

Human Coenzyme Q₁₀ Deficiency

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Abstract Ubiquinone (coenzyme Q₁₀ or CoQ₁₀) is a lipid-soluble component of virtually all cell membranes and has multiple metabolic functions. Deficiency of CoQ₁₀ (MIM 607426) has been associated with five different clinical presentations that suggest genetic heterogeneity, which may be related to the multiple steps in CoQ₁₀ biosynthesis. Patients with all forms of CoQ₁₀ deficiency have shown clinical improvements after initiating oral CoQ₁₀ supplementation. Thus, early diagnosis is of critical importance in the management of these patients. This year, the first molecular defect causing the infantile form of primary human CoQ₁₀ deficiency has been reported. The availability of genetic testing will allow for a better understanding of the pathogenesis of this disease and early initiation of therapy (even presymptomatically in siblings of patients) in this otherwise life-threatening infantile encephalomyopathy.

Keywords CoQ₁₀ · Mitochondria · Encephalopathy · Myopathy · Cerebellar ataxia

Introduction

Coenzyme Q₁₀ (CoQ₁₀) is the predominant human form of endogenous ubiquinone. Synthesized in the mitochondrial inner membrane, CoQ₁₀ is comprised of

a ubiquinone head group attached to a tail of 10 five-carbon isoprenoid units, that anchors the molecule to the membranes [1]. In addition to its central role in the mitochondrial respiratory chain as electron carrier from complex I and II to complex III [2], CoQ₁₀ is now thought to be involved in a number of cellular functions (Table 1) [1]. Intracellular synthesis is the major source of CoQ₁₀, although a small proportion is acquired through diet. The complexity of the biosynthesis (Fig. 1) suggests that defects in different biosynthetic enzymes or regulatory proteins may cause different clinical syndromes.

Primary CoQ₁₀ deficiency is an autosomal recessive condition with a clinical spectrum that encompasses at least five major phenotypes: (1) encephalomyopathy characterized by the triad of recurrent myoglobinuria, brain involvement and ragged red fibers; (2) severe infantile multisystemic disease; (3) cerebellar ataxia; (4) Leigh syndrome with growth retardation, ataxia and deafness; and (5) isolated myopathy [12–26].

Generalized weakness, exercise intolerance, and recurrent myoglobinuria are the distinctive features in the first four patients reported with the encephalomyopathic form, [12–15]; however, myoglobinuria was absent in another patient [16]. All the patients described so far have proximal muscle weakness [12–16]. The brain involvement is variable; seizures are a common finding [12, 13], in association with cognitive impairment [12] and cerebellar symptoms [12, 15, 16].

The second variant, described in three families, manifests as an infantile encephalopathy with renal involvement. Rötig and colleagues initially described two siblings with defects of multiple quinone-dependent enzymes ascribed to a deficiency of CoQ₁₀ in various tissues [17]. The patients presented with

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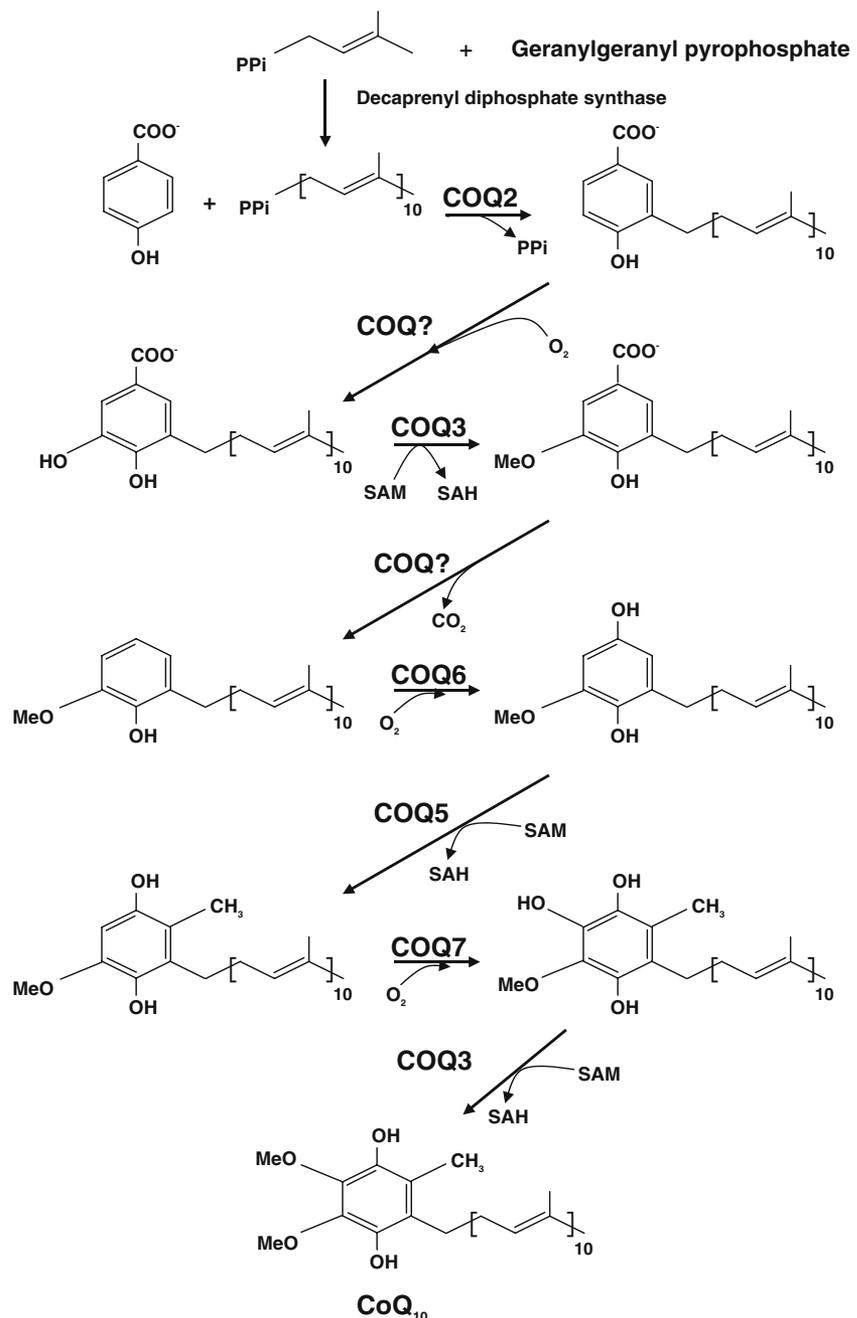
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Table 1 Functions of coenzyme Q (modified from [1])

Electron carrier in mitochondrial respiratory chain [3]
Extra-mitochondrial electron transport [4]
Antioxidant [5]
Regulation of mitochondrial permeability transition pore [6]
Regulation of physicochemical properties of membranes [7]
Modulation of the amount of β -integrins on the surface of blood monocytes [8]
Modulator of endothelial function [9]
Oxidation of sulfide in yeast [10]
Introduction of disulfide bonds in bacteria [11]

retinitis pigmentosa, optic nerve atrophy, bilateral sensorineuronal deafness, nephrotic syndrome, progressive ataxia, and cardiomyopathy. In Rahman's patient, hypothermia, lactic acidosis, cerebral and cerebellar atrophy, and developmental delay were associated with renal tubulopathy and ventricular hypertrophy [18]. Last year, we described two siblings who presented with nephrotic syndrome due to glomerulosclerosis, and the older sibling developed hypotonia, psychomotor delay, seizures, stroke-like

Fig. 1 CoQ₁₀ biosynthetic pathway with eight known biosynthetic enzymes denoted as COQ1-8. CoQ₁₀ is composed of a benzoquinone and a decaprenyl side chain. While the quinone ring is derived from amino acids tyrosine or phenylalanine, the isoprenoid side chain is produced by addition of isopentenyl pyrophosphate molecules to geranylgeranyl pyrophosphate (derived from mevalonate pathway) by decaprenyl diphosphate synthase. After para-hydroxybenzoate and decaprenyl pyrophosphate are produced, at least seven enzymes (encoded by COQ2-8) catalyze condensation, methylation, decarboxylation, and hydroxylation reactions to synthesize CoQ₁₀



episodes, and cerebellar and cerebral atrophy [19]. Interestingly, in these infantile-onset patients, deficiency of CoQ₁₀ is present not only in skeletal muscle, but also in other tissues and cells including skin fibroblasts. In addition, two adult sisters with encephalopathy, growth retardation, infantilism, ataxia, deafness and lactic acidosis have been described by Van Maldergam [23].

Cerebellar ataxia is the most common phenotype associated with CoQ₁₀ deficiency with 21 reported patients [20–22, 26]. Cerebellar ataxia and cerebellar atrophy are present in all the patients. Epilepsy is the most common associated feature, but pyramidal signs, mental retardation, myopathic weakness, and delayed motor milestones are other variably associated symptoms and signs. Except for two adult brothers with cerebellar ataxia and hypogonadism [22], the condition begins in childhood or adolescence. Muscle morphology does not show ragged-red fibers and lipid storage myopathy and CoQ₁₀ is moderately reduced in skin fibroblasts.

The clinical presentation of the variant isolated myopathy, recently described in four patients, is subacute onset of exercise intolerance and proximal limb weakness at variable ages. All patients have lipid storage and ragged-red fibers in muscle, as well as increased serum lactate and creatine kinase (CK) [24, 25]. In all the patients with different phenotypes, respiratory chain enzymes analyses show reduced activities of complex I + III and II + III with normal activities of isolated complex I and III.

In most of the reported patients, the exact site and nature of the defects in the biosynthesis of CoQ₁₀ have not yet been identified. Because ubiquinone biosynthesis is complex and not fully defined (Fig. 1), identification of the molecular genetic defect is not straightforward.

Undetectable CoQ₁₀ and low levels of decaprenylpyrophosphate, an intermediate compound in the synthesis of the lateral chain of CoQ₁₀ were found in the fibroblasts of the patient reported by Rötig and colleagues suggesting a defect in the synthesis of the decaprenyl side-chain, but they did not find any mutation in the cDNA of *COQ1*, the gene encoding transprenyltransferase, the enzyme that synthesizes decaprenylpyrophosphate [17].

This year, in two siblings with the infantile form of CoQ₁₀ deficiency, we reported a homozygous missense mutation (Y297C) in the *COQ2* gene, which encodes para-hydroxybenzoate (PHB) polyprenyl transferase. PHB-polyprenyl transferase mediates the conjugation of the benzoquinone ring with the decaprenyl side chain. Biochemical assays measuring incorporation of

radiolabeled PHB or decaprenyl-PP into CoQ₁₀ in skin fibroblasts from the proband showed 23–25% of control fibroblasts activity [27] confirming the defect of CoQ₁₀ biosynthesis.

The finding of a homozygous stop codon mutation in the *APTX* gene which is known to cause ataxia-oculomotor-aprataxia 1 (AOA1), in three siblings with cerebellar ataxia and CoQ₁₀ deficiency, supports the hypothesis that the ataxic form is a genetically heterogeneous disease in which CoQ₁₀ deficiency can be secondary [28]. Aprataxin is a member of the histidine triad superfamily and may be involved in nuclear DNA single strand break repair [29–31]. Despite the lack of an obvious link between aprataxin and regulation of CoQ₁₀ synthesis or catabolism, our findings, coupled with the clinical improvement of patients after CoQ₁₀ supplementation, suggest that CoQ₁₀ deficiency plays a pathogenic role in AOA1. Intriguingly, both CoQ₁₀ and cholesterol share a common biosynthetic pathway, therefore, in AOA1, altered levels of these molecules could be due to aberrant biosynthesis.

Patients with all forms of CoQ₁₀ deficiency have shown clinical improvement with oral CoQ₁₀ supplementation. The beneficial effects of exogenous CoQ₁₀ require high doses and long-term administration [32, 33]; its oral bioavailability is poor due to its extreme hydrophobicity; therefore, only a small fraction of orally administered CoQ₁₀ reaches the circulatory system, and augmentation of mitochondrial CoQ₁₀ content is even less effective. Beneficial effects of CoQ₁₀ supplementation are supported by in vitro correction of biochemical and histological abnormalities [12–14, 17]. However, while muscle abnormalities improve clinically and biochemically, in general, cerebral symptoms are only partially ameliorated [16]. This difference could be explained by the presence of irreversible structural brain damage before treatment or the poor penetration of CoQ₁₀ across the blood-brain barrier. Increases in plasma concentrations of CoQ₁₀ after oral supplementation in both humans and animals has been well-documented, but early work questioned whether CoQ₁₀ accumulates in tissues [34] and studies of 45-day-old rodents showed little or no change in rodent brain CoQ₁₀ concentrations after oral administration perhaps because levels of CoQ₁₀ are tightly regulated in young animals or may be saturated in membranes [34, 35]. In contrast, administration of very high doses of CoQ₁₀ (200 mg/kg daily) to 12–24 month-old rats produced significant increases in brain CoQ₁₀ levels [36], but a more recent study of the regional distribution of CoQ in 16 week-old rat brain before and after 4 weeks of moderately high exogenous dietary CoQ₁₀ (20 mg/kg daily) supplementation

showed that the concentration of CoQ was essentially unchanged in the cortex and in the striatum [37]. That study also demonstrated that the cerebellum, of the 7 brain regions dissected, contains the lowest levels of CoQ. If human brain has the same regional distribution of CoQ₁₀ as rat brain, the cerebellum may have the narrowest safety margin and therefore would be the first tissue to suffer from a pathological shortage of CoQ₁₀. Moreover, to function as an antioxidant, CoQ₁₀ must be in the reduced form but normally only 20% of the lipid is reduced in the brain. The high proportion of oxidized CoQ₁₀ in the brain could be a reflection of the high oxygen consumption in this tissue, causing an increased demand of anti-oxidants [38]. Therefore, CoQ₁₀ deficiency could be another form of inherited ataxia due to oxidative damage, as vitamin E deficiency.

Oxidative damage and mitochondrial dysfunction have also been implicated in neurodegenerative diseases such Parkinson disease (PD), Alzheimer disease (AD), and Friedreich's ataxia (FRDA) [39–41]. Pre-clinical studies have indicated that CoQ₁₀ can protect the nigrostriatal dopaminergic system and high doses (1200 mg daily) of CoQ₁₀ for 16 months appeared to slow progression PD [40, 42]. In 10 FRDA patients treated for 47 months high doses of CoQ₁₀ (400 mg daily) with vitamin E (2100 IU daily), improved bioenergetics in heart and skeletal muscle, improved cardiac function by echocardiography, and, possibly less clinical decline compared to historical controls [43]. Larger studies are necessary to better define the short- and long-term effects of CoQ₁₀ as primary or adjunctive therapy in neurodegenerative diseases.

Deficiency of CoQ₁₀ has been associated with a variety of neurological disorders that respond to oral supplementation. We have demonstrated that CoQ₁₀ deficiency can be primary due to a defect of biosynthesis or secondary as in patients with *APTX* mutations. The response of both groups of patients to oral supplementation suggests that exogenous CoQ₁₀ is taken up by affected tissues and can correct biochemical derangements. Further studies to define CoQ₁₀ deficiency syndrome will reveal new causes, enhance our understanding of its pathogenesis, and may provide novel insights that may be relevant to other neurodegenerative diseases.

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