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Case Report

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Patent Foramen Ovale and Inherited Thrombophilia in the Pathogenesis of Arterial Thrombosis in a Young Patient: A Case Report and Literature Review

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Abstract

Background: A Patent Foramen Ovale (PFO) is frequently associated with cryptogenic stroke in young patients with paradoxical embolism as the presumed mechanism. Moreover, hypercoagulable states that are known in the pathogenesis of venous thrombosis, can sometimes be found in patients with stroke, which can be explained by the PFO, that provides the missing link. The association between PFO and prothrombotic state may hence increase the risk for paradoxical embolism. Yet, the cause-and-effect relationship between these pathologies is not clearly established and the best therapeutic and preventive strategy are unelucidated.

Case Report: We report a case associating ischemic stroke, left internal carotid occlusion, and pulmonary embolism with the discovery of a PFO and inherited thrombophilic disorders, in a young woman under combined contraceptives.

Conclusion: We believe that this case is important since it shows the importance of searching for a PFO in young patients with arterial events and thrombophilia and also the interest of systematic screening for procoagulant disorders in those with stroke and PFO, and highlights the challenge in the multidisciplinary management of such patients.

Keywords

Patent foramen ovale; Thrombophilia; Arterial thrombosis

Introduction

A PFO is frequently associated with cryptogenic stroke in young patients with paradoxical embolism as the presumed mechanism. Moreover, hypercoagulable states that are known in the pathogenesis of venous thrombosis, can sometimes be found in patients with stroke, which can be explained by the PFO, that provides the missing link. The association between PFO and prothrombotic state may hence increase the risk for paradoxical embolism. Yet, the cause-and-effect relationship between these pathologies is not clearly established and the best therapeutic and preventive strategy are unelucidated.

We report a case associating ischemic stroke, left internal carotid occlusion, and pulmonary embolism with the discovery of a PFO and inherited thrombophilic disorders, in a young woman under combined contraceptives. We believe that this case is important since it shows the importance of searching for a PFO in young patients with arterial events and thrombophilia and also the interest of systematic screening for procoagulant disorders in those with stroke and PFO, and highlights the challenge in the multidisciplinary management of such patients.

Case presentation

We report the case of a 37-year-old woman, with no known history of cardiovascular nor thromboembolism risk factors, except for combined Estrogen–Progestogen contraceptives' intake during 10 years, who presented to the Emergency Department (ED) for an acute left hemiplegia. Cerebral Computerized Tomography (CT) scan was normal, we then performed a Magnetic Resonance Angiography (MRA) that was in favor of an extended subacute ischemic stroke in the right parietal lobe with right thalamic hemorrhage, in addition to an occluded Left Internal Carotid Artery (LICA) with no haematoma (Figure 1).

Physical examination found a conscious patient with left hemiplegia, dysarthria and right facial paralysis, a blood pressure of 110/70 mmHg, a pulse of 102 beats/min (regular), and saturation on room air of 99% with no murmur nor signs of lower limb Deep Vein Thrombosis (DVT) in the cardiovascular examination. The 12-lead ECG on admission showed sinus tachycardia and a S1Q3 pattern in addition to negative T waves in anteroseptal leads (Figure 2). Transthoracic Echocardiography (TEE) revealed right ventricular dilatation and dysfunction, with a calculated right ventricular systolic pressure of 78 mmHg, in addition to an interatrial septal aneurysm and a PFO with right to left shunt (Figure 3). No thrombus nor vegetation were found and Left Ventricular (LV) function was normal with an estimated LV Ejection Fraction (LVEF) of 60%, despite the paradoxical septal motion.

Further investigations were carried out starting with a thoracic CT angiography (Figure 4) that showed proximal occlusion of the Left Pulmonary Artery (LPA). When digging the patient's medical history with the help of her family given her dysarthria, a history of acute dyspnea was reported 2 months prior to her admission, for which the patient did not present to the ED and chose to treat symptomatically.

We also performed a transesophageal echocardiography that confirmed the PFO with a positive bubble study (Figure 5), followed by supra-aortic vessels angiography that confirmed the total occlusion of the LICA (Figure 6). 24 hours holter monitoring findings were unparticular and lower limb doppler ultrasonography showed no sign of DVT.

All the patient's baseline laboratory investigations are shown on Table 1. As we can see, the patient was found to have Protein C and Antithrombin III deficiency.

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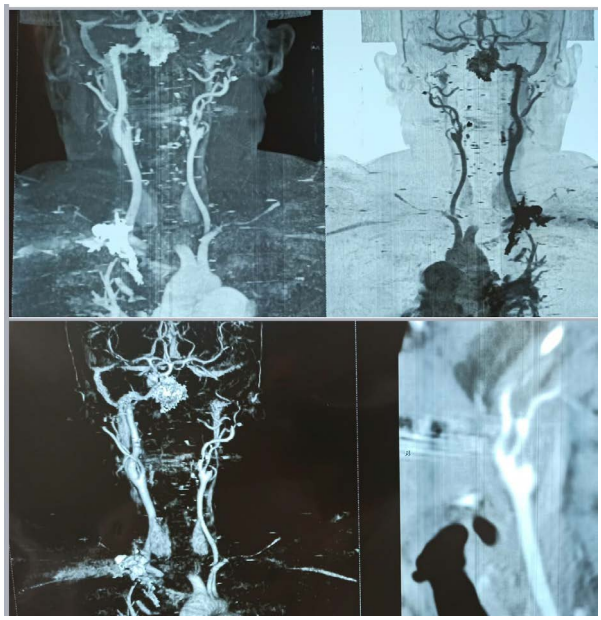

Figure 1: Occluded left internal carotid artery.

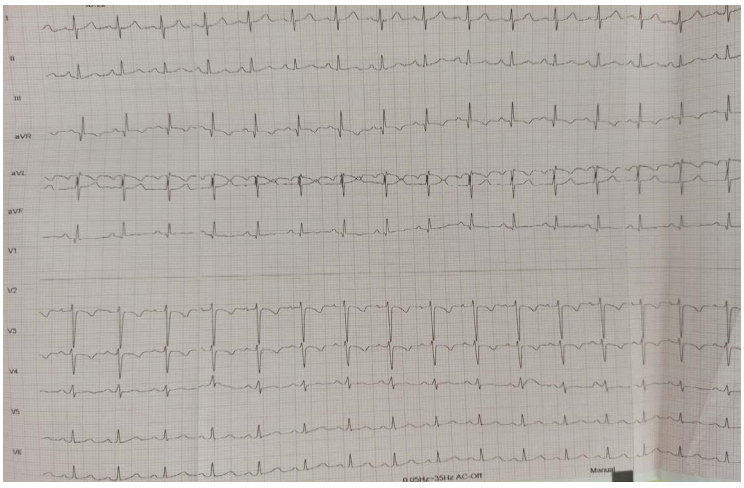

Figure 2: Sinus tachycardia and a S1Q3 pattern.

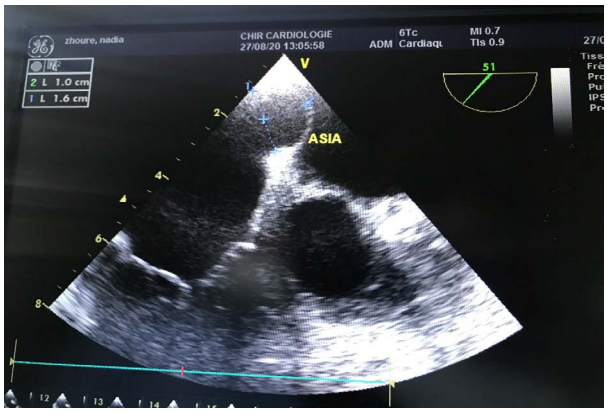

Figure 3: Interatrial septal aneurysm.

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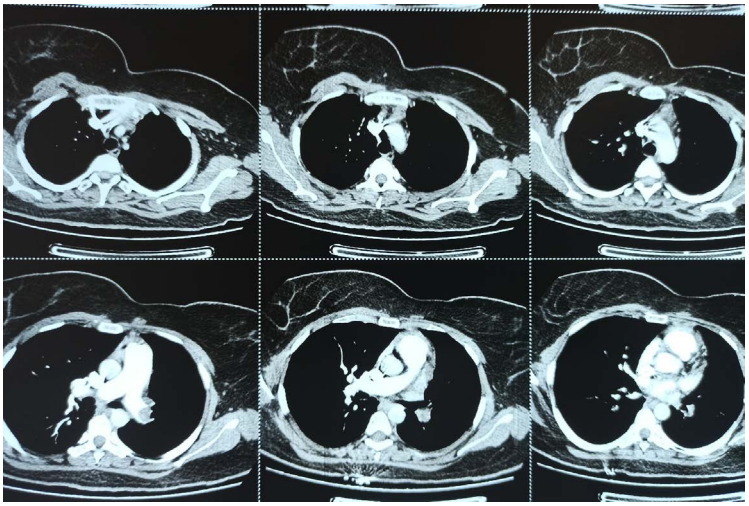

Figure 4: Thoracic CT angiography showed proximal occlusion of the left pulmonary artery (LPA).

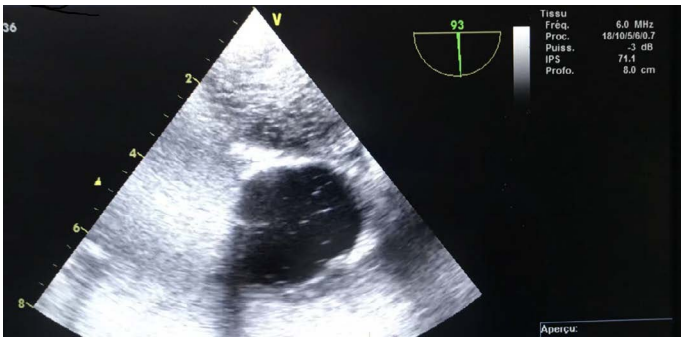

Figure 5: Transesophageal echocardiography that confirmed the PFO.

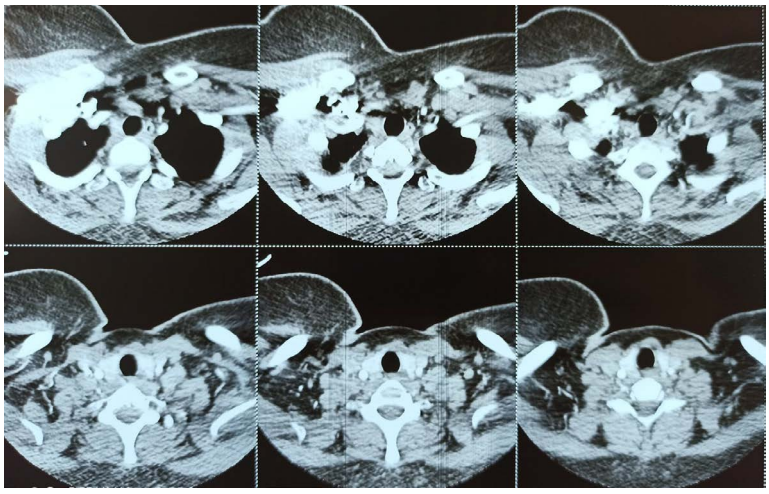

Figure 6: Supra-aortic vessels angiography that confirmed the total occlusion of the LICA.

Concerning the treatment, given the patient's high thrombotic risk, with both arterial and venous embolism in addition to her hypercoagulable state, it was decided, in concertation with the neurologists to immediately start Anticoagulant (AC) therapy with intravenous Unfractionated Heparin (UFH) starting with 18 UI/Kg/D with a close monitoring of the Partial Thromboplastin Time (PTT).

A control cerebral CT scan was performed on the 8th day and showed stationary ischemic lesions with no sign of cerebral hemorrhage (Figure 7), after which, we decided in collaboration with the heart and neurology teams to start oral AC with Vitamin K Antagonists (VKA) with an International Normalized Ratio (INR) target of 2.0 to 3.0.

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Table 1: Baseline characteristics of the final cohort.

Parameter	Result	Normal range
High sensitive Troponin	12 ng/L	0-34 ng/L
Hemoglobin (Hb)	14.2 g/L	13-16 g/L
Hematocrit (Ht)	0.44	0.41-0.50
White blood cells (WBC)	9.17 G/L	4-10 G/L
Neutrophils	5.71 G/L	2-8 G/L
Platelets	174 G/L	150-400 G/L
Prothrombin Time (PT)	97%	70-100%
Partial Thromboplastin Time (PTT)	39“	34“
Fibrinogen	2.3 g/L	1.8-4 g/L
Urea	0.29 g/L	0,1-0.55 g/L
Creatinin	6.7 mg/dL	0.7-1.3 mg/dL
Na+	138 mmol/L	135-145 mmol/L
K+	3.7 mmol/L	3.5-5 mmol/L
Ca++	2.2 mmol/L	2-2.6 mmol/L
Protein S	6	>2
Protein C	3	>10
Antithrombin III	1	>3
Factor V	2.7	2.2 – 3.2
Activated protein C resistance	5	>2.1
Antiphospholipid antibodies	Absent	
Antinuclear antibodies	Absent	
Tumor markors	Negative	
Tumor markors	Negative	

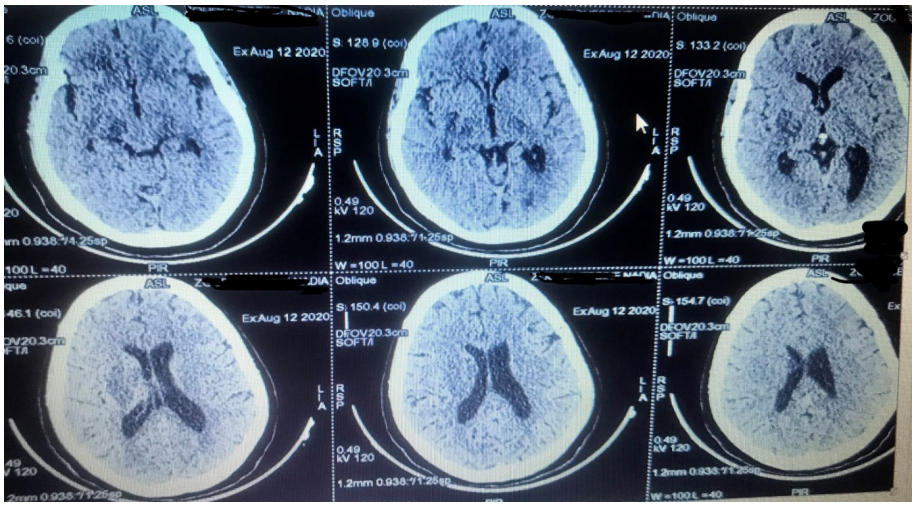

Figure 7: Sinus tachycardia and a S1Q3 pattern.

Moreover, the patient's Pulmonary Arterial Hypertension (PAH) was treated symptomatically using low doses of diuretics.

The patient's progress was favorable after 1 month of treatment and motor function rehabilitation, with progressive neurological improvement and dyspnea regression.

She was discharged from hospital, under acenocoumarol and diuretics and was followed-up as outpatient by a multidisciplinary team of cardiologists, neurologists and hematologists, with a good clinical evolution. A control TEE and thoracic CT angiography after 3 months of AC were indicated to see the pulmonary embolism and the PAH evolution. A ventilation/perfusion (V/Q) scan to detect chronic cor pulmonale was also scheduled. Depending on these investigations' results, surgical indication of Pulmonary Endarterectomy (PEA) in addition to the PFO closure, would be under discussion by the heart team.

Discussion

Overview

Ischemic stroke is common among the elderly and is usually associated with atherosclerotic risk factors such as arterial hypertension, diabetes mellitus, dyslipidemia etc. In younger individuals under 55 years, almost 50% of cerebral infarction remains cryptogenic despite extensive diagnostic work-up [1-4].

Paradoxical embolism through a PFO may account for a significant proportion of Cryptogenic Stroke (CS) cases; the mechanism is postulated to be a Pulmonary Embolism (PE), where clots originate in the venous circulation and go to the arterial one through an RLS [2-5]. Yet, a direct causal relationship is sometimes difficult to establish since the existence of a RLS alone, is not sufficient to explain the increased risk of ischemic stroke. The hypothesis of the existence of other risk factors associated with paradoxical embolism through the PFO, has been raised.

Some studies evoked other pathogenic processes, such as embolization from thrombi formed within the atrial septum [6,7] and transient atrial arrhythmias [8].

Other studies suggested the potential role of an underlying hypercoagulable state in predisposing young PFO carriers to brain embolism. Inherited thrombophilias are known to be at increased risk for Venous Thromboembolism (VTE), however, the causal relationship with arterial thrombosis remains unclear [9-11]. In the present literature, patients with prothrombotic state PFO, and paradoxical embolization have not been adequately studied, and there are no available guidelines for the management of this high-risk population.

Our case report features a patient with a constellation of findings, including hypercoagulable disorders, pulmonary embolism, PFO, an ischemic stroke and a total occlusion of the LICA. Two hypotheses were raised : Was the paradoxical embolism favored by the prothrombotic state, responsible for the ischemic stroke ? or did the hypercoagulable disorder provoke both the PE and the LICA occlusion resulting in a stroke ?

The aim of this report was to understand the pathophysiological process involved in such patients and to explore whether there might be any association between the condition of PFO and the hypercoagulable state in order to identify a possible high-risk subgroup in this population. If the presence of PFO is indeed associated with an increased likelihood of a thrombophilia, then the screening for prothrombotic disorders is justified in young patients with PFO and stroke, which may have an impact on the risk stratification. Likewise, patients with thrombophilia and arterial events might require a screening transthoracic echocardiogram for PFO, in order to guide decisions on AC or PFO closure [4,12].

PFO risk factors for cryptogenic Stroke

The prevalence of PFO in patients with CS was found to be significantly greater compared with patients with stroke of known cause. However, although PFO is very common, not all PFOs are the same. In fact, the risk of stroke is higher in the case of large oval opening, conditions promoting RLS (pulmonary hypertension, right ventricular infarct, severe insufficiency of tricuspid valve), Atrial Septal Aneurysm (ASA), like it was the case of our patient, and in certain morphological variants of the right atrium (persistent Eustachian valve, Chiari's network) [13]. Patients with PFO can thus, be subgrouped according to many characteristics (large vs. small PFO, provoked vs. unprovoked trans-septal gas passage, presence vs. absence of associated anatomical structures). Several investigators have reported an increased incidence of CS in patients with PFO associated with RLS of more than 20 microbubbles, evidence of shunt at rest, and ASA [14,15], although direct arterial embolism of thrombus from the atrial septum is another potential mechanism. These anatomical and functional characteristics may provoke transient RLS enabling the transfer of embolic material from the venous system to systemic circulation. Hence, this increased risk of PFO related systemic embolism should be carefully evaluated in TEE in order to properly identify a PFO "at risk", possibly suggesting the opportunity for PFO closure. According to the RESPECT trial, in this high risk population, closure of the PFO was 75% better than on-going blood thinners [16]. In the same way, a recent meta-analysis showed that the weighted incidence of recurrent stroke was 1.7% in the closure group versus 2.9% in the best medical therapy group and a lower relative risk for stroke after PFO closure, which was especially noted in patients with ASA and a large RLS [17].

Hypercoagulable states and cryptogenic stroke

The literature on prothrombotic states in stroke patients with PFO is mostly anecdotal. Inherited thrombophilias such as factor V Leiden, protein C deficiency, protein S deficiency, antithrombin deficiency, Antiphospholipid Syndrome (APS) and prothrombin gene mutation, are not described as a common cause for stroke in the adult population [18]. Factor V Leiden mutation, the most prevalent congenital hypercoagulable disorders, has been associated with a higher risk of stroke in younger patients [19]. Di Tullio et al. [10] found a significantly higher prevalence of protein C deficiency among 25 stroke patients with PFO compared with 195 without PFO. Barinagarrementeria et al. [11] and Chaturvedi [9] obtained similar findings in small case series. The results of a recent meta-analysis support the assumption that an underlying hypercoagulable state may be a predisposing condition for PFO-related cerebral infarcts and might be used as a further criterion for risk stratification among subjects with PFO [20]. In our patient's case, TEE revealed PFO, constituting a potential etiological mechanism of paradoxical embolism in addition to Antithrombin III and Protein C deficiency, both promoting thrombosis and increasing the probability of paradoxical embolism causing stroke. Other coagulation testing, including prothrombin and activated partial thromboplastin times, antiphospholipid antibodies, fibrinogen, activated protein C resistance, and antithrombin III, all came out negative.

All in all, the hypothesis that cardioembolic stroke might be the result of a combination of anatomic and hemostatic defects suggesting the concept of "vascular bed-specific hemostasis" first proposed by Rosenberg and Aird, was raised [21,22]. A systemic prothrombotic disorder affecting the coagulation process on the heart's endocardial surface, might be the first event in the pathophysiological mechanism leading to "local thrombus" formation ; the second one being the presence of anatomic abnormalities within the heart like PFO [22].

Pulmonary embolism in patients with PFO

One way in which hypercoagulability lead to ischemic stroke is by the simultaneous occurrence of a venous thrombus and a mechanism for paradoxical embolization to the arterial circulation. Patients with thrombophilia might sustain multiple subclinical DVT, which could embolize to the pulmonary circulation.

Although paradoxical embolism is the favored hypothesis in CS, PE or DVT in stroke patients with PFO is usually undetectable [23]. However, some studies suggest that this mechanism has probably been underdiagnosed. In fact, Pelvic vein thrombosis was documented in 20% of CS cases included in the PELVIS trial, after an extensive work-up [24]. And more recently, Cramer et al. [25] diagnosed paradoxical embolism in 29% of patients in a small series of subjects with CS and suggested that DVT may be missed in a significant number of cases if

an extensive study of pelvic and calf vein is not performed, in addition to the routine popliteal and femoral veins investigation.

In other cases, the thrombi is not visualized but can be guessed by its consequences ; for instance, chronic PE could raise pulmonary pressures and cause RLS in patients who have an atrial septal defect, thus providing a mechanism for arterial embolization of DVT in susceptible patients.

In our patient's case, TEE revealed right ventricular dilatation and dysfunction, with pulmonary and the thoracic CT angiography confirmed proximal occlusion of the Left Pulmonary Artery (LPA).

In such patients who develop PE, the presence of a PFO is associated with significantly increased mortality [26] and patients with large RLS are more likely to have ischemic stroke [27]. Thus, it would be helpful to explore the prevalence of both a hypercoagulable defect and a PFO, and to perform the proper investigations to find the DVT, in young patients with stroke.

Management and treatment

The optimal management of patients with CS and who have both a thrombophilia and a PFO has not been fully elucidated and represents a challenge requiring multidisciplinary management. The possible strategies of treatment in hypercoagulable patients with CS and PFO include administration of Antiplatelet Therapy (APT), Oral AC (OAC) with Vitamin K Agonists (VKA), combined therapy with APT and VKA, and transdermal or surgical closure of PFO. Current guidelines strongly recommend the initiation of an antiplatelet or anticoagulant therapy [28] The guidelines mention that AC is indicated in hypercoagulable patients, depending on the stroke characteristics, or an inferior vena cava filter if AC is contraindicated (Class IIA, C) [28]. According to some authors, VKA should constitute first line treatment in patients with thrombophilia and stroke of embolic etiology [29]. To date, in all PFO randomized controlled trials, (PICSS, CLOSURE, RESPECT, PC), the superiority of any of these approaches was not confirmed regarding the reduced risk of recurrent stroke in patients with PFO [16,30-32]. However, in the PICSS trial [32], warfarin group showed a significant increase in bleeding complications. Consequently, according to the American College of Chest Physicians and the American Heart Association guidelines, APT was preferred over VKA in patients with CS and PFO, except for individuals with thrombophilia and DVT [33].

In our case, considering the high thrombotic risk of our patient who had venous and multiple arterial thrombosis, we chose to first treat our patient with UFH and then with VKA with an INR target of 2.0 to 3.0 after a control cerebral CT scan and in concertation with the neurology team.

Concerning invasive closure of PFO, the safety of implantion a PFO device with a known thrombophilia remains unclear. In the literature, it is hard to find any evidence-based data supporting transdermal closure of PFO in thrombophilic patients with stroke since thrombophilia usually constitutes an exclusion criterion in the case of clinical trials dealing with the problem in question. In Giardini et al. [34] study comparing results of percutaneous closure of PFO for paradoxical embolism in patients with versus without thrombophilia, transcatheter PFO closure was found effective for preventing recurrences in patients with thrombophilia [34]. Likewise, in Rigatelli et al. [35] study, transcatheter closure was as safe and effective in patients with thrombophilia as in general population with no difference in device thrombosis or recurrent CVA events, with almost no additional therapy rather than aspirin.

To sum up these recommandations, patients with CS and PFO and documented thrombophilia should have a lower threshold for PFO closure than the non-thrombophilic CS/PFO population. If a venous source of embolism is found, OAC is indicated for 6 months, then followed by long-term APT; or closure of PFO associated with APT, depending on the presence of « high-risk » PFO. In the case of unfound venous source, long-term APT or PFO closure with APT can be considered depending on the PFO risk.

In our patient, due to the lack of strong evidence of benefits associated with transdermal closure of PFO, and taking into consideration the preference of our patient, we have temporarily resigned from invasive treatment and the patient was discharged our patient under VKA. Nevertheless, indications for PFO closure will be reconsidered if stroke recurs despite pharmacotherapy and depending on the evolution of her PE that might require a pulmonary endarterectomy (PEA) depending on the heart team concertation.

Conclusion

In conclusion, the current evidence suggest that when PFO is diagnosed in a young adult with CS, paradoxical embolism is a very probable causative mechanism, and is usually associated to other triggering factors such us hypercoagulable states. Our case highlights the importance of searching for PFO in young patients with arterial events and inherited thrombophilia. Likewise, as coagulation abnormalities were found in 30% of young patients with CS and PFO, screening for thrombophilia in cases of such strokes is of interest. Such patients' management represent a challenge requiring a multidisciplinary team including cardiologists, neurologists and hematologists. Several treatment strategies are described in the literature but no clear recommendation exist for this particular population of thrombophilic patients with CS and PFO. There is a need for clinical randomized trials analyzing the effects of PFO closure in patients with cryptogenic stroke and thrombophilia, in whom the presence of clotting abnormalities increases the risk of paradoxical embolism.

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