# Cryptogenic anterior circulation stroke in a young woman with a patent foramen ovale

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## Introduction

Asymptomatic patent foramen ovale (PFO) is found in about 25% of the general population. However, its prevalence increases to nearly 50% among young stroke patients following an extensive diagnostic evaluation of acute ischemic strokes (1, 2). Mechanism of cryptogenic stroke in PFO includes facilitating thrombus formation or creating a short route for paradoxical embolism where a thrombus bypasses lung filtration and travels from the venous system to the arterial system through the foramen ovale potentially causing cerebral ischaemia (3). However, confirming a direct causal relationship between PFO and stroke is often challenging due to limited and speculative evidence, underscoring the need for a through diagnostic evaluation. Moreover, treatment strategies for PFO remain debated, as guidelines are lacking and both invasive and non-invasive approaches carry associated risks.

## Case presentation

A 35-year-old woman presented to the emergency department of the Teaching Hospital, Batticaloa with sudden onset of left sided hemiparesis, slurred speech and facial droop for 5 hours. Her past medical history was otherwise not significant, showing no previous neurological impairments or cardiovascular concerns. As an active and healthy mother of two children, she had no history of miscarriages, smoking, substance abuse, use of oral contraceptive pills or a significant family history of cardiovascular or neurological diseases. She denies any history of trauma and no history of fever at presentation.

Her vital signs were stable on admission. Her Glasgow coma score was 15/15. Neurological examination revealed a left sided hemiparesis with power of 2/5 in the left upper and lower limbs and left side upper motor neuron type of facial nerve palsy and had a National Institutes of Health (NIH) stroke scale score of 6. Other systemic examinations were unremarkable.

An urgent non-contrast CT (NCCT) brain revealed no evidence of intracranial hemorrhage or space occupying lesions (Figure 1). A cryptogenic stroke was considered, considering the patient's age and lack of traditional risk factors of stroke. Due to unavailability of MRI at our facility, a NCCT brain was repeated after 24 hours of admission, and it revealed an infarction in the right middle cerebral artery territory (Figure 2). Since window period for thrombolysis had exceeded on admission, she was managed medically with high dose of aspirin (300 mg) nocte for two weeks and high intensity statins and started early intense physiotherapy.

A comprehensive diagnostic evaluation was undertaken to determine potential underlying causes. The initial assessments which included a transthoracic echogram, identified a PFO with a right to left shunt, which was further confirmed

by a bubble contrast trans-oesophageal echocardiogram, which showed a PFO with a size of 4 mm and a significant right to left shunt, while no other structural abnormalities of the heart were found. No evidence of thrombus was identified in the study. A further evaluation to look for other potential causes of young stroke was also undertaken. Table 1 summarizes the investigations performed on her.

After 2 weeks of treatment with high dose aspirin, she was treated with oral clopidogrel 75 mg nocte and a statin. Her neurological symptoms showed gradual improvement through rehabilitation and by the 6 months follow up, she had achieved almost full recovery, with only mild residual weakness remaining in her left lower limb. Closure of the PFO to reduce risk of recurrent stroke was discussed.

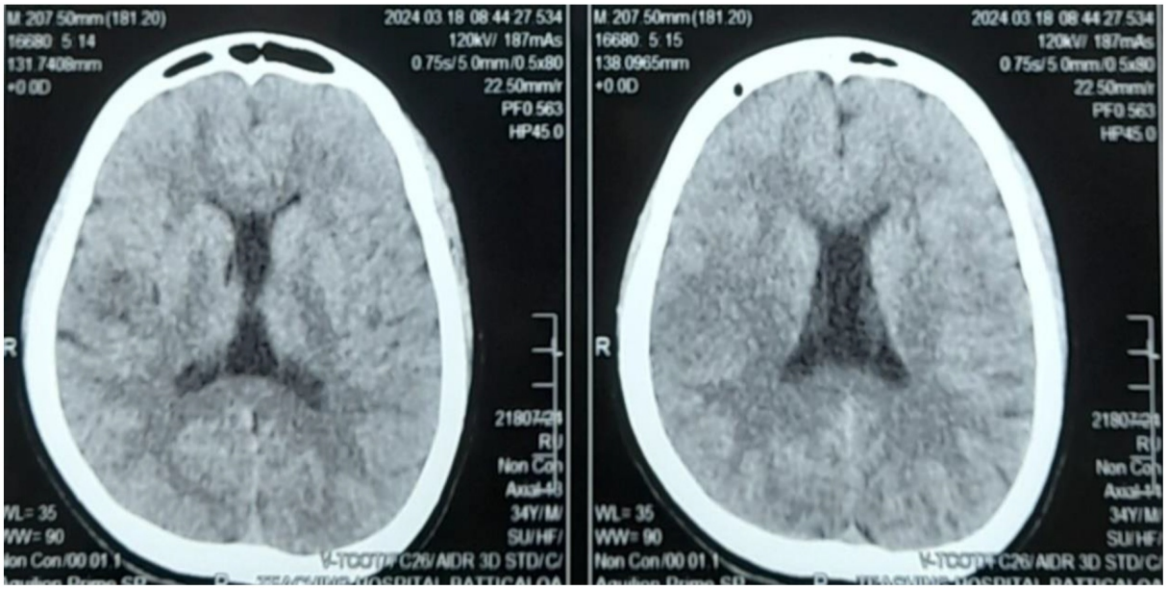


**Figure 1:** NCCT brain revealed no evidence of intracranial hemorrhage/ space occupying lesions.

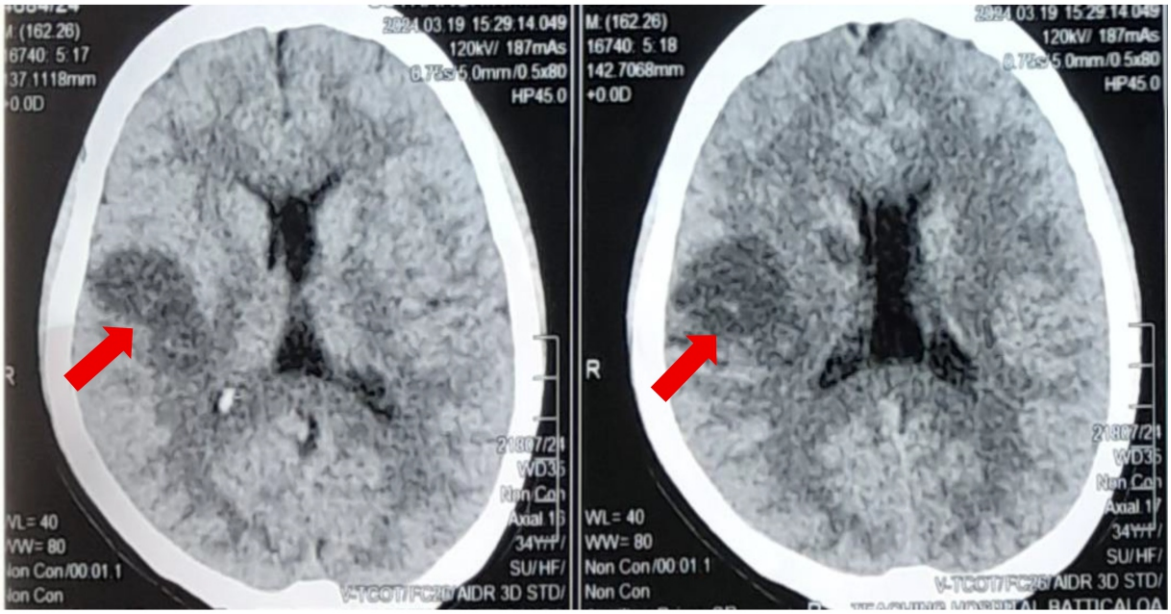


**Figure 2:** The NCCT brain revealed an infarction in the right middle cerebral artery territory (red arrow).

**Table 1:** Summary of investigations

| Test (unit) | Value |
|---|---|
| WBC ($\times 10^3/mm^3$) | 9.52 (4 - 11) |
| Haemoglobin (g/dL) | 11.4 (11 - 15) |
| Platelets ($\times 10^3/mm^3$) | 207 (150 - 450) |
| Urine full report | Normal |
| Blood picture | No abnormal cell lines |
| ESR (mm/hr) | 10 (<10) |
| eGFR (ml/kg/1.73$m^2$) | 126 |
| Serum Sodium (mmol/L) | 139 (136 - 145) |
| Serum Potassium (mmol/L) | 4 (3.5 - 5.1) |
| Serum Total Calcium (mmol/L) | 2.16 (2.12 - 2.62) |
| Serum Magnesium (mmol/L) | 0.8 (0.6 - 0.9) |
| Aspartate transaminase (U/L) | 21 (15-37) |
| Alanine transaminase (U/L) | 29 (12-78) |
| Serum bilirubin (mg/dL) | 0.7 (0.2-0.8) |
| Serum Albumin (g/L) | 42 (34-50) |
| Serum Globulin (g/L) | 35 (22-48) |
| INR | 0.97 (1.08) |
| APTT | 30.0 (27-42) |
| ANA (AU/mL) | 29 (0-40) |
| Lupus anticoagulant screen (ratio) | 1.12 (0.8-1.2) (Negative) |
| Cardiolipin IgM Antibody (MPL U/mL) | 9.1 (Negative) |
| Cardiolipin IgG Antibody (GPL U/mL) | 12.7 (Equivocal) |
| Beta 2 glycoprotein IgM antibody(U/mL) | Negative |
| Beta 2 glycoprotein IgG antibody(U/mL) | Negative |
| FBS (mmol/L) | 5.3 |
| $HbA_1C$ (%) | 5.0 |
| 24 hours Holter monitoring | Normal |
| Chest radiograph | Normal |
| Doppler scan of neck vessels | No evidence of thrombus/ plaque |
| Thyroid Stimulating Hormone (uIU/mL) | 1.108 |
| JAK2 mutation & Factor V Leiden mutation | Not detected |
| Protein C and S level | Normal |
| Lipid profile | Normal |
| Venous duplex of lower limbs | No evidence of thrombus |

## Discussion

Patent foramen ovale is a one of the congenital heart defects that often persists into adulthood (3, 4). The most important potential manifestation of PFO is ischemic stroke due to paradoxical embolism and otherwise majority of patients with a PFO remain asymptomatic. Other common manifestations include migraine, vascular headache, decompression sickness, air embolism, and the platypnea-orthodexia syndrome (3, 4). A cryptogenic stroke is defined as a stroke that occurs in the absence of an identified traditional aetiologic factors such as cardioembolic or large vessel source and with distribution that doesn't align with small vessel disease. Patients with cryptogenic stroke show a higher prevalence of PFO, suggesting that paradoxical embolism through the PFO may be a likely mechanism contributing to strokes in this group (5). Other possible mechanisms include thrombus formation directly within the PFO and atrial arrhythmias caused by abnormal electrical signaling (5).

The diagnostic process in this case underscores the difficulty of determining the cause of stroke in young patients with no apparent risk factors, especially in distinguishing whether a PFO is incidental or pathogenic.

PFO-related stroke is determined by different factors including younger age, larger PFO size, and the degree of right to left shunting, PFO morphology and the presence of an atrial septal aneurysm. Additional contributors, such as coagulation disorders and atrial abnormalities (*e.g.* Eustachian valve, Chiari network, or right atrial septal pouch) may independently or collectively heighten the likelihood of embolic events. Importantly, the PFO in cryptogenic stroke study (PICSS) observed a greater occurrence of large PFOs in patients with cryptogenic stroke compared to those with known stroke risk factors explained larger size is main determining factor in stroke (6). In our case, the PFO was 4 mm in size with significant right to left shunting. Even though it is smaller in size, in the absence of traditional risk factors for stroke, the PFO as a cause for ischemic stroke is justified.

The primary diagnostic method for detecting a PFO is an echocardiogram with bubble contrast. In a bubble study, agitated saline is injected, and the test is considered positive if contrast appears in the left atrium during early ventricular systole. Trans-oesophageal echocardiography (TEE) is then performed to confirm the PFO and assess its severity. TEE also helps rule out other cardioembolic stroke sources, such as thrombi, masses or vegetations, Since PFOs can be incidentally identified on echocardiograms, additional imaging (*e.g.* cerebral angiogram, MRI brain) or cardiac monitoring (*e.g.* electrocardiogram) may be necessary to investigate alternative stroke etiologies (7). MRI brain was not done for our patient due to its unavailability in our hospital.

The CLOSE trial, a randomised clinical study, evaluated whether PFO closure combined with antithrombotic therapy was effective than antithrombotic therapy alone in preventing strokes and alleviating migraines. The results indicated no significant difference between the two groups in terms of migraine relief (8). However, for stroke prevention, the trial demonstrated that PFO closure was more effective than antithrombotic therapy alone in patients who had experienced an initial cryptogenic stroke (9). The decision to pursue PFO closure depends on the probability that the existing PFO contributed to the cerebrovascular accident (CVA). The Risk of Paradoxical Embolism (RoPE) score was created to estimate the likelihood of a CVA being linked to a PFO (10). Scores range from 1 to 10, with higher values suggesting a stronger association. A score greater than 7 is considered the most indication of a PFO being the likely cause of a CVA.

PFO treatment is guided by the RoPE score and the exclusion of cryptogenic stroke. For patients with a low RoPE score (<7), antithrombotic therapy alone may be adequate and a high RoPE score (>7), a combination of PFO closure and antithrombotic therapy may be a more appropriate treatment approach. For patients with concurrent venous thromboembolism, anticoagulation therapy is strongly recommended. Our patient had a RoPE index score of 8, placing her at the higher end of the spectrum and no evidence of concurrent venous thromboembolism was found. So, she was started

on antiplatelet therapy and decided to undergo PFO closure. Unfortunately, due to the unavailability of device at our country, PFO closure has been postponed. However, during the six months follow-up, the patient showed significant neurological improvement with mild residual weakness in the right lower limb.

## Conclusions

Acute ischemic stroke is relatively rare in younger individuals and requires thorough evaluation to determine the cause and guide effective secondary prevention. In this population, PFO can be a potential source of cardioembolic stroke, but it should only be considered once all other possible causes have been excluded, which is highlighted by the presented case.

Managing a stroke in patients with a PFO requires a risk-based approach. Risk stratification score like RoPE index has proven effective in estimating the probability that a stroke is linked to a PFO. This case highlights the need to include PFO in the differential diagnosis of cryptogenic stroke in younger patients.

Informed written consent has been obtained from the patient to publish this case report.

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