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Editorial

Cerebellar Ataxia and *CoQ10* Deficiency

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EDITORIAL

In 2001, we described six patients with cerebellar ataxia and severe deficiency of coenzyme Q10 (CoQ10, ubiquinone) in skeletal muscle [1]. Within one year, we described 13 additional patients [2]; therefore, we suspected this was not a very rare syndrome. Twelve years after our original report, cerebellar ataxia and atrophy has emerged as the most common clinical presentation of CoQ10 deficiency, and now we know that it can be primary (associated with mutations in genes coding proteins involved in the biosynthesis of CoQ10 or its regulation), or secondary to other causes. In fact, 3 of the first patients reported by Musumeci et al. have a homozygous mutation in *APTX*, encoding aprataxin [3], a protein involved in DNA break repair, and one of the patients reported by Lamperti et al. carried heterozygous mutations in *ADCK3/CABC1*, which encodes a kinase required for CoQ10 biosynthesis [4]. To date, mutations in *ADCK3/CABC1* have been identified in 21 patients (14 families), some of them presenting with cerebellar ataxia and atrophy, plus exercise intolerance, dystonia and mild cognitive impairment [4-9]. Secondary CoQ10 deficiency has been confirmed in additional patients carrying *APTX* mutations [3,10-12].

The clinical picture is characterized by cerebellar ataxia and atrophy variably associated with peripheral neuropathy, seizures, mental retardation, migraine, psychiatric manifestations, muscle weakness, exercise intolerance, upper motor neuron signs, ptosis and ophthalmoplegia, retinitis pigmentosa, optic atrophy, hearing impairment, lipomas, Dandy-Walker syndrome, agenesis of the corpus callosum, hypogonadism, and other endocrinological problems [13]. CoQ10 levels are low in muscle, and frequently fibroblasts and lymphoblasts. Complex I+II and II+III activities are reduced in severely affected patients, but have been reported normal in muscle from less severely affected patients. Although muscle biopsies showed only non-specific myopathic changes in the first report, subsequent publications noted that skeletal muscle of some patients revealed mitochondrial proliferation and lipid accumulation, and COX-deficient fibers, but no typical ragged red fibers (RRF). The condition usually begins in childhood or adolescence; however, patients with adult-onset, very mild phenotype, have been described [13,9].

Interestingly, functionally impaired variants of *COQ2* were recently associated with an increased risk of multiple-system atrophy, a neurodegenerative disease characterized by autonomic failure in addition to various combinations of cerebellar ataxia, parkinsonism, and pyramidal dysfunction [14].

Supplementation with CoQ10 was associated with increased strength and disappearance of seizures in the affected individuals with aprataxin mutations we described [1,3], and with mild clinical improvement in patients with cerebellar ataxia associated with mutations in *ADCK3/CABC1* [4,5]. In a recent study, Pineda et al. assessed the clinical outcome in 14 patients with cerebellar ataxia with and without documented CoQ10 deficiency in muscle and/or fibroblasts and unknown molecular defect and observed that all patients with CoQ10 deficiency responded to therapy [6]. Therefore, muscle CoQ10 levels should be investigated in patients with autosomal recessive cerebellar ataxia, to diagnose and treat patients with this condition and to increase our understanding of this expanding group of disorders.

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