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Cryptogenic stroke and patent foramen ovale: Clinical clues to paradoxical embolism

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ABSTRACT

Background: Patent foramen ovale (PFO) is an independent risk factor for cerebral infarction. Since ~25% of the population have a PFO, the simple association of PFO with stroke is not enough to establish the diagnosis of paradoxical embolism. We evaluated possible clinical clues to the diagnosis of paradoxical embolism.
Methods: Among patients with cryptogenic ischemic stroke (CS) who were investigated for a right-to-left shunt (RLS), we compared clinical, coagulation and biochemical parameters in patients with PFO versus without PFO.
Results: Among 1689 new patients referred for TIA/non-disabling stroke between 2001 and 2007, 175 with cryptogenic stroke (CS) were investigated for RLS by transcranial Doppler (TCD) bubble studies; 89 (5.5%) with positive TCD had a PFO confirmed by TEE. In multivariate logistic regression, a history of DVT or pulmonary embolism (OR, 4.39; 95% CI, 1.23–15.69; $p=0.023$), prolonged travel (OR, 8.77; 95% CI, 1.775–43.3; $p=0.008$) , migraine (OR, 2.30: 95% CI, 1.07–4.92; $p=0.031$), a Valsalva maneuver preceding the onset of focal neurological symptoms (OR, 3.33; 95% CI, 1.15–9.64; $p=0.026$) and waking up with stroke/TIA (OR, 4.53, 95% CI, 1.26–16.2; $p=0.018$) were independently associated with PFO-associated cerebrovascular events. Patients with PFO had higher plasma total homocysteine levels than patients without PFO (8.9±3 versus 7.9±2.6 μmol/L respectively; $p=0.021$).
Conclusions: A history of DVT or pulmonary embolism, migraine, recent prolonged travel, sleep apnea, waking up with TIA or stroke or a Valsalva maneuver preceding the event are clinical clues to the diagnosis of paradoxical embolism among patients with CS.

1. Introduction

Patent foramen ovale (PFO), a persistence of the embryonic defect in the interatrial septum, is present in ~25% of the general population [1]. The cause of stroke remains undefined in ~25% of cases despite intensive investigation [2]. Paradoxical embolism via a PFO is associated especially with cryptogenic stroke and, though often considered rare, accounted for 4% of ischemic strokes in a 20-year natural history study by Hutchinson and Acheson [3]. They diagnosed paradoxical embolism in 4% of their consecutive 2000 patients with stroke, and confirmed it in 4% of over 600 autopsies. A meta-analysis of case-control studies demonstrated a strong association of PFO with cryptogenic stroke in patients under age 55 [4].

PFO and atrial septal aneurysm (ASA) may predispose to stroke through several mechanisms including paradoxical embolism from a venous source [5], thrombus formation in the atrial septum within the conduit of the PFO [6,7], or atrial arrhythmias causing thrombus formation and emboli to the brain [8].

Since ~25% of the population have a PFO [1], the mere association of PFO with stroke is not enough to establish the diagnosis of paradoxical embolism. In a recent review of cryptogenic stroke and PFO [9], clinical clues to the diagnosis were not mentioned. Here we review our experience with cryptogenic stroke and suspected paradoxical embolism. Clinical features of patients with and without PFO were studied to expose clues to the diagnosis of paradoxical embolism. To accomplish this purpose, we retrospectively reviewed and compared the clinical, hematological and biochemical parameters between patients with cryptogenic stroke investigated for right-to-left shunt (RLS), contrasting those with and without PFO.

2. Methods

Data were analyzed for all patients age <70 years with cryptogenic ischemic stroke or transient ischemic attack (TIA) who had a transcranial Doppler (TCD) bubble study because of suspected paradoxical embolism, from the database of the Stroke Prevention

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and Atherosclerosis Research Centre (SPARC) in London, Ontario, between October 1, 2002 (when we began routinely performing TCD bubble studies in patients with suspected paradoxical embolism) and December 31, 2006. The detailed clinical records of these patients were retrospectively reviewed by a research assistant and a stroke neurologist.

The diagnosis of ischemic stroke was based on the symptoms and signs of a focal cerebral deficit of sudden onset, and the corresponding findings on computed tomography (CT) or magnetic resonance imaging (MRI) scans. TIA was defined as a focal neurological deficit resolving within 24 h [10] Criteria derived from the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification were used to exclude defined cause of stroke [11]; additionally we used measurement of total carotid plaque area to assess the burden of atherosclerosis. Cerebrovascular events were considered the result of paradoxical embolism if the following conditions were met: 1) exclusion of any other identifiable cardiac or cerebrovascular cause; 2) clinically confirmed ischemic stroke or TIA; 3) presence of PFO with or without atrial septal aneurysm on transesophageal echocardiography (TEE) with right-to-left shunt during the passive or Valsalva phase of the TCD bubble study and/or TEE.

All patients underwent neurological examination, brain CT and/or MRI scan, 12-lead ECG, extracranial Doppler ultrasonography and B-mode carotid total plaque area measurement and TCD and transthoracic echocardiography (TTE). All patients with TIA or stroke with a positive TCD bubble study underwent a TEE. MR/CT angiography and/or conventional angiography of the extracranial and cerebral vessels were performed in selected cases.

Standard blood tests, plasma total homocysteine (tHcy) and vitamin B12 levels were performed in all cases; coagulation testing, including prothrombin and activated partial thromboplastin times, antiphospholipid antibodies, protein C, protein S and anti-thrombin III, and genetic analysis for inherited prothrombotic conditions including the G1691A mutation in the factor V gene and the G20210A mutation within the 3-untranslated region of the prothrombin (PT) gene were performed in selected patients with or without PFO.

3. Clinical data

Clinical data recorded for patients with CS included 1) age, sex, traditional vascular risk factors, and the baseline characteristics of the cerebrovascular event; 2) shortness of breath during or preceding the cerebrovascular event; 3) features suggesting paradoxical embolism, such as a history of deep-vein thrombosis (DVT), pulmonary embolism (PE), a Valsalva maneuver [5] (e.g. weight lifting, straining for a bowel movement, vomiting, sexual intercourse, coughing) preceding the onset of focal neurological symptoms, and a history of recent prolonged travel (PTH) suggesting "Economy Class stroke syndrome" [12] during the two weeks preceding the cerebrovascular event. A positive travel history was defined as travel, mainly in a sitting position for at least 4 h in a train, car or bus [13]: 4) waking up with neurological deficit; 5) history of migraine according to International Headache Society criteria [14].

4. Assessment of PFO

A Power M-mode digital transcranial Doppler (TCD) system (Spencer Technologies, Inc; PMD 100 mol/L) was used to diagnose right-to-left interatrial shunt (Fig. 1). This technology includes 2-MHz spectral single-gate TCD information at a specific dept and a power M-mode image from 33 sample volumes placed at 2-mm intervals from 24 to 88 mm dept of insonation. The insonation method for this equipment has been described [15]. Microembolic signals were assessed according to international consensus recommendations [16]. TCD diagnostic testing procedures were performed on all patients in the semirecumbent position with a pillow beneath their head. We injected a microbubble (MB) bolus prepared by mixing 9 mL isotonic saline and 1 mL air agitated between two 10-mL syringes connected by a 3-way stopcock. The mixture was injected as a bolus into a right antecubital vein by means of an 18-or 20-gauge intravenous catheter. This procedure was performed first during normal breathing and then again during a Valsalva maneuver. The subjects had been previously instructed in performance of the Valsalva maneuver, the efficacy of which was shown by a reduction in the mean velocity of the MCA of at least 25%. The patients began the Valsalva maneuver 5 s after the MB bolus injection and maintained it for 10 s. We classified the right-to-left shunt (RLS) grade according to a 6-level logarithmic scale that was used for both resting and Valsalva for subsequent injections as follows: grade 0 = 0 embolic tracks (ETs), grade I = 1–10 ETs, grade II = 11–30 ETs, grade III = 31–100 ETs, grade IV = 101–300 ETs, and grade V > 300 ETs [17]. We classified the RLS as small if the patients had grade 1 or II shunts, and large if they had grade III–V shunts.

All patients who had a positive TCD bubble test underwent TEE with a contrast study performed at rest and during Valsalva maneuver by use of 5-MHz transducer. The contrast study was considered positive if ≥3 microbubbles appeared in the left atrium, either spontaneously or after Valsalva maneuver, within 3 cardiac cycles after complete opacification of the right atrium. ASA was defined a bulging >15 mm beyond the plane of the atrial septum as measured by TEE.

4.1. Statistical analysis

Clinical and demographic data were compared between patients with and without PFO. Statistical analysis was performed with SPSS for Windows (Version 14). Normal distribution of variables was tested by QQ plot and Kolmogorov–Smirnov's 1-sample test. Comparisons between patients with PFO and without PFO were performed by a X^2 test, Fisher's exact test, or t test. The non-parametric Mann–Whitney test was used for comparison between two groups. Multivariate logistic regression analysis was performed to determine the multivariate predictors for the diagnosis and mechanism of PFO-associated cerebrovascular events.

5. Results

Among 1609 consecutive new patients with TIA or stroke entered into our database between October 1, 2002 and December 31 2006, 175 with CS underwent TCD bubble studies because of suspected paradoxical embolism; of these 89 (5.5% of all new patients referred, and 51% of the TCD study group) had positive studies and were confirmed on TEE to have a PFO; 86 (49%) had a negative TCD bubble study confirmed by TTE and/or TEE. Of the 89 patients with PFO, 25 patients (28%) also had an atrial septal aneurysm.

Baseline characteristics and traditional risk factors of stroke or TIA did not differ significantly between groups as shown in Table 1. Posterior circulation cerebrovascular events accounted for 44% of patients with PFO compared to 56% in the non-PFO group ($p = 0.113$).

5.1. Symptoms, clinical features and baseline TCD bubble study findings

A history of DVT or PE was more common in patients with PFO (16%) than in patients without PFO (5%) ($p = 0.016$) (Table 2). A positive PTH (economy class stroke syndrome) was more common with PFO (13.4%) than without (3.48%) ($p = 0.018$) (Table 2). Valsalva activity was more common in the PFO group (16.8%) than in the non-PFO group (6.9%; $p = 0.042$) (Table 2). Waking up with TIA/stroke symptoms was more common in patients with PFO (17%) than in patients without (5%) ($p = 0.009$) (Table 2). There was a trend to higher prevalence of shortness of breath at the time of the TIA or stroke among patients with PFO (17% vs 8.1%; $p = 0.093$) (Table 2).

In the TCD bubble study, 71 of the 89 patients with PFO (79.8%) had a RLS during the passive phase. The presence of ASA was associated