

Methylenetetrahydrofolate reductase homozygous mutation in a young boy with cerebellar infarction

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Abstract

Posterior circulation vascular occlusive disease in children is a rare and uncommonly reported event. Among the numerous risk factors, the methylenetetrahydrofolate reductase (MTHFR) mutation is considered to be a common genetic cause of thrombosis in adults and children. Recently, a link between the MTHFR mutation and cerebrovascular disorders was reported in children. Diffusion tensor imaging (DTI) is a great improvement on magnetic resonance imaging (MRI), making the *in vivo* anatomical and pathological study of the brain and its fibers possible. In our patient cerebellar infarction was associated with MTHFR mutation and, in a standard neurological examination, DTI revealed normal white matter tracts.

Introduction

Posterior circulation vascular occlusive disease is rare in children whereas in adults underlying vascular disease accounts for a high percentage of posterior circulation infarction. The most commonly reported cause of vertebrobasilar occlusion in children is traumatic injury to the cervical vertebral artery.¹ Recently, a link between the methylenetetrahydrofolate reductase (MTHFR) mutation, which is considered to be a common genetic cause of thrombosis in adults and children, and cerebrovascular disorders was reported in children.² The observation that most children with the MTHFR mutation do not present with cerebrovascular disorders may be a result of the requirement for additional thrombogenic risk factors.³ However, the concurrent effects of other circumstantial or genetic thrombogenic risk factors have not been established clearly, and further studies are needed to determine which associated exogenous and endogenous risk factors predispose infants with the

MTHFR mutation to cerebrovascular disorders. We report on a patient in whom cerebellar infarction was associated with MTHFR homozygous mutation.

Case Report

Our patient, a boy, was born at 36 weeks' gestation by normal vaginal delivery and had Apgar scores of 9 and 10 after 1 and 5 minutes. The family history was positive for vascular disorders: two relatives died from heart attacks. Neurological developmental milestones were normal according to age. At the age of seven years the child was hospitalized for head trauma with consequent vertigo and vomiting. No changes were observed on neuro-radiological investigation and the neurological examination was normal. At the age of 13 years he had an acute episode of headache associated with vomiting. For these reasons he was referred to our Pediatric Emergency Department where he presented with headache, further vomiting, and marked vertigo. On neurological examination he showed no meningeal signs, no deficit of the cranial nerves, a positive Romberg's sign, difficulty in performing coordination tests, and marked ataxia. In addition, nystagmus was present bilaterally. A CT scan was performed and demonstrated a marked hypodense lesion in the left cerebellar hemisphere. Magnetic resonance imaging (MRI) showed four areas of hyperintensity signal in T2 and Flair views without contrast enhancement. These areas were localized in the left cerebellar hemisphere, inferior part of the vermis, and right cerebellar hemisphere, respectively. Furthermore, slight compression laterally on the fourth ventricle was observed. This picture was compatible with multiple cerebellar ischemic areas (Figure 1).

The boy was hospitalized and rapidly started on anticoagulant therapy. High molecular weight heparin was administered according to the following schedule: 75 U/kg given intravenously over ten minutes, followed by a maintenance dose of 18 U/kg/h for ten days. Then the child was treated with oral anticoagulants (dicoumarol), monitoring coagulation parameters daily, and maintaining an INR index of between 2 and 3. The anticoagulation regimen was administered over two months, then dicoumarol was substituted with aspirin (100 mg/day). Furthermore, since the boy's diet was poor in vitamins, a multivitamin was given with the antiplatelet agent, notwithstanding the incompletely established role of vitamins in preventing endothelial damage. Over the next few days extensive coagulation studies were performed, including a complete blood count. Prothrombin time, activated partial

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thromboplastin time, concentrations of total and free protein S, and antithrombin III were normal; protein C was low (70%; normal range 70-140%). In addition, serum cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, homocysteine, and complement components C3 and C4 concentrations were normal. Lupus anticoagulant tests and serum titers of anticardiolipin IgG and IgM, β 2 glycoprotein 1 IgG and IgM, and anti-nuclear and anti-DNA antibodies were normal. An evaluation for the prothrombin G20210A gene mutation was negative. The patient was found to be heterozygous for the factor V Leiden mutation and homozygous for the 677TT mutation of the MTHFR gene by polymerase chain reaction analysis; factor VII was normal. Moreover, the father was found to be homozygous for the MTHFR mutation and the mother was heterozygous for the MTHFR mutation.

A cardiac evaluation including electrocardiography and echocardiography was normal, and no other cause for the cerebral infarction in the child was found. A second MRI together with diffusion tensor imaging (DTI) confirmed the previous findings of cerebellar damage of recent origin. MRI of the neck showed changes at the level of the left external carotid artery and left vertebral artery. Over the next few days the clinical condition of the boy improved markedly. MRI performed one month after the event was stable. The boy was discharged from the Pediatric Department in a good neurological condition; no clinical signs of neurological deficit were observed. A follow-up MRI remained stable; no other episodes of stroke were observed. During the two years and six months of follow-up, MRI plus DTI revealed a stable neuroradiological picture of the lesion previously observed and no anomalies of the major white matter tracts, such as corpus callosum, superior longitudinal fasciculus, and

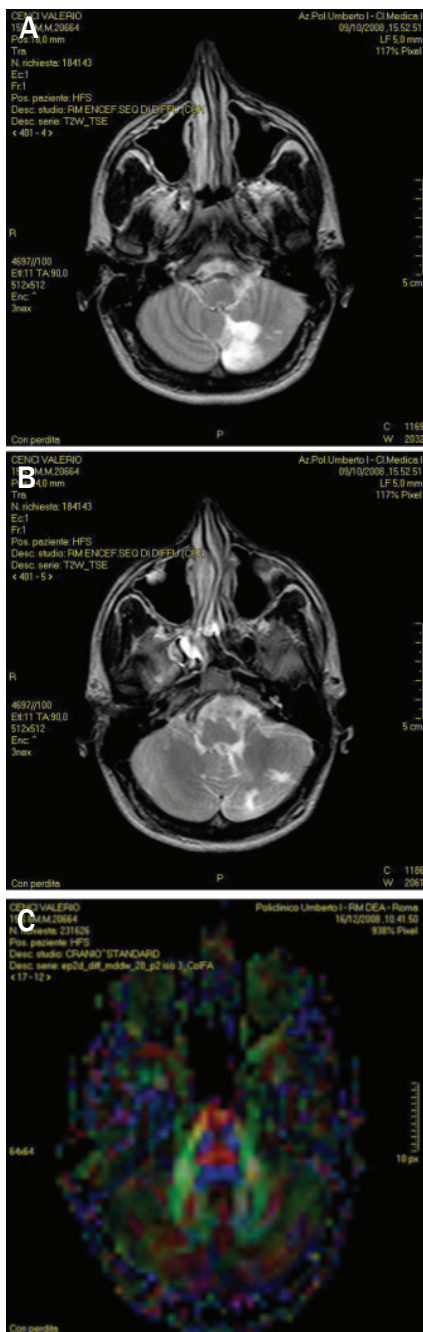


Figure 1. (A) and (B) T2-weighted axial views showing four areas of hyperintensity signal without contrast enhancement. These areas are localized in the left cerebellar hemisphere, inferior part of the vermis, and right cerebellar hemisphere. Note the slight compression laterally on the fourth ventricle. (C) Diffusion tensor imaging with fiber tracking, showing no anomalies of the major white matter tracts; corpus callosum (red), superior longitudinal fasciculus (blue), and corticospinal tracts (green).

corticospinal tracts. At present the boy is in good clinical health.

Discussion

The clinical presentation of cerebellar infarction is diverse, and can resemble many other disorders. The main symptoms of dizziness, nausea and vomiting, gait instability, and headache are nonspecific, and are caused usually by more common and benign disorders. The important components of the neurological examination that help to identify cerebellar stroke: coordination, gait, and eye movements, are commonly omitted or abridged in primary care, particularly when symptoms might not suggest a central nervous system cause. Headache is more common in strokes in the posterior circulation than in the anterior circulation, and particularly in cerebellar infarction with nearly 40% of patients with cerebellar infarction presenting with a headache. Notably, in our patient the main clinical symptom was a posterior *thunderclap headache*. Although the superior cerebellar artery is the largest branch of the vertebrobasilar tree, a superior cerebellar artery territory infarction is much less common than the posterior inferior cerebellar artery syndrome of Wallenberg.⁴ Isolated cerebellar artery infarctions have been reported in adults,⁴ but cerebellar infarction is a rare event in children and the young adult. The mechanism of such infarctions may be an artery-to-artery embolism from the vertebrobasilar arteries, a cardiac source of emboli (patent foramen ovale), dissection, or fibromuscular dysplasia of the superior cerebellar artery.⁵ Among the risk factors for cerebral stroke, the MTHFR mutation might lead to elevation of the plasma concentrations of homocysteine, which has been associated with an increased risk of ischemic stroke.^{2,6-7} However, this mutation might exert its effect via a mechanism other than elevating homocysteine concentrations. Factor V Leiden represents the most common mutation of Factor V. It is a result of a point mutation at nucleotide 1691 of the *FV* gene, inducing an Arg-506-Glu substitution in the FV protein. The consequence of this mutation is the loss of one of three sites of cleavage for activated protein C (aPC) in the FV molecule, so when aPC is added to the plasma from patients with Leiden, it resists the anticoagulant effect of aPC on thrombin production. This phenomenon is known as aPC resistance (aPCR). It has been reported that there is a prevalence for FV Leiden of 20-60% in white persons with thrombosis. The heterozygous state increases the risk for thrombosis up to 10%, while the homozygous condition increases the risk

50,100-fold.⁸ While FV Leiden represents a well-demonstrated risk for thrombosis, the question about the role of the C677T polymorphism of the MTHFR gene in thromboembolism includes some aspects that need to be discussed. First, although the relationship between the increased homocysteine plasma level and cardiovascular diseases is well-documented, the molecular mechanism of endothelial damage still is not completely understood. Second, the 677C>T polymorphism in the homozygous as well as the heterozygous state is not associated always with an increased Hct level. Meta-analyses have supported these observations. For example, Kelly and co-workers⁹ reported a 21% greater mean value for homocysteine plasma levels in patients with stroke, but the homozygous state of the mutation (MTHFR 677TT genotype) did not show statistical significance.⁹ We found the homozygous mutation of the *MTHFR* gene originating from the father can be considered the only risk factor for vascular accidents. The changes at the level of the left external carotid artery may be considered a normal anatomical variant and not a potential risk factor.

DTI is a great improvement on MRI in brain investigations, enabling the *in vivo* study of the anatomical and pathological structures of the brain and fiber tracts. Compared with routine MRI, DTI has many advantages. First, it finds the focal site of ultra-acute cerebral infarction that is displayed poorly by routine MRI; second, it clearly reveals the interruption of white matter fibers; third, it has a higher rate of spatial resolution and fewer artifacts; fourth, DTI-generated color tensor images reveal the relationship between the region of cerebral ischemia and the damaged fibers, and the three-dimensional fibrous reconstruction clearly presents the condition of the corticospinal tracts.¹⁰ In our patient, DTI demonstrated the normality of the white matter tracts. This finding is in accordance with the normal neurological condition of the boy and the absence of neurological consequences of the cerebellar stroke. As previously reported, structural abnormalities of white matter fibers are the dominant pathological change after cerebral ischemia and infarction. Such pathological changes in the microstructure of brain tissue may lead to severe ischemic stroke. In recent years, DTI has emerged as a noninvasive method to study the structure of brain white matter fibers *in vivo* and is promising in the evaluation of ischemic brain injury.¹⁰

In conclusion, when there are no other causes for cerebellar infarction, MTHFR mutation must be investigated. For example, when a pediatric patient presents with acute headache, a screening test for a genetic cause of thrombosis should be performed, together with MRI with DTI where possible. MRI should

be preferred to a CT scan in the pediatric age-group. Moreover, DTI seems to be the neuroradiological investigation of choice to evaluate the clinical and neuroradiological follow-up.

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