Recurrent Stroke in a Young Patient with Celiac Disease and Hyperhomocysteinemia

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A young man with a longstanding history of asymptomatic anemia and two episodes of stroke within a period of 18 months was found to be suffering from celiac disease (gluten-sensitive enteropathy). Hyperhomocysteinemia, presumably secondary to the folic acid deficiency associated with his celiac disease, may be a major contributor to the coronary arteriosclerosis and cerebrovascular disease seen in this patient.

Patient Description

A 33 year old man was hospitalized because of right hemiparesis of sudden onset. Eighteen months earlier he had suffered stroke in the left hemisphere. His medical history included anemia of at least 15 years duration. Family history with regard to manifestations of atherosclerotic vascular disease was non-contributory. On physical examination he appeared asthenic, with signs of mild right hemiparesis. His weight was 45 kg and his body mass index 16 kg/m^2. A computerized tomography scan of the brain showed an old left basal ganglia infarction, a similar finding to that obtained 18 months earlier.

Electrocardiography demonstrated a pattern compatible with an old anteroseptal myocardial infarction. Echocardiography revealed anteroapical hypokinesis and a 9 x 14 mm mass assumed to be a thrombus at the apex of the left ventricle. Cardiac catheterization demonstrated diffuse arteriosclerosis of the left anterior descending coronary artery and probable apical thrombus. Duplex scanning of the neck showed total occlusion of the right internal carotid artery. Laboratory evaluations for prothrombotic conditions revealed anemia, folic acid deficiency and a high level of plasma homocysteine.

Questioned on the etiology of the anemia, the patient recalled a few episodes of loose stools over a period of many years, with a weight loss of about 10 kg. Barium-contrast small intestinal radiologic examinations demonstrated dilatation of small bowel loops and dispersion of the X-ray contrast material compatible with celiac disease. Anti-endomysial and antigliadin antibody titers were high. Jejunal biopsy specimens showed partial villous atrophy and severe diffuse infiltration of plasma cells. The above findings were compatible with a diagnosis of celiac disease with secondary folic acid deficiency, hyperhomocysteinemia, and left ventricle apical thrombus. Treatment with the oral anticoagulant agent ferrous sulfate and folic acid were recommended along with a life-long gluten-free diet.

After 4 years of follow-up, the patient was recently found to be in complete clinical and laboratory remission [Table 1]. He had gained 17 kg in weight, and his neurologic state was normal. Echocardiography showed no evidence of the probable apical thrombus demonstrated previously. A second series of X-rays of the upper gastrointestinal tract, as well as the result of a

Table 1. Laboratory values

Variable	Reference intervals (N)	Value on admission	Value 1 year later
Hemoglobin (g/dl)	(13–17)	10	15
MCV (m^3)	(80–100)	71	N
Serum iron (g/dl)	(60–160)	19	N
Ferritin (ng/ml)	(20–300)	7	N
Serum folate (ng/ml)	(3.1–12.4)	2	11
Homocysteine (mol/L)	(4–11)	14.9	9
Anti-endomysial Ab titer	(<2.5)	1280	< 2.5
Antigliadin Ab titer	(0–20)	134	< 20
Vitamin B12		N	N
INR, aPTT, fibrinogen		N	N
Activated protein C resistance		N	N
Protein C activity		N	N
Antithrombin activity		N	N
Lupus anticoagulant activity		N	N
Anticardiolipin Ab titer, VDRL		N	N
ANA, RF, CRP, ESR		N	N
LDL cholesterol		N	N
HDL cholesterol		N	N
Triglycerides, TSH, Free T_4		N	N

aPTT = activated partial prothrombin time, ANA = antinuclear antibody, RF = rheumatoid factor, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, LDL = low density lipoprotein, HDL = high density lipoprotein, TSH = thyroid-stimulating hormone, T_4 = thyroxine.

jejunal biopsy obtained a few months after initiation of a gluten-free diet, were interpreted as normal.

Comment

Recent data indicate that an elevated plasma level of the thiol-containing amino acid homocysteine is a common, independent, easily modifiable and possibly causal risk factor for atherosclerosis, which may be no less important than hypertension, hypercholesterolemia or smoking [1].

Hyperhomocysteinemia has been associated with chronic renal failure, low plasma levels of vitamin co-factors (B6, B12 and folate), aging, menopause, and cardiac or kidney transplantation. Mutations in any of the three enzymes related to homocysteine metabolism – namely cystathionine-β-synthase, methylenetetrahydrofolate reductase, or methionine synthase – critically affect the eventual plasma level of that thiol-containing amino acid [2]. Studies both *in vitro* and *in vivo* point to several possible mechanisms of vascular damage mediated by high homocysteine levels. These include endothelial dysfunction, activation of factor V and tissue-type plasminogen activator, enhanced platelet aggregation, and inhibition of protein C.

Thromboembolic complications (deep vein thrombosis, stroke, cardiac thrombosis), though rare, have been described in chronic ulcerative colitis and Crohn's disease [3]. These vascular complications have been attributed to hypercoagulation manifested by thrombocytosis, increased thromboplastin generation time, and increase in fibrinogen and clotting factor VIII. The literature contains few solid data on a possible link between celiac disease and thromboembolic events.

A Medline search revealed four reports: two from Switzerland and Norway describing an association between hyperhomocysteinemia and celiac disease, and two from Australia and France on deep venous thrombosis and splenic thrombosis (respectively) as the presenting feature of celiac disease and hereditary hyperhomocysteinemia [4,5].

The present report appears to be the first description in an English-language journal of a patient suffering from a possibly related combination of celiac disease with acquired folic acid deficiency due to malabsorption causing secondary hyperhomocysteinemia, cardiac thrombosis, coronary arteriosclerosis, carotid arteriosclerosis, and recurrent stroke. We suggest that future studies investigate vitamin status and homocysteine metabolism in celiac disease and other malabsorption syndromes.

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