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Case Report

Headache and *MTHFRT677T* Genotype in a Young Woman - Clinical Case

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Abstract

Introduction: The *MTHFRC677T* polymorphism is involved in several pathologies.

Objectives: We report one case of headache associated with the *MTHFR T677T* genotype in a woman.

Observation: A 39-year-old woman was admitted in neurology department on March 12, 2012 for headaches with feet and hands parathesia for several months. The physical examination had noted a decrease in osteotendinous reflexes and an abolition of the plantar cutaneous reflex. Hamilton's 17-item depression score was 7. In the etiological investigation of probable polyneuropathy, homocysteine was 88.39 µmol/l (standard < 15 µmol/l), folates 2.34 nmol/l (standard ≥ 11 nmol/l) and vitamin B_{12} 132 pmol/l (standard ≥ 147 pmol/l). The aetiological investigation of this hyperhomocysteinemia revealed an *MTHFRT677T* genotype.

Conclusion: The *MTHFRT677T* genotype is associated with a variety of manifestations ranging from metabolic (B_{12} deficiency), headache and polyneuropathies.

Keywords: *MTHFR* Polymorphism; Headache; Polyneuropathy

Introduction

There are multiple polymorphisms of the methylene tetrahydrofolate reductase *(MTHFR)* gene. The *MTHFRC677T* polymorphism including the *MTHFRT677T* genotype induces a significant deficiency in the activity of the enzyme MTHFR which compromises the conversion of homocysteine into methionine [1]. Homocysteine metabolism involves vitamins B_6, B_9, and B_{12}. The *MTHFRT677T* genotype has been associated with vitamin B_{12} deficiency. Vitamin B_9 deficiency may also be linked to several causes, including nutritional factors [2]. The *MTHFRC677T* genotype is described in vascular diseases through Hyperhomocysteinemia, in other neurological conditions such as migraine, peripheral neuropathies and psychiatric conditions such as depression [2].

Objectives

We report one case of headache associated with the homozygous *MTHFR T677T* genotype in a woman.

Case Report

A 39-year-old patient was admitted in neurology department on March 12, 2012 for headache, paraesthesia on the feet and hands

for several months. The headaches were sometimes occipital or in whole head, with a sensation of heaviness, burning head almost permanent, without nausea or vomiting, not calmed by antalgic drugs. Headaches were rated at 40/100 on the analog visual scale. Headaches were associated with permanent vertigo, an impression of lightness with unstable walking. She sometimes had sleep paralysis. The patient had a depressive episode in 2009 that had regressed after 6 months with psychiatric care. Before her admission in neurology department, the patient had undergone several treatment including vitamin B complexes, which resulted in significant regression of paresthesia of feet and hands. In her background, she has 6 children, including a 24-year-old asthmatic girl, and a 14-year-old epileptic boy. She has a 28-year-old (maternal) half-sister with chronic headaches, a 38-year-old half-brother with chronic psychosis, a 34-year-old half-brother with eye pain, and a 43-year-old half-brother with sensory polyneuropathies. At the physical examination, the blood pressure was 120/80 mm Hg in both arms, the weight was 75 kg for a height of 1m 69 (Body Mass Index =26.2 kg/m^2). There was neither deep nor superficial sensory disturbance. The osteotendinous reflexes were diminished and the cutaneo-plantar reflexes were abolished. There was no nystagmus. The rest of the physical examination was normal. The patient was assessed by 2 psychiatricians who concluded that she was not depressed. Two evaluations with an interval of two weeks of Hamilton scale at 17 items [3] displayed an average score of 7. The biologic test including creatinine, blood glucose, total cholesterol, HDL, LDL, triglycerides, transaminases and Gamma Glutamyl Transferases (Gamma GT) were normal. Blood count, C-reactive protein (CRP), erythrocyte sedimentation rate, thyroid hormones and blood ionogram were normal. Human immunodeficiency virus (HIV) serology was negative. In the aetiological investigation of probable polyneuropathy, homocysteine was 88.39 µmol/l (standard < 15 µmol/l), folates 2.34 nmol/l (standard ≥ 11 nmol/l) and vitamin B_{12}, 132 pmol/l (standard ≥ 147 pmol/l). The high level of homocysteinemia associated with vitamin folates and B_{12} deficiencies motivated the investigation of the polymorphism *MTHFRC677T*. For the genotyping, the patient had given verbal consent. The *MTHFRC677T* polymorphisms were genotyped by TaqMan SNP genotyping tests according to the manufacturer's instructions. The genotype was called using QuantStudioTM 7 Flex (v 1.0) (Applied Biosystem) real-time PCR system and software on DNA samples extracted from saliva samples. The search for this polymorphism displayed a homozygous genotype *MTHFRT677T*. The electroneuromyogram (Figure 1), Electroencephalogram (figure 3), and brain CT scanner were normal. We have retained the diagnosis of *MTHFRT677T* genotype associated with chronic headaches by somatization disorders according to the criteria of the International Headache Society [3] with probable polyneuropathy according to the medical history and biological findings. She was treated with 10 mg per day of folic acid, 250 µmol/l of vitamin B_{12} for 6 months and 10 drops of amitriptyline in the evening for three months. After 6 months of treatment, the headaches had regressed to 15/100 with much more spaced intervals. The biologic control test of folate was 45.4 nmol/l, the vitamin B_{12} was 449 pmol/l and homocysteine was 33.03 µmol/l. She was diagnosed open-angle glaucoma in 2016 and treated with a beta-blocker (timolol) with normalization of intraocular pressure. Since July 2020, she has had tinnitus of motor-sound type in both ears with a slight hearing impairment of the right ear on the audiogram (Figure 2).

Electroneuromyographic recording

Right external popliteal sciatic nerve

Site	latency	amplitude	limb segment	latency	distance	Conduction velocity
Ankle	3.4 ms	5.0 mV	Ankle-Under collar	7.0 ms	340 mm	49 m/s
Under collar	10.4 ms	4.2 mV	Under collar - Upper collar	1.9 ms	90 mm	47 m/s
Upper collar	12.3 ms	4.1 mV		ms	mm	m/s

F wave

Nerve	Latency - M	Latency - F
Ulnar	2.5	27.3

Sensory and mixed nerve conduction

Figure 1: Normal electroneuromyography.

Figure 2: Audiometry showing a mild right-sided hearing loss on the low frequencies.

Figure 3: Normal EEG pattern with alpha posterior dominant rhythm.

Discussion

The *MTHFRT677T* genotype was described in vascular pathologies such as hypertension, in psychiatric conditions such as depression and migraine. This clinical case raises the multiplicity of pathologies involving the *MTHFR* gene. Although the majority of the literature associates the *MTHFRT677T* genotype with migraine, the headaches in this clinical case raises the characteristics of psychogenic headaches [4]. Recent studies have pointed out the association of a migraine without aura and the *MTHFRC677T* polymorphism in its homozygous or heterozygous form [5]. However, the headaches in our patient did not have the diagnostic criteria for migraines. Homocysteinemia remained high (33.03 µmol/l) despite the normalization of folate (45.4 nmol/l) and vitamin B_{12} (449 pmol/l), which ruled out vitamin deficiency as the cause of hyperhomocysteinemia. In homozygous TT forms of the *MTHFR* gene, the enzymatic activity of *MTHFR* is no longer sufficient to ensure normal homocysteinemia [6]. Glaucoma is one of the most common ophthalmic conditions with progressive atrophy of the

optic nerve and loss of vision. Multiple meta -analyses have established the correlation between polymorphism of *MTHFRC677T* and open-angle glaucoma, however the pathophysiological mechanism remains poorly elucidated and a vascular cause including hyperhomocysteinemia is suspected [7]. We do not have sufficient arguments for the diagnosis of sensitive polyneuropathy in this patient. However, folate-deficiency neuropathy is reportedly characterized by a predominance of sensory symptoms with a slow progression. This study shows the importance of folate deficiency in the differential diagnosis of neuropathy, in our developing countries. Hyperhomocysteinemia is described in diabetes-related neuropathy with a complex pathophysiology [8]. Hyperhomocysteinemia is known as a predisposing factor for peripheral neuropathy may be directly or indirectly through the folate and vitamin B_{12} deficiencies, two factors that provide peripheral neuropathy. The B_{12} deficiency described in Biermer's disease gives a picture of combined sclerosis of the spinal cord with pyramidal symptoms and ataxic sensory [9] Several studies have established the link between the *MTHFRT677T* genotype and vitamin B_{12} deficiency, but the mechanism of action is poorly understood. Cobalamin participates in biochemical reactions to the constitution of the basic protein of myelin and in the production of tetrahydrofolates for the synthesis of DNA [10]. If the folate deficiency in our patient is probably nutritional, the less common B_{12} deficiency in the population would be related to the homozygous genotype *MTHFRT677T* [11-13]. Folic acid may interfere with the synthesis of myelin. There is an interdependence between vitamin B_{12} and folic acid.

Conclusion

The *MTHFRT677T* genotype is associated with a variety of manifestations ranging from metabolic (B_{12} deficiency), headaches, polyneuropathies and psychiatric conditions. *MTHFR T677T* genotype greatly reduces the enzymatic activity of *MTHFR.* Hyperhomocysteinemia due to *MTHFRT677T* genotype cannot be reduced by vitamin B supplementation.

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