Patent foramen ovale and stroke: a possible association with deep vein thrombosis

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ABSTRACT

Patent foramen ovale (PFO) is a congenital heart abnormality consisting of the persistence of a tunnel between the right and left atrium; it is associated with a higher prevalence of strokes. A 52-year-old man was admitted to the emergency room for confusion and deep vein thrombosis with signs of pulmonary embolism; he started treatment with fondaparinux. After admission, there was an ischemic stroke. Blood tests, thrombogenic screening, and infectious diseases showed no alterations. Holter-electrocardiogram, echocardiography, and positron emission tomography-computed tomography were negative except for the presence of PFO. Apixaban and cardioaspirin were started. The surgical treatment was planned, but despite the therapy, there was a new ischemic stroke, so the treatment with mechanical thrombectomy was attempted but failed. The patient was continuing therapy until a new cerebral ischemic episode caused his death; the etiopathogenesis of brain events appears to be associated with the presence of PFO; association with deep venous thrombosis is described in the literature.

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Key words: patent foramen ovale, stroke, deep vein thrombosis.

Contributions: all the authors made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare there are no competing interests.

Ethics approval and consent to participate: not applicable.

Patient consent for publication: the family members gave consent to publication as the patient was deceased.

Funding: none.

Availability of data and materials: data available from the corresponding author upon request.

Received: 26 September 2024.
Accepted: 30 September 2024.

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Licensee PAGEPress, Italy
Italian Journal of Medicine 2024; 18:1801
doi:10.4081/itjm.2024.1801

Introduction

Foramen ovale is an embryonic defect in the interatrial septum that allows the passage of oxygenated blood from the right atrium to the left atrium.[1] Patent foramen ovale (PFO) is a highly prevalent finding in cryptogenic ischemic stroke, particularly in young adults.[2] An association between cryptogenic stroke related to PFO and venous thromboembolism is also reported in the literature.[3]

Case Report

A 52-year-old man was admitted to the emergency room for a confusional state and paresthesia in the fifth finger of the right hand. He exhibited a muscle-tendinous ultrasound of the left lower limb performed the same day, which showed "dilatation of the femoral-popliteal-tibial venous axis with the lumen subtotally occupied by echogenic material as by venous thrombosis deep".

On admission, the vital parameters were as follows: blood pressure 170/90 mmHg, heart rate 81 beats/minute, respiratory rate 22 breaths/minute, and oxygen saturation 98% on room air.

His medical history does not report any relevant pathologies; he reports plantar fasciitis and a recent episode of tracheitis treated with antibiotics and corticosteroids; the patient also had a smoking habit.

In the emergency room, the patient practiced routine exams and a computed tomography (CT) angiography of the lower limbs that showed "on the left, venous thrombosis of

the articular region of the knee extending to the distal middle third of the leg, absent arterial pathology with patency of the aorto-iliac-femoral-popliteal-tibial axis bilaterally"; he also underwent a chest CT scan and a brain CT: the first showed "non-homogenous opacification of the lower lobar pyramids bilaterally as per thromboembolism, ground glass area with thickening of the intra and inter lobular septa in the medial segment of the right lower lobe, right basal parietal effusion with a maximum thickness of approximately 18 mm and atelectasis of the contiguous parenchyma", the second showed "no evidence of densiometric alterations referring to acute lesions, ischemic outcome in the left inferior cerebellar region". The patient began therapy with antibiotics and fondaparinux and was transferred to the Internal Medicine Department.

Discussion

In the hospital, the patient appeared in stationary conditions, awake, alert and cooperative, and oriented in space and time. Routine tests and an electrocardiogram (ECG) were carried out; the following day, he suddenly appeared dysarthric with a speech that was at times not fluent in the absence of motor deficits. Head CT with angio sequences, echocardiography, and 24-hour Holter ECG were required: the first showed absence of hemorrhagic areas, subacute cortico-subcortical ischemic lesion in the left prieto-temporal location, further ischemic focalities in the left anterior frontal and right posterior parietal locations, and normal opacification of the supra-aortic trochia; the second and third showed no relevant alterations.

The following day, the general condition improved together with the ability to speak; a follow-up brain CT scan was requested after 24 hours; a blood sample was taken for thrombophilia screening (Table 1) in the absence of anticoagulant therapy; and a trans-esophageal echocardiography was also requested.

Brain TC confirmed the areas of evolutionary ischemic hypodensity, the largest of which was in the left parietal area and the other minor ones in the left frontal and right posterior parietal areas; trans-esophageal echocardiography showed the presence of patent tunnel-like foramen ovale measuring 2×5 mm; after the administration of saline solution and at the end of the Valsalva maneuver, the severe passage of microbubbles from right to left was observed.

The patient then began therapy with apixaban 5 mg every 12 hours and cardioaspirin 100 mg once daily.

The clinical conditions appeared stationary. Given the results of the tests, a screening for autoimmune [antineutrophil cytoplasmic antibodies (ANCA), perinuclear-ANCA, antinuclear antibodies, myeloperoxidase, proteinase 3, C3, C4, extractable nuclear antigen] diseases, a direct and indirect COOMBS test, a screening for infectious diseases [toxoplasma immunoglobulin (Ig) G-IgM, cytomegalovirus IgG-IgM, herpes simplex virus 1-2 antibodies, HIV 1-2 immunoblotting antibodies, rosolia IgG-IgM, anti-mycoplasma pneumoniae IgG-IgM antibodies, mycoplasma real-time polymerase chain reaction, Parvovirus B 19 IgG-IgM], serial blood, nasal and rectal cultures, a total body positron emission tomography-CT in the suspicion of paraneoplastic thrombophilia, and genetic tests for the detection of thrombophilic conditions were requested. Surgical closure of the PFO was planned.

All investigations carried out were negative for autoimmune, infectious, and neoplastic pathologies; the genetic

Table 1. Thrombophilia screening.

Laboratory examination	Result	Normal values
PT, prothrombin activity (%)	57.0	70-120
PT, INR	1.46	0.9-1.2
PT, ratio	1.43	-
aPTT (seconds)	33.0	28-40
aPTT, ratio	1.11	-
PLT (10^3/uL)	89.0	150-300
Fibrinogen (mg/dL)	352	150-400
Coagulating protein C (%)	70.0	70-140
Protein S free (%)	68.0	75-140
APC resistance (normal ratio)	1.14	>0.80
Anti-cardiolipin IgM antibodies (MPL/mL)	0.00	<10.0
Anti-cardiolipin IgG antibodies (GPL/mL)	0.00	<10.0
LAC diagnostics: DVVRT		
LAC screen (ratio)	1.52	-
LAC confirm (ratio)	1.43	-
Normalized ratio (NR)	1.07	<1.20
LAC diagnostics: SCT		
SCT screen (ratio)	1.28	-
SCT confirm (ratio)	1.15	-
Normalized ratio (NR)	1.11	<1.20

PT, prothrombin time; INR, international normalized ratio; aPTT, partial thromboplastin time; PLT, platelets; APC resistance, resistance to activated protein C; Ig, immunoglobulin; MPL, microgram of IgM antibody; GPL, microgram of IgG antibody; LAC, lupus anticoagulant; NR, normalized ratio; DVVRT, Russell viper venom test; SCT, silica clotting time.

analysis to search for the Factor V Leiden mutation and the G20210A mutation of prothrombin was negative.

After a few days, the patient suddenly showed confusion, focal deficits, and neglect affecting the left side. He underwent an emergency brain CT angiography, which showed an ischemic cerebral stroke of the right middle cerebral artery; he was promptly taken to the Stroke Unit, where mechanical thrombectomy was attempted three times, all with negative results. Therefore, he was kept under observation, and medical therapy was administered, but unfortunately, he died after a few days.

Conclusions

As described in the literature,[3] the patient's cerebral events appear to be associated with the presence of deep vein thrombosis and his unrecognized condition of PFO, events that appeared despite therapy with anticoagulant and antiaggregant therapy.

References

1. Teshome MK, Najib K, Nwagbara CC, et al. Patent foramen ovale: a comprehensive review. Curr Probl Cardiol 2020;45:100392.
2. Miranda B, Fonseca AC, Ferro JM. Patent foramen ovale and stroke. J Neurol 2018;265:1943-9.
3. Zietz A, Sutter R, De Marchis GM. Deep vein thrombosis and pulmonary embolism among patients with a cryptogenic stroke linked to patent foramen ovale-a review of the literature. Front Neurol 2020;11:336.