Case Report

Patent Foramen Ovale and Recurrent Transient Neurological Symptoms: A Case Report and Review of Literature

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Stroke is a common cause of morbidity and mortality in adults worldwide. Because patent foramen ovale (PFO) is commonly found in normal population, we need to identify a subset of cryptogenic stroke patients who are likely to have experienced paradoxical embolization. Various factors need to be considered such as atrial anatomic variation (PFO size, atrial septal aneurysm, eustachian valve anatomy), hemodynamic parameters, presence of venous thrombosis and presence of hypercoagulable state. The presence of any of these findings increase the chance of PFO contributing to stroke. We describe a 54-year-old patient with a history of well controlled hypertension and dyslipidemia who presented with 3 attacks of expressive aphasia lasting 5 minutes each. General medical and neurological examinations were normal. Transesophageal echocardiography with agitated saline injection revealed presence of PFO flap. Transcranial Doppler ultrasonography with three agitated saline injections showed multiple unilateral microembolism signals in the M1 of left middle cerebral artery. Aspirin was given as well as percutaneous endovascular PFO closure was performed with no immediate complication. Patient has had no further attack of stroke after 6 months follow-up.

Keywords: *Patent foramen ovale, Stroke, Atrial septal aneurysm, Paradoxical embolization*

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The definite etiology of ischemic stroke in young patients is often not found despite extensively systematic investigations. Such strokes are classified as cryptogenic[1]. In patients with cryptogenic strokes patent foramen ovale (PFO) can be detected in more than 50%, whereas its prevalence in the general population is at least 25%[2]. Therefore, PFO likely associated with cryptogenic stroke. The presumed mechanism is paradoxical embolism of venous thrombotic material across the right-to-left shunt. Earlier studies have suggested that PFO is an incidental finding in patients with cryptogenic strokes and does not represent a risk factor for cerebral ischemia. On the other hand, later studies and a meta-analysis support PFO as a risk factor for stroke, and also found a strong association between the morphological characteristics of the PFO and the risk of embolic cerebrovascular events. The coincidence of an atrial septal aneurysm (ASA) seem to increase the risk of brain infarct further.

Even assuming the PFO is related to the stroke, optimal treatment is uncertain. Antiplatelet therapy, anticoagulation, and closure of the PFO are all options. However, little definitive data nowadays exist to guide the best choice of treatment.

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Case Report

A 54-year-old nurse with a history of well controlled hypertension and dyslipidemia for 10 years. She had 3 consecutive attacks of expressive aphasia last about 5 minutes each, 3 days apart. She denied weakness, numbness, headache, transient monocular blindness and palpitation. General medical and neurological examinations were normal. Complete blood count, chemistry profile and coagulation were all normal.

Brain MRI showed a signal hyperintensity on T2W and FLAIR image with restriction on DWI at left periventricular area (Fig. 1), representing acute

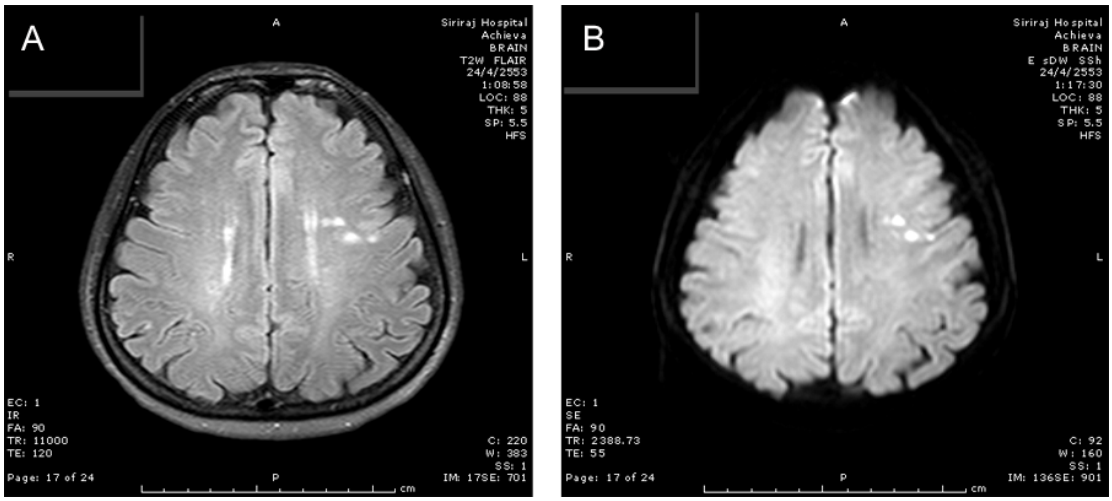

Fig. 1 Increase signal intensity on FLAIR image (A) with restriction on DWI (B) at periventricular area

infarction and multiple small hyperintensity on T2W and FLAIR images without restriction on DWI at right periventricular area, representing white matter changes. The brain and carotid MRA were normal. Transthoracic echocardiography was normal but transesophageal echocardiography with agitated saline injection revealed the presence of PFO flap, negative agitated saline injection test and no intracardiac thrombus (Fig. 2). Transcranial Doppler ultrasonography (TCD) with three agitated saline injections showed multiple unilateral microembolism signals in the left middle cerebral artery at M1 level with the average of 13-14 MES/signal injection (Fig. 3). The right to left cardiac shunt should be considered. Doppler ultrasound of deep veins in both lower extremities demonstrated no evidence of deep vein thrombosis.

Discussion

The foramen ovale is necessary for blood flow across the fetal atrial septum[3]. During fetal development, the interatrial septum arises from two septa, the septum primum and the septum secundum[4]. At birth this interatrial passage closes as pulmonary pressure falls and the left atrial pressure exceeds those on the right. Within a few months of life, the foramen ovale seals shunt in most individuals. This fusion is complete by the age of two years in about 75% of individuals, but patency occurs in the other 25%. It is a residual, oblique, slit-shaped defect resembling a tunnel. The reasons PFO fail to closed are unknown, but they likely related to multifactorial inheritance[5]. Greater PFO size increases the risk of paradoxical embolism.

Patent foramen ovale may be detected by transthoracic echocardiography (TTE), transesophageal echocardiography (TEE). One study revealed that TEE detected PFO with the most sensitivity, showing the prevalence of 39%. In this study, TTE found PFO in 18% and TCD was found in 27%[6]. All PFO detected by TTE and TCD were also detected by TEE. TCD may miss small defects. Transcranial Doppler is comparable to contrast TEE for detecting PFO-related right-to-left shunts, and is easy to perform at the bedside. One study compared the sensitivity of transcranial color-coded sonography with TEE for detecting right-to-left cardiac shunts and this is as sensitive as contrast TEE[7].

The etiology of a stroke is either hemorrhagic or ischemic. Lechat et al were the first to report an unusually high prevalence of PFO in patients who had cryptogenic stroke[8]. They studied the prevalence of PFO, detected by contrast surface echocardiography, in a population of 60 adults younger than 55 years with ischemic stroke. A PFO was found in 40% of the study population compared with 10% of a control group without stroke ($p < 0.001$). Not all studies have confirmed this association. Two population-based studies addressed the issue of PFO-related first-ever stroke risk prospectively[9,10], one in Olmsted county, MN and the other in the northern Manhattan population of New York. Both studies failed to establish the role of PFO as an independent risk factor for stroke in general population. There was only a non-significant trend towards a higher stroke incidence in persons with PFO in both studies. Several conditions must be met

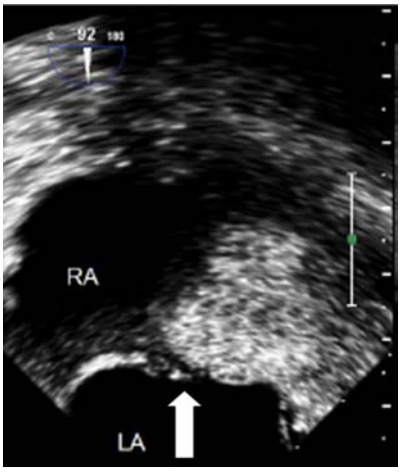

Fig. 2 Transesophageal echocardiogram of a patent foramen ovale (arrow).
LA = left atrium, RA = right atrium

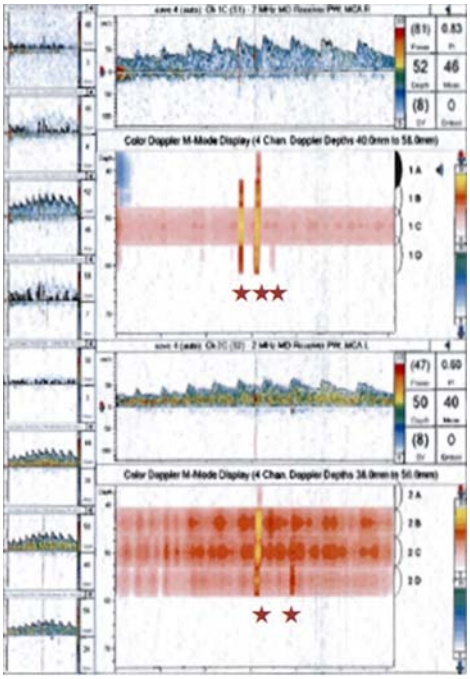

Fig. 3 Transcranial Doppler (TCD) with three agitated saline injections showed multiple unilateral microembolic signals were found in left middle cerebral artery (left M1). ★ Note: represent the embolic signals

for a paradoxical embolization through a PFO to occur. First, there must be a source of venous thrombus[11]. The thrombus must then embolize and while passing through the heart, it must be subjected to increased right heart pressure allowing thrombus to pass through the PFO to systemic circulation. The source of thrombus in patients with PFO and suspected paradoxical embolus is uncertain. Deep venous thrombosis is found in only a minority of patients. In one study of patients with PFO and suspected paradoxical emboli, only 14% had a clinically evident DVT, but contrast venography show venous thrombus in 57%[12]. Pelvic vein are likely an important source of paradoxical emboli in patients with PFO.

The strongest potentiator of stroke risk related to PFO is the coexistence of an ASA. In the French study, patients with both PFO and ASA the actuarial risk of a first stroke was 9.0% at 2 years[13]. In the meta-analysis ASA alone was associated with both stroke and cryptogenic stroke but the combination of PFO and ASA greatly magnified the risk[14]. An additional potential risk stratification variable is the anatomic size of the PFO. Larger PFO may be associated with greater volumes of paradoxical blood flow and allow passage into the arterial circulation of larger clots move likely to cause symptomatic stroke. Several case-control studies have found that larger PFO size is associated with both cryptogenic stroke, but others have failed to confirm this finding. Similarly, several studies have found that stroke patients with PFO have a greater frequency of right-to-left shunting at rest compared with controls. The degree of right-to-left shunting is related not only to PFO size, but also to the presence of a prominent Eustachian valve. Coagulation abnormalities may promote paradoxical emboli in patients with PFO and cryptogenic stroke. Chaturvedi studied 17 patients who presented with both cryptogenic stroke and a PFO[15]. A complete hematologic evaluation was performed in 16 patients. Hemostatic abnormalities were presented in 5 (31%) of 16 patients, including abnormal activated protein C resistance; this suggests hypercoagulability might be more prevalent in patients with PFO and stroke.

As we report, a 54-year-old woman presented with 3 recurrent episodes of expressive aphasia last about 5 minutes each. Transesophageal echocardiography revealed presence of PFO flap but transthoracic echocardiography failed to demonstrate this finding. We suspected her symptoms associate with PFO because transcranial Doppler ultrasonography with agitated saline injection evidenced multiple unilateral microembolism signals in the left middle cerebral artery at M1 level and right to left shunt at rest, but failed to demonstrate source of embolism. Aspirin and percutaneous endovascular PFO closure was performed and there was no

immediate complication.

There are no compelling clinical trial data available to guide treatment for patient with both cryptogenic stroke and a PFO and no studies have investigated treatments for primary prevention in a asymptomatic individuals. Treatment options for PFO in patient with stroke include antiplatelet therapy, anticoagulants, endovascular closure, or surgical closure. Treatments with antiplatelet therapy and anticoagulant therapy are intended to reduce venous thrombus formation and embolization whereas closure of the interatrial septal defect with surgery or with an endovascular device is intended to eliminate access by embolic particles to the artery. In several studies no significant differences were found between aspirin and warfarin in secondary prevention of stroke associated with PFO[13,16-18]. The retrospective study by Mas et al in 132 patients younger than 60 years with PFO and cryptogenic stroke, patients were treated with either aspirin (250-500 mg/d) or oral anticoagulation (target international normalization ratio [INR], 2.0-3.0). The average annual rate of recurrence was 1.2 % for stroke and 3.4% for the combined end point of TIA and stroke[13]. Surgical closure of the PFO provides an alternative to lifelong antiplatelet or anticoagulation therapy. Surgical treatment can potentially permanently close the interatrial defect, eliminating the need for medical therapy. The major disadvantage of surgical closure is that it requires thoracotomy and cardiopulmonary bypass. Percutaneous endovascular PFO closure theoretically offers benefit of eradication of the right-to-left shunt without the risks associated with surgical intervention; nevertheless, complications can also occur. Comparisons between antithrombotic theatment and percutaneous endovascular PFO closure in patients with cryptogenic stroke are scarce and mostly at the level of case-control studies. Windecker et al[19] compared the risk of recurrence in 308 patients with cryptogenic stroke and PFO, who were treated either medically (158 patients) or underwent percutaneous PFO closure. Patients undergoing percutaneous PFO closure had a larger right-to-left shunt (p = 0.001; 95% confidence interval [CI] 1.38 to 3.07) and were more likely to have suffered more than one cerebrovascular event (p = 0.03; 95% CI 1.04 to 2.71). At four years of follow-up, percutaneous PFO closure resulted in a non-significant trend toward risk reduction of death, stroke, or transient ischemic attack (TIA) combined (8.5% vs. 24.3%; p = 0.05; 95% CI 0.23 to 1.01) and of recurrent stroke or TIA (7.8% vs. 22.2%; p = 0.08; 95% CI 0.23 to 1.11) compared with medical treatment. They concluded percutaneous PFO closure appears at least as effective as medical treatment for prevention of recurrent cerebrovascular events in cryptogenic stroke patients with PFO. It might be more effective than medical treatment in patients with complete closure and more than one cerebrovascular event.

Potential conflicts of interest

None.

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จุมพล อานามนารถ, นิพนธ์ พวงวรินทร์

โรคหลอดเลือดสมองอุดตันเป็นสาเหตุสำคัญของความพิการและเสียชีวิตในประชากรผู้ใหญ่ทั่วโลก patent foramen ovale (PFO) พบบ่อยในประชากรทั่วไป และอาจเป็นสาเหตุของโรคนี้ จึงมีความจำเป็นที่จะต้องยืนยันว่า PFO เป็นสาเหตุที่แท้จริง หรือพบโดยบังเอิญ มีปัจจัยหลายชนิดที่บ่งว่า PFO อาจเป็นสาเหตุที่แท้จริงของโรคหลอดเลือดสมองอุดตันได้แก่ PFO ขนาดใหญ่ พบ atrial septal aneurysm และ/หรือมี eustachian valve ร่วมด้วยภาวะเลือดแข็งตัวง่าย และภาวะหลอดเลือดดำอุดตัน คณะผู้รายงานได้นำเสนอผู้ป่วยหญิง อายุ 54 ปี มีปัญหาผิดปกติด้านการพูด (expressive aphasia) ซึ่งเกิดแบบเป็นๆ หายๆ 3 ครั้งติดต่อกัน ครั้งละ 5 นาที การตรวจร่างกายทั่วไปและระบบประสาทอยู่ในเกณฑ์ปกติ ตรวจ transesophageal echocardiography with agitated saline injection พบ PFO flap ตรวจ transcranial Doppler ultrasonography with three agitated saline injections พบ microembolic signals จำนวนมากที่ left middle cerebral artery ตำแหน่ง M1 จึงเป็นการยืนยันว่าผู้ป่วยรายนี้เกิดโรคหลอดเลือดสมองอุดตันจาก PFO จริง ผู้ป่วยได้รับการรักษาด้วยยา aspirin และผ่าตัดปิด PFO โดยผ่านทางผิวหนังโดยไม่มีผลแทรกซ้อนใดๆ ผู้ป่วยสบายดี และไม่พบว่ามีอาการเกิดซ้ำอีก หลังจากติดตามผู้ป่วยไป 6 เดือน