MTHFR C677T AND PROTHROMBIN G20210A MUTATIONS IN A WOMAN FROM DALMATIA WITH SILENT BRAIN INFARCTION

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SUMMARY – A 55-year-old, previously healthy woman, presented with frequent headaches. She had no neurological disturbances, but had a positive family history; her father died from stroke. Magnetic resonance imaging showed brain infarction; therefore detailed diagnostic evaluation of thrombophilia markers and genetic testing were performed. The patient was found to be homozygous for the C677T mutation of the methylenetetrahydrofolate reductase gene and heterozygous for the mutation of the prothrombin G20210A gene. No other cause of cerebral infarction was found in the patient.

Key words: *MTHFR C677T; Prothrombin G20210A; Stroke; Silent brain infarction; Case reports*

Introduction

Silent stroke, and in particular silent brain infarction (SBI), is a term widely used to describe cerebral infarcts seen on brain imaging without any, or with unrecognizable corresponding stroke episode. Often, routine screening imaging is performed in healthy people as part of medical evaluation, resulting in SBIs detected in people of all ages. SBI was usually defined as focal T2 hyperintensities >3 mm with correlative T1 hypointensities[1].

Stroke is a multi-factorial polygenic, complex disease resulting from a combination of vascular, environmental and genetic factors. Many meta-analyses demonstrated positive associations of ischemic stroke with methylenetetrahydrofolate reductase (MTHFR) C677T and prothrombin G20210A polymorphisms[2,3].

A patient with SBI associated with MTHFR C677T homozygous mutation and prothrombin G20210A heterozygous mutation is described.

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Case Report

A 55-year-old woman was referred to the Clinical Department of Neurology, Split University Hospital Center because of frequent headaches. She had diffuse, persistent pain of mild to moderate intensity, vomiting and vertigo excluded. Headache occurred frequently and lasted for more than 24 hours. Taking analgesics decreased the pain, but not completely. Her family history was positive for vascular disorders, i.e. her father died from stroke. She had no other chronic disease and had not been taking drugs by that time. Neurological examination showed no meningeal signs, no cranial nerve deficits, negative Romberg's sign, no difficulty in performing coordination tests, and no signs of ataxia or nystagmus. Routine laboratory tests were negative too. Due to the family history and frequent headaches that had not resolved completely after taking analgesics, she was referred to undergo magnetic resonance imaging (MRI), which recorded vascular lesions (Figs. 1 and 2). After these findings, she was referred for diagnostic evaluation of thrombophilia markers. The patient was found to be homozygous for the C677T mutation of the methylenetetrahydrofolate reductase (MTHFR) gene and

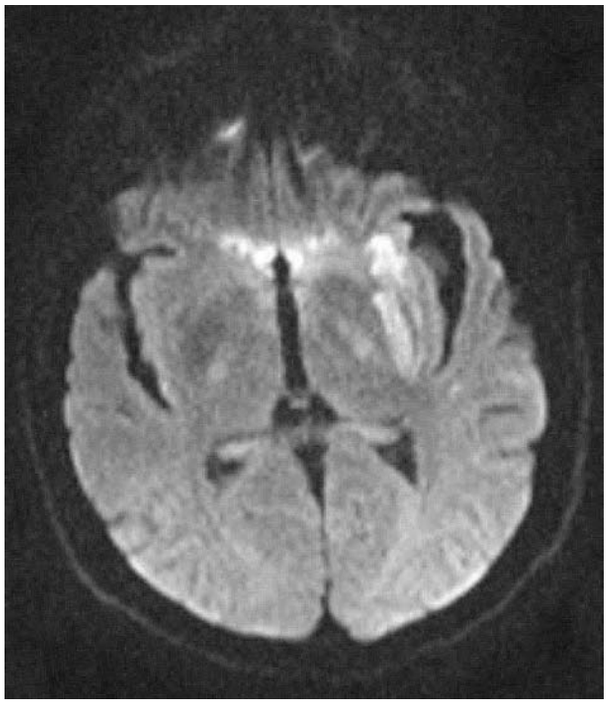

Fig. 1. Magnetic resonance imaging (diffusion-weighted imaging, DWI).

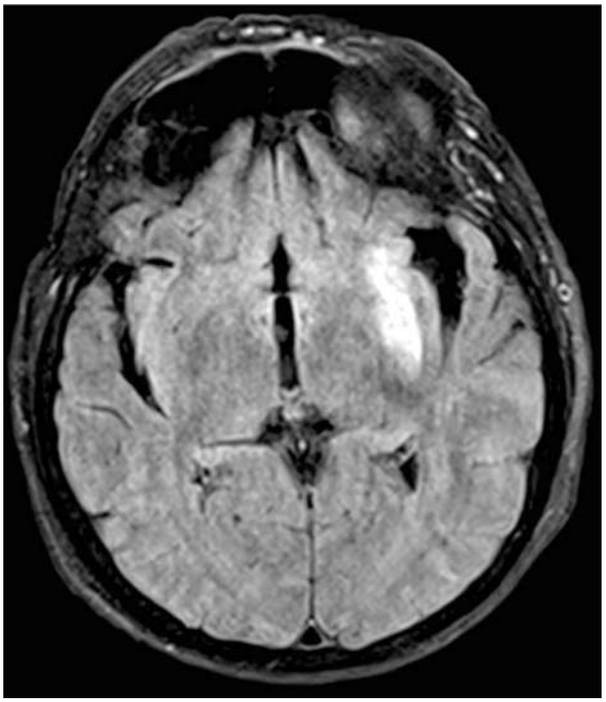

Fig. 2. Magnetic resonance imaging (fluid attenuated inversion recovery, FLAIR).

heterozygous for the mutation of the prothrombin G20210A gene by polymerase chain reaction (PCR) analysis. Genetic analysis of Factor V Leiden, plasminogen activator inhibitor (PAI) and angiotensin converting enzyme (ACE) was normal. Other thrombophilia markers including protein S, protein C and antithrombin III proved normal. Lupus anticoagulant tests and serum titers of anticardiolipin IgG and IgM, β2 glycoprotein 1 IgG and IgM, and antinuclear and anti-DNA antibodies were normal. Routine laboratory tests for the most common autoimmune diseases were also negative. In addition, serum cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, and complement components C3 and C4 concentrations were normal. Homocysteine level was also normal (5.6 μmol/L). She was referred to the cardiologist as well. Electrocardiogram, cardiac ultrasonography and cardiac examinations did not yield any pathologic findings and no other cause of cerebral infarction was found in the patient. The patient did not have any other risk factors such as obesity, smoking, high blood pressure, diabetes, or using some hormone therapy.

She was treated with oral anticoagulants, monitoring coagulation parameters daily, and maintaining the INR index between 2 and 3. The anticoagulation regimen was administered over two months, and then it was substituted with aspirin (100 mg/day). Her diet was not poor in vitamins, but a multivitamin (folic acid and other B vitamins) was given with the antiplatelet agent, notwithstanding the incompletely established role of vitamins in preventing endothelial damage. On the last follow up, her neurological finding was stable.

Discussion

In general population, the prevalence of SBI as defined by MRI ranges from 8% to 28%, with a higher prevalence with increasing age[1,4,5]. Although silent infarcts, by definition, lack clinically overt stroke-like symptoms, they are associated with subtle deficits in physical and cognitive function that commonly go unnoticed. Moreover, the presence of silent infarcts more than doubles the risk of subsequent stroke and dementia. Because of that, screening and treating

high-risk patients can effectively reduce the risk of further infarcts, stroke and dementia[1].

Headache is more common in strokes in the posterior circulation and in cerebellar infarctions than in strokes in the anterior circulation, but then it occurs with dizziness, nausea, vomiting, and gait instability[6]. In our case, we show that vascular lesions can also go with nonspecific headache, but without other symptoms or neurologic disturbances. Because of that, we classified these vascular lesions as SBI.

There are multiple genes involved in the pathogenesis of stroke, e.g., factor V Leiden Gln506, ACE I/D, MTHFR C677T, prothrombin G20210A, PAI-1 5G allele and glycoprotein IIIaLeu33Pro polymorphisms. Mutation of the prothrombin G20210A gene and especially mutation of the MTHFR C677T gene appear to be risk factors for stroke in adults, but also in children[2,3].

Among the risk factors for cerebral stroke, the MTHFR C677T mutation might lead to elevation of plasma concentration of homocysteine, which has been associated with an increased risk of ischemic stroke. Although the relationship between the increased plasma homocysteine level and cardiovascular diseases is well-documented, the molecular mechanism of endothelial damage has not yet been completely understood[7-10]. However, this mutation might exert its effect *via* a mechanism other than elevating homocysteine concentration, as in our case. Further studies are needed to verify how C677T mutation of the MTHFR gene can be a risk factor for stroke, regardless of high homocysteine concentration.

Prothrombin G20210A mutation was found to cause elevated levels of blood prothrombin (by one-third above normal), which is more than the extra 15% needed to develop thrombosis. Also, it has been proven that prothrombin G20210A mutation leads to increased mRNA and protein expression for prothrombin[11]. In a sample of adult north Mediterranean population younger than 65, the prevalence of prothrombin G20210A mutation was greater in patients with ischemic stroke than in matched controls[12]. It is important to point out that the prevalence of prothrombin G20210A mutation is higher in south Europe countries than in north Europe countries, in spite of the overlapping between the north and south. The prevalence of prothrombin G20210 mutation in general healthy population in Croatia is 2.5%-4.0%[13].

One of 7 patients with first-ever acute ischemic stroke will test positive for one of the inherited thrombophilias, but the relation is likely to be coincidental rather than causal in almost all cases, irrespective of the pathogenic subtype of ischemic stroke[14]. The situation is not different in Croatia. These results suggest that routine testing for thrombophilia in most patients with acute ischemic stroke may be unnecessary. Whether thrombophilias may still be important in younger patients with ischemic stroke or in predicting complications and stroke outcome, remains uncertain.

In conclusion, in middle-aged patients with findings of brain vascular lesions on MRI, it is important to examine the most common genetic mutations that are referred to as the risk of stroke, which include C677T mutation of the MTHFR gene and mutation of the prothrombin G20210A gene, especially in patients with no other risk factors such as obesity, smoking, high blood pressure, diabetes, or using some hormone therapy. Identification of these mutations is important in the overall assessment and management of patients at high risk. It is also important because of initiation of antithrombotic therapy for either primary or secondary thromboprophylaxis, duration of therapy, the potential of avoiding clinical thrombosis by risk factor modification, and genetic counseling of family members.

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Sažetak

MTHFR C677T I PROTROMBIN G20210A MUTACIJE U BOLESNICE IZ DALMACIJE S TIHIM MOŽDANIM UDAROM

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Prikazuje se slučaj dotad zdrave 55-godišnje bolesnice koja se javlja s učestalim glavoboljama. Nije imala nikakve neurološke ispade, ali je imala pozitivnu obiteljsku anamnezu. Otac joj je umro od moždanog udara. Magnetna rezonanca je pokazala infarkt mozga zbog čega je napravljena detaljna dijagnostička evaluacija tromboembolijskih biljega te genetska ispitivanja. Utvrđeno je da je bolesnica homozigot za mutaciju C677T gena metilentetrahidrofolat reduktaze i heterozigot za mutaciju gena protrombina G20210A. Nije pronađen nijedan drugi uzrok moždanog udara.

Ključne riječi: *MTHFR C677T; Protrombin G20210A; Moždani udar; Tihi moždani udar; Prikazi slučaja*