INSOLOGI: Jurnal Sains dan Teknologi
https://journal.literasisains.id/index.php/INSOLOGI
ISSN 2828-4984 (Media Online) | ISSN 2828-4992 (Media Cetak)
Vol. 1 No. 6 (Desember 2022) 808-814
DOI: 10.55123/insologi.v1i6.1143
Diterima Redaksi: 20-11-2022 | Selesai Revisi: 10-12-2022 | Diterbitkan Online: 30-12-2022

A Case Report : Patent Foramen Ovale Closure in Young Male Patient with Recurrent Cryptogenic Stroke

Kino Kino[1], Wenny Widyastuti[2], Denada Florencia Leona[3]
[1,2,3]RSUP dr. M. Djamil Padang/Medical Faculty of Andalas University, Padang, Indonesia
Email: [1]Kinokino@med.unand.ac.id, [2]Wenny@gmail.com, [3]Denadaflorencial@gmail.com

Abstract

Patent foramen ovale is one of the most common congenital abnormalities in children. In PFO, there is a valve-like opening between the atrial septum secundum and primum at the fossa ovalis of the heart. A cryptogenic stroke is a stroke for which no clear cause can be identified. In some cases, the PFO can be wide open, allowing paradoxical embolism to pass from the vein into the arterial circulation, that cause cryptogenic stroke. The prevalence of PFO associated with cryptogenic stroke are relatively high, especially in young age. The thorough evaluation was needed to assure the causative relationship between the PFO and stroke or just a merely coincident, which can help to decide the best treatment strategy. Many studies recommend the closure of PFO in patient with cryptogenic stroke to prevent recurrent incident of stroke. This case report transcatheter PFO closure in a young male patient with history of recurrent stroke after serial examination to evaluate the likelihood of PFO as the cause of his stroke.

Keywords: *PFO, Cryptogenic Stroke, PFO Closure*

1. INTRODUCTION

In about a third of patients, the etiology of acute ischemic stroke is still elusive; it is cryptogenic. Diagnosis is established by ruling out alternative reasons for stroke through prolonged rhythm monitoring to exclude atrial fibrillation; transoesophageal echocardiography or alternative imaging of the aorta, left atrial appendage to rule out aortic atherothrombosis or left atrial clot; and carotid ultrasonography, computed tomography, or magnetic resonance imaging to rule out cerebrovascular disease (Parrini, I, et al., 2020).

Patients diagnosed with cryptogenic stroke are less likely to have classic risk factors for atheroembolic stroke such as older age, hypertension, hyperlipidemia, and diabetes mellitus. They are more likely to have a Patent foramen ovale (PFO) than patients in the general population. Several studies show the association between PFO and cryptogenic left circulation thromboembolism including cryptogenic stroke (Kottoor, SJ, et al., 2018). PFO occurs when abnormal remnants of normal fetal anatomy persist into adulthood. The foramen ovale normally exist in fetal heart and close spontaneously after birth. It is a tunnel-like space between the overlying septum secundum and septum primum. However, in PFO, the hole between both atrials is remained. PFO also can be known as Atrial Septal Defect (ASD). The majority of adult patients with PFO are asymptomatic. However, in some adults, PFO can cause right-to-left interatrial shunting of deoxygenated blood and venous thromboembolic shunting into the arterial circulation. These changes explain the pathophysiological determinants of several conditions associated with PFO. This includes cryptogenic stroke (with no other apparent cause),

decompression sickness, migraine, platinia-orthodeoxya syndrome, and acute limb ischemia secondary to embolism (Hampton, et al., 2022).

Cryptogenic stroke is defined as a stroke that cannot be unequivocally attributed to cardioembolism, aortic atherosclerosis, or arteriolar disease. Patent foramen ovale is associated with cryptogenic stroke. With conflicting data, it remains unclear whether PFO is a direct cause, a risk factor, or an incidental finding. Possible stroke mechanisms include paradoxical embolization from venous clots across the PFO, in situ clot formation within the PFO, and atrial arrhythmias due to disruption of electrical signals. The major risk factors associated with PFO-induced stroke are young age, PFO size, and degree of right-to-left shunt (Stefanos G, et al., 2020). Clinical observational studies and RCTs show that PFO closure reduces stroke recurrence in comparison with medical therapy. But it remains challenging to risk stratify patients with suspected PFO-related stroke and to decide if device closure is indicated (Abdelghani, M, et al., 2019).

2. CASE REPORT

A 35 years old male presented with weakness in the left side of body since 1 year ago and worsened in the last three months. He experienced three episode of ischemic stroke in 2007, 2009 and 2021 with sequele of left-sided weakness, slightly slurred speech and left-sided facial droop and history of seizure once in 2020. Currently he was prescribed with phenytoin 2 x 100 mg, Topiramate 1 x 100 mg, and Acetylsalicylate acid 1 x 80 mg. Hypertension, diabetes mellitus, dyslpidemia, family history of stroke or epilepsy were denied.

Physical examination revealed the patient was fully alert, blood pressure 143/76 mmHg, heart rate 65 beat/minute, respiratory rate 16 breath/minute, SpO2 98% on room air. Cardiovascular and pulmonary examination were good with regular heartbeat, no murmur nor gallop were found, vesicular breath sound and no rales. Neurological examination showed parese of left nervous VII and XII (central type) with motoric strength of left extrimities were 333/333, and no sign of increasing intracranial pressure.

Laboratory findings were normal with Hb 13.2 gr/dl, leucocyte 5680/mm3, thrombocyte 261.000/mm3, ureum 26 mg/dl, creatinine 1.0 mg/dl, sodium 139 mmol/L, potassium 3.9 mmol/L, chloride 113 mmol/L, calsium 9.3 mg/dl, PT 0.98, APTT 27.9.

ECG showed sinus rhythm and no record of atrial fibrillation. Chest x-ray also appeared normal. Brain CT scan with no contrast were done on the onset of third episode of stroke showed hypodense lesion in right temporoparietooccipital region representing large subacute cerebral infarct. For investigation the cause of stroke, Digital Subtraction Angiography (DSA) were also done with result multiple total occlusion and stenosis of intracranial arteries, hypoplasia of sigmoid sinus and left internal jugular vein, and also aplasia of left transversus sinus. From Carotid Doppler were found non stenotic plaque in right and left CCA bifurcation, and hypoplasia of left vertebral artery.

Transthoracal dan transesophageal echocardiography were done to exclude the cause of stroke from cardiac source. The result were there was Patent Foramen Ovale (PFO) showed with bubble test, diameter 1.0 – 1.5 mm, good LV function (EF 56%), good RV function (TAPSE 2.1), global normokinetic, MR mild ec functional, TR mild low probability pulmonal hypertension, IVS intact, no atheroma plaque on descendent aorta.

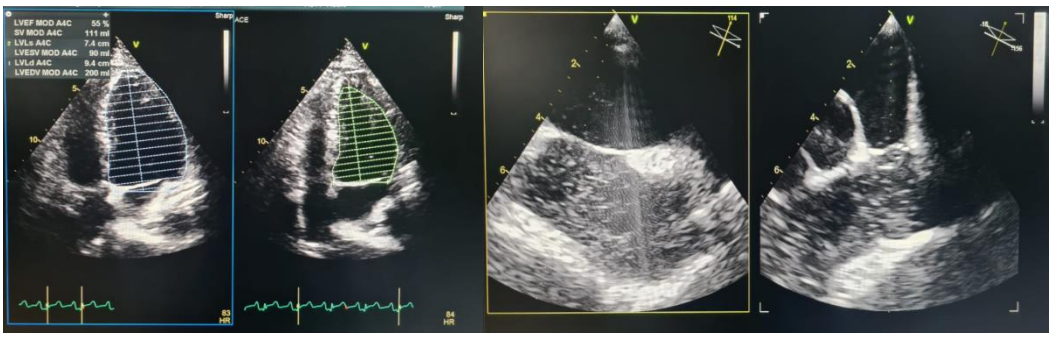


Figure 1. Transthoracal Echocardiography and Transesophageal Echocardiography with Bubble test

Autoimmune marker results (Anticardiolipin Antibody (ACA) were negative (ACA IgG < 2GPL U/ml, ACA IgM < 2 MPL U/mL), Lupus Anticoagulant (LA) was positive moderate, and Sm (Sm) SLE was negative) exclude the possibility of antiphospholipid syndrome disease in this patient.

Patient was diagnosed with cryptogenic stroke and patent foramen ovale (PFO) and given medication : phenytoin 2 x 100 mg, topiramate 1 x 100 mg, and acetylsalicylate acid 1 x 80 mg and underwent transcatheter closure with Amplatzer PFO Occluder.

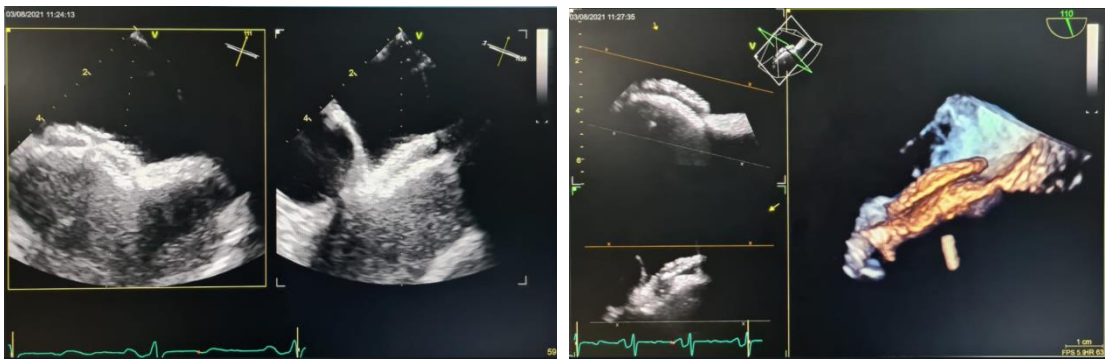


Figure 2. PFO Occluder Device after Implantation

3. DISCUSSION

Patent foramen ovale (PFO) is incomplete apposition of septum primum and septum secundum that creates a 'tunnel' between right atrium and left atrium. The prevalences of the cases are about 25 – 35 % and more frequent in patients with a cryptogenic stroke than in the general population. PFO diameter could range from 1 to 19 mm allows the passage of emboli from the venous system that are large enough to occlude up to the middle cerebral artery stem (3 mm) to reach the cerebral circulation and cause embolic / ischemic stroke (Parrini, I, et al., 2020).

Etiology of ischemic stroke are vary such as atherosclerotic, cardioembolic, and lacunar (a small vessel occlusion). Approximately, 25% to 39% of ischemic strokes do not have an identifiable cause and are termed as cryptogenic stroke (CS). Based on Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, cryptogenic stroke defines as a brain infarction that is not attributable to definite cardioembolism, large artery atherosclerosis, or small artery disease, despite extensive vascular, cardiac, and serologic evaluations. Causative Classification System divides cryptogenic stroke into 2 categories: cryptogenic embolism and other cryptogenic. Cryptogenic embolism refers to a stroke in which there is angiographic evidence of abrupt cut off consistent with a blood clot within otherwise angiographically normal-looking intracranial arteries, imaging evidence of

complete recanalization of previously occluded artery, or the presence of multiple acute infarctions that have occurred closely related in time without detectable abnormality in the relevant vessels. Other cryptogenic is reserved for those not fulfilling the criteria of cryptogenic embolism (Yaghi, S, et al., 2017).

Each year, 345,000 patients aged 18–60 years (up to 40%) present with a PFO and an embolic stroke of otherwise undetermined source worldwide. The NOMASS (Northern Manhattan Stroke Study) observed that CS disproportionately affects younger patients (55% in subjects <45 years old versus 42% in subjects who are ≥45 years old). The risks of recurrent stroke after CS at 1 month was 4.2% in the Oxford meta-analysis and 3% in the National Institute of Neurological Disorders and Stroke Data Bank. At 2 years, recurrence risk ranges from 14 to 20%, and 33% at 5 years in Olmstead country (Kottoor, SJ, et al., 2018).

We suspect this patient to had cryptogenic stroke due to the young age, recurrent event, and there was no risk factor for cerebrocardiovascular disease. We did serial evaluation to ensure the diagnosis and help to chose the best treatment strategy. Cryptogenic stroke is a diagnosis of exclusion after ruling out known causes. Routine evaluation of the patient with ischemic stroke includes several components as shown in algorithm (figure 4). Topographic features of the stroke could be assessed by MRI of the brain, or computed tomography (CT) of the brain. The topographic features provide important etiologic clues: infarcts in multiple territories suggest emboli from a proximal aortocardiac source; infarcts of different ages in a single territory suggest emboli of arterial origin; infarcts along the borders between brain artery territories suggest systemic hypotension or multiple emboli; and a small, deep infarct along with white-matter hyperintensities suggests intrinsic small-vessel disease. The brain, neck, and thoracic arteries are assessed by CT or magnetic resonance angiography (which have similar sensitivity and specificity) or, if these are contraindicated or unavailable, carotid duplex ultrasonography and transcranial Doppler ultrasonography (Saver, JL, et al., 2016).

The presence of structural cardiac disease is evaluated by means of echocardiography, either Transthoracic echocardiography (TTE) or Transesophageal echocardiography (TEE). TEE identifies potentially abnormalities in approximately 50 to 75% of young patients with otherwise cryptogenic stroke, including patent foramen ovale, atrial septal aneurysm, endocarditis, aortic atherosclerosis, regional myocardial-wall dysfunction, dilated left atrium, and atrial appendage thrombi. Cardiac dysrhythmias are initially assessed by 12-lead ECG and inpatient cardiac telemetry or 24-hour Holter monitor. The stroke may be considered to be cryptogenic after standard evaluation when clinical examination and brain imaging suggest a superficial or large, deep cerebral infarct, but none of the above routine vessel-imaging, cardiac, or hematologic tests has revealed a probable cause. Patients with a small, deep infarct also may be considered to have cryptogenic stroke if they are younger than 50 years of age, have no standard vascular risk factors, and have no white-matter hyperintensities or prior small, deep infarcts (Pristipino, C., 2019).

The first incident of stroke in this patient was in 2009, but there was no other evaluation after that. The work up to evaluate the cause of stroke in this patient were done after the third incident, with Brain CT scan, DSA, Electrocardiography, Echocardiography and Carotid Doppler. After standard evaluation, we conclude the paradoxical embolism through PFO is the possible mechanism of stroke in this patient.

Paradoxical embolism is the passage of a clot or other embolic particle from the venous circulation to the arterial circulation through a right to- left shunt, that allow venous thromboembolic to avoid filtration in the pulmonary vasculature and enter the systemic arterial circulation. The mean diameter of a patent foramen ovale is 4.9 mm, which is more than sufficient to permit the passage of emboli that are large enough to occlude the trunk of the middle cerebral artery (3 mm) and major cortical branches (1 mm). The important factors that determine the significance of a PFO are its size and the degree of a right-to-left shunt. Those patients with a PFO size of >4 mm are at a greater risk of a paradoxical embolism. It has also been noted that, in patients with CS, the PFOs are larger, have long tunnels, and are frequently associated with an ASA. Nakayama et al. proposed an echocardiographic score to define high-risk PFO. The presence of two or more high-risk PFO features (score > 2) is associated with CS. These hallmarks are large-size PFO (>2mm in height), long-tunnel PFO (>10mm in length), ASA, hypermobile AS, prominent Eustachian valve, or Chiari's network, large right-to-left shunt at rest and during Valsalva manoeuvre, and low angle PFO ($<10^0$ of PFO angle from inferior vena cava) (Saver, JL, et al., 2016).

The RoPE (risk of paradoxical embolism) score combines some criteria to identify stroke-related versus incidental PFO in cryptogenic stroke. The RoPE score is a 10-point score, where a high score suggests a high association between PFO and CS (young patients, few or no vascular risk factors, cortical infarcts with risk of recurrence of 2% at 2 years), while a low score suggests that the PFO is an incidental finding (elderly patients, deep infarcts, and vascular risk factors with a 2 years risk of recurrence of 20%). In addition, predictors of stroke recurrence differed based on the RoPE scores, that is, in patients with ROPE scores >6, factors related to the PFO such as a minimal degree of shunting and the presence of an atrial septal aneurysm were predictive of recurrent stroke risk, whereas in patients with ROPE scores ≤6, predictors of recurrent stroke were older age and antiplatelet versus anticoagulation therapy. This patient have RoPe score 7 that suggest PFO as likely mechanism of stroke. (Abdelghani, M, et al., 2019).

Patient Characteristic	Points
No history of hypertension	1
No history of diabetes mellitus	1
No history of TIA or stroke	1
Nonsmoker	1
Cortical infarct on imaging	1
Age, y	
18 to 29	5
30 to 39	4
40 to 49	3
50 to 59	2
60 to 69	1
>70	0

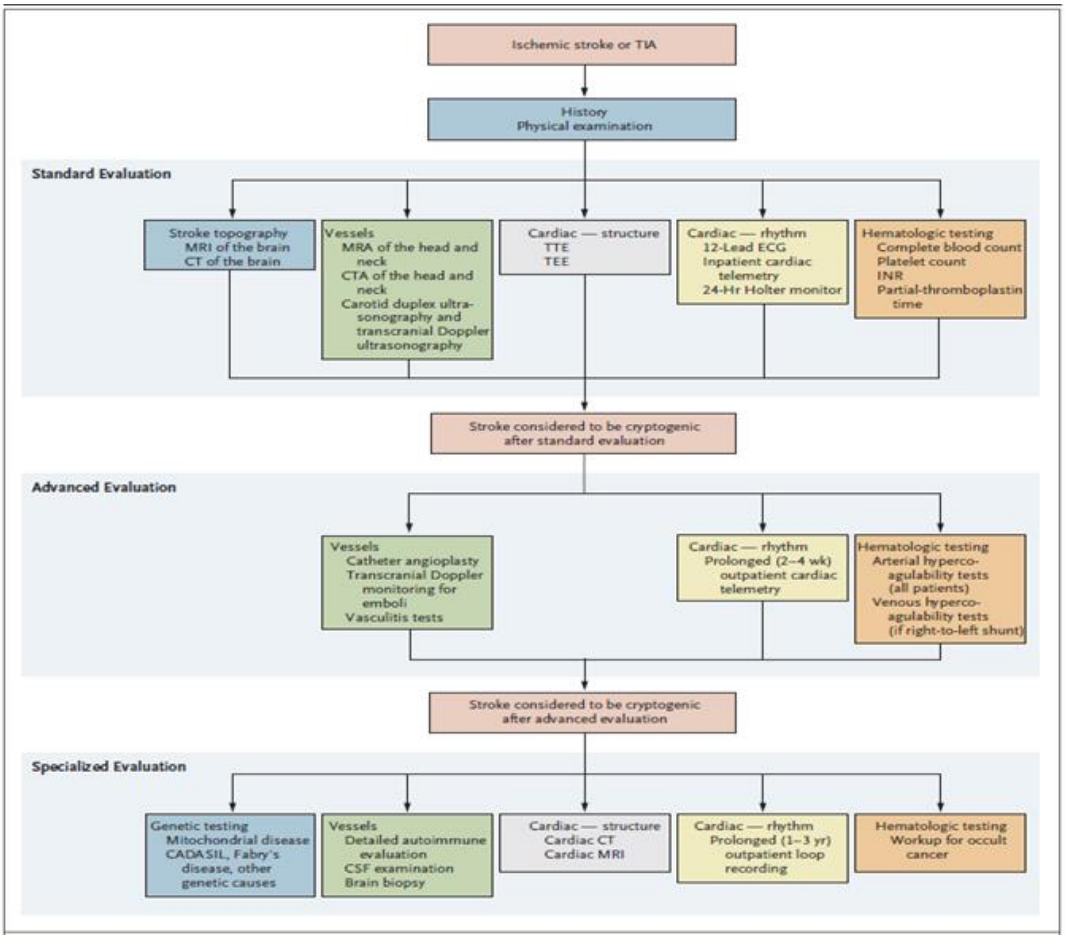
Figure 3. RoPE Score

Prevention recurrent events among stroke patients with a PFO include anticoagulant or antiplatelet agents, percutaneous PFO closure, and surgical PFO closure. Aanticoagulation might be superior to antiplatelet therapy in preventing PFO-related stroke, because it prevents thrombi arising in veins. However, anticoagulation is also associated with increased bleeding, and comparative studies have shown only modest evidence of an efficacy advantage. Several studies showed no benefit of anticoagulation therapy over antiplatelet therapy in patients with ischemic stroke and PFO. A substudy of WARSS (Warfarin Aspirin Recurrent Stroke Study) showed that risk of recurrent stroke or death at 2 years was similar in patients with ischemic stroke between aspirin and

warfarin. Therefore, in the absence of a DVT or pelvic DVT that warrants anticoagulation treatment, antiplatelet therapy remains the mainstay of treatment in patients with ischemic stroke and evidence of PFO (Yaghi, S, et al., 2017)..

Recent Position Papers of the European Society of Cardiology support PFO closure in high-risk patients. These recommendations are based on the evaluation of two factors: probability that the PFO has a role when other aetiologies of CS have been excluded and the probability of recurrent CS. Currently, PFO closure is recommended only as a secondary prevention indication for patients aged from 18 to 60 years with a CS of probable cardioembolic origin in the previous 6months, when PFO is associated with ASA or to high degree shunts (>20–25 microbubbles), especially in presence of concomitant DVT and when other causes of cardiac thromboembolismhave been ruled out. It is not currently recommended for subjects without these specific criteria, like CS more than 6 months before, TIA, age over 60 years, asymptomatic ischaemic lesions occasionally found at cerebral MRI, PFO with moderate shunt (<20 microbubbles), and, moreover, patients who need anticoagulation for other indications (Parrini, I, et al., 2020)..

Extended follow up of RESPECT trials and two new randomized trials, CLOSE and REDUCE, showed that transcatheter PFO closure significantly reduces the risk of recurrent stroke compared with medical therapy in patients with cryptogenic stroke, with no increased risk of serious adverse events or influence on major bleeding. (15). After PFO closure there is evidence to start medical therapy (aspirin 75mg with clopidogrel 75mg) from 1 to 6 months; followed by monotherapy for 5 years (Messe, SR, et al., 2020)



Figue 4. Algorithm for the Identification and Diagnostic Evaluation of Patients with Cryptogenic Ischemic Stroke or Transient Ischemic Attack (TIA).

4. CONCLUSION

In this case, we can conclude that despite the lack of some examination such as holter monitoring to exclude occult atrial fibrillation as cause of stroke, immunologic testing, and even with small and non-high risk feature PFO, there was history of recurrent stroke that made us considered that PFO closure will benefit the patients. With all consideration from multidiscipline team, we decide to close the PFO with Amplatzer PFO Occluder and followed with medical treatment of aspirin.

REFERENCES

Abdelghani M, El-Shedoudy SAO, Nassif M, Bouma BJ, de Winter RJ. 2019. Management of patients with patent foramen ovale and cryptogenic stroke: an update. *Cardiology*.143(1):62-72

Hampton T, Alsaleem M, Heather M, Lavoie M. 2022. Patent foramen ovale. *National library of medicine*.

Kottoor SJ, Arora RR. 2018. Cryptogenic stroke: To close a patent foramen ovale or not to close. *J Cent Nerv Syst Dis*. 10:1-9

Messe SR, Gronseth GS, Kent DM, Kizer JR, et al. 2020. Practice advisory update summary : Patent foramen ovale and secondary stroke prevention. *Neurology*. 94(20):876-85

Parrini I, Cecchi E, Forno D, Lyon AR, Asteggiano R. 2020. Device closure for patent foramen ovale in patients with cryptogenic stroke : which patients should get it ?. *Eur Heart Journal*. M43-M50

Pristipino C, Sievert H, Ascenzo FD, Mas JL, et al. 2019. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. *European Heart Journal.* 40(38): 3182-95.

Saver JL. Cryptogenic Stroke. 2016. *N Engl J Med*. 374:2065-74

Stefanos G, Ioannidis, Panayiotis DM. 2020. Patent foramen ovale in cryptogenic ischemic stroke: direct cause, risk factor, or incidental finding?. *Frontiers in neurology*.

Yaghi S, Bernstein RA, Passman R, Okin PM, Furie KL. 2017. Cryptogenic Stroke. 120(3):527-40