Case Report

Cerebral venous sinus thrombosis associated with hyperhomocysteinemia due to methylenetetrahydrofolate reductase homozygous gene mutation: A case report

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ABSTRACT

Cerebral venous sinus thrombosis (CVST) is a rare but potentially life-threatening condition requiring a high index of suspicion for diagnosis. We report a case of a 20-year-old vegetarian male presenting with acute severe headache, vomiting, and papilledema, diagnosed with left transverse and sigmoid sinus thrombosis secondary to hyperhomocysteinemia caused by a homozygous methylenetetrahydrofolate reductase gene mutation. Treatment with anticoagulants, mannitol, therapeutic lumbar puncture, and vitamin supplementation led to significant clinical improvement and partial thrombus recanalization at 6 months. This case underscores the importance of considering genetic causes of hyperhomocysteinemia in young patients with CVST, even in populations with dietary risk factors such as vegetarianism.

Key words: Folic acid, Headache, Stroke, Vitamin B12

Cerebral venous sinus thrombosis (CVST) is an uncommon cause of stroke, accounting for 0.5–3% of cases, with an incidence of 3–4 per million in adults and 7 per million in children [1]. It predominantly affects individuals under 50 years and is three times more common in women due to gender-specific risk factors such as pregnancy and hormonal therapies [2]. Clinical presentations vary, including headache (present in 90% of cases), intracranial hypertension, and focal neurological deficits. Hyperhomocysteinemia, often linked to dietary deficiencies and sometimes to genetic mutations such as methylenetetrahydrofolate reductase (*MTHFR*) gene variants, is a recognized risk factor for thrombosis [3]. The suspicion for genetic causes of hyperhomocysteinemia is low due to an inaccurately low estimate of its prevalence, despite it being quite common.

We present a case of CVST in a young male with hyperhomocysteinemia due to an MTHFR homozygous mutation to highlight the importance of considering genetic evaluation in atypical presentations of CVST where homocysteine elevation cannot be explained by dietary deficiency alone.

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CASE PRESENTATION

A 20-year-old vegetarian male presented with a 4-day history of rapid-onset, diffuse, pulsatile headache (Visual Analog Scale [VAS] 8/10) accompanied by left-sided neck pain. On day 4, he developed three episodes of early morning vomiting, prompting hospital admission. The headache persisted despite analgesics, worsening to VAS 10/10 by day 7, with new-onset photophobia and sleep disturbance. There was no history of visual disturbances, diplopia, altered sensorium, fever, substance use, seizures, or relevant past medical or family history.

General examination revealed stable vital signs. Neurological assessment showed normal higher mental functions, cranial nerves, motor, sensory, and cerebellar systems. Fundus examination confirmed bilateral papilledema. No neck stiffness or systemic abnormalities were noted. The clinical presentation suggested raised intracranial pressure (ICP).

A non-contrast brain computed tomography (CT) revealed hyperdensity in the left transverse and sigmoid sinuses, with no cerebral infarcts or hemorrhage. Magnetic resonance (MR) venography confirmed acute thrombosis with filling defects in these sinuses. Laboratory evaluation showed low-normal serum Vitamin B12 (362 pg/mL,

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reference: 211–911 pg/mL) and folate, but elevated homocysteine (125 mg/dL, reference: 0–15 mg/dL). Grossly elevated homocystenemia despite low normal Vitamin B12 and folate levels leads to suspicion of a genetic abnormality in homocysteine homeostasis. Genetic testing identified a homozygous *MTHFR* gene mutation (A1298C). Therapeutic lumbar puncture revealed an elevated opening pressure of 480 mm H_2O, with acellular cerebrospinal fluid and normal protein and glucose levels.

The treatment was initiated with subcutaneous low-molecular-weight heparin (LMWH; enoxaparin 60 mg twice daily). Intravenous mannitol was administered for 1 week to manage raised ICP, followed by a therapeutic lumbar puncture in the 3rd week. Symptoms improved over several days. After 4 weeks of LMWH, the patient was transitioned to dabigatran (150 mg twice daily), acetazolamide (250 mg twice daily) for intracranial hypertension, and Vitamin B12 and folic acid supplementation for hyperhomocysteinemia. At 6-month follow-up, MR venography showed partial thrombus recanalization, and homocysteine levels normalized to 13 mg/dL. Dabigatran was discontinued, but vitamin supplementation continued due to the genetic mutation and a vegetarian diet. At 1-year follow-up, homocysteine levels remained controlled, and MR venography demonstrated further recanalization.

DISCUSSION

CVST presents a diagnostic challenge due to its variable clinical spectrum, ranging from isolated headache (25% of cases) to severe complications such as seizures, hemorrhage, or intracranial hypertension [4]. Early diagnosis is critical to prevent adverse outcomes. Risk factors include prothrombotic states, infections, and genetic predispositions. Hyperhomocysteinemia, often linked to Vitamin B12 or folate deficiency in vegetarians, is a key contributor, but MTHFR mutations, particularly the C677T polymorphism, significantly elevate thrombosis risk by impairing homocysteine metabolism [3,4]. A meta-analysis confirmed hyperhomocysteinemia's role in venous thrombosis, including CVST, with MTHFR mutations amplifying this risk [5]. Recent studies highlight the C677T polymorphism's prevalence and clinical implications, particularly in populations with dietary folate deficiencies [3]. In India, CVST's higher prevalence necessitates a low diagnostic threshold with a high degree of suspicion, especially in young patients with acute headache and intracranial hypertension [6].

Prasad *et al*. described a young Indian male with CVST and hyperhomocysteinemia due to MTHFR mutation who improved with anticoagulation and vitamin supplementation [7]. Bostan *et al*. reported a case of recurrent venous thrombotic events in a female during pregnancy and in the post-partum period who was later found to have MTHFR mutation and was treated with lifelong anticoagulation and vitamin supplementation [8]. In case reports by Prasad *et al*., [7] Alswij *et al*., [9] and Sun *et al*. [10], their patients had the C667T mutation, which was considered to be more severe than the A1298C mutation. The most severe form is the combined C667T and A1298C mutations. Yu *et al*., [11] reported such a heterozygous mutation with persistently elevated homocysteine levels despite treatment. Our patient had a homozygous mutation in A1298C, which causes a mild-to-moderate increase in homocysteine levels. He was a vegetarian with normal serum Vitamin B12 and folate levels, suggesting that the hyperhomocysteinemia was solely attributable to the MTHFR mutation. The patient has improved completely, and there have been no further/recurrent thrombotic events.

High index of suspicion prompting neuroimaging (contrast-enhanced CT or MR venography) and anticoagulation remain critical for diagnosis and treatment. This case underscores the genetic (MTHFR homozygous mutation) factor in CVST, advocating for genetic screening in atypical presentations to guide prevention of further vascular events.

The challenges associated with this disease diagnosis and management are: (a) CVST's nonspecific symptoms, such as headache, risk of diagnostic oversight without thorough history, examination, and imaging. (b) Distinguishing dietary versus genetic causes of hyperhomocysteinemia is essential for tailored management and preventing further vascular events. (c) India's higher CVST prevalence requires heightened clinical awareness.

CONCLUSION

This case emphasizes the need for a high index of suspicion for CVST in young patients with acute headache, particularly with symptoms of raised ICP (vomiting). While dietary deficiencies often cause hyperhomocysteinemia, genetic etiologies such as MTHFR mutations must be investigated, especially when homocysteine levels are out of proportion to vitamin deficiencies. Prompt neuroimaging, anticoagulation, and vitamin supplementation can achieve favorable outcomes.

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