

SUCCESSFUL TREATMENT OF BRAIN ISCHEMIA WITH SUPPLEMENTATION THERAPY IN A PATIENT WITH HYPERHOMOCYSTEINEMIA

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SUMMARY – The effectiveness of homocysteine-lowering therapy on stroke prevention is still unclear. Although randomized controlled epidemiological trials have yielded mixed findings, a multicenter trial did not show any beneficial effect. Genetic studies are still lacking. Therefore, we report on a female patient with transient ischemic attacks and the thermolabile variant of methylenetetrahydrofolate reductase (TT genotype), who benefited from supplemental therapy for homocysteine lowering.

Key words: *Hyperhomocysteinemia; Ischemic attacks, transient; Methylenetetrahydrofolate reductase; Vitamins; Dietary supplement*

Introduction

Over the last decade, following *in vitro* and *in vivo* observations of a homocysteine-associated vascular pathology, convincing epidemiological evidence has been gathered on the relation between moderate elevation of plasma homocysteine (Hcy) and vascular disease, including cerebral ischemia¹. On the other hand, randomized controlled epidemiological trials have yielded mixed findings regarding the effectiveness of therapeutic Hcy lowering on stroke prevention. Furthermore, a large multicenter trial has shown that folic acid supplementation, despite Hcy lowering, does not demonstrate a major effect in averting stroke². However, increased plasma Hcy due to a mutation in the methylenetetrahydrofolate reductase (MTHFR) gene is associated with a procoagulative state as well as accelerated atherosclerosis, independently of other risk factors. Therefore, in certain patients with ce-

rebral ischemic events, supplemental therapy with a Hcy-lowering strategy could be beneficial. In this context, we present a case of a young woman with the thermolabile variant of MTHFR (TT genotype) in association with low serum vitamin B12 who suffered multiple transient ischemic attacks (TIAs).

Case Report

A 40-year-old Caucasian right-handed female was admitted to the Department of Vascular Neurology and Neurological Intensive Care, University Medical Center in Ljubljana, Slovenia, in the fall of 2008, for a detailed diagnostic work-up to establish the etiology of several TIAs in the previous six months. TIAs had presented as temporary dysarthria with paresis of the right corner of her mouth and mild right-sided hemiparesis with no weakness, paresthesias or clumsiness of any of her limbs. Her symptoms lasted from a couple of minutes to 90 minutes and resolved spontaneously with no permanent deficit. Her medical therapy on admission consisted of extended-release dipyridamole with acetylsalicylic acid, and a thyroxine analogue for hypothyroidism due to autoimmune

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thyroid disease. At the age of 13, she was diagnosed with Henoch-Schönlein purpura with skin and renal involvement, and at the age of 29 she developed acute myeloblastic leukemia, which was successfully treated with chemotherapy and irradiation. Her mother had suffered multiple ischemic cerebrovascular strokes due to patent foramen ovale and her father had an ischemic cerebrovascular stroke at the age of 70. On admission, the patient was cognitively intact, euphasic, and no slurred speech was observed. Examination of the cranial nerves was normal, meningeal signs were not present, and no murmurs were heard over the neck arteries. Further neurologic examination did not reveal any abnormality in muscle bulk, muscle tone, muscle strength or tendon jerks. There were no signs of incoordination, clumsiness or pronator drift. Sensory testing, including vibration and position sense, was normal, as were her stance and gait. Cardiac, pulmonary and abdominal examinations were normal. There was no rash. Computed tomography (CT) scan performed shortly after the first TIA attack revealed no abnormalities. Transthoracic cardiac echosonography was normal. Twenty-four-hour ECG monitoring revealed sinus rhythm with no significant paroxysmal rhythm disturbances, while blood pressure values were in the upper normal range throughout twenty-four-hour monitoring. During her hospital stay at our department, magnetic resonance (MR) scan of the head combined with MR angiography of the cerebral arteries and angiosonography of the cervical arteries showed no abnormalities. Transcranial Doppler (TCD) with the Valsalva maneuver showed no signs of right-to-left shunt. Transesophageal cardiac echosonography using contrast medium revealed a normally-shaped interatrial septum with a closed foramen ovale. Blood lipids, blood glucose and tests of hemostasis were all normal, inborn hypercoagulability disorders (such as factor V Leiden variant, prothrombin 20210G>A mutation) were excluded and no significant elevations of anticardiolipin antibodies or lupus anticoagulant were detected. During her stay at Neurology Department, no further neurologic deficits occurred. On discharge, her neurologic examination was completely normal. She continued antiplatelet therapy (dipyridamole and acetylsalicylic acid) and treatment with a thyroxine analogue.

At the beginning of 2009, she was also seen by a rheumatologist for further rheumatologic work-up.

Additional laboratory tests performed at her first visit revealed only mild erythrouria, while serologic tests showed a low titer of IgG anticardiolipin antibodies and transient IgA anti-beta 2 glycoprotein I antibodies. Their values did not suffice to support the diagnosis of the antiphospholipid syndrome. She continued with her antiplatelet therapy, but despite regular treatment she experienced two additional TIAs in the following months, both of which resolved spontaneously. The neurologist who suspected Hashimoto's encephalopathy (further thyroid testing revealed a euthyroid state and a high titer of anti-thyroglobulin antibodies) replaced the combination of extended-release dipyridamole and acetylsalicylic acid with a combination of acetylsalicylic acid and clopidogrel. In the light of the previous negative tests for thrombophilia and antiphospholipid antibodies, the patient was additionally tested for Hcy, which was found to be elevated (20.9 $\mu\text{mol/L}$). Supplementation therapy with folic acid and other B vitamins (vitamin B6, thiamine, riboflavin, niacin and pantothenic acid) and with the addition of vitamin B12, after confirmation of hypovitaminosis B12 (with no antibodies against intrinsic factor), was started immediately. Additional genetic testing confirmed homozygosity for the thermolabile variant of MTHFR (TT genotype). After a month of supplementation treatment, her Hcy level was in the normal range. Soon after starting replacement therapy, the patient also reported a considerably improved state of health. She continued to receive combined antiplatelet therapy and vitamin supplementation and suffered no TIAs in the next two years of follow-up.

Discussion

Moderate to intermediate elevations of the plasma Hcy concentration, occurring in 5%-7% of the population, are recognized as a risk factor for premature cerebro- and cardiovascular disease^{3,4}. These elevated plasma Hcy levels are due to various genetic defects (such as polymorphisms in the MTHFR gene)⁵, vitamin deficiencies (vitamin B6, vitamin B12 and folic acid, necessary vitamin cofactors), renal impairment (the kidneys perform up to 70% of the clearance of Hcy), various drugs (antiepileptic drugs, methotrexate, theophylline, nicotinic acid, fibrates, levodopa, metformin)⁶, hypothyroidism, hyperproliferative dis-

orders (such as certain cancers, psoriasis), sickle-cell anemia, increasing age, high protein intake and low intake of vegetables or fruit⁷.

Elevated plasma Hcy is a strong, graded, independent risk factor for various vascular events including stroke, recurrent stroke and silent brain infarct^{8,9}. In the Rotterdam study, it was estimated that each 1 $\mu\text{mol/L}$ increase in plasma Hcy concentration was associated with a 6%–7% increase in the risk of stroke¹⁰. In the Physicians' Health Study, a slight increase (1.4-fold) in the risk of stroke was observed in subjects with plasma Hcy $>12.7 \mu\text{mol/L}$ compared to subjects with Hcy concentrations below this value¹¹. Several studies have suggested that hyperhomocysteinemia is also a risk factor for small vessel cerebrovascular disease, resulting in cerebral white matter hyperintensities on magnetic resonance imaging and development of cognitive impairment and dementia^{12,13}.

Due to the dependence of Hcy metabolism on folate, vitamin B12 and vitamin B6, it was expected that the administration of these vitamins could reduce plasma Hcy levels. According to previous trials, vitamin therapy reduces total Hcy¹⁴, and reverses endothelial dysfunction induced by high total Hcy¹⁵. However, it is still unclear whether vitamin supplementation prevents vascular events such as stroke and/or silent brain infarct.

The Vitamin Intervention for Stroke Prevention (VISP) trial originally did not show the efficacy of combined high-dose vitamin therapy for recurrent vascular events in patients with previous nondisabling stroke². However, after exclusion of patients with vitamin B12 malabsorption, those who had received parenteral vitamin B12 and other vitamin B12 supplements and those with renal failure from the original VISP patient group, the stroke incidence was statistically significantly lowered by treatment with high-dose vitamin therapy¹⁶. Other reports also show the beneficial effect of vitamin supplementation therapy on stroke risk reduction, including the Heart Outcomes Prevention Evaluation 2 (HOPE-2) study¹⁷ and a meta-analysis of eight relevant randomized trials reported by Wang *et al.*¹⁸.

Despite these initial convincing data, they were not confirmed by later studies. Lee *et al.*¹⁹ published a meta-analysis of thirteen randomized controlled trials that included participants receiving therapy with

folic acid to decrease plasma Hcy levels. Folic acid supplementation did not demonstrate any major effect on averting stroke among persons with high cardiovascular risk. Similarly, in a recent meta-analysis of eight randomized vitamin treatment trials, Clarke *et al.*²⁰ found no significant effects of dietary supplementation with folic acid on stroke and other cardiovascular events. In the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), reductions in blood Hcy levels with folic acid and vitamin B12 supplementation in patients after myocardial infarction did not show any beneficial effects on further major vascular events²¹. Despite the suggestion that such treatment might preferentially reduce stroke^{17,18}, SEARCH found no significant effect of vitamin therapy on stroke reduction²¹.

In summary, hyperhomocysteinemia is recognized as an independent risk factor for cerebrovascular disease⁴. However, according to the results of recent studies, vitamin supplementation has no beneficial effect on secondary prevention of cerebrovascular disease. At present, screening for hyperhomocysteinemia and vitamin therapy is therefore not recommended. In our young patient with no other well-known cardiovascular risk factors (smoking, hyperlipidemia, arterial hypertension or diabetes mellitus), different types of thrombophilia (including factor V Leiden, mutation in the prothrombin gene, antiphospholipid syndrome) and structural diseases of the heart and vessels were all excluded. Since she suffered further TIAs despite appropriate antiplatelet therapy, it was also decided to test her for hyperhomocysteinemia, which was confirmed and found to be caused by homozygosity for the thermolabile variant of MTHFR (TT genotype) in association with low serum vitamin B12 (possibly due to irradiation of the stomach region during leukemia treatment). After starting vitamin supplementation therapy, the patient had no further TIA episodes in the next two years of follow-up. Vitamin supplementation therapy was beneficial, with an evident clinical response. Despite the present diagnostic and treatment recommendations for secondary prevention, we believe that Hcy lowering could be beneficial in some patients with cerebrovascular disease, as, for example, in younger patients with no additional well-known cardiovascular risk factors or in the very early stages of vascular disease elaboration. Further studies

should attempt to clearly define which patients might benefit from screening for hyperhomocysteinemia and subsequent vitamin supplementation therapy.

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Sažetak

USPJEŠNO LIJEČENJE MOŽDANE ISHEMIJE DODACIMA HRANI U BOLESNICE
S HIPERHOMOCISTEINEMIJOM

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Učinkovitost terapije snižavanja homocisteina u prevenciji moždanog udara ostaje nejasnom. Iako su randomizirana kontrolirana epidemiološka ispitivanja polučila mješovite nalaze, jedna multicentrična studija nije pokazala nikakav koristan učinak, dok genetičke studije još uvijek nedostaju. Prikazuje se slučaj bolesnice s prolaznim ishemijskim napadajima i termolabilnom varijantom metilen-tetrahidrofolat reduktaze (TT genotip) u koje se terapija dodacima hrani radi snižavanja homocisteina pokazala korisnom.

Ključne riječi: *Hiperhomocisteinemija; Ishemijski napadaj, prolazni; Metilen-tetrahidrofolat reduktaza; Vitamini; Dodaci hrani*

