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CASE REPORT

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Navigating thrombotic terrain: unveiling a novel homocystinuria mutation associated with thrombophilia in a 16 year old

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Abstract

Background Thrombophilia is characterised by an abnormality of blood coagulation that increases thrombosis. Homocystinuria encompasses a group of disorders marked by increased levels of homocysteine and other amino acids detectable in the bloodstream and urine. Conversely, homocystinuria due to methylenetetrahydrofolatereductase (MTHFR) deficiency, a rarer disorder, stems from impaired folate metabolism due to deficient MTHFR enzyme.

Case presentation A 16-year-old boy presented with walking difficulties, headaches, and thrombotic events, thrombophilia workup led to a diagnosis of homocystinuria due to a novel mutation in MTHFR gene. Anticoagulant therapy was initiated which showed clinical improvement, but financial constraints hindered follow-up.

Conclusions This case highlights the complexities of diagnosing and treating paediatric thrombophilia, particularly in resource-limited settings. Notably, the identified homozygous autosomal recessive (AR) missense variation in the MTHFR gene (Exon 4—c582C>G) represents a novel mutation, suggesting the ongoing significance of genetic research in elucidating the underlying mechanisms of thrombotic disorders.

Keywords Anticoagulation, Methylcobalamin, MTHFR, Thrombophilia, Thrombosis

Background

Thrombophilia is characterised by an abnormality of blood coagulation that increases thrombosis. Homocystinuria encompasses a group of disorders marked by increased levels of homocysteine and other amino acids detectable in the bloodstream and urine. They present with diverse symptoms, including neurological manifestations, premature arteriosclerosis, and venous and arterial thrombotic events (Shay et al. 2007). The primary genetic form arises from the deficiency of the cystathionine beta-synthase (CBS) enzyme. Conversely, homocystinuria due to methylenetetrahydrofolatereductase (MTHFR) deficiency, a rarer disorder, stems from impaired folate metabolism due to deficient MTHFR enzyme.

While newborn screening can detect homocystinuria, diagnosing the rare variety is challenging—particularly in cases presenting later in life. Dietary modifications and vitamin supplementation have been used with ongoing research on enzyme replacement (Shay et al. 2007). This study highlights a novel genetic variant of homocystinuria in the MTHFR gene.

Case presentation

A 16-year-old boy, born to a non-consanguineous couple with an unremarkable birth and development history, presented with a one-year history of walking difficulties accompanied by pain that radiated to his groin area with an antalgic gait. The pain would alleviate after rest, and he also encountered difficulties rising from a seated position. No weakness in the upper limbs was reported.

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Additionally, he had experienced past episodes of intermittent lower limb swelling and headache. Notably, he experienced paraparesis following a fall in the past. He was evaluated outside for the same, and imaging studies (computed tomography of the brain and magnetic resonance imaging (MRI) of the spine) were performed to exclude any central nervous system (CNS) pathology and revealed no significant findings. Following this, as his symptoms persisted, he presented to us. The clinical examination indicated findings consistent with an upper motor neuron lesion. Hence, he was admitted for a workup of the same. It was noted that the mother also had paraplegia and was wheelchair-bound due to Schwannoma.

During his hospitalisation, an MRI of the brain revealed a bleed in the bi-thalamic regions and venous thrombosis involving the superior sagittal sinus and deep cerebral veins. Prompted by the history of intermittent lower limb swelling, venous Doppler of lower limbs revealed bilateral deep vein thrombosis (DVT). Consequently, the coagulation profile indicated an elevated activated partial thromboplastin time (aPTT) and international normalised ratio (INR) (Prothrombin time—17.3 s, aPTT—85.3 s, INR—1.2). However, Warfarin therapy was initiated with dose adjustment based on INR values.

Considering a deranged coagulation profile with evidence of thrombosis, a detailed thrombophilia-based etiological workup was planned; however, considering cost-effectiveness, whole exome sequencing was performed. The results unveiled a homozygous AR missense variation in the MTHFR gene (Exon 4—c582C>G), affirming a diagnosis of homocystinuria due to MTHFR deficiency with AR inheritance. The child was started on vitamin B12 at 1000mcg per day for two weeks, followed by 1000mcg weekly along with folate at 0.4 mg per day along with dietary modification, and anticoagulation with warfarin was continued and was doing well for two months but failed to follow up.

Conclusions

The incidence of childhood thrombosis is 0.07–0.14 per 10,000 (Celkan and Dikme 2018). Children with thrombophilias have an elevated risk of developing complications like deep vein thrombosis, pulmonary embolism, and other clot-related complications. Thrombophilia involves multiple factors, comprising both congenital and acquired risk factors. MTHFR plays a crucial role in synthesising 5-methyltetrahydrofolate, a key methyl donor for remethylating homocysteine to methionine. Severe MTHFR deficiency manifests as an autosomal recessive disorder associated with severe hyperhomocysteinemia and homocystinuria, leading to various neurological and vascular complications such as developmental delay, mental retardation, seizures, motor and gait abnormalities, and thromboses (Sibani et al. 2003). Milder forms of the condition have been described and are associated with higher residual enzyme activity, later symptom onset, and predominantly psychiatric symptoms, intellectual disability, and movement disturbances (Goyette et al. 1995).

Exome sequencing of our case demonstrated homocystinuria due to MTHFR deficiency, caused by a mutation on Exon 4, identified as a homozygous autosomal recessive variant c.582C>G (p.lle194Met), a novel finding, not previously reported. Our case demonstrated MTHFR deficiency contributing to thrombophilia, necessitating anticoagulation therapy.

As per the American College of Chest Physician guidelines, anticoagulation therapy is recommended for at least three months in children with provoked venous thromboembolism (VTE), with an extension to 12 months or lifelong if the underlying risk factor persists (Monagle and Newall 2018). The primary conventional anticoagulants include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and vitamin K antagonists (VKA). UFH is typically reserved due to concerns over long-term osteoporosis risk. LMWHs, such as enoxaparin, have emerged as the preferred choice over UFH, demonstrating greater inhibitory activity on factor Xa, administered via subcutaneous injection, with lower risks of heparin-induced thrombocytopenia and osteoporosis (Monagle and Newall 2018). Warfarin, a VKA, inhibits vitamin K-dependent clotting factor carboxylation and is orally administered at 0.1–0.2 mg/kg (max 5 mg). Monitoring and adjusting warfarin dosage are crucial, requiring INR testing to maintain the therapeutic range between 2 and 3 (Monagle and Newall 2018). A significant concern is its narrow therapeutic range, its interactions with various drugs and dietary components, which can lead to elevated drug levels and an increased risk of bleeding. Considering our child's risk factors and due to financial limitations, warfarin was chosen.

Furthermore, homocystinuria with an MTHFR mutation can be treated with a combination of dietary adjustments and supplements like a methionine-restricted diet to mitigate homocysteine production (Majtan et al. 2019). Various other treatments attempted are a combination of folic acid, vitamin B6, vitamin B12, methionine supplementation, and betaine (Kliegman 2019). Early intervention with betaine yields favourable outcomes by reducing homocysteine levels in bodily fluids by remethylating homocysteine into methionine (Kliegman 2019).

Furthermore, enzyme replacement therapy (ERT), orally administered enzyme CDX-6512, has demonstrated favourable outcomes. However, it remains at an experimental stage and is challenging to obtain (Majtan

et al. 2018; Skvorak et al. 2023). Liver transplantation has served as a curative measure in rare instances (Kerkvliet et al. 2021).

The range of phenotypical outcomes associated with MTHFR gene mutations spans from severe neurological decline and premature death to asymptomatic adults. Unfortunately, our ability to follow up with our child was hindered by financial constraints and through subsequent phone conversations, we learned of the child's demise.

This case underscores the intricate interplay between genetic disorders, diagnostic challenges, and therapeutic complexities in paediatric thrombosis. The influence of financial constraints on diagnostic pathways and treatment decisions highlights the need for accessible healthcare resources. Despite limitations, insights gained contribute to understanding rare genetic variants and their clinical implications in thrombotic disorders.

Abbreviations

AR	Autosomal recessive
CBS	Cystathionine beta-synthase
MTHFR	Methylenetetrahydrofolatereductase
CNS	Central nervous system
DVT	Deep vein thrombosis
aPTT	Activated partial thromboplastin time
INR	International normalised ratio
VTE	Venous thromboembolism
UFH	Unfractionated heparin
LMWH	Low-molecular-weight heparin
VKA	Vitamin K antagonists
ERT	Enzyme replacement therapy

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Author contributions
PT analysed patient data and contributed in writing the manuscript. AV analysed patient data and contributed in writing the manuscript. NK analysed and interpreted the patient data, managed the case, and contributed in writing the manuscript. DRR analysed and interpreted the patient data, managed the case, and contributed in writing the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
As per institutional policy, case reports do not need ethics approval; however, the committee was intimated regarding this submission.

Consent for publication
Written informed consent was obtained from the patient's parents/legal guardians for publication of this case report. A copy of the written consent is available for the review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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