and the PFO-attributable fraction was ~90%.60 Beside right-to-left shunt, AF-like pathophysiology (atrial dysfunction and concomitant AF) has been suggested as a mechanism of stroke related to PFO.81,82 Therefore, a longer ECG monitoring should be considered for patients with large infarcts or echocardiographic findings of left atrial dysfunction.

Tests for Coagulopathy and Cancer Screening

Measurement of D-dimer and screening tests for concealed cancer may be needed in patients with cryptographic stroke, who had (1) vascular risk factors that cannot sufficiently explain the stroke, (2) atypical presentation of symptoms, and (3) multiple infarcts involving multiple vascular territories.15 Patients with cancer-related stroke often present with progressive neurological deficits for hours to days (or even weeks) rather than sudden catastrophic events with initial maximum deficits at onset. In many patients, multifocal thromboembolism culminates in widespread infarcts of various sizes, producing confusion, lethargy, or dementia.

Conclusions

The proportion of patients diagnosed with cryptographic stroke using current classification systems remains high, thereby potentially exposing several people to an underdiagnosis of underlying causes that may be amenable to treatment for preventing recurrences. Our review of the literature, as well as cases presented within this article, suggest the need for broader yet systematic application of advanced technologies in patients with suspected cryptographic stroke. Conceivably, such application of advanced diagnostic technologies may reduce the proportion of patients diagnosed with cryptographic stroke (Figure 6).
Continuous efforts are needed to refine the approach to working up cases of suspected cryptogenic stroke. For example, it was recently reported that genetic risk factors for stroke may be stroke subtype-selective,\textsuperscript{8,14} and genetic expression in conjunction with infarct pattern might predict possible causes in patients with cryptogenic stroke.\textsuperscript{15} In the meantime, the methodological approach to working up cases of suspected cryptogenic stroke discussed in this article may provide a useful and practical approach for clinicians caring for patients with ischemic stroke and TIA.

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None.

References
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The version of the article, “Evaluation of Cryptogenic Stroke With Advanced Diagnostic Techniques” by Bang et al (Stroke. 2014;45:1186–1194) that published online ahead-of-print on February 24, 2014, a correction was needed.

The Abstract section has been removed and Key Words modified.

This has been corrected in the online and print version of the article.