Recurrent stroke in a patient with vitamin B₁₂ deficiency and *MTHFR* mutation

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We report an unusual case of recurrent stroke in a patient with vitamin B₁₂ deficiency who was also homozygous for the methylene tetrahydrofolate reductase (*MTHFR*) gene mutation. The patient was a 35-year-old male vegetarian with no known medical history who initially presented with global aphasia, slurred speech, right facial weakness, and right-sided hemiplegia and was found to have a stroke (NIH Stroke Scale score of 25). At that time a CT scan of the head ruled out intracranial hemorrhage and a CT angiogram of the head and neck was done. The patient was found to have occlusion of the M1 segment of the left middle cerebral artery. Because he was within the time frame for thrombolytics, systemic thrombolysis with alteplase was given without improvement. He therefore underwent a cerebral angiogram that demonstrated occlusion of the M1 segment of the left middle cerebral artery and very poor leptomeningeal collaterals from the left anterior and posterior cerebral artery territories (figure 1). He underwent mechanical thrombectomy of the left middle cerebral artery thrombus with Penumbra aspiration device (Penumbra Inc., Alameda, CA) and SOLITAIRE stentriever (Covidien, Irvine, CA) with complete recanalization of the occluded segment (figure 2). He had a remarkable early recovery as the hemiplegia resolved. During the hospital course he was placed on a statin and low-dose aspirin and was later discharged to a rehabilitation unit for treatment of his right-sided hemiparesis and residual expressive aphasia. Workup for secondary stroke prevention, including telemetry and a transesophageal echocardiogram, was unremarkable.

On follow-up MRI 3 months later, a small new acute left middle cerebral artery stroke was found. At that time he underwent a workup for a hypercoagulable state. The workup was negative for the following: lupus anticoagulant, anticardiolipin antibody, factor V Leiden mutation, prothrombin gene mutation, protein C and S deficiency, and antithrombin deficiency. However, the patient was found to have a markedly elevated homocysteine level of 55.7 μmol/L (normal 5–15 μmol/L) and relatively low levels of vitamin B₁₂ and folate at 206 ng/L (normal 180–914 ng/L) and 5.2 μg/L (normal ≥4 μg/L), respectively. Serum creatinine was 0.98 mg/dL and complete blood count showed hemoglobin of 14.4 g/dL and mean corpuscular volume of 88 fL. Genetic testing revealed the presence of homozygous *MTHFR* 677 TT genotype.

The patient was then treated with supplemental vitamin B₁₂ 1,000 mcg daily, initially IM and then orally. He also received folic acid supplementation. Two months later, the patient's symptoms improved dramatically, with resolution of his expressive aphasia and marked improvement of his right-sided hemiparesis. Laboratory data also showed improvement, as

Practical Implications

In certain patients with recurrent stroke, such as those with elevated homocysteine and *MTHFR* gene mutations, supplemental vitamin B₁₂ may be beneficial.

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Figure 1 Left common carotid artery stump occlusion

Digital subtraction angiography of the left common carotid artery in anteroposterior projection demonstrates stump occlusion of the M1 segment of the left middle cerebral artery (MCA) at the beginning of the procedure. There are very poor leptomeningeal collaterals from the left anterior cerebral artery to the left MCA territory.

vitamin B₁₂ level increased to 1,249 ng/L and homocysteine level decreased to 28.5 μ mol/L. Eighteen months after his initial diagnosis, homocysteine levels further decreased to 12 μ mol/L while receiving supplemental vitamin B₁₂ and folic acid.

DISCUSSION

In the past, studies have demonstrated that elevated homocysteine level is a risk factor for vascular disease, specifically myocardial infarction and stroke.^{1,2} The association between hyperhomocysteinemia and stroke was even shown in a population of young adults with a history of ischemic stroke.³ A recent randomized trial showed that the combination of enalapril and folic acid is beneficial in the primary prevention of stroke.⁴ However, other clinical trials have failed to reveal a benefit when using homocysteine-lowering vitamins in patients with known vascular disease or recurrent stroke.⁵⁻⁷

Homocysteine is thought to contribute to vascular disease by a variety of mechanisms. Raised plasma homocysteine concentrations have been associated with increased coagulation of the blood, increased cholesterol synthesis, increased oxidative stress, reduced synthesis of apolipoprotein A1 leading to reduced concentrations of high-density lipoprotein, upregulated adhesion molecules, and several other mechanisms that impair endothelial function.⁸

This case illustrates that markedly elevated homocysteine in the setting of a vitamin B₁₂-deficient vegetarian patient with *MTHFR* mutation can be associated with increased thrombosis, as the rest of his workup was negative. It also demonstrates clinical improvement in the setting of vitamin B₁₂ supplementation concordant with laboratory improvement in homocysteine levels. Even though most studies have shown no significant benefit from vitamin supplementation for stroke prevention, a subgroup analysis of a large randomized trial showed that vitamin B₁₂ played a key role in vitamin therapy for total homocysteine and suggested that vitamin B₁₂ supplementation may be needed for some patients.

Figure 2 Left common carotid artery complete recanalization

Digital subtraction angiography examination of the left common carotid artery in anteroposterior projection demonstrates complete recanalization of the left middle cerebral artery and distal branches after mechanical thrombectomy.

Vitamin B₁₂ is an underrecognized player in homocysteine levels and vascular disease, particularly in elderly and vegetarian patients.⁸ In addition to the increase in total homocysteine that results from vitamin B₁₂ deficiency, there are neurologic sequelae such as neuropathy, dementia, and subacute combined degeneration of the spinal cord. These findings can easily be overlooked in elderly patients. Lastly, because most dietary vitamin B₁₂ is obtained from meat, strict vegetarians are more likely to be deficient than nonvegetarians, as was the case in our patient.

Currently the guidelines for the prevention of stroke in patients with stroke and TIA advise against screening for hyperhomocysteinemia and vitamin supplementation for prevention of stroke.⁹ However, large-scale stroke prevention studies identifying high-risk patients through genetic testing (e.g., *MTHFR* 677C→T) that target populations with vitamin B₁₂ deficiency have not been performed. We suggest that vitamin B₁₂ supplementation may be beneficial in patients with stroke and *MTHFR* mutation who are also vitamin B₁₂ deficient. Large prospective studies in patients who have homozygous *MTHFR* 677 TT genotypes will be helpful to assess the role of vitamin B₁₂ supplementation.

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Dr. Zacharia: acquisition of data and drafting of the manuscript. Dr. Shani: acquisition of data and critical revision of the manuscript for important intellectual content. Dr. Ortiz: critical revision of the manuscript for important intellectual content.

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