Case Report

Cerebellar stroke in a young female associated with elevated homocysteine levels and heterozygous MTHFR *C677T* gene: A case report.

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Abstract

Homocysteine is an amino acid, which is an intermediate in the metabolism of methionine and cysteine. Elevated homocysteine levels are recognized as a cause for both arterial and venous thrombotic phenomena. Methylenetetrahydrofolatereductase -encoded by *MTHFR* gene- is the rate-limiting enzyme of the remethylation of homocysteine to methionine. Homozygous *MTHFR T677T* gene mutation can independently cause raised homocysteine levels and increase the risk of thrombosis whereas heterozygous *MTHFR C677T* gene mutation usually does with an acquired cause such as folate or vitamin B12 deficiency, and is with lesser risk for thrombosis. We report a case of a previously healthy 23-year-old female, who was excluded from other inherited and acquired thrombophilic conditions, but was found to be having heterozygous *MTHFR C677T* gene mutation and elevated level of homocysteine presented late with right cerebellar stroke. Therefore, when young patients present with thrombotic phenomena, homocysteine levels should be assessed in the absence of other common thrombophilic conditions.

Keywords: Young stroke, Homocysteine, *MTHFR*, Thrombosis

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Introduction

There are multiple causes for ischemic stroke in the young [1]. Hyperhomocysteinaemia is increasingly recognized as one of the causes. Homocysteine is an amino acid produced in methionine metabolism, of which the rate-limiting enzyme is methylenetetrahydrofolate reductase, encoded by the *MTHFR* gene [2]. Mutations of this gene can cause elevated levels of homocysteine, especially the homozygous *MTHFR T677T* variant [3]. We report a case of a young female having heterozygous *MTHFR C677T* gene mutation and elevated level of homocysteine presented late with a right cerebellar ischemic stroke.

Case presentation

A previously healthy 23-year-old right-handed girl presented with sudden onset slurred speech and right upper limb weakness and difficulty in walking for two days duration. She had a tendency to fall to her right. She had no episodes of loss of consciousness or seizures. On examination, she had marfanoid body habitus, i.e. tall stature, arm span to height ratio 1.08, high arched palate and hyperextendable joints. Her blood pressure was 110/70 mmHg and her pulse rate was 72 beats per minute with a regular rhythm. Bilateral upper and lower limbs were with normal tone, power and reflexes. There was no sensory impairment, however, coordination was affected in the right upper limb and lower limb along with dysarthria. An urgent non-contrast computed tomography (NCCT) of the brain revealed a hypodense lesion in the right cerebellum, consistent with an acute ischemic stroke. The magnetic resonance imaging (MRI) of the brain (Figure 1) done three months later confirmed this diagnosis with the gliosis noted in the right cerebellum. As the National Institutes of Health Stroke Scale (NIHSS) was 03, she was started on dual antiplatelet therapy with high dose atorvastatin for three weeks and continued with a single antiplatelet drug (clopidogrel 75mg) with atorvastatin there onwards. With occupational therapy for hand skills, physiotherapy balance training and speech therapy, she gained back her normal functional status by two months.

The full blood count showed normal cell counts and a haematocrit of 35.9% excluding polycythemia. Her renal function tests and liver function tests were within the normal limits. The prothrombin time was 11.2s with the international normalized ratio (INR) of 1.019, while activated partial thromboplastin time (APTT) was 26.1s; all of which were within the normal ranges. Her HbA1c was 4.8% (normal <5.6%). The lipid profile was within normal limits; low-density lipoprotein cholesterol 92mg/dl, triglycerides 43mg/dl and high-density lipoprotein cholesterol 58.5mg/dl. Serum-corrected calcium level was 2.35mmol/l(2.15-2.65mmol/l). Her two-dimensional echocardiogram was normal and the CT-cerebral angiogram depicted normal vasculature. The erythrocyte sedimentation rate was 5mm/1st hour and anti-cardiolipin antibodies (IgM and IgG) were negative. Diluted Russell viper venom time (dRVVT) done three months after the presentation was negative, for lupus anticoagulant. Protein C level and protein S level were within the normal range. JAK2 V617F mutation, factor 5(F5) Leiden mutation and prothrombin G20210A mutation were not detected. Her serum homocysteine level was elevated to 25.8µmol/l (5-15µmol/l) while the vitamin B12 level was within the normal range;525pg/ml (200-1100pg/ml), and the *MTHFR C677T* gene mutation was detected. Therefore, she was started on oral folate 1mg daily and the homocysteine level came down to 15µmol/l after three months.

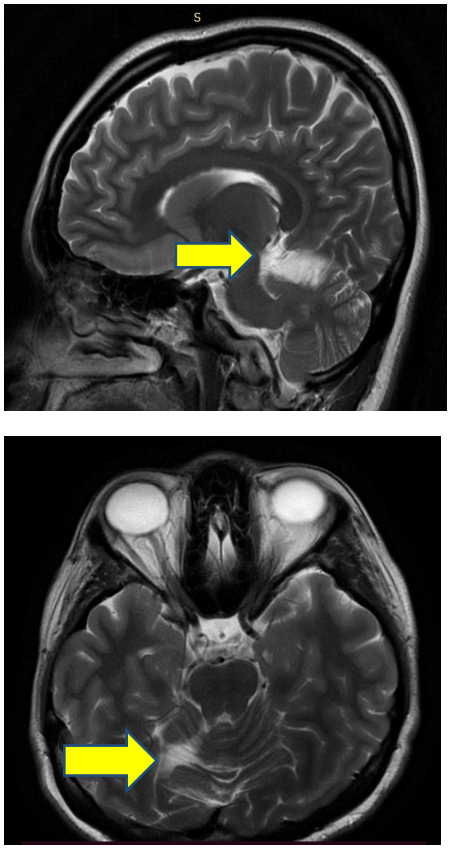

Figure 1: Yellow arrows indicating right cerebellar gliosis in T2 weighted MRI brain

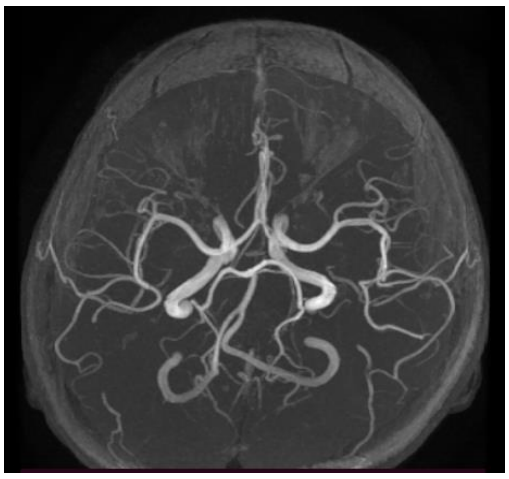

Figure 2: Normal MR angiogram

Discussion

This case highlights the importance of seeking homocysteinemia as a cause of stroke in the young even in the presence of heterozygous MTHFR gene mutation. It was not considered to be pathogenic in the past unless associated with vitamin B12 or folate deficiency. However, the current studies have suggested elevated homocysteine level alone as a risk factor for stroke and heterozygous MTHFR gene mutation is correlated.

According to the Trial of Org 10172 in acute stroke treatment(TOAST) there are five types of ischemic stroke; atherosclerosis in large arteries, cardiac thromboembolism, small vessel occlusion, stroke of other determined etiology and stroke of undetermined etiology [4]. Large artery atherosclerosis is rare in the young. Causes for cardiac thromboembolism are atrial fibrillation, cardiac tumours, cardiomyopathy, endocarditis and atrial-septal defects, which were excluded in this patient with the normal ECG and 2D-echocardiography. Fabry disease and small vessel diseases are unlikely in this patient as her MRI brain did not show any white-matter hyperintensities or microbleeds apart from the cerebellar infarction, which she presented with. Strokes of determined aetiology include multiple causes as follows. Antiphospholipid syndrome and other autoimmune conditions were excluded in this patient. Factor II deficiency, factor V Leiden mutation, protein C and S deficiency were excluded as well. Intracranial arterial dissections, Moyamoya disease, reversible cerebral vasoconstriction syndromes and vasculitis were unlikely in this patient with the normal cerebral angiography findings (Figure 2). Pregnancy was excluded. There was no family history suggestive of mitochondrial diseases and she was not engaged in any illicit drug use [1].

The abnormalities seen in Marfan syndrome are also described with homocysteinemia. In this patient, although she had Marfanoid body habitus, she did not have lens subluxation or cardiac defects which are involved in Marfan syndrome.

Homocysteine is an amino- acid produced in the middle of the metabolism of methionine and cysteine in the body. Homocysteine is methylated to methionine by methionine synthase with vitamin B12 as the co-enzyme, while folate is converted to tetrahydrofolate by methylenetetrahydrofolate reductase (MTHFR), which is the rate-limiting enzyme of the remethylation pathway. It is the MTHFR gene that encodes the enzyme. Defects in this enzyme, folate deficiency or vitamin B12 deficiency can result in elevated homocysteine levels [2]. Elevated homocysteine levels as a cause of thrombosis are recognized [5,3]. The mechanism of it is yet to be understood. It is shown in studies that homocysteine can induce atherosclerosis by a C-reactive protein-mediated inflammatory process in the vascular smooth muscle [6]. *MTHFR* gene mutation could be homozygous*(T677T)* or heterozygous*(C677T).* The homozygous mutation is associated with higher homocysteine levels than the heterozygous mutation, hence correlating with a higher risk of thrombosis [3]. A deficiency of folate or vitamin B12 can augment the enzyme deficiency in a heterozygous mutation.

A meta-analysis has shown 27% increase in venous thrombosis for 5µmol/l increase in homocysteine level in prospective studies and 60% in retrospective studies [7]. One study conducted in India suggested that *MTHFR C677T* is a strong risk factor for arterial strokes [8]. In a Chinese study among a large population of ischemic stroke patients, a significant association with elevated homocysteine has been demonstrated, and the level of homocysteine was observed to be highest with *TT* variant which was followed by *CT* and *CC* variants. Although both *TT* and *CT* variants were correlated with stroke, only the *TT* variant had a significant association with an increased risk of ischemic stroke [3]. Therefore, in the absence of other possible causes of ischemic stroke in this young patient the presence of *MTHFR C677T* gene mutation and hyperhomocysteinemia despite the normal vitamin B12 level is the most likely cause for the ischemic cerebellar stroke. Folic acid supplementation has been shown to reduce the level of homocysteine level by 25%, however a meta-analysis has found that it had no significant 5-year-risk reduction in cardiovascular disease [9,10].

Conclusion

Elevated homocysteine level is a recognized risk factor for thrombotic phenomena. Heterogenous *MTHFR C677T* gene mutation alone may cause elevated levels of homocysteine. Therefore, it is necessary to exclude hyperhomocysteinemia in young patients with ischemic stroke in the absence of other common risk factors. More research is needed in South-Asians to understand the prevalence and behaviour of *MTHFR* gene mutations and their risk in thrombosis.

Consent

Informed written consent was obtained from the patient**.**

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