

HYPERHOMOCYSTEINEMIA AND CEREBRALVENOUS SINUS THROMBOSIS

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Pak J Neurol Sci 2006; 1(3):136-7

Though cases of ischemic arterial thrombosis due to hypercoagulability caused by hyperhomocysteinemia (CVT) have been reported¹ cerebral venous thrombosis due to hyperhomocysteinemia is a rarely reported cause of venous strokes.

Elevated level of homocysteine is strongly associated with premature arterial or venous thromboembolism. Factors related with the pathogenesis of venous thrombosis include blood stasis, hypercoagulability, and vessel damage. Increased thromboembolic risk has been attributed to antithrombin III, protein C, or protein S deficiencies as well as factor V Leiden, prothrombin mutation G20210A, or hyperhomocysteinemia.²

A more recent study demonstrated that elevation of plasma factor VIII level proved to be the most prothrombotic risk factor for cerebral venous thrombosis (CVT).³

We report two cases of young males, without any significant identifiable risk for hypercoagulability, presenting with headaches, seizures and altered mental status, who were found to have cortical venous sinus thrombosis. During workup of hypercoagulable state, these patients were found to have hyperhomocysteinemia, a rare cause of venous thrombosis.

CASE 1

A 23 year-old male developed symptoms of persistent diffuse headaches for about a month. He took different 'over-the-counter' medications. His symptoms improved completely. About a week prior to his admission to the hospital, he developed double vision. CT scan of the head and lumbar puncture were normal. He was treated with oral steroids.

His diplopia resolved. After 3 or 4 days, he developed vomiting, drowsiness and staggering gait.

On the day of admission, the patient had a seizure for which he was brought to the hospital. Examination, except for drowsiness, was unremarkable. MRI brain showed an ischemic lesion in the right parietal cortex with gyriform enhancement suggestive of venous cortical infarction. MR venogram showed irregular defect in the superior sagittal sinus suggestive of cerebral venous thrombosis and partial recanalization.

EEG, a repeat lumbar puncture, echocardiogram, routine chemistries, blood counts, protein C, protein S, antithrombin III, and Factor V Leiden were normal. The blood cultures and antiphospholipid antibodies were negative. Plasma homocysteine level was 20.52 $\mu\text{mol/l}$ (normal reference value 4.45-12.42 $\mu\text{mol/l}$).

The patient was treated with heparin infusion (intravenous) and a PTT was maintained around twice that of normal. He was also started on folic acid. His symptoms resolved over a week and he was discharged on warfarin and folic acid.

CASE 2

A 37 year-old male with a history of diabetes mellitus presented to ER with new onset of headaches, seizures and altered mental status.

On initial examination, the patient was drowsy. An urgent plain CT scan of brain revealed left parieto-occipital hemorrhage. An emergent cerebral angiogram showed thrombosis of the superior sagittal sinus, the confluence, the left transverse sinus and right transverse sinus. Further workup revealed normal protein C, protein S, antithrombin III and factor V Leiden. The antiphospholipid

antibodies were also negative. However, the plasma homocysteine levels were elevated i.e. 20.17 $\mu\text{mol/l}$ (4.45-12.42 $\mu\text{mol/l}$).

During hospital stay, the patient deteriorated and required craniotomy and removal of the clot. After the surgery, he showed dramatic improvement.

DISCUSSION

Cerebral venous thrombosis is a diagnostic challenge due to its nonspecific symptoms and its relative infrequency. This is probably more common for underdeveloped countries where investigations are not readily available. Even when diagnosed, the cause sometimes remains elusive.

McCully extensively studied children with homocysteinuria and showed a relationship between homocysteinuria and development of premature coronary artery disease and stroke.⁴

A correlation between hyperhomocysteinemia and arterial vascular disease is also well established. Several studies have investigated the role of hyperhomocysteinemia in recurrent vein peripheral thromboembolism.^{5,6,7,8} There are, however, very few reports of cortical venous thrombosis and hyperhomocysteinemia.

Homocysteinuria primarily comes from methionine. Methionine is a by-product of protein catabolism. There are two distinct pathways whereby homocysteine is metabolized:

1. Transsulfuration pathway requires cystathionine beta synthetase. This converts homocysteine to cystathionine and then to cysteine, which is excreted in the urine. Vitamin B6 is a required co-factor in this pathway. Deficiency causes homocysteinuria, an inborn error of metabolism.

2. Remethylation pathway requires methylene tetrahydrofolate reductase (from folate metabolism) which helps methionine synthetase to convert homocysteine back to methionine. Vitamin B12 is a co-factor in this reaction. Pathology in this pathway is responsible for hyperhomocysteinemia.

High levels of auto-oxidation of homocysteine reacting with highly reactive oxygen species cause lipid peroxidation which in turn leads to vascular matrix damage and smooth muscle cell proliferation leading to atherogenesis. The same phenomenon also causes vascular endothelial injury and is responsible for prothrombogenesis.

CONCLUSION

The two reported cases in our study had moderately elevated homocysteine level. These patients did not have other risks for CVT. These cases had almost similar presentations. Both showed good improvement with treatment on long-term folate replacement. Further studies are required to analyze the importance of checking homocysteine level in cases of CVT, especially where a clear risk factor has not been identified.

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