Editorial

Prime Time for Dissecting the Entity of Cryptogenic Stroke

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The term cryptogenic ischemic stroke (or stroke of undetermined pathogenesis) encompasses ischemic strokes without specific cause detected after adequate diagnostic workup. Cryptogenic stroke is, thus, a diagnosis done by exclusion. Strokes may remain cryptogenic if diagnostic evaluation is incomplete for one or another reason or in the presence of multiple competitive causes, such as atrial fibrillation (AF) and atherosclerotic stenosis in an ipsilateral relevant artery. Choosing the particular diagnostic investigation should always be balanced between the cost and potential yield, considering patient characteristics and the effect on treatment decisions. The only patients with stroke in whom thorough pathogenic workup may be unnecessary are those whose poor prognosis cannot be improved reasonably by pathogenic diagnosis. A substantial proportion of all strokes end up being cryptogenic. Among the 5017 patients in the German Stroke Data Bank, cryptogenic strokes accounted for 23%. Notably, the cryptogenic category is even larger among younger patients reflecting major challenges in defining their pathogenesis and interpreting causally relevant findings. A total of 40% of patients aged <50 years remained without elusive cause for their stroke in a recent large multicenter survey. Furthermore, another prospective study with MR-imaged patients aged <55 years showed higher rates of cryptogenic strokes with lower age.

There is paucity of data to guide secondary prevention after cryptogenic stroke. Current guidelines either did not give statements specifically on cryptogenic stroke or recommended antiplatelet therapy. Anticoagulation (warfarin with target international normalized ratio, 1.4–2.8) has been compared against aspirin (325 mg/d) only in 1 randomized trial subgroup of cryptogenic stroke (n=576), with no difference in the primary outcome of ischemic stroke or death >2 years (15.0% versus 16.5%). About patent foramen ovale, a prevalent feature in both general population and in younger patients with cryptogenic stroke, warfarin was not superior to aspirin, and patent foramen ovale closure in unselected patients with unselected device was not beneficial compared with the best medical treatment to reduce the risk of recurrent strokes in the recently completed randomized trials.

Among these limited data on secondary prevention, clinical and subclinical recurrence risk after cryptogenic stroke remains significant. A South Korean study showed a very high rate (30%) of recurrent stroke after cryptogenic stroke in a relatively short 1-year follow-up. Furthermore, another recent study found a 14.5% rate of new silent ischemic MRI lesions at 90-day follow-up although 1.2% had a clinical recurrent stroke during that time period. Even the young patients with stroke of undetermined pathogenesis experience recurrent events, with an annual rate of ≈1%. These figures suggest an active pathology underlying most cryptogenic strokes and justifies the use of advanced and often expensive diagnostic equipment targeting to improve the secondary prevention of these patients.

Development and the use of modern equipment and technology have indeed allowed revealing the most likely cause in strokes formerly deemed cryptogenic in cases where causal relationship has been unclear. For instance, carotid plaques with less than the arbitrary 50% stenosis, as well as intracranial plaques, that may seem harmless may be thromboembolic. This plaque vulnerability can be assessed with multicontrast MRI, 3-dimensional, or contrast-enhanced ultrasound and carotid Duplex or transcranial Doppler ultrasound microemboli detection. In the setting of embolic imaging lesion distribution in suspected cryptogenic stroke, a prolonged telemetric or implantable loop recorders may allow recording ECG even up to months or years to detect atrial arrhythmias.

In the current issue of this journal, Bang et al present a rigorous review on the most recent advances in diagnostic techniques and propose a practical approach to select appropriate tests in the workup of suspected cryptogenic stroke. Their insightful approach starts with analysis of brain MRI diffusion-weighted imaging and fluid-attenuated inversion recovery patterns that guide the selection of advanced vascular and cardiac imaging, prolonged ECG, and additional testing, such as surrogate markers for atrial arrhythmia or screening for cancer.

Because a considerable proportion of cryptogenic strokes has an embolic imaging pattern (for instance, in our institution 24% of all ischemic strokes among 541 consecutive patients during a 6-month period were cryptogenic with imaging pattern suggestive of embolism; unpublished observation), it is plausible to hypothesize that much of the diagnostic yield may come from prolonged ECG. Indeed, small pilot studies applying implantable loop recorders detected new paroxysmal AF in as many as one quarter of patients with cryptogenic stroke. Furthermore, also other types of supraventricular arrhythmias might be relevant to stroke mechanisms as pointed out by recent observations. The soon-to-be released Cryptogenic Stroke and underlying AF results will likely shed light on the prevalence of these electrocardiographic features in a large poststroke population.
Although the current American and European guidelines suggest 24-hour Holter to detect paroxysmal AF,\(^5\)\(^6\) its detection rate is \(\approx5\%\) at best and cost-effectiveness questionable (number needed to screen 47, cost per one new diagnosis would be \$9400 and cost per decision to initiate oral anticoagulation \$17000).\(^7\) Moreover, even serial ECGs may detect AF more efficiently.\(^8\) Only 1 randomized study has been completed whether prolonged ECG monitoring changes the decision making on anticoagulant therapy.\(^9\) That study found zero rate of new AF. Therefore, the most optimal cost-effective ECG monitoring technology and monitoring duration remain important open questions. Although novel ECG monitoring equipment is certainly not cheap, blood biomarkers, electrophysiological, and cardiac structural, and functional characteristics may be needed to select high-risk patients for such long-term monitoring.

Rigid classification systems with arbitrary cut-offs (such as the \(\ge 250\%\) criteria for relevant carotid stenosis) increase the proportion of cryptogenic strokes and may lead to unnecessary overuse of expensive advanced diagnostic testing. The more recent classification systems, such as ASCO (A for atherosclerosis, S for small vessel disease, C for cardiac source, O for other cause)\(^2\)\(^0\) and Causative Classification System,\(^2\)\(^1\) are able to better perceive the presence of multiple concomitant competing mechanisms and characterize patient phenotype, and thus improve the fidelity for subtype classification when compared with the traditional Trial of Org 10172 in Acute Stroke Treatment (TOAST).\(^2\)\(^2\) Development and the use of more advanced classification schemes and algorithms would be essential to improve the subtyping accuracy particularly for genetic and epidemiological studies, as well as for clinical decision making.

The approach provided by Bang et al\(^1\)\(^2\) neither removes the clinician’s pitfalls of delayed workup in case of, for example, dissection with normalized angiographic appearance or a mobile thrombus that has disappeared at the time of diagnostic imaging nor helps proving causality in uncertain conditions, such as patent foramen ovale–related strokes.\(^2\)\(^3\) Moreover, devices are unable to detect transient risk factors for arterial thrombosis, such as infections\(^2\)\(^4\) or psychosocial stressors\(^2\)\(^5\) and their interplay with blood coagulation and hemostasis. The authors provide a largely mechanistic approach for revealing the potentially underlying cause of cryptogenic stroke, but drawing the big picture likely necessitates a far more multidisciplinary perspective.

Although the review by Bang et al\(^1\)\(^2\) will definitely be helpful for stroke physicians, choosing the approach for advanced pathogenetic evaluation in suspected cryptogenic stroke, there are many open questions to be resolved. Cryptogenic stroke is a major health issue and should be among the top research focuses in the field. This research necessitates multidisciplinary approach involving a broad knowledge on not only vascular neurologists and cardiologist but also experts of other fields, such as hematology, genetics, and imaging device engineering. An example of such multidisciplinary attempt is the recently initiated investigator-driven multicenter study, Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Etiology, Triggers, and Outcome (SECRET0; NCT01934725).

**Disclosures**

None.

**References**

5. European Stroke Organisation (ESO) Executive Committee, ESO Working Committee on Subtypes of Ischemic Stroke, Stroke of Unknown Origin Study Group. Rigid classification systems with arbitrary cut-offs (such as ASCO A for atherosclerosis, S for small vessel disease, C for cardiac source, O for other cause) and Causative Classification System, are able to better perceive the presence of multiple concomitant competing mechanisms and characterize patient phenotype, and thus improve the fidelity for subtype classification when compared with the traditional Trial of Org 10172 in Acute Stroke Treatment (TOAST). Development and the use of more advanced classification schemes and algorithms would be essential to improve the subtyping accuracy particularly for genetic and epidemiological studies, as well as for clinical decision making.

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