

Letters to the Editor

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Cryptogenic Stroke: Cryptic Definition?

To the Editor:

We have read with great interest the article entitled "May-Thurner Syndrome in patients with cryptogenic stroke and patent foramen ovale" which appeared in *Stroke*.¹

The article is innovative, being the first large-scale analysis of the association between May-Thurner Syndrome, cryptogenic stroke, and patent foramen ovale (PFO). Nonetheless, it arises some uncertainties concerning the definition of "cryptogenic stroke". In the present study, cryptogenic stroke was defined as "a sudden focal neurological event in the absence of an identifiable cause such as uncontrolled hypertension, intracranial hemorrhage, ipsilateral carotid lesion, atrial fibrillation, intracardiac thrombus, degenerative neurological disorder or neoplasm."¹

In literature, the term cryptogenic stroke usually refers to strokes with no clearly definable cause even after extensive workup.² Approximately 30% to 40% of ischemic strokes are cryptogenic.³ This means that in a large part of our patients we are unable to identify stroke etiology because: (1) the cause is reversible, and the workup is not performed at the appropriate time; (2) the causes of stroke are not fully investigated; and (3) some causes of stroke remain unknown.³ In the TOAST classification, the stroke is of undetermined etiology when the presence of multiple, concomitant risk factors force the physician to be unable to determine a final diagnosis.⁴

Paradoxical embolism via PFO has been documented as a stroke mechanism. Nevertheless, data are still conflicting, and PFO remains associated with cryptogenic stroke. In the present study all patients had undergone PFO closure, but a comprehensive workup was also performed to rule out other causes of stroke. Interestingly, they found a statistically significant higher incidence of thrombophilia screen abnormalities in the May-Thurner Syndrome group. Some of these factors are known to be independent risk factors for arterial stroke (ie, 1 patient had antiphospholipid syndrome). Others are independent risk factors for venous thrombosis, but also a probable cofactor for arterial stroke (2 patients had Factor V Leiden mutation, 2 patients had prothrombin gene mutation, 4 patients had anticardiolipin antibody titer).⁵

We believe that these cases reported above exclude the definition of cryptogenic stroke. As a matter of fact, the presence

of a thrombophilic abnormality (especially if acting in the venous system) and the PFO are not only concomitant risk factors, but pathophysiologically connected to the etiology of these strokes. Therefore, these are not cryptogenic strokes.

This consideration is not only speculative, because it relates to the diatribe concerning the indication of percutaneous closure of PFO. In presence of a thrombophilic factor, when lifelong antithrombotic or anticoagulant therapy is recommended, the advantage of closure is minor, while the risk of its complications are still not trivial.

To conclude, in the light of studies investigating new putative risk factors for stroke, it is urgent to revise the definition of cryptogenic stroke, to clarify the diagnostic doubts, and the possible clinical approach.

Disclosures

None.

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