Ischemic Stroke in a Young Adult: a diagnostic challenge. Exploring the association between Patent Foramen Ovale and Chiari Network

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Introduction

Globally, strokes are the second leading cause of mortality,[1,2] and are broadly categorized into hemorrhagic and ischemic types.[1,2] In 2019, ischemic stroke accounted for 62.4% of all cases, totaling 7.63 million episodes.[1] Projections indicate a substantial increase in stroke prevalence, from 3.9% in 2020 to an estimated 6.4% by 2050.[3] Despite comprehensive etiological investigations, the underlying cause of cerebrovascular ischemic events remains undefined in 10% to 40% of the cases,[4] known as cryptogenic stroke.

Stroke is often a disabling condition and poses a major threat to the socioeconomic stability of a country, particularly in developing nations. The incidence of ischemic stroke has been increasing, particularly among individuals under 55 years of age.[5] Approximately 10% to 15% of all strokes manifest in young adults aged 18 to 49.[5,6] This trend underscores the critical importance of stroke prevention strategies, even within this younger demographic.[5]

Among the main risk factors for ischemic stroke, such as systemic arterial hypertension and atrial fibrillation, a growing association with patent foramen ovale (PFO) is gaining recognition. Although often considered clinically "innocent," PFO has been implicated in cryptogenic stroke,[7] especially in young adults.[7,8] Furthermore, given that 83% of the patients with a Chiari network also have a PFO,[9] several reported cases suggest that this specific concurrence of PFO and a Chiari network may substantially elevate the risk of ischemic stroke.

Case Report

A previously healthy 25-year-old man, with no history of smoking or illicit drug use, was admitted to the Emergency Room approximately 36 hours after the onset of right hemiparesis. Concomitant symptoms included dysarthria, aphasia, loss of consciousness, and sphincter incontinence. On examination, he exhibited dysarthria along with decreased motor strength in the right hemibody. Cardiopulmonary auscultation revealed no significant findings.

The initial non-contrast head Computed Tomography (CT) revealed no detectable abnormalities. Given the neurological symptomatology, further investigation required a Brain Magnetic Resonance Imaging (MRI) with intravenous contrast. The MRI demonstrated a T2 hyperintensity in the left corona radiata, immediately contiguous to the posterior limb of the ipsilateral internal capsule. This lesion showed no diffusion restriction, post-contrast enhancement, hemorrhage, or surrounding vasogenic edema, consistent with a previous ischemic vascular injury (Figure 1).

Following initial evaluations, a diagnostic workup was performed to determine the underlying etiology of his condition. A transthoracic echocardiogram (TTE) indicated preserved ventricular function. Subsequently, a bubble study with agitated saline, conducted through peripheral venous circulation, unequivocally demonstrated a right-to-left shunt, consistent with a PFO, along with an exuberant Chiari network (Figures 2 and 3). Doppler ultrasound studies of the carotid and vertebral arteries yielded normal results. Confirmation of both the PFO and the exuberant Chiari network was subsequently obtained via transesophageal echocardiogram (TEE). Notably, this study revealed a significant passage of microbubbles across the atrial septum into the left chambers, even at rest. The TEE also provided precise measurements for the PFO: a tunnel length of 10mm, with left and right atrial rims measuring 2mm and 3mm, respectively. The angle between the inferior vena cava and the PFO was also less than 10 degrees.

A chest computed tomography angiography (CTA) was performed to rule out pulmonary thromboembolism, showing normal findings. Additionally, a color Doppler ultrasound of the deep and superficial venous systems of the lower limbs showed no signs of deep vein thrombosis or venous insufficiency.

Further investigations included serological assays for HIV 1 and 2, syphilis, hepatitis B, and hepatitis C, all of which proved to be negative. The patient's lipid profile remained within target ranges, and thyroid function (TSH and free T4) was normal. A comprehensive thrombophilia investigation was also meticulously conducted. This included genetic testing for Factor V Leiden (r506q) and the prothrombin gene (g20210a), as well as the evaluation of homocysteine, anticardiolipin IgM and IgG antibodies, lupus anticoagulant, antithrombin III, functional protein C, and free protein S. All of these tests collectively yielded negative results, effectively ruling out the most common thrombophilias.

Keywords

Ischemic Stroke; Stroke; Patent Foramen Ovale

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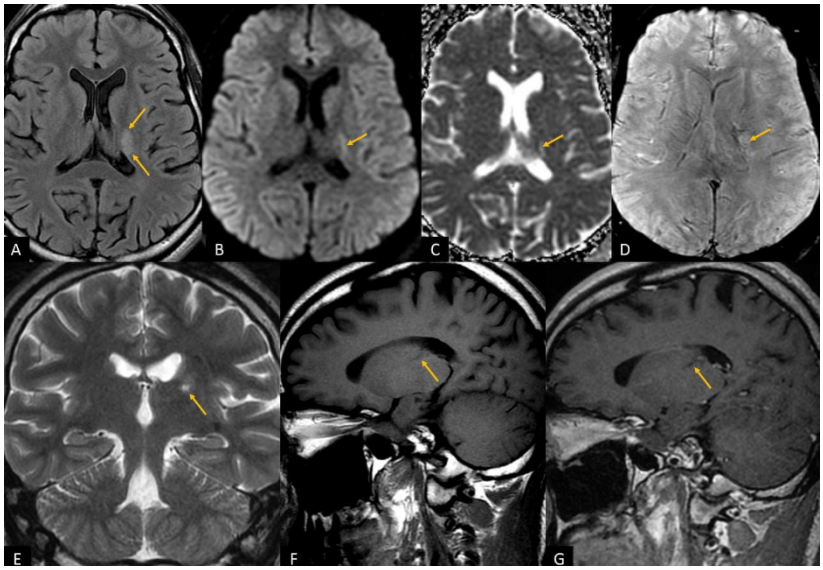

Figure 1 – *Brain MRI Findings. An area of T2-weighted hyperintensity is noted in the left corona radiata, immediately adjacent to the posterior limb of the ipsilateral internal capsule. This lesion shows no diffusion restriction, post-contrast enhancement, hemorrhage, or surrounding vasogenic edema, consistent with prior ischemic vascular injury. (A) FLAIR; (B) Diffusion-weighted imaging (DWI); (C) Apparent diffusion coefficient (ADC) map; (D) Susceptibility-weighted angiography (SWAN) / Gradient recalled echo (GRE) T2*; (E) Coronal T2-weighted image; (F) Sagittal T1-weighted pre-contrast image; (G) Sagittal T1-weighted post-contrast image.*

Percutaneous PFO closure was recommended for the patient and, due to a limited economic situation, he is awaiting the procedure through the public health system. He was discharged with instructions to use Rivaroxaban, 20 mg/day.

Discussion

The foramen ovale plays a fundamental role in maintaining intrauterine life[10,11] and is classified as a subclass of ostium secundum defects.[12] After birth, it typically undergoes functional closure due to changes in systemic and pulmonary pressure differentials. The Koutroulou review reported a PFO prevalence of approximately 24% across all age groups in the general population, based on autopsy and TEE studies.[13] Although often considered an incidental finding, PFO has been associated with cryptogenic stroke[8] and even less common conditions, such as migraine, peripheral embolism, and Alzheimer's dementia.[7]

Ioannidis et al. postulated that PFO in stroke patients might represent an incidental finding, a contributing risk factor, or even a direct causal agent.[14] Proposed mechanisms include paradoxical embolism, in situ thrombus formation, and arrhythmogenesis.[15] Hausmann et al. observed that patients presenting PFO and ischemic arterial events generally exhibit more pronounced right-to-left contrast shunts and larger PFO openings.[16] The SAFAS study indicated that decreased levels of galectin-3 and osteoprotegerin could potentially serve as biomarkers for PFO-related stroke.[17]

In 1897, Austrian pathologist Hans Chiari elucidated the presence of fibrous networks in the right atrium, later named the Chiari Network.[18] Autopsy studies have reported Chiari network prevalences ranging from 1.3% to 4%.[19-24] More contemporary echocardiographic techniques, notably TEE, have identified a 2% prevalence of the Chiari network among 1,436 individuals.[9] The same study revealed associations with PFO and atrial septal aneurysm (ASA) in 83% and 24% of patients with a Chiari network, respectively.[9] The Chiari network likely promotes the persistence of the PFO and may facilitate paradoxical embolism.

Manerikar et al. documented an occipital stroke in a 46-year-old man attributed to the combined presence of a Chiari network and PFO.[25] An additional finding in the case was a mass on the mitral valve consistent with a Lambl's excrescence.[25] Although its echocardiographic diagnosis is typically straightforward, it can occasionally be mistaken for thrombi in the right atrium.[26] The Chiari network itself can serve as a nidus for thrombus formation, potentially leading to a stroke when associated with a PFO through paradoxical emboli that cross from the right to the left atrium and subsequently enter systemic circulation.

The embolic potential of a PFO is primarily attributed to paradoxical embolism through its opening.[15,27] This occurs when a thrombus originating in the venous system

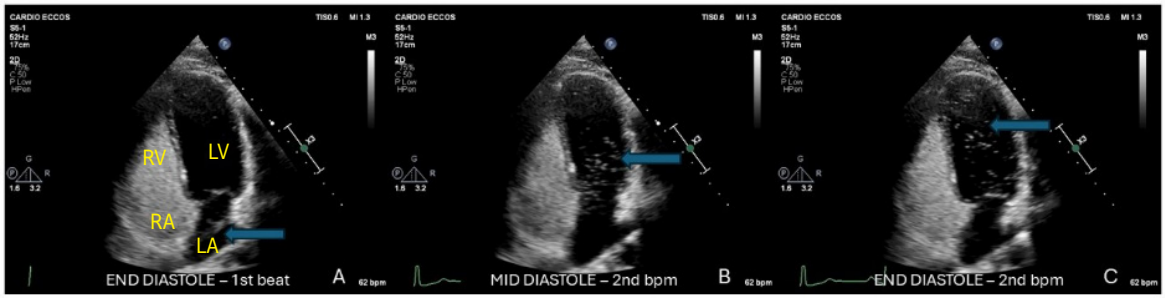

Figure 2 – *Transthoracic Echocardiogram (TTE): Apical 4-chamber view following intravenous infusion of agitated saline solution (microbubbles – blue arrow). (A) First cardiac cycle after opacification of the right chambers and microbubble passage into the left atrium at end-diastole; (B) Microbubbles passing through the opened mitral valve during mid-diastole of the second cycle; (C) Microbubbles within the left ventricle at end-diastole of the second cycle. RV: Right Ventricle; RA: Right Atrium; LV: Left Ventricle; LA: Left Atrium.*

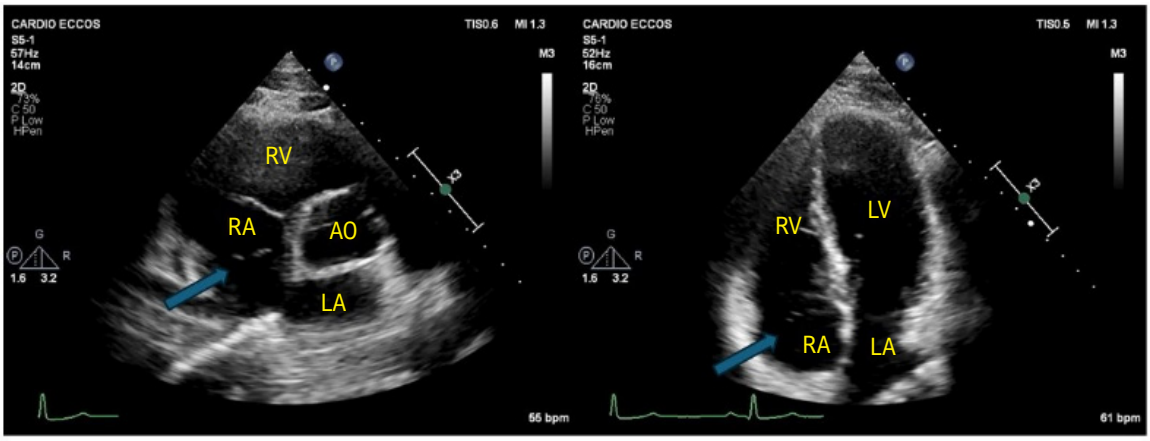

Figura 3 – *Transthoracic Echocardiogram (TTE): The exuberant Chiari network (blue arrow) is shown in (A) short-axis view and (B) apical 4-chamber view. RV: Right Ventricle, RA: Right Atrium, LV: Left Ventricle, LA: Left Atrium, AO: Aorta.*

bypasses pulmonary circulation, passes through the PFO to the left chambers, and subsequently embolizes to the brain, culminating in an ischemic stroke. In patients with a PFO, it is of utmost importance to verify the occurrence of a right-to-left shunt. This is most commonly performed via TTE or, with greater sensitivity, via TEE, both with an infusion of agitated saline. The visualization of microbubble passage from the right to the left atrium confirms the presence of the shunt between these chambers. Another tool is Transcranial Doppler (TCD), which is highly sensitive but cannot differentiate between cardiac and pulmonary shunts. It is the best method to quantify the severity of the shunt, as it is more sensitive than either the TTE or the TEE.[28]

The CLOSE study recommends that after a PFO-associated stroke, secondary prevention is necessary, with options including antiplatelet therapy, anticoagulation, and percutaneous PFO closure, the latter being superior to antithrombotic therapy (antiplatelets or anticoagulants) in preventing new strokes in individuals who have had a cryptogenic stroke.[29] The indication for percutaneous PFO closure is strongest in young patients (up to 60 years), after a cryptogenic ischemic stroke, and especially in the presence of high-risk features, such as an Atrial Septal Aneurysm or a large volume shunt.[30]

Conclusions

Ischemic stroke, particularly when it occurs in young adults, requires an exhaustive etiological investigation. In the present case, the patient's symptoms manifested beyond the window for thrombolysis. The detection of a PFO on both the TTE and the TEE initially suggested a paradoxical embolism, a recognized cause of ischemic stroke. However, the absence of clinical signs or venous Doppler findings indicative of current or previous deep vein thrombosis made this hypothesis less likely, although certainly not excluded.

zOther potential etiologies, such as thrombophilia, were systematically ruled out. The TTE confirmed normal cardiac chamber dimensions and the absence of valvular abnormalities. The 12-lead ECG and 24-hour Holter monitoring were normal, thus ruling out arrhythmias, particularly atrial fibrillation, as the cause of the ischemic stroke.

Therefore, a plausible mechanism for the pathophysiology of the ischemic stroke in this patient (Figure 4), which finds support in the existing literature, involves the in situ formation of a thrombus within the Chiari network, its subsequent passage from the right atrium to the left atrium through the PFO, and the resulting embolization to the carotid system and brain.

Author Contributions

Conception and design of the research: Frota RS, Passos MD, França LS.

Acquisition of data: Frota RS, Passos MD, Santos SN, França LS.

Analysis and interpretation of the data: Frota RS, Passos MD, Santos SN, Alves LM, França LS.

Writing of the manuscript: Frota RS, Passos MD, Santos SN, Alves LM, Ferreira DP, França LS.

Critical revision of the manuscript for intellectual content: Frota RS, Passos MD, Santos SN, Alves LM, Ferreira DP, França LS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Critical revision of the manuscript for intellectual content

This study was approved by the Ethics Committee of the Fundação de Ensino e Pesquisa em Ciências da Saúde – FEPECS/SES/DF under the protocol number 83023524.0.0000.5553. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

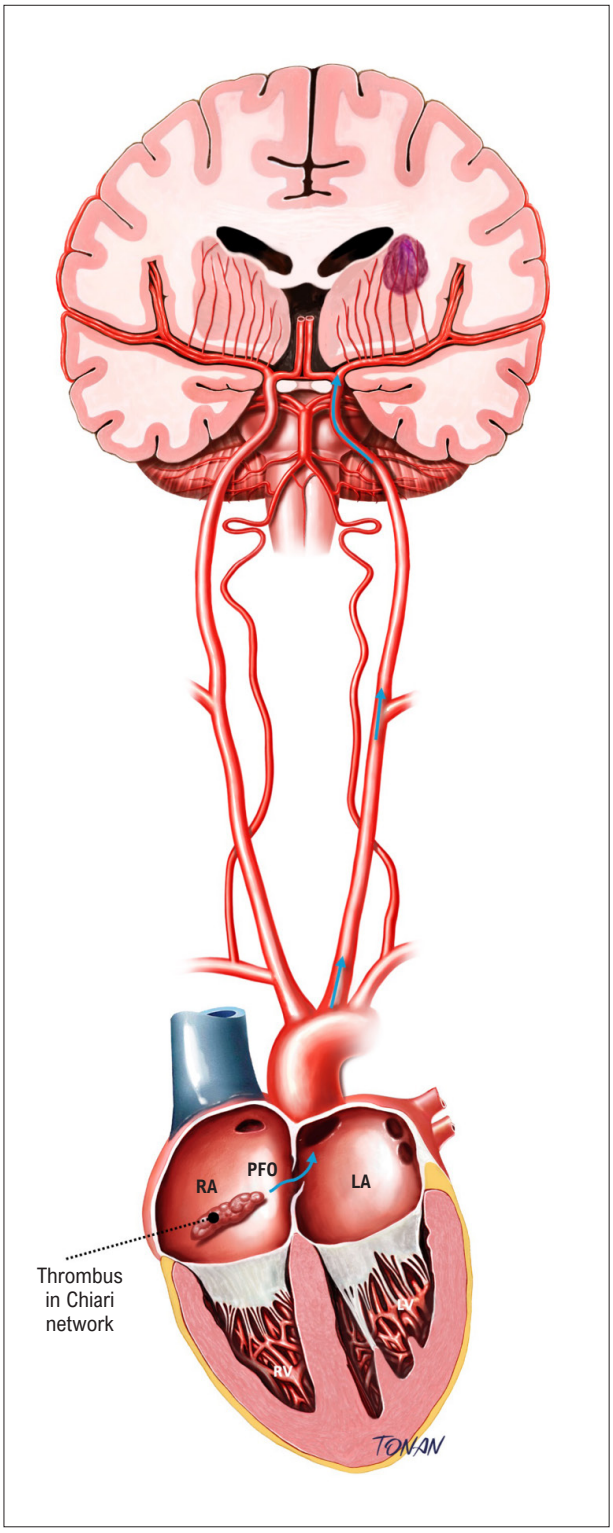

Figure 4 – *Proposed Pathophysiology of Stroke. This illustration elucidates the probable mechanism of the patient's ischemic stroke: the genesis of a thrombus within the Chiari network, its subsequent paradoxical embolization from the right atrium (RA) to the left atrium (LA) through the patent foramen ovale (PFO), and its ultimate transit to the left carotid system and brain, precipitating the ischemic stroke. (Medical illustration by Rodrigo Tonan).*

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