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Manifestations of neurological symptoms and thromboembolism in adults with MTHFR-deficiency

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ABSTRACT

Background: Methylenetetrahydrofolate-reductase (MTHFR) deficiency is a rare autosomal recessive disorder affecting intracellular folate metabolism with affection of different organ systems and clinical manifestation usually in childhood.
Objective: We report on four adult members of a family with MTHFR deficiency presenting with neurological and thromboembolic complications in adulthood.
Methods: Extensive diagnostic work-up including genetic testing was performed in four adult members.
Results: The male siblings aged 42 and 32 years presented with various neurological symptoms, and a recent history of deep vein thrombosis. Extensive diagnostic work-up revealed total homocysteine (tHcy) plasma concentrations of 135 μmol/L and 231 μmol/L. and compound heterozygosity for two novel *MTHFR* gene mutations in exon 2 (c.202C > G, p.Arg68Gly) and intron 10 (c.1632 + 2T > G), and the known polymorphic variant *MTHFR* c.665C > T (p.Ala222Val, *MTHFR* 677C > T). Their mother was heterozygous for *MTHFR* c.1632 + 2T > G and c.665C > T, and a paternal relative was heterozygous for *MTHFR* c.202.C > G and *MTHFR* c.665C > T mutation. Both brothers showed partial response to therapy with betaine and multivitamins with clinical improvement. MTHFR activity was determined in fibroblast extracts and was around 4% of the mean control. Cell culture analysis indicated a re-methylation defect due to MTHFR deficiency.
Conclusion: Severe hyperhomocysteinemia due to two mutations of the *MTHFR* gene resulted in severe neurological symptoms in adulthood. Vitamin and methionine supplementation stabilize tHcy plasma levels. Severity of clinical manifestation varied greatly between the siblings. Damages to the nervous system may be present for years before becoming clinically manifest.

1. Introduction

Increased plasma levels of total homocysteine (tHcy) can result from various causes including rheumatoid arthritis, kidney diseases, or B-vitamins deficiencies (B_6, B_{12} and folate). Severely increased tHcy with concentrations (> 100 μmol/L) are frequently due to enzyme defects including 5-methylenetetrahydrofolate-reductase (MTHFR), methionine-synthase, or cystathionine-beta-synthase deficiencies [1,2].

Severe MTHFR deficiency is an autosomal recessive disorder affecting the intracellular folate metabolism and represents the most common inborn error of the folate cycle. More than 40 different mutations of the *MTHFR* gene have been described [3]. These have been identified during the neonatal period and early infancy with manifestations including cardiomyopathy, bowel disease, and vascular system disorders. Clinical manifestations in adolescence or in adults are rare [3]. Neurological symptoms usually occur during childhood including

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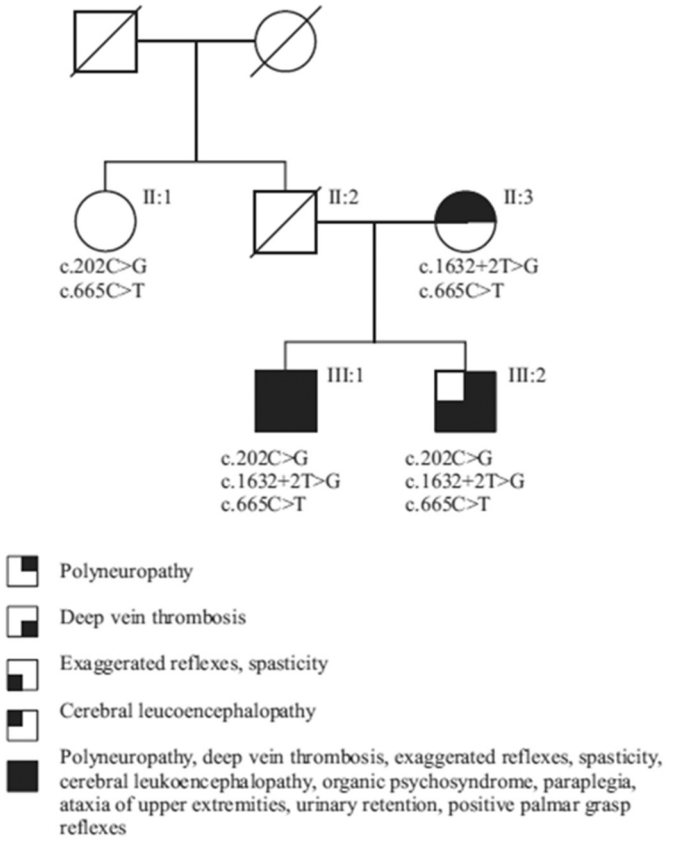

Fig. 1. Pedigree of the family. Clinical findings as well as mutations in the *MTHFR* gene are shown. Case 1: III:1; case 2: III:2; case 3: II:3; case 4: II:1 of the pedigree.

pyramidal and cerebellar signs, polyneuropathy, dementia, seizures and stroke [3–5].

The most common mutation is the variant c.665C > T (p.Ala222Val, also known as *MTHFR* 677C > T) with an estimated prevalence between 30% and 58% [1,6]. An association with an increased risk for neural tube defects, coronary artery disease, stroke and deep vein thrombosis has been described in homozygous patients [4,5,7].

In the present study we report on four adult members of a family with severe MTHFR deficiency showing neurologic and thromboembolic symptoms.

All evaluations were carried out in accordance with the declaration of Helsinki. The patients presented in the manuscript are aware of the submission and gave written consent.

2. Patients

2.1. Clinical signs and presentations

The index patient (case 1, male, 42 years) was referred to the neurological department because of dizziness, organic psycho-syndrome, and unsteady gait for about half a year. The dizziness worsened over one month leading to immobility. Neurological examination revealed paraplegia with pyramidal signs, spasticity, hypaesthesia in both legs, and urinary retention. Primitive reflexes were present. Six months before referral deep vein thrombosis occurred in one lower limb.

Simultaneously, his brother (case 2, male, 32 years) suffered from a deep vein thrombosis. Neurological examination revealed exaggerated reflexes and clinical signs of polyneuropathy with disturbances of pain sensation and reduced vibration sensation. Additionally unsteady gait was obvious since an undefined period of time. The mother of the siblings (case 3, female, 62 years) showed only signs of mild polyneuropathy on neurological evaluation. Repeated transient ischaemic attacks with hemiparesis, aphasia and double vision were reported for a paternal female relative of the siblings (case 4). Clinical examination revealed no abnormalities. The pedigree of the family is shown in Fig. 1.

2.2. Diagnostic work-up

2.2.1. Cranial magnetic resonance imaging (cMRI)

cMRI was performed in the siblings as well as the mother (cases 1, 2 and 3). Unspecific abnormalities in the white matter (leukoencephalopathy) were detected in case 1 (see Fig. 2). cMRI of case 2 showed no pathologies, and age-appropriate mild leukoencephalopathy was detected in case 3. No brain imaging was available for case 4.

2.2.2. Electrophysiology

Evoked nerve action potentials and nerve conduction velocity were reduced suggestive for presence of axonal polyneuropathy in subject 1, 2 and 3.

2.2.3. Laboratory studies

Very long chain fatty acids were determined in the plasma and were within normal ranges. Highly increased tHcy plasma concentrations were measured in case 1 (135.5 μmol/L) under vitamin supplementation (5 mg of folic acid, 1000 mg of vitamin B_{12} daily intravenously) and in case 2 (231 μmol/L) at time of presentation. The tHcy plasma level in the mother (case 3) was slightly elevated with 17 μmol/L (normal range 5.5–16.2 μmol/L) in the absence of decreased concentrations of plasma folate or vitamin B_{12}. After detection of hyperhomocysteinemia, methionine plasma levels were determined by high-performance liquid chromatography, and folate and vitamin B_{12}

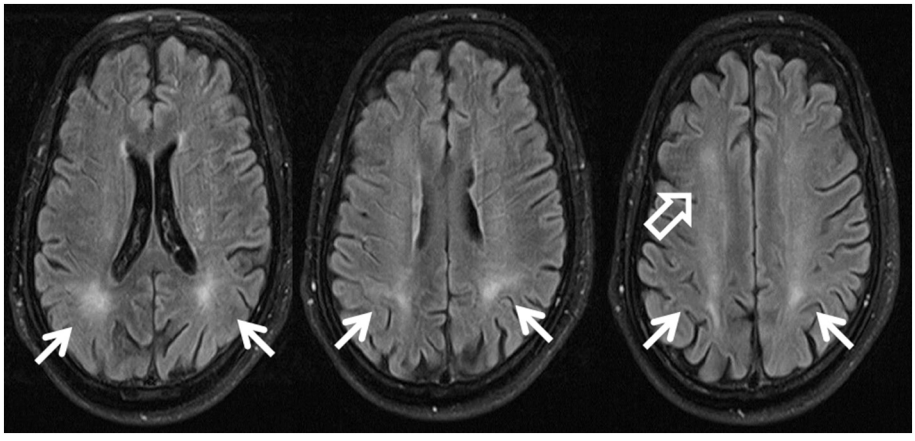

Fig. 2. Cranial magnetic resonance imaging (cMRI) in case 1. The patient presented with organic psychosyndrome, unsteady gait, and paraplegia with pyramidal signs. Primitive reflexes were present with positive palmar grasp reflexes. cMRI showed bilateral symmetric hyperintensities in the white matter parietooccipal (white arrows) as well as hyperintensities in the frontal regions more pronounced on the right side (transparent white arrow) on T2-Fluid Attenuated Inversion Recovery (Flair) sequences.