A Family With Spinocerebellar Ataxia Type 8 Expansion and Vitamin E Deficiency Ataxia

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Background: Ataxia with vitamin E deficiency is a recessive autosomal neurodegenerative disorder resembling the Friedreich ataxia phenotype but is due to mutations in the α-tocopherol transfer protein (TTPA) gene. In a recent article, we described a patient with ataxia carrying reduced serum vitamin E levels and showing CTA/CTG expansions of 320 triplet repeats in the SCA8 gene.

Objectives: To perform a screening of the TTPA gene in the patient and to evaluate the effects of treatment with vitamin E on the patient's neurologic disturbances.

Patient and Methods: We performed a single-strand conformation polymorphism and nucleotide sequence analysis of the 5 exons of the TTPA gene in the patient's family members.

Results: The results indicated the patient to be a compound heterozygote for 2 mutations (in exon 3), each transmitted by one of the 2 parents, yielding a nonfunctional protein.

Conclusions: We describe for the first time, to our knowledge, a mutated form of the TTPA gene in a patient also carrying an expansion in the SCA8 gene. The lack of improvement in the patient's symptoms on supplementation with α-tocopherol suggests that the SCA8 mutations may act in the neurodegeneration process, worsening the neurologic signs caused by the vitamin E deficit, and it could be speculated that the co-occurrence of mutant alleles for 2 distinct loci may influence the clinical course of the disease.

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We recently reported a clinical and genetic analysis of spinocerebellar ataxia type 8 (SCA8) in Italian patients. In particular, we described a patient with ataxia (PN-1 family) carrying reduced serum vitamin E levels and showing CTA/CTG expansions of 320 triplet repeats in the SCA8 gene, inherited via maternal transmission. In this patient, we recently identified a mutated form of the α-tocopherol transfer protein (TTPA) gene, which has been reported to cause ataxia with vitamin E deficiency (AVED). Vitamin E (α-tocopherol) has an important antioxidant role and its plasma levels are regulated by oral intake and absorption and transfer into circulating lipoproteins secreted by the liver. The α-tocopherol transfer protein seems to regulate this latter step.

Ataxia with vitamin E deficiency is a recessive autosomal neurodegenerative disorder characterized by progressive ataxia, areflexia, decreased proprioceptive and vibratory sensations, and dysarthria. The clinical symptoms of vitamin E deficiency resemble the Friedreich ataxia (FA) phenotype but the two can be distinguished in terms of genetic defect, consisting in AVED of mutations in the TTPA gene located on 8q13. Patients with AVED usually have low levels (<1 µg/mL) of vitamin E, but the clinical symptoms show at least some improvement when supplemented with α-tocopherol at an early stage of the disease.

REPORT OF A CASE

A 30-year-old woman belonging to the PN-1 family had a clinical history of progressive ataxia. Her early development was normal but at the age of 7 years she started to experience gait disturbances and was diagnosed as having FA without cardiac abnormalities and diabetes. Cerebral magnetic resonance imaging revealed pure cerebellar atrophy without clinical and radiologic signs of brainstem involvement. By the age of 17 years, she had become wheelchair bound, and genetic studies revealed no specific FA GAA expansion in the FRDA gene. Laboratory tests revealed a low serum vitamin E concentration (0.3 µg/mL [0.012 µmol/L]; normal range, 5.0-15.2 µg/mL [0.215-0.654 µmol/L]); thus, the patient was treated with vitamin E at a dose of 300 mg, 3 times per day. However, after a follow-up period of 1 year, the patient's neurologic disturbances showed no clinical improvement.

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We performed a single-strand conformation polymorphism and nucleotide sequence analysis of the 5 exons of the TTPA gene in the PN-1 patient’s family members (Figure). Informed consent was obtained for the genetic analysis after the nature of the procedure had been fully explained. The results indicated the patient to be a compound heterozygote for 2 mutations (in exon 3), carrying both the 400 C/T mutation (paternally inherited) and the 513 TT-insertion (maternally inherited), each transmitted by one of the 2 parents. The genetic defects characterizing our patient are truncating mutations (400 C/T, causes an Arg/ter substitution; 513 TT-insertion causes a frameshift with the insertion of 4 aberrant amino acids, leading to a shortened product), yielding a nonfunctional protein.

Both parents did not show any neurologic alterations despite having the 2 TTPA gene mutations in heterozygosity; however, they decided to start taking the same vitamin E supplementation. The healthier brother of the proband, whom we examined more recently, was found to carry an expansion of 169 triplet repeats in the SCA8 gene and have the heterozygous mutation (400 C/T, paternally inherited) in the TTPA gene. He had normal serum vitamin E levels.

About 20 different mutations in the TTPA gene have been reported worldwide in AVED families of different ethnic origins (North African, European, North American, and Japanese). Compound heterozygotes for different mutations have been described in a few families, but to our knowledge, no patient carrying a combination of the 400 C/T and 513 TT-insertion mutations has ever been reported. To our knowledge, this is the first time a mutated form of the TTPA gene in a patient also carrying an expansion in the SCA8 gene has been described.

The lack of improvement in the patient’s symptoms on supplementation with α-tocopherol suggests that the SCA8 mutations may act in the neurodegeneration process, worsening the neurologic signs caused by the vitamin E deficit. In addition, it could be speculated that the co-occurrence of mutant alleles for 2 distinct loci may influence the clinical course of the disease.

Since previous evidence suggests that extremely long (>250 CTA/CTG repeats) expansions in the SCA8 gene are not necessarily always pathogenic, we hypothesize that the 320 repeat expansion identified in our patient might play a role in her neurologic dysfunction only because the patient is carrying another genetic defect, in the α-tocopherol gene, leading to ataxia. This hypothesis is strengthened by the fact that the mother and brother of this proband, although carrying, respectively, a 105 and 169 CTA/CTG repeat expansion in the SCA8 gene and 1 mutated allele in the TTPA gene, show no evidence of neurologic alterations. This case confirms the uncertain role of CTA/CTG expansions in SCA8 pathogenesis. The reported low penetrance of SCA8 among patients with ataxia (<1%), the wide variability in disease expression, and the presence of this expansion in nonataxic subjects as well (eg, in 2 patients with Alzheimer disease), suggest that mutations in another gene, as well as other epigenetic factors, should significantly influence the ataxia phenotype in families carrying an SCA8 mutation. These results suggest that, in our patient, vitamin E deficiency at a genetic level together with the previously detected SCA8 expansion may play an important role in the pathogenesis of spinocerebellar degeneration.

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