Case Reports

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Case Series Coexistence of Patent Foramen Ovale with Other Conditions: Who's The Culprit?

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Abstract

Background: Patent foramen ovale is a major cause of cryptogenic stroke (CS). However, it is still possible that patent foramen ovale comes with those other conditions during evaluation. This paper presents a series of CS cases highly suspected due to patent foramen ovale origin with each of its special presentations.

Case illustration: We present three cases of CS with patent foramen ovale as a possible contributing factor. Case 1 showed a patient with repeated ischemic strokes that was investigated to be cryptogenic in origin. Case 2 showed CS with patent foramen ovale and occult atrial fibrillation. Case 3 showed CS at a young age caused by a patent foramen ovale with protein C/S deficiency.

Conclusion: The role of patent foramen ovale as a culprit, risk factor, or a coincidental finding in CS is still debatable and is a controversial issue. Determining patent foramen ovale as a cause of CS requires a thorough consideration of clinical and patent foramen ovale anatomical/morphological factors.

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Keywords: Cryptogenic Stroke, Patent Foramen Ovale, Occult Atrial Fibrillation, Thrombophilia.

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Background

Cryptogenic stroke (CS) is an ischemic stroke without apparent etiology even after adequate diagnostic evaluation.[1] 25% of all ischemic stroke cases are cryptogenic, and more than two-thirds originate from emboli. Cardiac embolism is believed to provide the most significant contribution to the occurrence of cryptogenic stroke.[2] Conditions that may cause a CS include a patent foramen ovale, aortic arch atheroma, occult paroxysmal atrial fibrillation, and inherited thrombophilias.[3]

Patent foramen ovale is indeed a major cause of CS, and its role as a culprit, risk factor, or a coincidental finding is questionable. The mechanism of the stroke that occurs is still uncertain.[4] This paper presents a series of CS cases highly suspected due to patent foramen ovale origin with each of its special presentations.

Case Illustrations

Case 1

A 43-year-old man with a history of transient ischemic attack (TIA) presented to the emergency department with severe cephalgia for three days. One month before, he had a history that he could not control his right limb when driving the car. Physical examination and electrocardiography (ECG) were normal. He had increased triglyceride (184 mg/dL) and uric acid (7.4 mg/dL) levels. A non-contrast-enhanced magnetic resonance angiography (NC-MRA) revealed an old infarction in the parasagittal left frontal lobe (Figure 1). The transthoracic echocardiogram (TTE) was unremarkable with normal heart functions, left ventricular ejection fraction (LVEF) 70%, and no thrombus. He underwent a transesophageal echocardiogram (TEE) and showed positive bubble contrast study (Figure 2). Holter monitoring for seven days showed no atrial fibrillation. The patient received antiplatelet, anticoagulant, and statin therapy.

Six months later, the patient came to the hospital with left facial weakness and a history of mild traffic accidents. Non-contrast head CT showed no bleeding due to anticoagulant therapy administration, and no new infarction. The patient was referred for percutaneous patent foramen ovale closure.

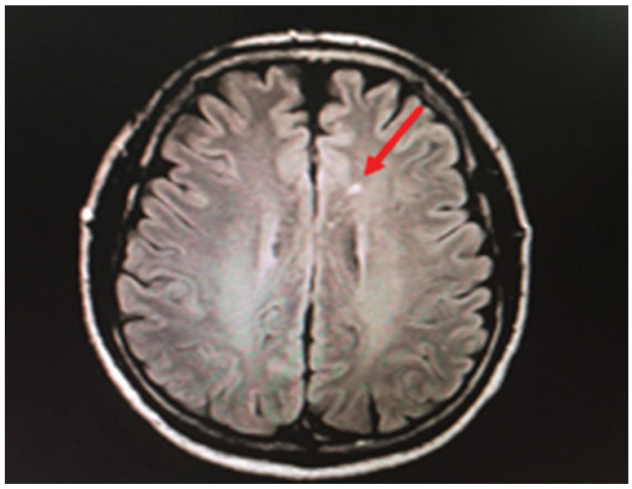

Figure 1. MRA of head showing old infarction in the parasagital left frontal lobe marked by red arrow.

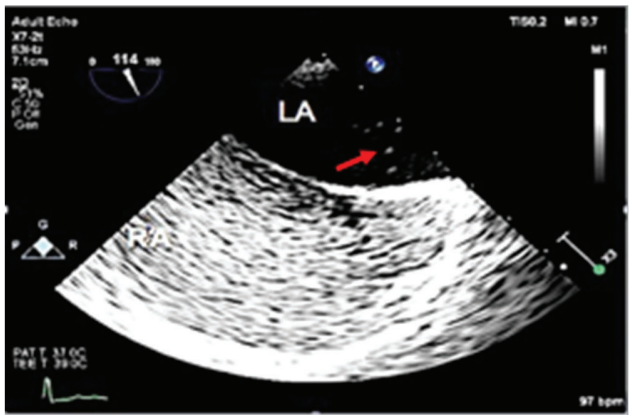

Figure 2. Bubbles (red arrow) are crossing from right atrium to left atrium through patent foramen ovale

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Case 2

A 53-year-old woman with a history of hypertension, dyslipidemia, and recurrent stroke came to the hospital for a medical check-up. The patient had a history of three strokes the last of which was three months ago as manifested by sudden speaking difficulties. Physical examination and ECG were normal. Lab results showed increased low-density lipoproteins (LDL) (164 mg/dL) and triglycerides (179 mg/dL). NC-MRA of the head revealed old infarctions in the right frontoparietal and left occipital area (Figure 3).

TTE showed mild aortic regurgitation with normal heart functions, normal cardiac chamber size, normal regional wall motion, and no LV thrombus. TEE

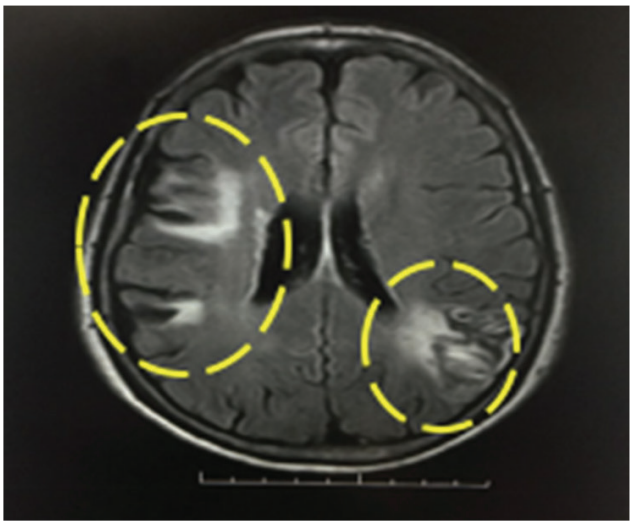

Figure 3. Multiple infarct marked by circles.

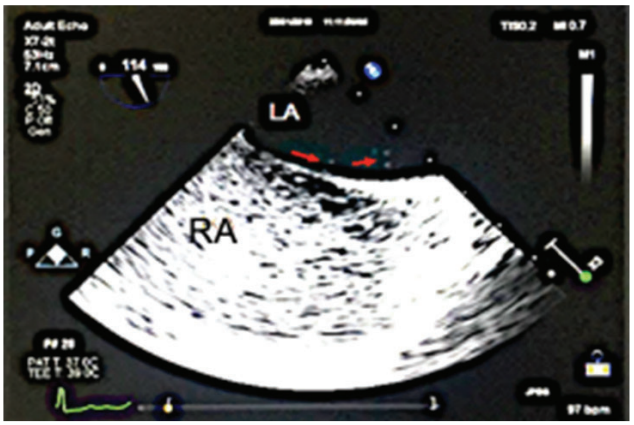

Figure 4. Bubbles (red arrow) are crossing from right atrium to left atrium through patent foramen ovale

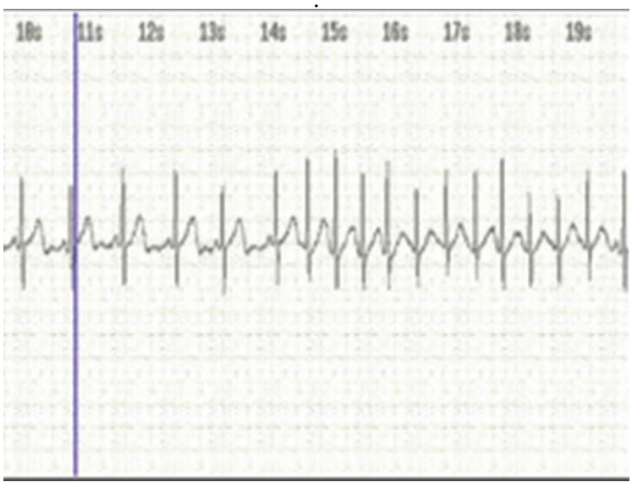

Figure 5. Occult Paroxysmal Atrial Fibrillation showed in 7d-Holter monitoring.

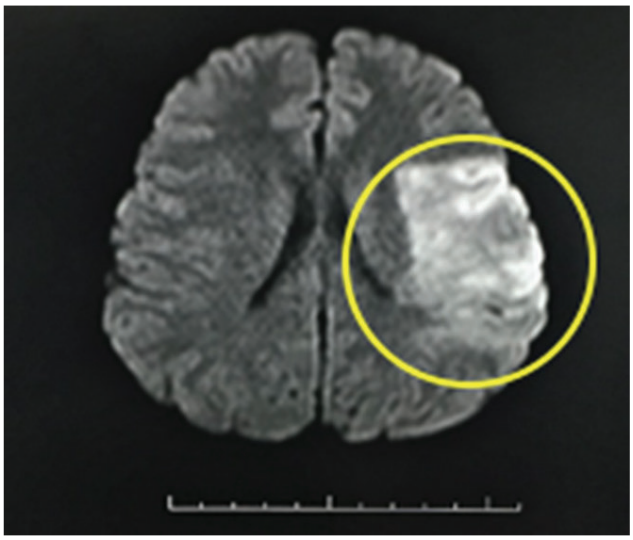

Figure 6. Frontotemporoparietal Infarct marked by circle.

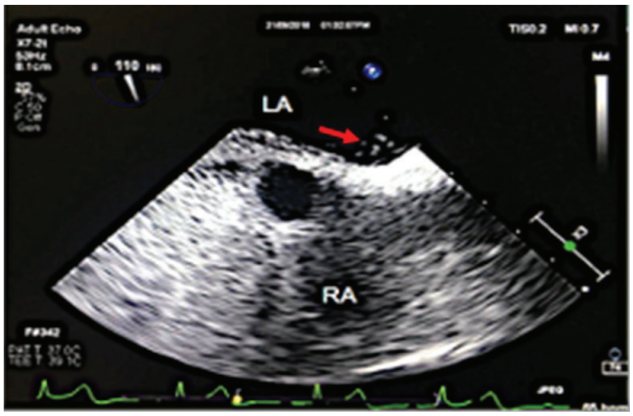

Figure 7. Bubbles (red arrow) are crossing from patent foramen ovale.

presented a small calcified atheroma plaque at the aortic arch and a positive bubble contrast study (Figure 4). Seven days holter monitoring recorded occult paroxysmal atrial fibrillation (Figure 5). She received statins, antihypertensive drugs, and anticoagulants.

Case 3

A 14-year-old boy presented with sudden weakness in his right upper and lower limbs, and difficulty speaking. Physical examination showed a decrease of motor strength in the right limbs and aphasia. ECG was normal, and his labs revealed an elevated d-dimer level (0.96). NC-MRA of the head was obtained, which demonstrated an acute infarction in the left

frontotemporoparietal and stenosis in the M3 segment of the left cerebral artery (Figure 6). TTE showed a small shunt in the atrium, suspicious of patent foramen ovale. TEE with bubble contrast study presented a patent foramen ovale type 1 with a left to right shunt (Figure 7). Further hypercoagulability testing showed that this child had a problem with protein C and S deficiency. The patient currently is not referred for percutaneous closure.

Discussion

CS has several definitions. The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) defines CS as a cerebral infarct not attributed to a definite source of cardioembolism, large-vessel atherosclerosis, or small-vessel disease, despite (1) extensive cardiac, vascular, hematologic, and serological evaluation; (2) evidence of more than one competing cause, or (3) incomplete diagnostic evaluation. Meanwhile, according to the Causative Classification of Stroke System (CCS), diagnostic of CS requires a minimum evaluation of 12-lead electrocardiogram, echocardiogram, and brain imaging (computed tomography (CT) / magnetic resonance imaging (MRI), and intravascular imaging. The CCS divides CS into two categories: cryptogenic embolism and other cryptogenic origin. Determination of the culprit is essential to improve secondary stroke prevention strategies.[5] In summary, CS is a diagnosis of exclusion — it is an ischemic stroke with no identifiable etiology.

The role of patent foramen ovale as a culprit, a risk factor, or coincidental finding is still debatable. The association between patent foramen ovale as a culprit is a controversial issue, paradoxical embolism (the systemic passage of thrombi of venous origin through an interatrial conduit) frequently remains a diagnosis of suspicion. The incidence of patent foramen ovale as a risk factor was found to be four times greater in patients under 55 years than in older patients.[4] There are several factors to consider when attributing a patent foramen ovale to be stroke-related rather than incidental. Kent et al. developed an index to identify stroke-related vs. incidental patent foramen ovale in CS. The study showed that decreasing age, the absence of conventional vascular risk factors, and the presence of a superficially located lesion are consistently associated with an increasing prevalence of patent foramen ovale in patients with CS.[6] Furthermore, patent foramen ovale morphologies that carry a higher risk of cerebrovascular accident include greater patent foramen ovale height during a Valsalva maneuver, larger septal excursion distance, concomitant atrial septal aneurysm, and a large right-to-left shunt.[7]

Several potential CS mechanisms due to patent foramen ovale are paradoxical embolism, insitu clot formation, and arrhythmias. In studies as early as 1877, an autopsy of a young stroke patient had shown significant lower limb thrombus along with a large patent foramen ovale. He hypothesized that the patent foramen ovale served as a pathway for an arterial embolism that paradoxically started in the venous circulation. Secondly, insitu clot formation is possible due to the deceleration of flow, blood stagnation and thrombi formation within the patent foramen ovale or atrial septal aneurysm. Thirdly, embolic events in patent foramen ovale are caused by atrial tachyarrhythmias and/or paroxysmal atrial fibrillation (AF), especially in the presence of a hypermobile atrial septum.[4] Occult paroxysmal AF is often asymptomatic and not identified by standard short term cardiac monitoring.[3] In a meta-analysis study, ECG at admission showed undiagnosed AF in 7.7% of cases. The length of monitoring to detect occult AF is still discussed. The current pathophysiology states that the relationship between AF and stroke starts from altered electrical activity in the atrial cells itself. This problem stimulates platelets, coagulation cascade, and thrombus formation, which are linked to stroke.[8]

The main target for therapy in CS is prevention of stroke recurrence and disability. Modalities of treatment include antiplatelet/anticoagulant and/or patent foramen ovale closure.[9] The relationship between CS and patent foramen ovale is mainly found in people under the age of 55 years. It is considered that after the first CS, there will be a risk of recurrent stroke by an average of 2% each year. The Risk of Paradoxical Embolism (RoPE) score is a scoring tool to predict the probability of CS associated with patent foramen ovale and is used to estimate the risk of 2-year recurrence of stroke / TIA. Variables of the RoPE score include age, information on imaging, smoking history, stroke or transient ischemic attack history, diabetes history, and hypertension. The higher score indicates the stroke is more patent foramen ovale related. patent foramen ovale is considered to be closed if the score above or equal to 7.[10]

In case 1, the patient had repeated strokes even with optimal medical therapy. The RoPE score was 7. This means that the probability of CS associated with patent foramen ovale is high. In this case, patent foramen ovale is considered pathogenic rather than an incidental finding. Patent foramen ovale closure is the best choice for preventing the recurrence of paradoxical embolism through patent foramen ovale.

In Case 2, the patient had a history of hypertension and dyslipidemia, well known risk factor for stroke. However, as the patient had experienced recurrent strokes, further TEE and holter evaluation was done. MRI revealed multiple infarct sites in the cortical area and lesions within multiple vascular regions. It is assumed that the stroke is cardioembolic, with patent foramen ovale and occult AF as a risk factor of CS. Both patent foramen ovale and atrial fibrillation is a condition linked to ischemic stroke. Daher et al, reported patent foramen ovale prevalence of 18.7% using TEE and 56.6% during the pulmonary vein isolation ablation procedure in AF patients.[11] As a structured congenital heart disease, patent foramen ovale is also linked to AF. Atrial arrhythmias increase with increasing age to up to 38% in 50-year-old patients. This also comes with a 13% risk of TIAs and stroke.[12]

Our patient had both patent foramen ovale and atrial fibrillation. Anticoagulation was used and no patent foramen ovale closure had been done. The presence of concurrent patent foramen ovale in this largely anticoagulated group of patients with AF was not associated with increased risk of ischaemic stroke. The presence of patent foramen ovale in patients with AF was not associated with embolic risk beyond those with right-to-left shunt and other established risk factors in this predominantly anticoagulated AF population.[13]

In case 3, CS was presented at a young age. The patient presented with patent foramen ovale and protein C/S deficiency. Thrombophilia is a known risk factor of thrombus formation. This hypercoagulable state is believed to be the primary cause in the creation of the paradoxical emboli in this patient. However, it is noted that the presence of thrombophilia typically predisposes a patient more frequently to venous rather than arterial thrombosis. There are several potential mechanisms that could contribute to the development of ischemic stroke. Ischemic stroke may arise in the setting of deep vein thrombosis and subsequent paradoxical embolism via a patent foramen ovale. Therefore, CS patients with patent foramen ovale should also be investigated for deep venous thrombosis in the legs and pelvic veins.[1415]

Ischemic stroke resulting from thrombophilic disorders may involve any arterial territory and often affects multiple arterial territories at the same time. In this case, the patient experienced CS manifesting as left temporal region infarction along with stenosis in the middle cerebral artery, as seen on the imaging study.[14]

The presence of a patent foramen ovale is associated with an increased risk of CS, especially in the young. However, there is only limited evidence with regards to the impact of thrombophilia and the risk of recurrent CS with patent foramen ovale. A systematic review by Hviid et al suggests that the presence of an acquired or inherited thrombophilia in patients with CS and patent foramen ovale increases the risk of recurrence, even after patent foramen ovale closure. Patent foramen ovale closure may reduce the risk of stroke recurrence but additional antithrombotic therapy is still needed to give a maximum protection to its recurrence.[14, 16] Therefore, in this case patent foramen ovale closure may be considered however, it may not be entirely necessary.

Conclusion

This paper presented 3 different cases of CS with patent foramen ovale. Determining patent foramen ovale as a CS cause remains a challenging task. Clinical presentation, morphology of patent foramen ovale and RoPE score could be used to determine patent foramen ovale pathogenicity and risk of stroke recurrence. The management goal of patients with patent foramen ovale and CS include the prevention of stroke recurrence and disability.

Acknowledgements

None.

Conflicts of interest

None.

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