Recurrent paradoxical embolic cerebral ischemia after patent foramen ovale closure

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Practical Implications

Consider all causes of paradoxical embolism before closing a patent foramen ovale.

About one-third of all ischemic strokes are classified as cryptogenic, with a significant rate of stroke recurrence in the first year (5%–30%).^{1,2} Patent foramen ovale (PFO) is a common finding among cryptogenic stroke patients,³ although its role as a stroke determinant is not always clear. We report a case of recurrent paradoxical brain embolism in spite of PFO closure.

Case

A 45-year-old Caucasian man presented to our emergency department with acute-onset perioral paresthesia, dizziness, and horizontal diplopia that had begun during physical effort and lasted about 15 minutes. Cerebral CT scan was negative for acute events. His past medical history was notable for recurrent epistaxis and episodes of dizziness and diplopia triggered by physical exertion. Brain MRI performed in another hospital had documented multiple cerebral lesions that were initially interpreted as demyelinating plaques and only later as multiple ischemic injuries (figure 1). Transcranial color-coded Doppler (TCCD) sonography with bubble study (BS) had detected a right-to-left shunt (RLS), while transesophageal echocardiography (TEE) had demonstrated the presence of a PFO. The characteristics of the shunt, in particular the time of appearance of the bubbles after injection, were not available. With no further clinical investigations the patient had undergone a PFO closure; however, he was never enrolled in a follow-up survey and when he came to our attention he was not on any antithrombotic treatment.

Physical examination revealed cyanosis of lips and fingertips, clubbing of fingernails, and telangiectasias on the tongue and chest; oxyhemoglobin desaturation was detected even with light physical effort. Neurologic examination was unremarkable. Laboratory tests showed considerable polycythemia, and hypercoagulable screening was negative. Serial ECGs and prolonged (i.e., 1 week) ECG monitoring never disclosed arrhythmias.

We repeated a TCCD with BS, according to the International Consensus Protocol,⁴ and documented a “curtain sign” reflecting a major RLS even at rest.

In order to exclude a deep vein thrombosis of the lower extremity or the pelvis, an echo color-coded Doppler sonography of the lower extremity and a contrast-enhanced venous magnetic resonance angiogram of the pelvis were performed: both tests were negative. TEE showed that the PFO closure device was not dislocated and that there were no peripheral leaks. A CT

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

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Figure 1 Brain MRI showing cerebellar (A, B) and thalamic (C, D) ischemic lesions in diffusion-weighted imaging and fluid-attenuated inversion recovery sequences

scan of the chest with contrast medium revealed multiple massive pulmonary arteriovenous malformations (PAVMs) (figure 2). The medical history of the patient and these current findings allowed us to make the diagnosis of hereditary hemorrhagic telangiectasia (HHT) according to the international criteria.⁵ Genetic testing detected a mutation in the *ENG* gene, and study of the patient's family members revealed HHT signs in many relatives. The patient underwent embolization of PAVMs and was placed on aspirin therapy; he has not had any recurrent events.

DISCUSSION

A major portion of ischemic strokes have no identifiable cause and are classified as cryptogenic.^{1,2} Some cryptogenic strokes may be the result of the transition of an embolus from the venous to the arterial circulation through an RLS. Indeed, a PFO, which is present in up to 60% of these patients,³ is a possible determinant of paradoxical embolism. However, even after the detection of a PFO, other causes of stroke must be taken into account in the diagnostic workup, including other sites of RLS. In particular, HHT, one of the most common genetic autosomal dominant diseases in the world (prevalence 1 case per 5,000), is characterized by recurrent epistaxis, telangiectasias, and multiple arteriovenous malformations.⁵ PAVMs reduce the filtering function of the lungs and increase the risk of stroke and brain abscess. It is important to note that obliteration of all angiographically visible PAVMs seems to significantly reduce ischemic stroke rate,⁶ emphasizing the importance of recognizing and treating even small PAVMs because of their harmful potential. TCCD with BS has excellent sensitivity for detecting RLS but low specificity for identifying the precise site of the shunt. International guidelines for HHT management recommend contrast echocardiography with BS for the detection of a pulmonary origin of the RLS.⁵ However, as shown by this report, these techniques are operator-dependent and

Figure 2 CT of the chest showing multiple pulmonary arteriovenous malformations (arrows) and patent foramen ovale closure device

echocardiography might not correctly identify the site of the shunt in cases with the simultaneous presence of PFO and PAVMs.

This case underlines that the detection of a PFO should not hamper a complete diagnostic workup in patients with multiple cerebral ischemic lesions. An accurate collection of the clinical history, a detailed clinical examination, and a complete diagnostic study aimed at disclosing alternative embolic sources should be performed before considering PFO a stroke determinant in order to avoid potentially harmful treatment without really abating the risk of a recurrence.

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STUDY FUNDING

No targeted funding reported.

DISCLOSURES

F.M. Farina reports no disclosures. C. Baracchini serves on the executive committee of the European Society of Neurosonology and Cerebral Hemodynamics; has received travel and/or speaker honoraria from Pfizer, Sanofi-Aventis, Guidotti, and Novartis; serves as Associate Editor for *BMC Neurology*; and has given expert testimony in a medico-legal case. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

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