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Severe methylenetetrahydrofolate reductase deficiency: Clinical clues to a potentially treatable cause of adult-onset hereditary spastic paraplegia

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Case Report/Case Series

Severe Methylenetetrahydrofolate Reductase Deficiency
Clinical Clues to a Potentially Treatable Cause of Adult-Onset Hereditary Spastic Paraplegia

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IMPORTANCE Hereditary spastic paraplegia is a highly heterogeneous group of neurogenetic disorders with pure and complicated clinical phenotypes. No treatment is available for these disorders. We identified 2 unrelated families, each with 2 siblings with severe methylenetetrahydrofolate reductase (MTHFR) deficiency manifesting a complicated form of adult-onset hereditary spastic paraparesis partially responsive to betaine therapy.

OBSERVATIONS Both pairs of siblings presented with a similar combination of progressive spastic paraparesis and polyneuropathy, variably associated with behavioral changes, cognitive impairment, psychosis, seizures, and leukoencephalopathy, beginning between the ages of 29 and 50 years. By the time of diagnosis a decade later, 3 patients were ambulatory and 1 was bedridden. Investigations have revealed severe hyperhomocysteinemia and hypomethioninemia, reduced fibroblast MTHFR enzymatic activity (18%-52% of control participants), and 3 novel pathogenic *MTHFR* mutations, 2 as compound heterozygotes in one family and 1 as a homozygous mutation in the other family. Treatment with betaine produced a rapid decline of homocysteine by 50% to 70% in all 4 patients and, over 9 to 15 years, improved the conditions of the 3 ambulatory patients.

CONCLUSIONS AND RELEVANCE Although severe MTHFR deficiency is a rare cause of complicated spastic paraparesis in adults, it should be considered in select patients because of the potential therapeutic benefit of betaine supplementation.

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Hereditary spastic paraplegia (HSP) is a highly heterogeneous group of neurogenetic disorders characterized by progressive spastic weakness of the lower limbs secondary to degeneration of the corticospinal tracts. Various forms of HSP are clinically distinguished by the presence of additional neurological and systemic manifestations, age at onset, and pattern of inheritance. To date, more than 50 distinct genetic loci and more than 30 causative genes have been identified.[1]

Despite significant progress in the diagnosis of HSP, no treatment is currently available, and about 40% of the various forms remain of unknown cause.[1] We report 2 families with severe methylenetetrahydrofolate reductase (MTHFR) deficiency, with some patients presenting with a treatable form of adult-onset HSP.

Report of Cases

Methods

Since 1990, we have evaluated and prospectively followed up 4 patients with severe MTHFR deficiency. The patients are 2 pairs of siblings from 2 unrelated families of Ashkenazi Jewish (family 1) and Georgian Jewish (family 2) origin, without parental consanguinity or additional affected family members (**Table**). Both families were registered in the Israeli HSP database in 2004. Diagnosis was based on the typical biochemical combination of severe hyperhomocysteinemia and hypomethioninemia in the absence of folate or vitamin B_{12} deficiency, malabsorption, megaloblastic anemia, methylmalonic aciduria, or abnormal fibroblast cobalamin metabolism. Enzymatic MTHFR activity in cultured skin fibroblasts of the probands and sequencing of the *MTHFR* coding regions in genomic DNA were performed by conventional methods.[2,3] Participants or their legal guardians provided written informed consent. The studies were performed with approval of the Hebrew University-Hadassah Medical Center institutional review board.

Results

The main clinical and laboratory findings at diagnosis are summarized in the Table. Both pairs of siblings presented

Table. Main Clinical and Laboratory Findings at the Diagnosis of Hyperhomocysteinemia

	Family 1		Family 2	
Finding	Patient 1	Patient 2	Patient 3	Patient 4
Age at diagnosis, y	53	67	34	45
Sex	Female	Male	Female	Female
Duration of symptoms, y	16	17	5	5
Initial manifestation	Seizures	Cognitive decline	Psychosis	Gait disorder
Behavioral impairment	+	+	+	–
Cognitive impairment	+	++	++	+
Attention and concentration	++	++	++	+
Language	–	–	–	–
Visuospatial skills	+	+	+	–
Memory	+	+	+	–
Executive functions	++	+++	+++	+
Seizures	+	–	–	–
Spastic paraparesis	+++	++	+++	++
Bilateral extensor plantar response	+	+	+	+
Reduced ankle reflexes	+	+	+	+
Distal sensory loss	+	+	+	+
Plasma values				
Total homocysteine (normal, 0-15), µmol/L	140	152	150	185
Methionine (normal, 20-35), mg/dL	0.16	0.090	0.075	0.12
Fibroblast *MTHFR* activity, nmol CHO/mg protein/h (control run concurrently)	6.9 (13.8) 8.6 (16.3)	2.5 (13.8) 3.2 (16.3)	5.0 (13.6) 4.7 (9.3)	5.7 (13.6) 2.9 (9.3)
MTHFR mutation	c.1141C>T/c.1535A>G	c.1141C>T/c.1535A>G	c.1130G>A/c.1130G>A	c.1130G>A/c.1130G>A
NCS sensorimotor polyneuropathy	+	+	+	+
Cerebral and spinal MRI				
Generalized cerebral atrophy	+	+	+	+
Leukoencephalopathy, mainly posterior periventricular	+	+	+	+
Spinal cord atrophy	+	ND	+	ND

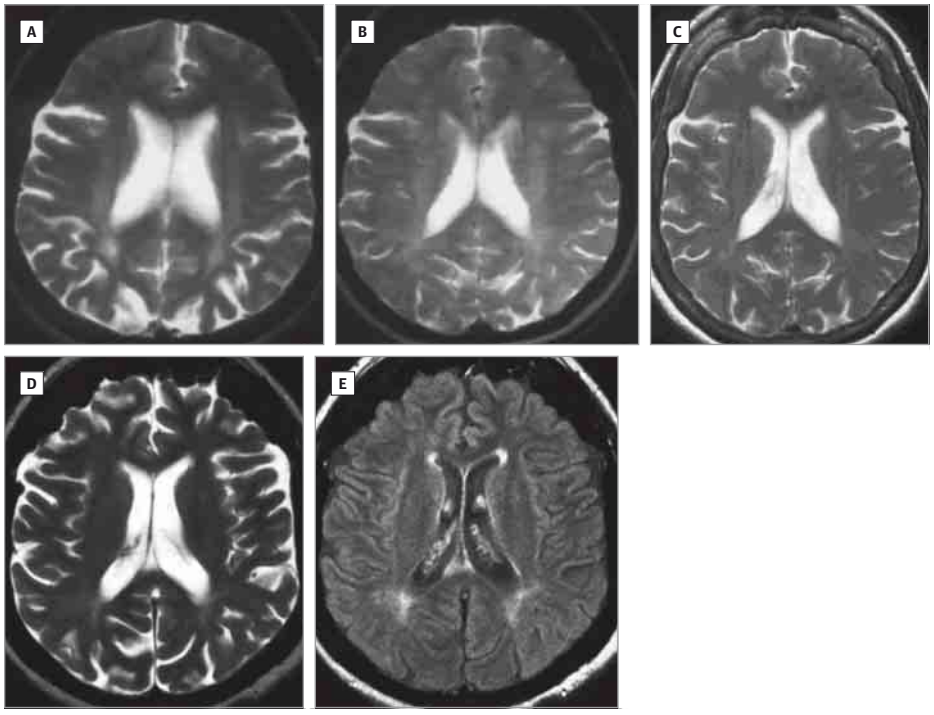
Abbreviations: CHO, carbohydrate; MRI, magnetic resonance imaging; *MTHFR*, methylenetetrahydrofolate reductase; NCS, nerve conduction study; ND, not done; +, mild; ++, moderate; +++ severe; –, not present.

SI conversion factors: To convert homocysteine to milligrams per deciliter, divide by 73.97; to convert methionine to micromoles per liter, multiply by 67.02.

with a similar combination of late-onset progressive spastic paraparesis and polyneuropathy associated with early behavioral changes and cognitive impairment. Patient 1 had generalized tonic-clonic seizures and depression from 37 years of age followed within a decade by unsteady gait. Evaluation elsewhere documented bilateral pyramidal signs in the legs and axonal peripheral neuropathy, confirmed by sural nerve biopsy. By 53 years of age, she became socially withdrawn and dependent on crutches. Patient 2 was evaluated at 67 years of age, following diagnosis of his sister. Seventeen years earlier, he retired because of behavioral and affective deterioration and gait disturbance. On examination, both siblings manifested prominent spastic paraparesis with severely limited aided walking associated with regressive behavior, labile affect, and markedly disturbed attention with perseverative executive dysfunction and relatively preserved language skills, suggestive of significant frontal-subcortical cognitive impairment.

Patient 3 had paranoid psychosis with catatonic episodes starting from 29 years of age. Weakness of the legs and unsteadiness were first noted at 30 years of age and were initially attributed to a sensorimotor polyneuropathy and treatment with antipsychotic medications. Within 3 years, her gait progressively worsened and she became bedridden and severely cognitively impaired. Patient 4, a younger sister of patient 3, presented at 45 years of age with progressive unsteadiness of 5-year duration, which led to severely limited aided walking. On examination, both sisters had spastic paraparesis associated with neuropsychiatric dysfunction. Patient 3 was psychotic and catatonic. When stabilized with electroconvulsive therapy and antipsychotic medication, she became apathetic and dull with impaired judgment. Formal cognitive assessment was difficult owing to lack of cooperation. Patient 4 had widespread cognitive decline most prominent in executive functions, attention, and short-term memory.

Figure. Cerebral Magnetic Resonance Imaging in Patients 1 and 4



Representative magnetic resonance images of patient 1 (A-C) and patient 4 (D and E) showing mild generalized atrophy and a predominantly posterior periventricular leukoencephalopathy on T2-weighted (A-D) and fluid-attenuated inversion recovery (E) sequences. Sequential magnetic resonance images of patient 1 obtained before (A), 3 years (B), and 7 years (C) after initiation of betaine anhydrous treatment showing gradual improvement of the white matter T2 hyperintensity and reduction of the ventricular size.

With the exception of patient 2, who had essential hypertension and chronic peripheral vascular and ischemic heart disease, none of the patients had symptomatic cerebrovascular or cardiovascular involvement and their cerebral magnetic resonance angiography findings were unremarkable.

Following the diagnosis of hyperhomocysteinemia, all patients were treated with sequential and then concomitant supplementation of vitamin B_{12} (cyanocobalamin or hydroxocobalamin, 1000 µg/mo), folic acid (15 mg/d), and folinic acid (45 mg/d), and with riboflavin (500 mg/d for 4 days in patient 4) and pyridoxine hydrochloride (600 mg/d for 14 days in patient 3). Some improvement of behavioral pattern, attention, and executive functions was noted over a few months on repeated examination. However, only betaine anhydrous (trimethylglycine), initiated at diagnosis of MTHFR deficiency and continued thereafter for 9 to 15 years at doses of 6 to 10 g/d, resulted in a rapid and sustained decline in homocysteine levels by 50% to 70% and in elevation of methionine level to within normal range. Over years, this was associated with additional cognitive improvement and increased walking distance of the 3 ambulatory patients who became functionally independent, with stabilization of the cerebral magnetic resonance imaging findings in 2 patients and improvement in 1 (**Figure**). Patient 3 remained bedridden and patient 2 was lost to follow-up soon after he clinically improved.

Sequencing the *MTHFR* gene identified 3 novel missense mutations segregating in an autosomal recessive pattern in both families. Patients in family 1 were compound heterozygotes for c.1141C>T (p.W381R) and c.1535A>G (p.Y512C) mutations, and patients in family 2 carried a homozygous c.1130G>A (p.R377H) mutation (numbering from A of the initiation codon ATG, GenBank NM_005957). These mutations affect evolutionarily conserved residues, are predicted to be pathogenic by the MutationTaster software,[4] and are not present among the variants in the Exome Variant Server (http://www.evs.gs.washington.edu/EVS/). A previously reported mutation, p.R377C, was also designated as c.1141C>T[2], but it did not involve the same sequence change as that reported here because the sequence numbering was based on GenBank U09806.

Discussion

Diagnosis of severe MTHFR deficiency in these patients was based on the typical laboratory findings and was confirmed by molecular analysis. The full clinical spectrum, taken together with the history of an affected sibling, was suggestive of a complicated HSP variant.[1] A similar combination of clinical features also occurs in adult-onset MTHFR deficiency[3,5-7]; however, in contrast to HSP, paraparesis usually develops late and is preceded by cognitive, behavioral, or psychiatric manifestations.[3,5,6] Indeed, initial presentation with seizures, behavioral changes, slow cognitive deterioration, or psychosis in 3 of our patients provided an important clue to the correct diagnosis.

Our patients represent the latest onset spectrum of MTHFR deficiency, probably related to the residual enzyme activity.[3] Only 3 patients with MTHFR deficiency of similar age have been reported previously, all without family history of HSP.[5-7] In addition to the characteristic slow progression, they manifested periods of rapid deterioration, which we did not observe. Triggered in part by environmental and iatrogenic factors,[8,9] such events represent another diagnostic feature in disorders of remethylation.

Whereas long axonal degeneration in the spinal cord is a common pathogenic mechanism in HSP,[1] demyelination, as in subacute combined degeneration, underlies severe MTHFR deficiency.[10] It is probably caused by low methionine and S-adenosylmethionine[11] and likely results in leukoencephalopathy, as in our patients, of a predominantly posterior-periventricular distribution[6,7,10] that may sometimes reverse with treatment.[6,12]

The beneficial effect of betaine in severe MTHFR deficiency is mediated through betaine-homocysteine methyltransferase with the use of an alternate methyl donor for remethylation of homocysteine to methionine.[11] Biochemical improvement in our patients was associated with significant behavioral and cognitive improvement and mild motor recovery in all except the most severely affected patient 3, suggesting the importance of early treatment to prevent irreversible deterioration.[6,7] Therefore, increased awareness of the possibility of severe MTHFR deficiency and screening for total homocysteine and methionine is indicated in select patients with adult-onset complicated HSP.

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Study concept and design: Lossos, Kohn.
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