Recurrent Paradoxical and Pulmonary Embolism, Hypercoagulable State, and Patent Foramen Ovale
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Case presentation: A 62-year-old woman presented to the emergency department with the acute onset of paresthesia and severe left arm pain; an aortogram revealed an occlusion of the proximal left subclavian artery (Figure 1). The patient underwent emergency right-to-left axillary-axillary bypass grafting and was discharged on aspirin 81 mg. She again presented to the hospital 4 weeks later with symptoms of a stroke; magnetic resonance imaging and angiography revealed multiple left-sided acute embolic infarcts and proximal occlusion of the left internal carotid and vertebral artery (Figure 2). The patient underwent emergency endarterectomy during which fresh thrombus was removed; of note, there was no underlying atherosclerotic plaque. Three days after surgery, the patient developed a deep venous thrombosis and subsequent bilateral pulmonary emboli of the left leg. A transesophageal echocardiogram revealed the presence of a patent foramen ovale (PFO), an atrial septal aneurysm, and a large right-to-left shunt (Movie I in the online-only Data Supplement). A hypercoagulable workup was positive for heterozygous factor V Leiden mutation.

Discussion
Overview
Ischemic stroke occurs annually in ≈700,000 patients in the United States and causes significant morbidity and mortality.1 Cryptogenic stroke occurs in ≈45% of cases.2 Paradoxical embolism through a PFO may account for a proportion of cryptogenic stroke cases. However, a direct causal relationship is sometimes difficult to establish.

There are several case reports that support paradoxical embolism as a cause for stroke,3,4 myocardial infarction,5,6 and other peripheral embolic events.6 These cases may visualize “clot in transit” within the PFO, which is identified by transesophageal echocardiography and requires open surgery to remove the thrombus and close the defect to prevent impending paradoxical embolism. According to autopsy findings, PFO is present in ≈27% of the population, with no sex differences. The size of a PFO can vary greatly between 1 and 19 mm (mean, 4.9 mm).7 In the last 2 decades, percutaneous closure of PFO to reduce the risk of recurrent cryptogenic stroke has been the subject of much debate. Data from randomized, controlled trials (RCTs) fail to support clear benefit of this procedure for secondary prevention beyond medical therapy.8−10

Patients with hypercoagulable disorders, PFO, and paradoxical embolization have not been adequately studied, and there are no guidelines concerning management of this high-risk population. This Clinician Update case features a patient with a constellation of findings, including hypercoagulable disorder, deep venous thrombosis, pulmonary embolism, and recurrent paradoxical embolization.

Association of PFO and Cryptogenic Stroke
The prevalence of PFO in patients with cryptogenic stroke has been shown to be significantly greater compared with patients with stroke of known cause. This association is stronger for those...
patients who have an atrial septal aneurysm. Furthermore, patients with PFO who suffer a cryptogenic stroke are 5 times more likely to have deep venous thrombosis than patients with stroke of known origin. Interestingly, patients with venous leads from implantable defibrillators and pacemakers who have PFO are at a 3-fold increased risk of systemic thromboembolism. These observations are indirect evidence of the causal association of PFO with cryptogenic stroke. Patients who suffer a cryptogenic stroke can be treated medically with antiplatelet drugs or anticoagulants or can have their PFO closed.

Long-term observational studies have shown that patients with prior stroke or transient ischemic attack who underwent percutaneous PFO closure were less likely to suffer recurrent events compared with medically treated patients. This was especially noted in those patients with atrial septal aneurysm and a large right-to-left shunt. However, 3 RCTs failed to show superiority of PFO closure.8-10 A recent meta-analysis that combined the results of these 3 RCT showed that the weighted incidence of recurrent stroke was 1.7% in the closure group and 2.9% in the best medical therapy group.14 The relative risk for stroke was lower after PFO closure (relative risk, 0.66; 95% confidence interval, 0.37–1.19; P=0.171).14 The results are not statistically significant but may indicate potential benefit favoring PFO closure. Because the events rate in these RCTs is so low, type 2 errors may exist; that is, the studies are statistically underpowered to show a significant result.

Hypercoagulable States and Cryptogenic Stroke

The optimal management of patients who suffer a cryptogenic stroke and who have both a hypercoagulable state and a PFO has not been fully elucidated. Inherited thrombophilias (such as factor V Leiden, protein C deficiency, protein S deficiency, antithrombin deficiency, and prothrombin gene mutation) are an uncommon cause for stroke in the adult population. However, they play a role in the mechanism of stroke in pediatric and neonatal populations. Factor V Leiden, the most prevalent of the thrombophilias, has been associated with a higher risk of stroke in younger patients. Some hypercoagulable states, in particular anti-cardiolipin antibody, lupus anticoagulant, or hyperhomocysteinemia, were excluded from 2 RCTs.8,9 Patients with factor V Leiden or prothrombin gene mutations were not routinely assessed in any of the RCTs. Both of these hypercoagulable states have been associated with cryptogenic stroke in patients with PFO.18 If a patient with a hypercoagulable state develops a cryptogenic stroke, current guidelines strongly recommend the initiation of an antiplatelet or anticoagulant therapy. The guidelines mention that anticoagulation might be considered in hypercoagulable patients, depending on the clinical

Figure 1. Aortogram revealing acute occlusion of the proximal left subclavian artery.

Figure 2. Magnetic resonance angiography of the brain revealing proximal acute occlusion of the left internal carotid and vertebral artery.
circumstances. A dilemma exists when a patient with a PFO in conjunction with a hypercoagulable state develops a stroke on both an antplatelet agent and an anticoagulant. No specific recommendation is made in such a high-risk patient population.

Pulmonary Embolism in Patients With PFO

The presence of a PFO is associated with significantly increased mortality in patients who develop pulmonary embolism. Magnetic resonance imaging of patients with pulmonary embolism shows higher rates of ischemic stroke in the presence of a PFO. Patients with large right-to-left shunts are more likely to have ischemic stroke.

Management of Present Case

In our case, the patient again presented to hospital 2 weeks later with the acute onset of impaired gait and memory. The patient was deemed to be at high risk for recurrent paradoxical embolism, given the failure of medical therapy. The PFO was closed with a 25-mm Amplatzer Cribriform device. After closure, the patient was maintained on aspirin 81 mg and rivaroxaban 20 mg daily. She has been symptom free since closure and was doing well at the 6-month follow-up visit.

Conclusion

Although data from RCTs do not clearly favor PFO closure over medical therapy, certain patients may benefit. This patient with a hypercoagulable state, deep venous thrombosis, pulmonary embolism, and multiple paradoxical emboli was easily treated with percutaneous closure with good short-term outcome.

Disclosures

None.

References


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