Bilateral Internal Carotid Artery Dissection in Cystathionine Beta-Synthase Deficiency

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Dear Sir,

Homocystinuria is the second most common congenital aminoacidopathy after phenylketonuria [1–3]. The most commonly involved enzyme is cystathionine beta-synthase (CBS) (MIM 236200), responsible for major hyperhomocysteinemia and homocystinuria. Commonly diagnosed during childhood, it is rarely revealed in adult life. Here we report a patient who presented strokes due to bilateral internal carotid occlusion. Etiological work-up found CBS deficiency. The mechanism of occlusion was bilateral artery dissection. Only one case of cervical artery dissection in major homocystinemia has been reported previously [4]. However, increased homocysteine levels were recently described [5, 6] in spontaneous cervical artery dissection in young adults.

Case Report

A 35-year-old white woman was admitted with headache, right arm weakness and painful neck that had commenced 3 days previously. She had a medical history of bilateral luxation of the lenses at the age of 30, gravidic hypertension, miscarriage and mild depression. Her only vascular risk factor was estroprogestative pill intake. Family medical history was unrevealing. Dihydroergotamine had been given for hypotension 4 days before the first symptoms. On admission to the neurological ward, she was conscious with a headache and right hemiparesis but no neck stiffness. General examination revealed marfanoid features with thin blond hair, arm span:height ratio

>1.05 and arched palate. Neither skin abnormalities nor hyperextensible joints were found. She was treated with aspirin at 250 mg daily. Three days later, she suddenly became comatose and was transferred to the neurological intensive care unit for respiratory assistance. Her Glasgow Coma Scale rated 6, she presented with spastic tetraparesis. Cerebral CT scan, Doppler sonography and cerebral MRI suggested ischemic stroke by occlusion of both internal carotid arteries (ICA). On MRA, the left ICA was missing and the right ICA had tapering narrowing aspect. Axial CT angiography confirmed the dissection of both ICAs with intracranial extension (fig. 1a). Transthoracic echocardiography and 24-hour Holter results were normal. Blood sampling found major hyperhomocysteinemia, with total

plasma homocysteine at 158 $\mu\text{mol/l}$ (normal <15 $\mu\text{mol/l}$). The plasmatic methionine level was in the upper normal range. Urinary amino acids chromatography confirmed homocystinuria at 160 $\mu\text{mol/l}$ (normal <10). Foliates and vitamin B₁₂ were mildly decreased. Antithrombin III, protein C and protein S were within the normal range. Mutation of factor V Leiden was not detected. She was heterozygote for the C677T mutation of the methylene tetrahydrofolate reductase (MTHFR), but enzymatic activity of MTHFR was normal. On thoraco-abdominal CT scan neither asymptomatic aorta aneurysms nor enlargement of the proximal aorta arch was found. Dural ectasia at lumbosacral level was ruled out by spine MRI. No sign of osteoporosis was found on bone X-ray. Al-

Fig. 1. a Axial neck CT angiography showing filling defects with mild dilatation of the left ICA and intimal flap (arrow) of the right ICA with no evidence of atherosclerosis. **b** Axial T₂ fat saturation MR at 2 months found hyperintensity around signal intensity void (arrow).

most no activity of CBS in cultured skin fibroblasts was measurable. Family screening revealed no additional affected member. Without the guidelines of randomized trials but solely on the basis of the clinical time-course and of radiological findings, we considered the ischemic risk to be greater than the bleeding risk, and decided to treat by intravenous heparine therapy. A low methionin diet, with betaine and vitamin supplements (pyridoxine, B₁₂ and folates) was started. After 1 month of appropriate treatment, total plasma homocysteine was down to 61 $\mu\text{mol/l}$, to 51 $\mu\text{mol/l}$ after 2 months and to 13 $\mu\text{mol/l}$ after 1 year. Heparin was switched to aspirin (250 mg/day) after regularization of homocysteine plasma levels. T₂ fat saturation sequence at 2 months is shown in figure 1b. Neurological improvement slowly ensued, but 1 year after discharge she still presented with right hemiparesis and severe frontal syndrome.

Discussion

CBS deficiency is the most common cause of major homocysteinemia [1, 2]. The clinical picture is highly variable, including ectopic lenses, osteoporosis, skeletal abnormalities, marfanoid features, mental retardation, psychiatric disturbances and vascular disease; arterial or venous thromboses are also experienced. Our patient presented with the normal features of the disease at age 30: ectopic lenses, marfanoid features and mild psychiatric disturbance. Dural sac:vertebral body ratio, using MRI, was normal. This ratio is known to identify Marfan syndrome with 95% sensitivity and 98% specificity [7, 8]. Miscarriage has been described previously and related to the disease [9]. Mudd [1] and McCully [10] were the first to describe the relationship between vascular events and CBS deficiency. A common pathogenesis of vascular occlusions in this disease is atherothrombosis. This was confirmed by anatomopathological and sonographic data [11].

Bilateral spontaneous internal carotid dissections are rare events but can occur without any known risk factor (4% of all internal carotid artery dissections) [12]. Previously, only 1 case of cervical artery dissection was described in CBS deficiency [4].

On the other hand, Konrad et al. [13], comparing spontaneous cervical artery dissection patients with matched healthy individuals, suggested that a moderately elevated homocysteine level is associated with the occurrence of spontaneous cervical artery dissection. Two additional recent studies revealed a link between mild hyperhomocysteinemia and cervical arteries dissection in young adults [5, 6]. Experimental data suggested activation of elastases and metalloproteases is associated with high levels of homocysteine [14]. Interaction between homocysteine and arterial elastic fibers could play a role in artery dissection [15]. Other connective tissue disorders – i.e. Marfan disease, Ehlers-Danlos type IV syndrome, osteogenesis imperfecta and pseudoxanthoma elasticum – are known to cause arterial dissections [16].

Our case report supports the hypothesis of a causal relationship between CBS deficiency and ICA dissection. It remains unclear why only 2 cases of artery dissection in CBS deficiency have been described. Other external factors such as drug intake could trigger dissection in previously altered arterial walls.

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