Familial Hyperhomocysteinemia-related Cerebral Venous Sinus Thrombosis and Pulmonary Embolism: A Case Report

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Abstract- Elevated plasma homocysteine levels are associated with an increased risk of deep vein thrombosis. Herein we report a case of familial hyperhomocysteinemia-related cerebral venous sinus thrombosis and pulmonary embolism in a 21-year-old man who presented with severe headache over bilateral frontal areas. Neurological examination revealed no evidence of focal neurological deficit. Chest CT showed pulmonary thromboembolism in bilateral basal lung fields and brain MRI disclosed right transverse and sigmoid venous sinus thrombosis. Routine immunological tests, coagulation factors and occult tumor screening were normal, as were vitamin B12 and folate levels. The DIC profile was negative. The only risk factor we were able to identify was an elevated serum homocysteine level, namely 46.23 µM/L.

Hyperhomocysteinemia was also noted in the patient’s asymptomatic elder brother (68.0 µM/L) and, to a lesser extent, in his parents (father 12.5 µM/L; mother 11.7 µM/L).

In conclusion, the cause of cerebral venous thrombosis and pulmonary embolism in this young patient was most likely related to familial hyperhomocysteinemia, with the thromboembolic events precipitated by a preceding systemic infection. After anticoagulation therapy; the patient recovered completely without any residual neurological deficit.

Key Words: Hyperhomocysteinemia, Cerebral venous sinus thrombosis, Pulmonary embolism

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INTRODUCTION

Cerebral vein thrombosis (CVT) is a distinct cerebrovascular disorder that mostly affects young adults. The estimated annual incidence is 3 to 4 cases per 1 million, with 75 percent of the adult cases occurring in women⁴. The clinical symptoms vary and may include severe headache (90%), focal lateralized signs (50%), seizures (40%) as well as behavioral symptoms such as delirium, amnesia and disturbances in consciousness.

In about 70% of the CVT cases, the cause is identifiable, and may be related to inflammatory disease, infection, trauma, neoplasm, autoimmune disease, or oral contraceptives⁵. CVT may also be associated with genetic prothrombotic conditions, such as deficit of antithrombin III, protein C, or protein S, mutation of the...
factor V or II genes\textsuperscript{(2-4)}, resistance to activated protein C, and hyperhomocysteinemia. While more than ~80 percent of all patients have good neurologic outcomes\textsuperscript{(1)}, mortality has been reported to be 5% to 30%\textsuperscript{(3)}.

Most often the treatment for CVT includes prevention or reversal of cerebral herniation with IV mannitol, or decompressive hemicraniectomy and/or removal of hemorrhagic infarct with surgical procedures. In addition, oral acetazolamide (500 to 1000 mg daily), a carbonic anhydrase inhibitor, may be administered to reduce the intracranial pressure. If effective and tolerated, this agent may be continued for weeks to months. Anticoagulation therapy with heparin may be applied to arrest the thrombotic process and to prevent pulmonary embolism (40% hemorrhagic infarction). Thrombolysis (endovascular thrombolysis) by administration of a thrombolytic enzyme, urokinase, into the sinus has also been tried in some DVT cases.

**CASE REPORT**

The patient was a 21-year-old unmarried male who had no previous history of systemic illness, including hypertension, diabetes mellitus, hyperlipidemia, hyperthyroidism, renal insufficiency, or anemia. The patient had no family history or personal history of venous thrombosis or any other CV events. He did not smoke or have abnormal dietary habits. The patient was admitted to the emergency ward in our hospital with the chief complaints of sudden intense continuous headache over bilateral frontal sites and mild neck stiffness for 2 days. Moreover, the patient had been admitted to another hospital, Taitung Mackay Memorial Hospital, for fever and progressive dyspnea one week before the onset of the headache. Fever and dyspnea soon ameliorated with careful medical management, which was given under a diagnosis of acute respiratory distress syndrome, although the cause was not identified.

When the patient was admitted to our department, there was mild dyspnea but the results of physical and neurological examinations were in general unremarkable. However, Chest CT showed acute right transverse and sigmoid venous sinus thrombosis (Fig. 2). MRI and MR venography also revealed venous sinus thrombosis in the same locations, with collateral drainages to the right jugular vein and prominent branches of the right superficial middle cerebral vein (Fig. 3).

An extensive survey for the etiology of the thrombotic disorder was performed. There were no laboratory signs of inflammation (WBC: 5390/mm\textsuperscript{3}) and no anemia (Hgb: 15.5 g/dl). Immunological tests, including those for lupus anticoagulant and anticardiolipin antibodies, reveal normal findings. General studies of the coagulation profiles disclosed no abnormalities: Fibrinogen 234.5 mg/dL (N: 200-400 mg/dL); fibrin degradation products <10 ug/mL (N: <10 ug/mL); Antithromin-III 75.8% (N: 80-120%); D-Dimer 93 ng/dL (N: <500 ng/dL); Protein C 84%; and Protein S.
The levels of vitamin B12 (506.9 pg/mL) (N: 200-500 pg/mL) and folate (4.26 ng/mL) (N: 3-17.0 ng/mL) were also normal. However, total plasma homocysteine, which was measured by a commercially available MEIA assay (Abbot Laboratories), was abnormally elevated to a level of 46.23 µM/L.

Moderate hyperhomocysteinemia (Hcy: 68.0 µM/L) with low folate (2.31 ng/mL) and a low-normal level of vitamin B12 (250 pg/mL) (N: 200-500 pg/mL) was also detected in his asymptomatic elder brother, who is also a nonsmoker and have no previous history of venous thrombosis or any other CV events. The patient's parents were also found to have mildly elevated Hcy levels (father 12.5 µM/L; mother 11.7 µM/L) (Fig. 4).

The patient was treated with heparin, followed by oral anticoagulant plus folate, vitamin B6, and vitamin B12. The patient recovered two months later (Fig. 5). The anticoagulant was discontinued, and he has been kept on folate and vitamin B12 therapy thereafter.

**DISCUSSION**

This patient presented intractable headache and was found to have multiple thrombotic phenomena involving the brain (CVT) and lung (pulmonary thromboembolism). Deep vein thrombosis has been associated with mild-to-high circulating levels of homocysteine. Based on four studies concerning tHcy and the relative risk of CAD, the Nutrition Committee of the American Heart Association proposed a fasting tHcy concentration of 10 µM/L as a reasonable cutoff level of hyperhomocys-
teinemia, though there is no general consensus on these cutoff values. Homocysteine is an intermediary amino acid formed by conversion of methionine to cysteine, which is metabolized by two divergent pathways--transsulfuration and remethylation. Elevation of plasma homocysteine concentrations can occur as a result of genetic defects (e.g. C677T mutation in the MTHFR gene), nutritional deficiencies in vitamin cofactors, cigarette smoking, or other factors including some chronic medical conditions and use of drugs (e.g. fibrates and nicotinic acid).

In this CVT patient, the only risk factor we were able to identify after extensive investigation was an elevated blood homocysteine level. Because genetic and nutritional factors are two important determinants of homocysteine metabolism, and also because there was no evidence that the hyperhomocysteinemia in this patient was an acquired disorder, we screened the patient and his family members for genetic markers of hyperhomocysteinemia. In all four subjects we found the C677T polymorphism in all alleles of the MTHFR gene, pointing to the possibility of familial hyperhomocysteinemia. If feasible, oral methionine (100 mg/kg) might be given to the patient’s parents who had only borderline high fasting homocysteine levels as a provocative test. More definite hyperhomocysteinemia may ensue.

Because his family was unwilling to participate in further studies, we could not perform extensive investigation. However, we do know that there was no family history of ischemic stroke or venous thrombosis. The common C677T mutation in the methylene tetrahydrofolate reductase (MTHFR) gene has been associated with a thermolabile variant and has approximately half-normal activity. Approximately 10% to 13% of the white population are homozygous for this mutation. On the other hand, because blood levels of folate, vitamin B12 and to a lesser extent vitamin B6, are inversely correlated with the level of homocysteine, anyone with nutritional deficiency of these vitamins may also be at an increased risk of hyperhomocysteinemia.

Hyperhomocysteinemia may be associated with thrombotic processes through several mechanisms, including increased platelet aggregation, increased activity of factor V, prothrombin activation, inhibition of protein C activation, and decreased tissue plasminogen activator binding to endothelial cells.

For the patient discussed in this report, we hypothesize that the cause of cerebral venous thrombosis and pulmonary embolism may be ascribable to familial hyperhomocysteinemia, with the thromboembolic events precipitated by a preceding systemic infection. After anticoagulation therapy, this young patient completely recovered without any residual neurological deficit. The anticoagulant was discontinued and he has been kept on folate and vitamin B12 therapy thereafter.

REFERENCES