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Spontaneous large right-to-left shunt and migraine headache with aura are risk factors for recurrent stroke in patients with a patent foramen ovale

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Abstract

Background: We sought to determine whether migraine headache with aura (MHA) and spontaneous large right-to-left (R–L) shunt are risk factors for recurrent cerebral ischemic events in cryptogenic stroke patients with a patent foramen ovale (PFO).
Methods: 140 patients with a PFO and cryptogenic stroke underwent transcatheter defect closure at our institution at a mean age of 45 ± 13 years. We retrospectively analyzed follow-up data from the first cerebral ischemic event to the time of PFO closure. Before the procedure, all patients underwent transesophageal echocardiography (TEE); Transcranial Doppler scanning (TCD) was additionally performed on the last 59 patients. We analyzed the impact of MHA, thrombophilia, spontaneous large R–L shunt, and atrial septal aneurysm (ASA) on the risk of recurrent cerebral ischemic events.
Results: 44 patients (31%) had had at least 1 recurrent event during a follow-up of 2.2 ± 2.6 years. Patients with recurrent events were more commonly females ($p = 0.0001$), had more often an associated thrombophilia ($p = 0.0077$), and had a higher prevalence of spontaneously large R–L shunt both at TEE and at TCD ($p < 0.05$). They also had more commonly a history of MHA ($p = 0.0009$) and more frequent episodes of MHA ($p = 0.0048$). Patients with MHA had a higher risk of recurrent events when compared to patients without (odds ratio 3.87, 95% CI 1.75 to 8.50). Thrombophilia ($p = 0.001$) and spontaneous large R–L shunt ($p = 0.02$) were independent predictors of recurrent stroke.
Conclusions: In cryptogenic stroke patients with a PFO, a history of MHA, large spontaneous large R–L shunt, and thrombophilia are all associated with a higher risk of recurrent events.

Keywords: Migraine; Stroke; Transcranial ultrasound; Patent foramen ovale

1. Introduction

Because of association studies, patent foramen ovale (PFO) has been implicated in the etiology of cryptogenic stroke secondary to paradoxical embolism [1,2], neurologic decompression illness in scuba divers [3,4], and migraine headaches [5,6]. Suggested risk factors for recurrent stroke in PFO patients are a large right-to-left (R–L) shunt, the presence of an atrial septal aneurysm (ASA), and the association of a thrombophilia [7–11]. In this setting, the potential role of migraine headache with aura (MHA) as a risk factor for recurrent events has not been evaluated extensively [12]. We hypothesized that, in patients with PFO and cryptogenic stroke, MHA and spontaneous large R–L shunt through the PFO would be associated with an increased risk of recurrent ischemic events.

2. Materials and methods

2.1. Patient population

Between April 1999 and June 2005, a total of 140 consecutive patients with a PFO and at least 1 documented cryptogenic stroke underwent transcatheter PFO closure at our

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institution at a mean age of 45 ± 13 years (range 18 to 71 years). Overall, 102 patients (73%) were ≤ 55 years old at the time of the first ischemic event. The first cerebral ischemic event was a stroke in 61 patients (44%) and a transient ischemic attack in 79 (56%). We analyzed retrospectively all patients' clinical records and we interviewed both patients and referring physicians. To analyze recurrence rates of cerebral ischemic events prior to transcatheter PFO closure and to identify risk factors for recurrent events, we reconstructed patient history from the first cerebral thromboembolic event to the time of PFO closure. All patients gave written informed consent to participate in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2. Patient selection

All patients who underwent transcatheter PFO closure in the present study fulfilled the following criteria:

1) Clinically and neuro-radiologically confirmed ischemic stroke or symptoms unequivocally due to a transient ischemic attack with or without neuro-radiologically identified intracranial ischemic lesions at contrast-enhanced cerebral magnetic resonance imaging;
2) Exclusion of any identifiable cause for the thromboembolic event other than PFO by submitting all patients to at least the following investigations: cerebral magnetic resonance imaging, echo Doppler of the carotid and vertebral arteries, transesophageal echocardiography (TEE) with examination of the heart and thoracic aorta;
3) Presence of PFO associated with an ASA or PFO alone with a large spontaneous or Valsalva-induced R-to-L at contrast TEE. Our baseline evaluation included a clinical examination and a screening for associated known cardiovascular risk factors and thrombophilia that were all performed before PFO closure, in a previously reported manner [7].

2.3. Definition of recurrent cerebral ischemic event

A recurrent event was defined as one episode of clinically or neuro-radiologically confirmed neurological impairment lasting less than 24 h (transient ischemic attack) or more than 24 h (stroke).

2.4. Echocardiographic definitions

All echocardiographic evaluations were made with a multiplane TEE probe. A previously shaken bolus of 10 ml of saline solution was used as contrast agent. The criteria used to define an ASA at TEE were a diameter of the base ≥ 15 mm and an excursion of the septum secundum ≥ 10 mm [13]. A PFO with R-to-L shunt (spontaneous or after Valsalva maneuver) was defined as the passage of at least 5 microbubbles from right to left atrium across the interatrial septum within 3 cardiac cycles from intravenous saline injection. The shunt through the PFO was defined as large when more than 30 microbubbles or cluster of bubbles were seen crossing the atrial septum at baseline or after Valsalva maneuver [14]. Power M-mode Transcranial Doppler (TCD) scanning performed through the temporal approach after injection of agitated saline was used as a complementary technique to assess the presence and degree of R-to-L shunt in the last 59 patients. Reported criteria were used to categorize shunt magnitude at TCD [15].

2.5. Assessment of MHA

Migraine headache with aura is a recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over 5–20 min, last for less than 60 min, and is usually followed by headache with the features of migraine without aura [16]. Presence or absence of MHA was based on the assessment made by the referring neurologist according to current recommendations and diagnostic criteria [16]. Migraine severity was assessed by using the validated Migraine Disability Assessment Questionnaire (MIDAS; [17,18]). Once the diagnosis of MHA was made, the referring neurologist made distinction between recurrent episodes of MHA and recurrent transient ischemic attacks.

3. Statistical analysis

Continuous variables are expressed as mean ± SD. Categorical variables are expressed as number (percentage). Statistical analysis was performed using Fisher's exact test and unpaired t test when appropriate. Kaplan–Meier estimates were used to determine survival with freedom from recurrent cerebral ischemic event in different subgroups of patients. Actuarial risk of recurrent cerebral ischemic events at mean follow-up was determined by using the Kaplan–Meier life-table analysis method. The 2-tailed log-rank test was used to compare the rate of recurrence in different patients' subgroups. To investigate independent risk factors for recurrent events, we applied multivariate logistic regression analysis to a model that accounted for presence or absence of any of the following variables: female gender, MHA, thrombophilia, ASA, spontaneous large R–L shunt at TEE. Since presence of a large R–L shunt after Valsalva maneuver was a selection criterion for PFO closure in the present study, it was not entered in the analysis. Statistical significance was assumed at $p < 0.05$.

4. Results

Forty-four patients (31%) had at least 1 recurrent cryptogenic stroke before transcatheter PFO closure (Table 1). The recurrent event was a stroke in 25 patients (57%) and a transient ischemic attack in 19 (43%).

Patients who experienced recurrent events were more commonly females ($p = 0.0001$) and had more often an associated thrombophilia ($p = 0.0077$). Details on the