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Case Report

Ischemic Stroke in a Child with Sickle Cell Anemia, Patent Foramen Ovale and Moya-Moya Syndrome: The Challenges of Implementing a Secondary Prevention Strategy

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Abstract: Strokes, traditionally regarded as conditions affecting adults, can also occur in the pediatric population, where their rarity often delays diagnosis. This report describes the case of a seven-year-old boy with sickle cell anemia who was admitted with left-sided motor deficits. The patient had been febrile and recumbent the previous day. Laboratory tests revealed severe anemia (hemoglobin 6.7 g/dL). During hospitalization, a transthoracic echocardiogram identified a patent foramen ovale (PFO) with left-to-right atrial flow and dilation of the left heart chambers. Brain imaging revealed lesions in the vascular border zones, while cerebral angiography confirmed severe stenosis in the internal carotid artery and a Moyamoya pattern. Following an etiological investigation, the symptoms were attributed to an ischemic stroke. Empirical antimicrobial therapy, blood transfusions, and antiplatelet therapy were initiated. Two potential mechanisms for the stroke were identified: PFO and Moya-Moya syndrome (MMS). The coexistence of these rare conditions in a pediatric patient presented unique diagnostic and therapeutic challenges. MMS was considered the primary cause of the stroke due to characteristic imaging findings and the patient's history of sickle cell anemia. This case highlights the complexities of managing pediatric strokes with dual pathologies and the importance of a multidisciplinary approach. It advances clinical understanding by demonstrating how PFO complicates secondary prevention in MMS and emphasizes the need for individualized treatment strategies and long-term follow-up to optimize outcomes.

Keywords: Moya-Moya Disease; Anemia, Sickle Cell; Ischemic Stroke; Secondary Prevention.

1. Introduction

Moya-Moya disease (MMD) is a chronic cerebrovascular condition characterized by progressive narrowing of the distal internal carotid arteries (ICA) and proximal branches, leading to the formation of abnormal collateral vessels, referred to as "moyamoya" due to their puff-of-smoke appearance on angiography [1]. Moyamoya syndrome (MMS) differs from MMD by being a secondary vasculopathy associated with underlying conditions such as sickle cell disease, Down syndrome, or neurofibromatosis type 1 [2]. The clinical presentation of MMS can vary, with ischemic strokes being the most frequent neurological manifestation in pediatric patients. The primary treatment goals for MMS include aug-

menting cerebral blood flow through revascularization procedures and alleviating hemodynamic stress on compromised moyamoya vessels, which reduces the risk of ischemic events [2].

Patent foramen ovale (PFO) is an incidental finding in approximately 20–25% of the general population, resulting from the failure of the foramen ovale to close after birth. This condition typically remains asymptomatic and is diagnosed during echocardiographic evaluation, particularly in individuals with cryptogenic strokes or other embolic events [3]. Although isolated PFO is often benign, it may predispose patients to paradoxical embolism, especially in the presence of hypercoagulable states, such as sickle cell disease [3]. This paradoxical right-to-left shunting can significantly increase the risk of ischemic stroke in vulnerable populations. Contrast transthoracic echocardiography is the preferred diagnostic tool in pediatric patients due to its high sensitivity and the elimination of the need for general anesthesia [4].

The coexistence of MMS and PFO in pediatric patients is exceedingly rare and poses unique challenges for clinicians. The diagnostic complexity arises from the overlapping risk factors for ischemic stroke, making it difficult to attribute the event to a single underlying cause. Furthermore, the management strategies for these conditions can diverge, with MMS often requiring surgical revascularization and PFO closure being debated in pediatric populations. While current guidelines do not advocate routine PFO closure for primary stroke prevention in children, individualized assessments may be warranted in select cases, particularly when recurrent embolic events occur despite optimal medical therapy [3].

A comprehensive review of the literature reveals that while both MMS and PFO have been extensively studied independently, their coexistence is poorly documented, particularly in pediatric populations. MMS, being a progressive condition, often leads to recurrent ischemic events without timely intervention, whereas PFO-related strokes are typically embolic in nature. Studies on PFO in children primarily focus on cryptogenic strokes, with limited emphasis on its coexistence with other significant cerebrovascular disorders [5,6]. This gap in the literature highlights the importance of reporting such cases to enhance clinical understanding and guide management strategies in similar scenarios.

This report presents the case of a seven-year-old boy with sickle cell anemia who experienced an ischemic stroke and was subsequently diagnosed with both MMS and PFO. The dual presence of these conditions posed significant challenges in establishing stroke etiology and determining the most appropriate management approach. Both conditions independently carry the potential for severe neurological outcomes, and their coexistence necessitates a multidisciplinary approach to optimize patient care.

The rarity of this coexistence, combined with the diagnostic and therapeutic dilemmas it presents, underscores the need for a detailed case discussion. This case aims to fill the gap in the current literature by providing insights into the diagnostic approach, clinical management, and potential outcomes of pediatric patients with MMS and PFO. Through this report, we seek to offer a valuable reference for healthcare professionals navigating similarly complex cases, ultimately contributing to the development of evidence-based guidelines for managing dual cerebrovascular conditions in children.

In conclusion, the coexistence of MMS and PFO in pediatric patients represents a rare but significant clinical scenario requiring a nuanced approach. The challenges of differentiating between potential etiologies of ischemic stroke, coupled with the need for tailored treatment strategies, highlight the importance of interdisciplinary collaboration. This case provides a foundation for further research and discussion, emphasizing the need for heightened awareness and a systematic approach to such complex clinical presentations.

2. Case Report

The patient was a 7-year-old boy of African descent from São Paulo, Brazil, with sickle cell anemia and a history of ischemic strokes in June and July 2023 (Table 1). He had

been followed irregularly at the pediatric hematology outpatient clinic and was already indicated for exchange transfusions. On the day of admission, his mother reported that, upon awakening, he exhibited left-sided weakness, particularly in his left leg, along with difficulty walking, paleness, and drowsiness.

Table 1. Timeline of Clinical Events.

Date	Event
Birth	Diagnosis of sickle cell anemia
June 2023	First ischemic stroke
July 2023	Second ischemic stroke
August 2023	Current hospitalization for neurological symptoms

On physical examination, the patient was underweight, pale (2+/4+), anicteric, tachydyspneic, and febrile (39.3°C). He had symmetrical carotid pulses, was drowsy, and presented with incomplete disproportionate left-sided hemiparesis, accompanied by an ipsilateral Babinski's sign. There were no meningeal signs, and the remaining neurological examination was unremarkable (Table 2).

Table 2. Neurological tests during hospital admission.

Exams	Results
CSF	Clear
Glucose	63 mg/dL
Proteins	52 mg/dL
Leukocytes	2.6/mm³
Bacteria culture	Negative

CSF. Cerebrospinal Fluid.

Further laboratory evaluation revealed anemia (hemoglobin 6.7 g/dL) and leukocytosis (10,800 cells/mm³) with a left shift (Table 3). Urine sediment analysis was normal.

Table 3. Blood count parameters during hospital admission.

Blood count parameters	Values
Hb	6.7 g/dL
Leukocytes	10,800/mm³
Rods	648/mm³
Segmented	4,212/mm³
Platelets	192,000/mm³
C-reactive protein	39.7 mg/L
Blood culture	Negative

Cerebrospinal fluid analysis revealed hyperproteinemia (52 mg/dL), and brain MRI showed hypersignal areas in the right temporoparietal region and left semi-oval center with restricted water diffusion (Figures 1A and 1B). Additionally, gliosis was observed in the right basal nuclei. Cerebral angiography revealed severe stenosis in the ICA (70%), M1 segments of the middle cerebral artery, A1 segments of the right anterior cerebral artery, and 80% stenosis in the left anterior cerebral artery, consistent with a Moyamoya pattern (Figure 2).

Figure 1. A. Axial Flair MRI sequence showing hypersignal. B. MRI showing hypersignal in diffusion sequence with restriction of water molecules, typical of a stroke.

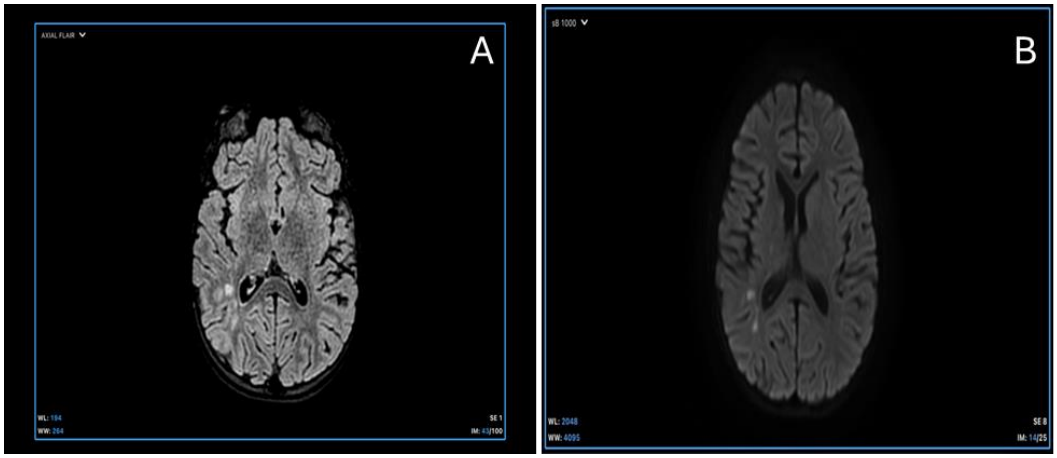
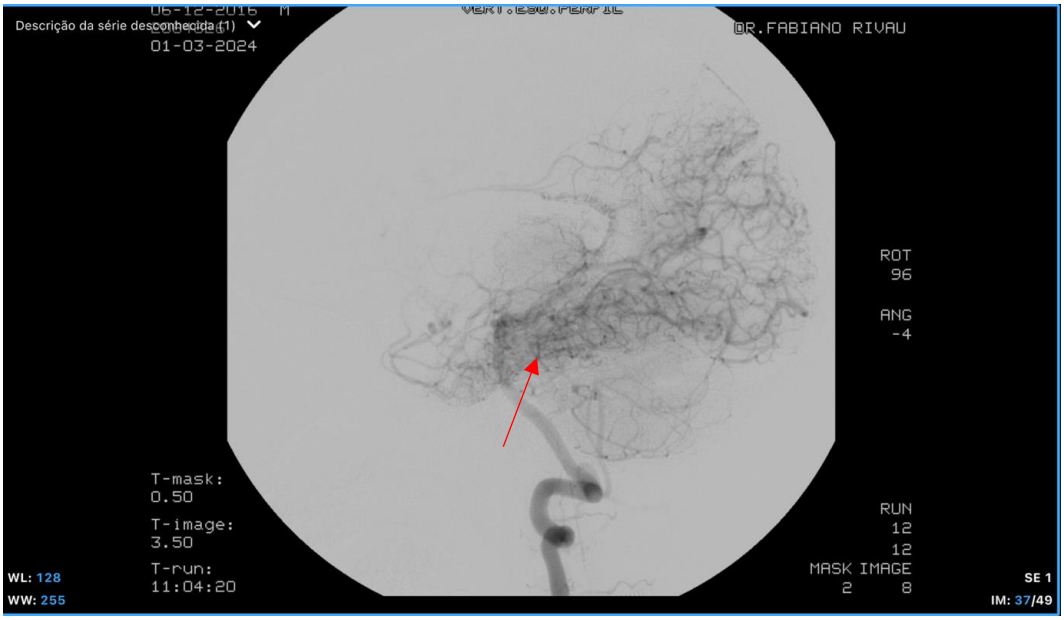


Figure 2. Cerebral angiography by catheterization of the femoral artery shows a "smoke-like" pattern (arrow), typical of the presence of Moyamoya syndrome (MMS).



2.1 Differential Diagnosis Discussion

The neurological findings, including restricted water diffusion and the Moyamoya pattern, align with ischemic stroke secondary to MMS. However, differential diagnoses such as vasculitis, thrombotic conditions, or metabolic encephalopathies were considered. Unlike MMS, vasculitis often presents with arterial wall thickening and diffuse involvement, while thrombotic events typically affect venous structures. The absence of infectious markers further supported the diagnosis of MMS combined with PFO, underscoring the importance of a comprehensive diagnostic approach.

2.2 Treatment and Prognosis

During hospitalization, the patient was treated with ceftriaxone for a suspected central nervous system infection, exchange transfusions, aspirin (ASA), and captopril to manage blood pressure. A transthoracic echocardiogram revealed a patent foramen ovale (PFO) with left-to-right atrial flow and left ventricular dilation. He received antibiotics

and a blood transfusion, remaining hospitalized for 24 days. Following discharge, the patient exhibited a complete resolution of neurological deficits. He continued with regular exchange transfusions for sickle cell disease and was referred for cardiology follow-up.

One-month post-discharge, the patient was evaluated by a cardiologist, who recommended conservative management. Meanwhile, a neurosurgeon proposed endovascular revascularization to address the Moyamoya syndrome. The hematologist maintained the patient on ASA 50 mg, monthly blood transfusions, and continuous folic acid supplementation. The patient remained asymptomatic during follow-up. The patient remained asymptomatic following discharge, with no reported neurological deficits or complications. However, the duration of follow-up to substantiate this claim was limited to one month after discharge. While the initial recovery was favorable, longer-term monitoring is crucial to evaluate the stability of clinical outcomes and the efficacy of the management strategy. Regular follow-up visits, including neurological and cardiological assessments, are essential to identify potential recurrence or late complications.

Future reports should prioritize detailing the duration and scope of follow-up to provide a comprehensive understanding of long-term outcomes in similar cases. This would enhance the credibility of the findings and offer valuable insights for optimizing secondary prevention strategies in patients with dual pathologies like MMS and PFO.

3. Discussion

This case demonstrates the complexities of managing ischemic stroke in a pediatric patient with concomitant MMS and PFO. Differentiating the primary etiology was particularly challenging, as both conditions independently increase stroke risk. Ultimately, the diagnosis of MMS as the primary cause was supported by specific imaging findings, such as severe ICA stenosis, vascular border zone lesions, and the characteristic "smoke-like" collateral pattern on angiography [1,2]. These findings, combined with the patient's history of sickle cell anemia and severe anemia on admission, strongly suggested MMS as the underlying cause.

The coexistence of PFO introduced additional complexity. PFO is associated with paradoxical embolism, especially in hypercoagulable states like sickle cell disease. This dual pathology necessitated careful consideration of antiplatelet therapy and potential PFO closure [3]. However, current evidence for the efficacy of PFO closure in pediatric stroke remains limited, emphasizing the need for individualized management plans.

Comparing this case to other reported instances highlights key differences. For example, in a 25-year-old patient with coexisting MMD and PFO, significant shunt contrast and membrane mobility were identified as contributors to stroke [9]. Such findings underscore the importance of advanced imaging techniques, such as transesophageal echocardiography, to better stratify PFO severity. Furthermore, transcranial Doppler could have provided valuable data on cerebral hemodynamics and microembolic events [6,10].

Differential diagnoses considered included cerebral vasculitis, metabolic encephalopathies, and thrombotic conditions. Vasculitis, often characterized by diffuse arterial wall thickening, was ruled out due to the lack of systemic inflammatory markers and the distinct angiographic pattern observed in MMS [7]. Similarly, the absence of metabolic derangements and venous involvement excluded other potential causes.

The interaction between PFO and MMS complicates both diagnosis and treatment. While MMS is primarily managed with revascularization, PFO introduces the risk of embolic events, warranting antiplatelet therapy or, in select cases, closure. The role of PFO in this case was further complicated by the patient's hypercoagulable state, which increases the risk of recurrent ischemic events. Studies suggest that managing these conditions concurrently requires a delicate balance to avoid exacerbating one pathology while addressing the other [4].

Emerging evidence highlights the need for a multidisciplinary approach in such cases. For instance, antiplatelet therapy, though effective in reducing embolic risks asso-

ciated with PFO, has uncertain benefits post-revascularization for MMS [8]. This underscores the importance of tailoring management strategies to each patient's unique clinical profile.

4. Conclusion

This case underscores the complexities of managing ischemic stroke in pediatric patients with coexisting Moyamoya syndrome (MMS) and patent foramen ovale (PFO). Differentiating the primary cause of the stroke posed a significant challenge, given that both conditions independently increase the risk of ischemic events. In this instance, the diagnosis of MMS as the primary cause was supported by characteristic imaging findings, clinical history, and risk factors. The presence of PFO further complicated management decisions, particularly regarding the use of antiplatelet therapy and the consideration of PFO closure.

A structured, multidisciplinary approach is essential for the management of such cases. This includes advanced diagnostic modalities, such as transcranial Doppler and transesophageal echocardiography, to better assess cerebral hemodynamics and PFO severity. Revascularization surgery remains the cornerstone of MMS management, while the decision to pursue PFO closure should be individualized based on clinical and imaging findings.

Future research should aim to establish evidence-based guidelines for managing dual pathologies like MMS and PFO. Emerging diagnostic tools and therapeutic advancements may further enhance clinical decision-making, ultimately improving patient outcomes. By sharing experiences and critically analyzing similar cases, healthcare professionals can refine strategies for secondary stroke prevention and optimize long-term care in these complex scenarios.

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