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Case Report

A 13-Month-Old Iranian Boy with Thrombosis of the Left Transverse and Superior Sagittal Sinuses Due to Homozygous Mutations in MTHFR A1298C: A Case Report & Review of Literature

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Abstract

Background and Aim: Cerebral sinus venous thrombosis (CSVT) is a rare stroke subtype in children, with limited data on its clinical presentation, etiology, and outcomes. This case report aims to describe a case of CSVT in a child, including their clinical presentation, imaging findings, and management, to increase awareness of this rare but serious condition.

Case presentation: A 13-month-old boy presented with swelling and deviation of the left eye after being hospitalized for left periorbital cellulitis. The patient was diagnosed with thrombosis of the left transverse and superior sagittal sinuses and underwent treatment with levetiracetam, folinic acid, rosuvastatin and enoxaparin followed by warfarin. Genetic testing was also performed to identify the underlying genetic basis of thrombophilia.

Results: Laboratory tests showed that there was one heterozygous mutation in the β-Fibrinogen gene and three homozygous mutations in MTHFR A1298C, PAI-I-675 4G/5G, and PAI-I-844 G/A genes. Additionally, Lipoprotein (a) was measured at 89.3 nmol/L and the patient's mother had two homozygous mutations in PAI-I-675 4G/5G and PAI-I-844 G/A genes.

Conclusions: It appears that the mutation in MTHFR gene is more prevalent in our region, which may be a contributing factor to the increased incidence of stroke in children and adolescents in the country. Further research is needed to determine the prevalence of this mutation and its impact on thrombophilia in the population. This case highlights the importance of prompt diagnosis and treatment of CSVT in children, as well as the need for genetic counselling and testing to identify underlying risk factors.

***Keywords:** cerebral sinus venous thrombosis, Pediatric Stroke, MTHFR gene defect.*

Introduction

With an estimated incidence of 0.67 incidences per 100,000 children per year, cerebral sinus venous thrombosis (CSVT) is a rare stroke subtype in children (1).

It is a complex condition with both acquired and inherited risk factors, including trauma, dehydration, cardiac or hematological disorders, and infection (especially of the head and neck, such as otitis media, sinusitis, meningitis, and mastoiditis) (1, 2). Infectious sinus thrombosis has been shown to be more common in children than in infants (3, 4). CSVT affects both the dural sinuses and the cortical and deep cerebral veins, and can present with a range of clinical manifestations, including seizures, headache, encephalopathy, and vomiting. Although focal neurological deficits are uncommon, optic nerve ischemia and papilledema can occur (5, 6).

The etiology of CSVT is not fully understood, but at least one abnormality was found in one-third of children with CSVT who were screened for prothrombotic disorders. In some studies, the most prevalent genetic disorder is factor V Leiden, while anti-cardiolipin antibody is the most prevalent acquired disorder (5,7). Elevated factor VIII levels, whether genetic or acquired, pro-thrombin G20210A mutation (F2 mutation) or homozygosity for the MTHFR mutation (A1298C/C677T mutation) polymorphism are also risk factors, though results vary across studies (8-13,15).

Given the rarity of the condition, there is limited data on the clinical presentation, etiology, and outcomes of CSVT in children (12).

This case report aims to describe a case of CSVT in a child, including their clinical presentation, imaging findings, and management. By sharing this case, we hope to increase awareness of this rare but serious condition and contribute to the growing body of knowledge on CSVT in children.

Case Presentation

A 13-month-old boy was admitted to Imam Hossein Medical & Educational Center, complaining of swelling and deviation of the left eye, which had begun 2 days prior. He was the second child of consanguineous marriage. The patient had been hospitalized a week earlier for pneumonia and left otitis media, which had been treated with intravenous (IV) ceftriaxone and vancomycin. On this occasion, he was referred to us for left periorbital cellulitis.

On examination, the patient had sixth nerve palsy in the left eye and had undergone debulking surgery for orbital abscess and FESS (Functional endoscopic sinus surgery), and was treated with meropenem, vancomycin, linezolid, and clindamycin. Four days later, the physicians consulted us with the suspicion of thrombosis on the patient's brain MRI. The ECG and echocardiogram were normal.

As a first step, the patient was given enoxaparin ($1_{mg/kg}$ subcutaneously every 12 hours), folinic acid ($3_{mg/kg}$ IV every 12 hours), and levetiracetam (20 mg/kg IV every 12 hours), and laboratory tests were requested to assess thrombophilia. After MRA and MRV, left transverse and superior sagittal sinus thrombosis on the patient's brain neuroimaging was confirmed. (Fig1: a, b, c, d).

seven days later, the patient was administered warfarin (0.5 mg/kg/day), and enoxaparin was discontinued when the INR was between 2-3.

To clarify the underlying genetic basis of thrombophilia in this family, the patient and his parents were referred for genetic counseling and testing. After obtaining informed consent in accordance with the Declaration of Helsinki principles, EDTA-anticoagulated peripheral blood samples were collected from the patient, and DNA was extracted. The results of laboratory tests showed that there was one heterozygous mutation in the β- Fibrinogen gene and three homozygous mutations in MTHFR A1298C, PAI-I-675 4G/5G, and PAI-I-844 G/A genes. Additionally, Lipoprotein (a) was measured at 89.3 nmol/L, which was significantly higher than the cut-off value for the presence of increased risk of CVD/CHD based on the Framingham study. Based on the abnormal findings in the child's tests, genetic testing was also performed on the parents' blood samples, and the results are summarized in Table 1.

MRV with contrast revealed that the left transverse sinus & superior sagittal sinus were almost completely opened 40 days after initiating treatment with subcutaneous enoxaparin followed by oral warfarin (Fig2: a, b, c).

Currently, the child is under further observation and treatment with syrup levetiracetam (15 mg/kg every 12 hours), folinic acid (15 mg daily), rosuvastatin (5 mg daily) and warfarin (5 mg daily), and INR is checked weekly. After 3 months of warfarin treatment, we changed it to rivaroxaban (2.5 mg daily).

After more than 6 months of follow-up, the child's general condition is very good, and the seizures have not recurred. Additionally, the deviation of the left eye has been resolved.

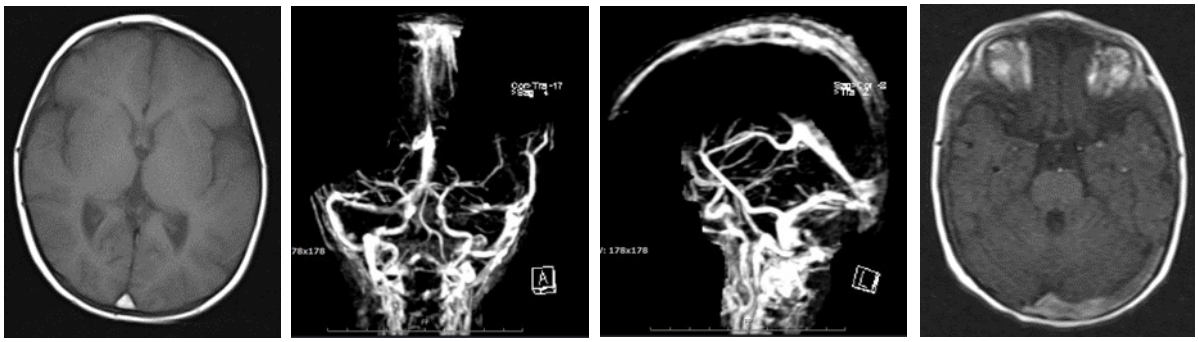

Fig. 1: A: *Empty Delta Sign in T1 weighted image* ***B, C, D:*** *The first MRV & SWI of the patient showed severe involvement of the superior sagittal sinus and the left transverse sinus.*

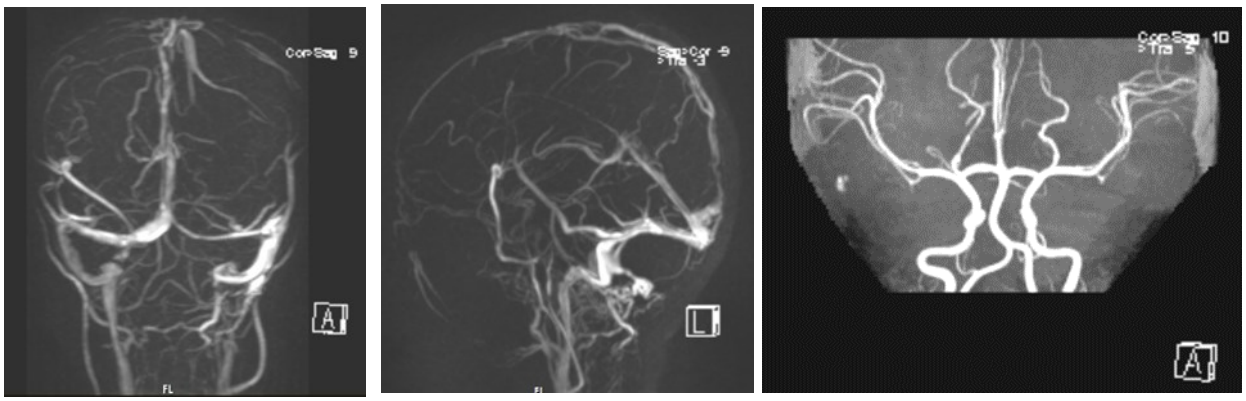

Fig. 2: A: *MRV with contrast revealed that the left transverse sinus was almost completely opened 40 days after initiating treatment with subcutaneous enoxaparin followed by oral warfarin.*
B: *MRV with contrast showed that the superior sagittal sinus was almost completely open 40 days after initiating treatment with subcutaneous enoxaparin followed by oral warfarin.*
C: *The arterial vessels and the circle of Willis appear healthy.*

Table 1: Molecular Detection of Multiple Hereditary Factors for Thrombophilia & Cardiovascular Diseases (CVD) in patient and his family.

Marker	Patient	Mother	Father
ß- Fibrinogen	Mutated, Heterozygous	Wild Type, Normal	Mutated, Heterozygous
Factor V Leiden G506A	Wild Type, Normal	Not requested	Not requested
Factor V HR2	Wild Type, Normal	Not requested	Not requested
MTHFR C677T	Wild Type, Normal	Wild Type, Normal	Mutated, Heterozygous
MTHFR A1298C	Mutated, Homozygous	Mutated, Heterozygous	Mutated, Heterozygous
Prothrombin G20210	Wild Type, Normal	Not requested	Not requested
PAI-I-675 4G/5G	Mutated, Homozygous	Mutated, Homozygous	Mutated, Heterozygous
PAI-I-844 G/A	Mutated, Homozygous	Mutated, Homozygous	Mutated, Heterozygous
Lipoprotein (a) (nmol/L)	89.3	20.6	236

Discussions

Cerebral sinus venous thrombosis (CSVT) is a rare and complex condition that can be difficult to diagnose and manage in children (1-9, 11-12). In this case report, we presented a case of CSVT in a 13-month-old boy with a history of pneumonia and left otitis media who presented with swelling and deviation of the left eye. This case highlights the importance of considering CSVT in the differential diagnosis of pediatric patients with a recent history of infection.

The etiology of CSVT is multifactorial and can be both acquired and inherited (5,12). In this case, the patient had a history of pneumonia and left otitis media, which are known risk factors for CSVT. The patient's laboratory results showed heterozygous mutation in the β- Fibrinogen gene and three homozygous mutations in MTHFR A1298C, PAI-I-675 4G/5G, PAI-I-844 G/A genes, which may also contribute to the development of CSVT (5-6,12-14). Therefore, clinicians should consider screening for prothrombotic disorders in children with CSVT to identify any underlying genetic or acquired risk factors (5,15). It appears that the mutation in MTHFR gene is more prevalent in our region, which may be a contributing factor to the increased incidence of stroke in children and adolescents in our country. Ongoing research is being conducted to further investigate this potential association (6,10-13).

The clinical presentation of CSVT in children can be variable, and the diagnosis can be challenging (5-6,12). In this case, the patient presented with sixth nerve palsy in the left eye and underwent debulking surgery for orbital abscess and FESS. However, the physicians suspected CSVT when MRI showed thrombosis of the left transverse and superior sagittal sinuses. Therefore, it is crucial for clinicians to have a high index of suspicion for CSVT in children with neurological symptoms, especially those with a recent history of infection, inflammation, trauma, or dehydration and prothrombotic states (5,6).

The management of CSVT in children involves anticoagulation therapy to prevent further thrombus formation and reduce the risk of complications such as stroke (3-6,8,12). In this case, the patient was initially treated with enoxaparin, folinic acid, and followed by warfarin when the INR was between 2-3. It is essential to monitor the INR closely to prevent bleeding complications associated with anticoagulation therapy (2,10,11,15).

Genetic counseling and testing are recommended for children with CSVT to identify any underlying genetic risk factors and provide appropriate management and follow-up. The identification of any homozygous mutations may have implications for the patient's future health and the management of any future thrombotic events (10,16).

Conclusion

CSVT is a rare but serious condition in children that can have a variable clinical presentation and be challenging to diagnose and manage. This case report highlights the importance of considering CSVT in the differential diagnosis of pediatric patients with neurological symptoms, especially those with a recent history of infection. It also emphasizes the need for screening for prothrombotic disorders in children with CSVT and the importance of genetic counseling and testing to identify any underlying genetic risk factors.

Conflict of Interest

The authors declare no conflict of interest.

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