Case Report

May headache be the first sign of mutation in the MTHFR gene?

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BACKGROUND: Cerebral venous thrombosis (CVT) is a rare disease and it has different etiologies. Inherited or acquired prothrombotic state plays a key role in the development of CVT.

METHODS: A 28-year-old man who presented to our emergency department with persistent headache and accompanied by complaints of nausea and vomiting over a week. Neurologic examination revealed bilateral papilledema. Brain computed tomography showed a hyperdense area on the posterior part of the occipital lobe. Brain magnetic resonance imaging and magnetic resonance venography revealed thrombosis of CVT. Homozygous mutations were found for methylenetetrahydrofolate reductase (MTHFR). MTHFR CG677T gene mutation and blood tests showed elevated homocysteine levels on the etiological screening. There was no other etiology for CVT.

RESULTS: Headache and other complaints were improved after treatment of heparin, warfarin, and vitamin B12. No recurrence of symptoms was observed upon outpatient follow-up.

CONCLUSION: Since CVT is an important cause of headache, we recommend etiology screening for patients who present with CVT for MTHFR gene mutations and family counseling should be provided.

KEY WORDS: Cerebral venous thrombosis; Headache; Methylenetetrahydrofolate reductase gene mutation

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INTRODUCTION

Cerebral venous thrombosis (CVT) is a relatively uncommon condition afflicting mostly young adults. Many clinical conditions have been described as risk factors for CVT, including hereditary thrombophilia, pregnancy and puerperium, postoperative state, intracranial or local infections and use of oral contraceptives. CVT is often misdiagnosed and rarely compared with stroke that has an arterial cause.

Homocysteinemia is a significantly independent, usually heritable, prothrombotic risk factor for atherothrombotic cardiovascular, cerebrovascular, and peripheral vascular diseases. The patients with methylene

tetrahydrofolate reductase (MTHFR) gene mutation usually have high levels of serum homocysteine.^[1] The common homozygous mutation in the MTHFR gene is associated with a significant risk factor for ischemic stroke and it is related to the increased level of total homocysteine.^[2] We report a case of a 28-year-old man with CVT in whom we recognized of MTHFR gene mutation and hyperhomocysteinemia.

CASE REPORT

A 28-year-old right handed man was admitted to our emergency department because of severe posterior

headache persisted over a week. The headache was mostly severe, tightening in quality and progressive in nature. Occasionally, headache was accompanied by nausea and vomiting. On admission, he was conscious, his blood pressure and temperature were within normal range. Physical examination revealed that he was an alert patient with bilateral papilledema. His visual acuity was reduced. Neurological examination was normal. Brain computed tomography showed a hyperdense area on the posterior part of the occipital lobe (Figure 1). Hereupon, magnetic resonance venography was obtained. Because of absence of signal on the location of bilateral transverse sinus, sinus rectus and superior sagittal sinus on magnetic resonance venography (Figure 2), the patient was admitted to the neurology clinic with the diagnosis of venous sinus thrombosis. Familial and personal history did not reveal any previous cerebrovascular diseases as vascular risk factors. He did not smoke nor drink alcohol. But there was a family history of miscarriage (his cousin 14 times). His differential blood cell count, biochemical results (including, C-reactive protein, prothrombin and partial thromboplastin times, serum glucose, electrolytes, liver enzymes, urea, creatinine, protein, calcium, magnesium) and urinalysis were normal. The results of thrombophilic screening tests involving antinuclear antibodies, anti-

single-stranded DNA and anti-double-stranded DNA antibodies, anticardiolipin IgG and IgM antibodies, anti-SS-A and anti-SS-B were all negative. No mutations were found for factor V Leiden, factor V H1299R, factor VIII, factor XIII, prothrombin G20210A, b-fibrinogen, plasminogen activator inhibitor type 1, angiotensin-converting enzyme, apolipoprotein BR3500Q, or apolipoprotein E. But the level of serum homocysteine was elevated (21 $\mu\text{mol/L}$; normally 5.00–12.00 $\mu\text{mol/L}$) and there was homozygous CG677T polymorphism of the MTHFR gene (genotype 677TT). The levels of serum vitamin B12 and folate were <150 (normally 193–663 pg/mL) and 4.23 ng/mL (normally 3–17 ng/mL) respectively.

MTHFR gene scanning of the patient's family was performed; his father, mother and elder brother had heterozygote CG677T polymorphism of MTHFR gene mutation, one of his brothers had homozygote CG677T polymorphism of MTHFR gene mutation. But, no clinical manifestations were observed in his 16-year-old brother so far.

Heparin, warfarin, vitamin B12 and folic acid were prescribed. After four days, patient's complaints subsided, and he was discharged without any sequelae. Neither recurrence of headache nor neurological complication was found during follow-up.

Figure 1. Non contrast-enhanced CT showing hyperdense vascular structure associated with venous thrombosis at bilateral transverse sinuses (A), sinus rectus (B) and superior sagittal sinuses (C).

Figure 2. MR venography showing that thrombosed bilateral transverse sinuses, sinus rectus and superior sagittal sinuses (A). Thrombosed transverse sinus showing at sagittal source image of MR venography (white arrow, B).

DISCUSSION

Thrombosis of the cranial venous sinuses and the cerebral cortical veins can lead to a distinct cerebrovascular disorder, which unlike arterial stroke, most often affects even young adults and children. Symptoms and clinical course are highly variable, etiological factors are even more heterogeneous making cerebral cortical vein thrombosis a unique clinical entity. The disorder can occur *de novo* as the first manifestation or can overlap with another existing clinical problem. Each component of the Virchow's triad (endothelial damage, stasis and hypercoagulability of blood) may in turn have several contributory factors/causes to produce the final manifestation of CVT.^[3]

CVT presents with a wide spectrum of manifestations. The most common presenting symptom is headache, and other associated symptoms and signs are seizures, focal neurological deficits, papilloedema and impaired consciousness. The clinical picture is determined by the age of patient, site of CVT and the presence or absence of parenchymal lesions.^[4] Our patient had only headache and papilloedema. Isolated headache, as the only presentation of CVT, has been described but it is rare.^[5]

Because of the heterogeneity in clinical presentation and etiology, the diagnosis of CVT is often missed, and even if a diagnosis is made, the contributory factors are often subclinical and are also missed or overlooked. Most often only one of the etiological factors is prominent enough to be picked up and it is a universal practice to look for rarer causes and some inherited causes of venous thrombosis. Diagnosis is often missed unless clinicians maintain a high index of suspicion and be aware of varied clinical presentations.^[3]

Venous thrombosis in the body results from exaggerated activity of one or more mechanisms of hemostasis or reduced activity of one or more natural

antithrombotic mechanisms or a combination of both.^[3]

The common conditions with tendency for thrombosis (thrombophilic states) to be routinely looked for are listed in Table 1.^[3]

Rarely only one of the contributory causes is an underlying hereditary thrombophilia-like condition: factor V Leiden, prothrombin gene mutation, hereditary hyperhomocysteinemia, deficiency of protein C, protein S, antithrombin deficiency, increased factor VIII, and dysfibrinogenemia.

The discussed patient was confirmed to have hyperhomocysteinemia and the homozygous form of C677T mutation in the MTHFR gene. Thus, C677T mutation in the MTHFR gene has not been considered an independent risk factor causing CVT, even though this mutation is frequently accompanied by hyperhomocysteinemia, a significant and strong risk factor for the development of CVT.^[4] In our patient, the level of plasma homocysteine was very high. Homocysteine has primary atherogenic and prothrombotic properties. Mildly increased levels of homocysteine were observed in patients with coronary artery, cerebrovascular, and peripheral artery diseases. Association of mild hyperhomocysteinemia with occlusive disease was independent of the presence of risk factors such as smoking, hyperlipidemia, hypertension, and diabetes mellitus. It can be familial or acquired due to vitamin deficiencies.^[3] Histopathological hallmarks of homocysteine-induced vascular injury include intimal thickening, elastic lamina disruption, smooth muscle hypertrophy, marked platelet accumulation, and the formation of platelet-rich occlusive thrombi. Homozygote for the thermolabile variant of MTHFR results from a common mutation Ala→677 Val and is found in 5%–15% of the general population. Subjects with MTHFR gene mutation have significantly elevated levels of plasma homocysteine.^[6]

The first step in CVT treatment consists of initiating full anticoagulant treatment by administering heparin or, quite frequently nowadays, by LMWH. Not even a rather extensive hemorrhage in venous cerebral infarcts is a contraindication to parenteral administration of heparin.^[7] The duration of heparin administration ranges from several days to three weeks. After this period, transition to an orally administered anticoagulant is recommended.^[7]

Both MTHFR homozygote gene mutation and hyperhomocysteinemia were detected in our patient. He had had no thrombotic event until the onset of the clinical manifestations. The general factor should be figured out by focusing on the etiological researches. Family

Table 1. Common conditions with a tendency for thrombosis (thrombophilic states)

Dehydration (even subclinical)	Unusual postures in travel or sleep
Prolonged immobilization	Surgery or trauma
Focus of infection/inflammation/abscess	Pregnancy/postpartum period
Hyperhomocysteinemia	Polycythemias
Thrombocytosis	Obesity
Diabetes	Oral contraceptives
Hormone replacement therapies	Antiphospholipid antibodies
Behcet's and other vasculitis	Congestive cardiac failure
Nephrotic syndrome	Smoking
Inflammation	Liver disease
Increasing age	Dyslipidemia
Atherosclerosis	Malnancies

screening was followed after detection of MTHFR gene mutation. Receiving genetic counselling service, the patient and his brother were subjected to anticoagulant therapy.

In conclusion, CVT should be considered when severe headache is found in a patient with either a headache free anamnesis or changes in the characteristics of primary headache. Etiological investigations should be carried out immediately. Genetic counselling should be provided for the family members in order to prevent possible complications.

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