When is a Stroke Really Cryptogenic? A Multidisciplinary Approach to a Complex Case

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Abstract
Patent foramen ovale (PFO) is a congenital heart defect, resulting from the incomplete closure of a communication in the interatrial septum at the level of the fossa ovalis, which physiologically allow blood flowing from the right to the left atrium during foetal circulation. The physiological increase in left atrial pressures after birth forces the septum primum against the septum secundum and determines the closure of such communication.

Introduction
However, PFO is diagnosed in up to 25% of individuals [1,2] and can be responsible for paradoxical embolism, that may eventually end up into transient ischemic attacks (TIA) or strokes [3]. Recent guidelines suggest that the presence of a PFO should be investigated in cases of cryptogenic stroke, especially in patients younger that 55 years, after all alternative aetiologies of recurrent stroke have been excluded [4]. Furthermore, guidelines recommend PFO closure in case of recurrent strokes despite adequate medical therapy with no other mechanism identified [4]. We report the case of a patient undergone percutaneous PFO closure after an ischemic stroke that had been considered cryptogenic and whose comorbidities warranted a multidisciplinary approach to tailor the best treatment during follow-up.

Case Presentation
A 63-year-old man, former smoker and with a familiar history of cerebrovascular accidents, underwent PFO closure with Amplatzer Septal Occluder 28 mm (St. Jude Medical, St Paul, Minnesota, USA) in April 2007 after the occurrence of an ischemic stroke, classified at that time as cryptogenic. Patient was discharged on double antiplatelet therapy (ticlopidine for 3 months and aspirin for 12 months). Postoperative course was uneventful until August 2016, when a TIA occurred with clinical similarities to previous event. Cerebral CT scan promptly excluded intracranial haemorrhage and coagulation tests were within the normal range. Eventually, the patient was referred to our outpatient clinic for a cardiologic assessment. Transthoracic echocardiography (TTE) evidenced the presence of a mass adherent to device (Figure 1). Subsequent transoesophageal echocardiography (TEE) better defined this mass as a pedicle adherent to the left atrial surface of the device (Figure 2 and 3). After that, considering the high risk of thrombo-embolic accidents, oral anticoagulation therapy with warfarin was recommended, with a target INR of 2.5.

Patient was followed-up with TEE on a monthly basis. Mass dimensions significantly reduced after the first month and thrombus completely solved after 6 months (Figure 4). During last visit, the patient exhibited the results of cerebral MRI, showing areas of previous necrosis, with concomitant cerebrovascular malformations suggestive of multiple cavernomatosis. A surgical therapy was excluded by neurosurgeons, because patient was asymptomatic after 6 months from the event and because the malformations were not approachable by surgery. Testing for thrombophilia evidenced a heterozygosis for Cystathionine-β-synthase (involved in the metabolism of homocysteine), beta fibrinogen G (-455) A/WT and isoforms of Apolipoprotein E, but such polymorphisms are not usually associated with an increased risk of thrombosis. Genetic counselling excluded the presence of CCM1, CCM2 and CCM3 mutations on chromosomes 3 and 7, typically involved in cases of familial multiple cavernomatosis [5] and therefore the screening was not extended to his relatives. Oral anticoagulation was stopped, considering the absence of intracardiac thrombosis and the potential risk of fatal intracranial haemorrhage and lifelong aspirin has been then recommended. The patient started a follow-up program, specifically designed to address the clinical and neuroimaging evolution of such cerebral malformations. From a cardiological standpoint, patient is followed-up on a yearly basis with TTE. Up to date, patient is in good clinical conditions and returned to usual
daily activities.

**Discussion**

The case reported here stress the need for thorough diagnostic evaluation to determine the pathogenesis in ischemic stroke, before it could be considered really cryptogenic. Cryptogenic strokes accounts for 25% [6] to 40% [7] of all ischemic strokes. Schnieder et al. [8] reported a 30.9% prevalence of PFO in patients with cryptogenic stroke. Recently, data from the Closure of Patent Foramen Ovale or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE) Trial, suggested that transcatheter PFO closure significantly reduced the rate of stroke recurrence over medical therapy alone, at the cost of an increased risk of occurrence of atrial fibrillation [9]. The results of the Gore REDUCE Clinical Study, specifically designed to address the topic of PFO and cryptogenic stroke, give supportive evidence of the superiority of PFO closure over medical therapy alone, but at an increased risk of device complications and atrial fibrillation [3]. However, current guidelines recommend percutaneous PFO only in selected patients, if medical therapy failed as a preventive strategy and only after having excluded any other potential underlying aetiology [4]. Cavernous malformations are clusters of abnormal and enlarged endothelial channels, with prevalence ranging from 0.16% to 0.5% of the population. Cerebrovascular malformations may be causative of neurological symptoms, varying from epilepsy to haemorrhage or ischemia, and are asymptomatic in a relevant percentage of cases. Their usual treatment is surgical resection, unless localized in unapproachable site of the brain [10]. In the case reported here, we have no data to support if the occurrence of the first ischemic stroke was related to a paradoxical embolism through a PFO or had been a clinical manifestation of a cerebrovascular malformation, because detailed neuroimaging records were provided only after the occurrence of the latter TIA. Oral anticoagulation was necessary, once the thrombosis of the device had been recognized, but was promptly discontinued when thrombus solved, in accordance with neurosurgeons to avoid the increased risk of intracranial bleeding. This report suggests that therapy should always be tailored on patient’s needs and that a multidisciplinary assessment of ischemic stroke helps providing the appropriate management, thus avoiding the occurrence of potentially lethal complications.

**References**

1. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen


