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Annals of Clinical Pathology

Review Article

Coenzyme Q10 Deficiency and Cerebellar Ataxia

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Submitted: 15 January 2014

Accepted: 18 May 2014

Published: 19 May 2014

Keywords
- Coenzyme Q10
- CoQ10
- Cerebellar ataxia
- CoQ10 supplementation
- Aprataxin
- ADCK3

Abstract

Coenzyme Q10 (CoQ10) deficiency is an autosomal recessive disorder presenting five main phenotypes: an enchephalomyopathic form, a severe infantile neurological syndrome, a nephrotic form, a pure myopathic form and an ataxic form. The last one, the focus of this review, is the most common phenotype, characterized by childhood/young adulthood-onset cerebellar ataxia and cerebellar atrophy as main neurological signs, and decreased CoQ10 levels in muscle (the hallmark of the disease), and sometimes in fibroblasts. Molecular defects have been described in two different genes: *APTX* and *ADCK3*. Early diagnosis is important because patients can benefit from CoQ10 supplementation.

ABBREVIATIONS

CoQ10: Coenzyme Q10; APTX: Aprataxin; AOA1: Ataxia Ocular Apraxia 1; ARCA2: Autosomal Recessive Cerebellar Ataxia 2; ICARS: International Cooperative Ataxia Rating Scale-scores; ADCK3: AarF Domaing Containing Kinase 3; CABC1: Chaperone ABC1

INTRODUCTION

Coenzyme Q10 (CoQ10) also known as ubiquinone, is an endogenously synthesized lipid, that transfers electrons from complexes I (*NADH-ubiquinone oxidoreductase*) and II (*succinate-ubiquinone oxidoreductase*) and from the oxidation of fatty acids and branched-chain amino acids (via flavin-linked dehydrogenases) to complex III (*succinate-cytochrome c oxidoreductase*) of the mitochondrial respiratory chain [1]. The reduced form of CoQ10, known as ubiquinol, has antioxidant properties, protecting membrane lipids, proteins and mitochondrial deoxyribonucleic acids (mtDNA) against oxidative damage [1]. Intracellular synthesis is the major source of CoQ10, although a small proportion is acquired through diet. Cells synthesize CoQ10 *de novo* starting with synthesis of the para-hydroxybenzoate ring, which is derived from the metabolism of tyrosine and phenylalanine. The decaprenyl side-chain, which anchors CoQ10 to membranes, is generated by the addition of isopentenyl diphosphate molecules, derived from the mevalonate pathway, to farnesyl diphosphate in multiple steps catalyzed by decaprenyl diphosphate synthase [1]. Farnesyl pyrophosphate is also substrate for the synthesis of cholesterol, dolichol, and dolichyl-posphate and prenylated proteins [1]. The length of the prenyl side-tail varies among different organisms. In humans, it is comprised of ten isopentenyl units producing CoQ10, whereas in rodents it is composed of 9 isopentenyl units thus given the name CoQ9 [1].

CoQ10 deficiencies have been associated with four major clinical phenotypes: 1) an encephalomyopathic form, characterized by the triad of recurrent myoglobinuria, brain involvement, and ragged-red fibers (RRF)/lipid storage in muscle [2-4]. 2) A pure myopathic form with lipid storage myopathy and respiratory chain dysfunction [5-7]. 3) A multisystemic infantile form [8,9]. 4) A nephropaty, typically nephrotic syndrome often in association with encephalopathy or other neurological manifestations [9-12]. 5) A cerebellar form characterized by cerebellar ataxia and cerebellar atrophy variably associated with other manifestations as neuropathy, seizures, mental retardation and muscle weakness [13-16]. The ataxic form is the most common phenotype and is the focus of this review.

CEREBELLAR ATAXIA AND COQ10 DEFICIENCY: CLINICAL PRESENTATION AND MOLECULAR DEFECTS

Autosomal recessive cerebellar ataxias (from the Greek words "a," meaning "not," and "taxis," meaning "order") are heterogeneous, complex, disabling inherited neurodegenerative diseases, mostly manifesting in children and young adults characterized by incoordination of movement and unsteadiness, due to cerebellar dysfunction. Clinical examination reveals gait disorder with imbalance, staggering, and difficulties with tandem walking, upper-limb and lower-limb dysmetria, dysdiadochokinesia (difficulty performing rapidly alternating movements), hypotonia, cerebellar dysarthria, and saccadic ocular pursuit [17].

Cerebellar ataxia associated with CoQ10 deficiency is generally characterized by childhood-onset cerebellar ataxia and cerebellar atrophy, associated with other manifestations such as neuropathy, seizures, mental retardation, hypogonadism, movement disorder and muscle weakness [18]. In 2001, Musumeci reported the first six patients presenting muscle CoQ10 deficiency associated with syndrome characterized by cerebellar ataxia as the main neurological sign. Noteworthy, all patients had cerebellar atrophy in brain MRI studies. Other features included pyramidal signs, nystagmus, absence of tendon reflexes and seizures [15]. This syndrome was confirmed in 13 more patients who presented childhood-onset ataxia and cerebellar atrophy together with seizures, developmental delay, mental retardation and pyramidal signs [15]. Muscle biopsies of patients from these studies did not show any significant abnormalities other than severe CoQ10 deficiency.

Follow up studies with linkage analysis in three of the affected patients who were siblings identified a previously known mutation (W279X) in the aprataxin (*APTX*) gene [19], encoding a protein involved in DNA single strand break repair. *APTX* mutations are known to cause ataxia oculomotor ataxia type 1 (AOA1) [20,21]. The clinical phenotype of these subjects, presenting early onset ataxia, oculomotor apraxia, cerebellar atrophy, hypoalbuminemia and hypercholesterolemia was consistent with those associated with AOA1. Muscle biopsies showed nonspecific myopathic changes in all patients studied [16]. The association between *APTX* mutations and CoQ10 deficiency has been subsequently confirmed in 5 more unrelated AOA1 patients who also improved considerably after CoQ10 therapy [22], however, because not all AOA1 patients present muscle CoQ10 deficiency, the significance and mechanism of CoQ10 deficiency in this disorder remains unknown.

A peculiar association of ataxia, hypogonadism with muscle CoQ10 deficiency was reported in two brothers [14], who, in the 4-5th decade of life developed cerebellar ataxia with dysarthria, broken ocular pursuit movements and severe limb ataxia. They also had azoospermia (noticed some years before the onset of ataxic signs) and moderate sensory-motor neuropathy of mixed axonal-demyelinating type. Hormonal blood analysis showed hypergonadotropic hypogonadism; muscle biopsies showed mild neurogenic changes in both patients. The molecular defect of this disorder is still unknown.

While the first patients described with cerebellar ataxia and CoQ10 deficiency carried mutations in genes encoding protein not directly involved in the CoQ10 synthetic pathway, subsequent mutations reported in genes encoding CoQ10 biosynthetic enzymes (PDSS1, PDSS2 and CoQ2) were identified in patients with severe infantile onset encephalomyopathy, renal failure or multisysemic disease, thus suggesting that cerebellar ataxia was most likely a secondary CoQ10 deficiency. However, in 2008 two different groups reported eleven patients (belonging to eight different families) with mutations in the *ADCK3/CABC1*, or *COQ8* gene [23-25], encoding a putative kinase, which appears to modulate the biosynthesis of CoQ10: studies of the yeast homologue, Coq8p, indicated that the protein is required to maintain the stability of Coq3p [26].

After these initial reports of small groups of patients, 24 additional patients have been described with cerebellar phenotype and mutations in ADCK3 [25-28].

The phenotype associated with *ADCK3* mutations, called Autosomal Recessive Cerebellar Ataxia 2 (ARCA2) usually manifests as childhood-onset ataxia, seizure, sometimes progressive to epilepsia partialis continua [24], cognitive impairment and muscle weakness with exercise intolerance [23,29], and increased serum lactate after physical effort. None of the patients carrying mutations in *ADCK3/CABC1* had peripheral neuropathy which is frequently present in AOA1. All patients with *ADCK3* mutations have evidence of cerebellar atrophy at the MRI [24,25].

Nevertheless, a recent study [30] described patients with mutations in *ADCK3* and adult-onset disease, who remained ambulatory into their late forties. Spasticity, dystonia, tremor and migraine were also variably present in this late-onset form, and cognitive impairment, severe in the early-childhood onset variant, was absent in the adults-onset one, which is slowly progressive, although acute worsening triggered by an episode of epileptic encephalopathy can occur.

Intriguingly, a very recent paper [27] described two sisters, harboring compound heterozygous mutations in *ADCK3*, with extremely variable clinical presentations. Cerebellar atrophy was present in both sisters; however, the younger sister had early onset progressive ataxia, cognitive decline, and psychiatric involvement; in contrast, the older one (32 years-old) manifested only dysarthria without ataxia. Muscle biopsy performed in the younger sister showed normal morphology, but decreased activity of complexes I+III and IV. CoQ10 levels were unfortunately not assessed, but CoQ10 supplementation led to improvement of the neurological and motor symptoms.

A review of the clinical features of ten new patients (from seven unrelated families) with ARCA2, and four previously published [31], suggested acute complications as stroke like episodes [24,31] can account for the clinical variability of the disease, and the rapid deterioration of cognitive functions and/or the rapid development progression of untreatable seizures and status epilepticus. The prognosis of ARCA2 is usually mild and not inexorably progressive as in most of the other recessive ataxias. Usually patients have a chronic evolution starting at around 20 years of disease, until death. Only few cases of ARCA2 presented with an infantile degenerative encephalopathy rather than an early adult-onset progressive ataxia, showing how this early neurological regression could be the extreme presentation of this disease [31].

Analysis of muscle biopsy is useful in *ARCA2* mutant patients: lipid accumulation, mitochondrial proliferation and COX-deficient fibers may be present, although typical RRF are usually absent. Deficiency in CoQ10-dependent enzyme activities (complex I+III or II+III) is usually evident at least in severely affected patients. As for CoQ10 level, it is usually decreased in muscle and sometimes in fibroblasts [30].

TREATMENT

The identification of CoQ10 deficiency in patients with cerebellar ataxia is very important because treatment response

has been remarkable in most cases highlighting the importance of an early diagnosis of this disorder.

Notable clinical improvements in strength, overall well-being, better control of seizures and some improvement of cerebellar function were noticed after CoQ10 supplementation in the first patients described with *AOA1* mutations and COQ10 deficiency. In addition postural stability, gait, speech articulation, and normalization of hormonal blood values improved with CoQ10, in the two brothers with ataxia and hypoganadism [19,14]. In contrast CoQ10 therapy did not produce overt benefit in patients harboring *ADCK3* mutations.

The reported clinical improvements in patients after 6 months of treatment with high doses (10 to 30 mg/Kg/day) varied from not at all [24,30,31] to mild improvements with stabilization of cerebellar ataxia [23,24]. However, one patient described in 2011 had a clear clinical improvement in motor skills and in the control of seizures after 6 months of CoQ10 supplementation, although no improvement of cerebellar atrophy was seen by repeated MRI [32]. Five patients, after CoQ10 supplementation, showed long lasting improvement of dystonia and myoclonus [28,31], balance and academic performance [27,28]. Interestingly, a study published in 2010 in 14 patients with recessive ataxia showed that CoQ therapy lead to an overall significant improvement in the international cooperative ataxia rating scale-scores (ICARS), mostly in posture and gait, only in the 7 patients with muscle CoQ10 deficiency [33,34].

However, it is difficult to assess the response to CoQ10 supplementation, as currently there is no standard protocol with regard to formulations or daily dosage of CoQ10, although several studies suggest that doses of up to 2400mg/day in adults [35] and up to 30 mg/kg/ day in pediatric patients [33,35] are therapeutically optimal.

CONCLUSION

Coenzyme Q10 deficiency is an example of a mitochondrial syndrome caused by the lack of a key metabolite in the mitochondrial respiratory chain that can be effectively treated in many cases through supplementation. However, the fact that not all patients respond to CoQ10 therapy indicates that further studies are necessary to optimize this treatable mitochondrial disorder.

ACKNOWLEDGEMENT

The project was supported by K23 HD065871 (CMQ) and 1R01 HD057543 (MH) from the Eunice Kennedy Shriver National Institute of Child Health & Human Development. MH is also supported by NIH grants R01 HD056103 and 1RC1 NS070232, a Muscular Dystrophy Association grant, and by the Marriott Mitochondrial Disorder Clinical Research Fund (MMDCRF).

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Cite this article

Peverelli L, Naini A, Hirano M, Quinzii CM (2014) Coenzyme Q10 Deficiency and Cerebellar Ataxia. Ann Clin Pathol 2(1): 1011.