Diagnosing and treating Patent Foramen Ovale (PFO) from various manifestations in adults: case series

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ABSTRACT

Background: Patent foramen ovale (PFO) is a part of atrial septal defects (ASD) entities. While mostly asymptomatic, some adults with PFO will develop symptoms, from mild complaints such as migraine or palpitation to more debilitating complications such as syncope or cryptogenic stroke. Therefore, it is highly crucial that PFO be diagnosed and treated promptly. Echocardiography, trans-thoracal and or trans-esophageal, is the main diagnosis modality. For treatment, antplatelet with or without anticoagulation, trans-catheter closure, and surgery are utilized in accordance with their indications.

Case Presentation: We present four adult patients referred with various symptoms: vertigo, migraine, palpitation, and cryptogenic stroke. Three of them had no explicit risk factors for the cerebrovascular event, with one patient having a co-existing hypercoagulable state. Echocardiography revealed a positive bubble test, which meant that PFO was the primary etiology of those cases. We then treated each of them with transcatheter device closure, which improved their symptoms, before adding antplatelet for six months.

Conclusion: Proper diagnosis and prompt treatment of PFO are imperative in reducing complications. Echocardiography, mainly TEE, is the main diagnostic tool for PFO. Antithrombotic (with or without anticoagulant), minimally invasive procedure and surgery in some cases are the modalities available.

Keywords: adults, manifestations, patent foramen ovale, transcatheter closure.

INTRODUCTION

Patent foramen ovale (PFO) is a part of atrial septal defects (ASD) entities. Normal or functional foramen ovale exists in neonates, and once the pulmonary circulation increases after birth, the structure will close itself in about 12 months; more than half of infants will have PFO at six months old. Nevertheless, in about 25% of patients, foramen ovale will persist throughout adulthood. It may be secondary to a deficiency in the membranous portion while the primum septum is fusing with the secundum membranes to form the interatrial septum.

Many adults with PFO stay asymptomatic throughout their lifetime, but some will develop symptoms. When the blood that is leaking from the left atrium contains a clot, it causes the PFO to be symptomatic. The symptoms of PFO are varied: from migraine-like headaches to cryptogenic stroke. Cryptogenic stroke is one of the most debilitating complications of PFO. Most cryptogenic strokes are thromboembolic, and PFO can be found in 40% of patients with a thromboembolic event. It is caused by paradoxical embolism, where PFO is a potential route for embolic transit and also could be the place where the embolic thrombus is formed.

Therefore, it is highly crucial that symptomatic PFO be diagnosed promptly and precisely. Transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and transcranial Doppler ultrasound (TCD) are the modalities used to assess and diagnose the PFO. The TEE is considered the gold standard because it allows better direct visualization. A bubble test using saline contrast will increase the sensitivity of echocardiography imaging. It is injected intravenously during the Valsalva maneuver to enhance the detection of the right-to-left shunt through the PFO.

The best treatment for PFO in patients with a thromboembolic event remains uncertain. Medical management using antplatelet and anticoagulant are commonly used with 3.8 – 12% recurrent stroke events annually. Transcatheter therapy using PFO closure devices has a better annual recurrence rate of stroke, that is 0 – 5%. The last option is surgical closure; although it is less appealing with stroke recurrent attack nearly 8% annually post-procedure, it may be attempted if the anatomy is unfavorable for transcatheter therapy.

We will describe a case series of PFO in adult patients with various clinical manifestations, one of whom has hematological co-morbid in the form of hypercoagulation syndrome, to provide further information on the importance of a proper approach in such cases.
CASE PRESENTATIONS

Case 1
Our first patient was a 41-year-old female with a history of an ischemic stroke earlier this year. It was the first event, and she had been healthy until now. Because there were no explainable risk factors such as hypertension, diabetes, obesity, dyslipidemia, smoking, and hormonal birth control, the patient was referred to our cardiology clinic for structural cardiac evaluation. We did not find any abnormality in heart sound and neurological status. Hematologic parameters showed normal results, and her electrocardiogram (ECG) showed no arrhythmia. However, TTE revealed a high suspicion of PFO, which was then confirmed by a positive bubble test in TEE (Figure 1).

For the closure procedure, first, we intubated the patient, then utilized cardiac catheterization to the right atrium. After making sure the catheter tip was in a proper place, we expanded the ASO (Figure 2 and Figure 3) to cover the PFO. Afterward, we made sure it was in place with a chest x-ray. We observed the patient for a day, then discharged her with aspirin 100 mg once a day for six months. In the outpatient clinic, we followed her for recurrent ischemic stroke, and she experienced no relapse in subsequent follow-ups.

Case 2
Our next patient was a 26-year-old female with recurrent lightheadedness during medium-high intensity exercise. The symptom was first experienced when she was in high school, and it was initially brief. Nevertheless, since last year, the complaint had become more severe, and she frequently visited various doctors to look for a diagnosis. She did not suffer from other neurologic symptoms, and hematologic screening showed no abnormality. There were no explicit hypoxic signs on the extremities. Her ECG showed no arrhythmia. We detected a faint pansystolic heart murmur in the left sternal border and found cardiomegaly with distention of pulmonary trunk in chest x-ray when she was referred to our clinic for further evaluation. We performed TTE, which revealed a PFO with a positive bubble test and mild pulmonary hypertension.

We completed PFO closure via cardiac catheterization, utilizing an atrial septal occluder (Figure 4). Chest x-ray post-closure showed that the occluder was set up on the PFO site (Figure 5). After a brief period of observation, she was discharged with aspirin 100 mg once a day for six months. We aimed for complete recovery of his lightheadedness, and three-monthly follow-ups from the outpatient clinic showed that she had remained asymptomatic with optimal exercise capacity.

Case 3
A 24-year-old male was referred from the neurologist for severe progressive right-sided migraine and vertigo accompanied by palpitation in the last two years. The patient had been prescribed various symptomatic medicine, anti-histamines, and analgesics with no obvious result. He had no history of hypertension, hearing problem, or smoking. The vertigo was not worsened by head movement, and the palpitation only occurred when he exercised. There was no murmur, but we found slight orthostatic hypotension (15 mmHg difference in systolic pressure when standing). There was no abnormality in her hematologic, electrolytes, kidney/liver function, and blood glucose level. Because of his persistent symptoms and the presence of palpitation, the neurologist
CASE REPORT

and hypercoagulable state in her first stroke. Yet, when those co-morbidities had been controlled by medication, the stroke still recurred. She received no hormonal birth control and was never pregnant. A brain scan showed multiple chronic lacunar infaracts in the bilateral frontal lobe, subcortical parietal lobe, and ganglia wards. She was given aspirin 80 mg once a day and rivaroxaban 15 mg once a day. Further tests revealed increased erythrocyte sedimentation rate and protein S deficiency with a non-significant antinuclear-antibody profile. There was no arrhythmia from 24-hour Holter. Nevertheless, TTE found a PFO with a size of 0.9 mm that was confirmed by a positive bubble test (Figure 6).

We performed PFO closure with ASO via cardiac catheterization (chest x-rays post-procedure: Figure 7a and Figure 7b) and discharged her with aspirin 100 mg once a day for six months and continued rivaroxaban indefinitely. We made a referral to hematology for further follow-ups but still monitored her bi-monthly for her neurologic deficit. After six months of PFO closure, she still had been asymptomatic.

DISCUSSIONS

Foramen ovale is a normal structure in the form of an opening between the right and left atrium. The structure will close itself in about 6-12 months postnatal once the pulmonary circulation increases. Although the prevalence of PFO is about 25% in the general population, this proportion increases to about 30-40% in young patients with a history of cryptogenic stroke.

There are various types of PFO: (1) The Eustachian Valve (EV), an embryological remnant of the inferior vena cava that during fetal life helps divert oxygenated blood from the IVC toward the foramen ovale to escape the pulmonary circulation; (2) Chiari network, an embryonic remnant of the right valve of the sinus venosus, most often associated with paradoxical embolism, and; (3) An atrial septum abnormality (ASA), a redundant bulging atrial septal tissue that can be caused by a sustained interatrial pressure difference or can be a primary malformation involving either the fossa ovalis or the entire atrial septum.

Case 4

Our last patient was more complicated. She was a 24-year-old female referred from the neurologist because of recurrent ischemic stroke four times within the last four months. She had temporary left hemiparesis and seventh/twelfth cranial nerve paralysis after her first event, and while the subsequent events did not cause her further disability, the frequency of ischemic stroke was alarming, and she underwent complete diagnostic procedures. The patient was found to have Hashimoto's hypothyroidism, hypercholesterolemia, and hypercoagulable state in her first stroke. Yet, when those co-morbidities had been controlled by medication, the stroke still recurred. She received no hormonal birth control and was never pregnant. A brain scan showed multiple chronic lacunar infaracts in the bilateral frontal lobe, subcortical parietal lobe, and ganglia wards. She was given aspirin 80 mg once a day and rivaroxaban 15 mg once a day. Further tests revealed increased erythrocyte sedimentation rate and protein S deficiency with a non-significant antinuclear-antibody profile. There was no arrhythmia from 24-hour Holter. Nevertheless, TTE found a PFO with a size of 0.9 mm that was confirmed by a positive bubble test (Figure 6).

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CASE REPORT

The presence of PFO with persistent or transient right-to-left cardiac shunting leads to paradoxical embolism. The PFO itself is also a potential conduit for venous emboli to enter the arterial circulation. Paradoxical embolization is more likely to produce symptoms when the embolization occurs in the posterior cerebral circulation. Twenty-five to 40% of such strokes have no identifiable cause; they are referred to as cryptogenic strokes.11

Incidental PFO can be found in up to 40% of patients with cryptogenic stroke.5 Recently, a prospective study found a significantly higher prevalence of PFO in patients with cryptogenic stroke compared with patients with stroke of known cause.12 While cryptogenic stroke is usually benign, in the long term, it is associated with a higher rate of recurrence and adverse outcome.13

Positive signs of PFO-mediated paradoxical embolic stroke include the cortical location of infarcts, strokes in multiple vascular distributions, and infarcts of different ages in the same vascular territory. A presumptive diagnosis of such stroke can also be inferred from the absence of conventional stroke risk factors, a history of deep vein thrombosis, recent travel, pulmonary embolus, or the presence of Valsalva maneuver before the stroke event.14 Our first and fourth case shows this very clearly.

Various non-stroke manifestations, particularly migraine or vertigo, can also occur because vasoactive amines and humoral substances, such as prostaglandin E1, E2, serotonin, bradykinin, and angiotensin I, reach the cerebrovascular circulation through the PFO. Another presumed mechanism is microthrombi or venous emboli pass through the PFO and enter the posterior circulation.15 Although a causal relationship between migraine or migraine-like symptoms and PFO remains unproven. Several studies have noted improvement in the patient who has undergone PFO closure.10

Diagnosis of PFO in adults is often overlooked because of the asymptomatic nature of this defect. Usually, a search for PFO is performed after a stroke or, in some cases, a severe neurologic manifestation. However, because of non-specific findings in the patients, we need to stress that primary care physician observation is highly important. In all of our cases save one, the hematological, other basic laboratory tests, and ECG was normal. While ischemic stroke in younger adults can be caused by hematologic or immunologic abnormality, e.g., hypercoagulable state, hematologic malignancy, and lupus, events from such diseases usually are more progressive and often can be explained by laboratory tests. Therefore, in such a situation, structural heart disease, including PFO, ASD, or valve abnormalities, need to be assessed by means of echocardiography.

A PFO can be detected by TTE, TEE, and or transcranial Doppler (TCD). It is defined on echocardiography as 15-mm of total septal tissue excursion or a 10-mm protrusion into either atrium from the septal midline. Transeosophageal echocardiography is the most sensitive test, mainly when combined with saline or contrast injection. The patient is made to do the Valsalva maneuver (usually by coughing), and crossing of saline or contrast bubbles from the right to the left atrium in apical 4-chamber view marks a positive bubble test due to PFO. Grade 1 PFO is diagnosed if there are < 5 bubbles; grade 2 if there are 5-25 bubbles; grade 3 if there are >25 bubbles; and grade 4 with opacification of the entire chamber.16

However, because of technical difficulties and sedation needs, TTE – to evaluate atrial septal aneurysm and quantify flow, usually is performed first. Transcranial Doppler is seldom utilized but can show a positive bubble test in the middle cerebral artery as a micro-embolic signal.14,15 It is important to note that the main difference between PFO and other atrial abnormalities such as ASD is the lack of abnormal heart murmur in PFO; therefore, it can point the physician to the correct defect.

In all of our cases, the diagnosis of PFO was made by means of TTE, which came as both fortunate – because the diagnosis could still be made without TEE – and weakness – because it showed that TEE availability was the main concern in our country. Even in a cryptogenic stroke setting, TEE was not routinely ordered. In addition, multi-disciplinary continuing care, particularly between neurologists and cardiologists, while vital, had not always been readily accessible in most settings.

In most patients, including pediatric and asymptomatic adult populations, PFO doesn’t require treatment. Furthermore, PFO is vital in some congenital heart defects that are dependent on atrial blood shunting. In symptomatic adults with cryptogenic stroke, the Risk of Paradoxical Embolism (RoPE), which includes a history of hypertension, diabetes, stroke, smoking, cortical infarction in imaging, and age, is calculated. In RoPE score >7, after excluding more obvious

**Figure 7a.** Posteroanterior chest x-ray post-procedure showed ASO in the correct place (arrow).

**Figure 7b.** Lateral view of the same patient post-procedure (arrow: ASO).
cases, for example, atrial fibrillation, hypercoagulable state, etc., patients should be undergone treatment.14

Treatments for PFO include (1) Antithrombotic medications for ≥ six months with the addition of anticoagulant if there is vein thrombosis; (2) Percutaneous device closure for reducing recurrence in < 60 years old patients; and, (3) Surgical approach, indicated in ≥ 25 mm PFO, device closure failure, or inadequate rim at the edge (making percutaneous closure difficult).14 In migraine patients, PFO closure potentially improves the symptoms.17

Amplatzer PFO Occluder was the first device to be approved for PFO closure; it has 2 self-expanding nickel-titanium discs composed of polyester wire mesh. The advantages of device closure are high effectiveness in reducing stroke risk (>50% to almost 100% reduced risk) with the minimally invasive method.18,20 After open-heart surgery, there is no need to prescribe antithrombotic or anticoagulants, though.14

The prognosis of PFO in adults is generally excellent, but several periprocedural complications can arise. Device embolism, cardiac perforation, residual shunt, thrombus formation on the device, and or atrial fibrillation may occur, even with a very low probability.21 The aim of post-intervention monitoring is to evaluate patients’ subjective symptoms such as vertigo or palpitation, objective signs such as recurrent neurologic events, and or aforementioned post-procedural complications.

CONCLUSIONS

Patent foramen ovale has various clinical entities, ranging from mild to morbid complications, including but not limited to: vertigo, migraine, near-syncpe, palpitation, and or stroke. It is imperative that PFO be diagnosed properly and treated promptly to reduce debilitating complications. Echocardiography, mainly TEE, is the main diagnostic tool for PFO. Antithrombotic (with or without anticoagulant), minimally invasive procedures and surgery in some cases are the treatment modalities.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ETHICS CONSIDERATION

All the subjects had already signed informed consent for their cases to be shared and or published in this journal.

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AUTHOR CONTRIBUTION

All the authors equally contributed to the study, from the conceptual framework, data gathering, and analysis to interpreting the study results.

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