Primary and secondary CoQ\textsubscript{10} deficiencies in humans

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Abstract
CoQ\textsubscript{10} deficiencies are clinically and genetically heterogeneous. This syndrome has been associated with five major clinical phenotypes: (1) encephalomyopathy, (2) severe infantile multisystemic disease, (3) cerebellar ataxia, (4) isolated myopathy, and (5) nephrotic syndrome. In a few patients, pathogenic mutations have been identified in genes involved in the biosynthesis of CoQ\textsubscript{10} (primary CoQ\textsubscript{10} deficiencies) or in genes not directly related to CoQ\textsubscript{10} biosynthesis (secondary CoQ\textsubscript{10} deficiencies). Respiratory chain defects, ROS production, and apoptosis variably contribute to the pathogenesis of primary CoQ\textsubscript{10} deficiencies.

Keywords
coenzyme Q\textsubscript{10}; respiratory chain activity; ROS; oxidative stress

1. Introduction
Human CoQ\textsubscript{10} deficiencies are clinically and genetically heterogeneous diseases. In most cases, family history suggests an autosomal recessive mode of inheritance. In 18 patients, pathogenic mutations in genes encoding for proteins involved in the biosynthesis of CoQ\textsubscript{10} have been identified (primary CoQ\textsubscript{10} deficiencies) [1–7].

2. Primary CoQ\textsubscript{10} deficiencies
In 1989, Ogasahara et al. first described patients with CoQ\textsubscript{10} deficiency, two sisters who presented with mitochondrial myopathy, elevated serum creatine kinase (CK), recurrent myoglobinuria, lactic acidosis, seizures, and mental retardation, associated with decreased activities of complexes I + III and II + III and markedly reduced CoQ\textsubscript{10} in muscle [8]. Since then, several patients with encephalomyopathy manifesting the same clinical triad of mitochondrial myopathy, recurrent myoglobinuria, and encephalopathy have been reported to have CoQ\textsubscript{10} deficiency [9–12]. In these patients, treatment with CoQ\textsubscript{10} supplementation improved mainly the muscle symptoms, and the molecular defect, compound heterozygous mutations in \textit{ADCK3/CABC1}, has been found only in the patient reported by Aure [6,12].

In 2000, Rötig et al. described for the first time an infantile-onset disorder associated with widespread CoQ\textsubscript{10} deficiency in three siblings who presented soon after birth with neurological symptoms, including nystagmus, optic atrophy, sensorineural hearing loss, ataxia, dystonia, weakness, and rapidly progressive nephropathy. The causative mutation in this family has not been reported; however, most of the patients with multisystemic infantile and CoQ\textsubscript{10} deficiency described so far have had genetically confirmed primary CoQ\textsubscript{10} deficiencies.

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deficiency. In 2006, we reported two siblings, who shared a homozygous missense mutation in the \textit{COQ2} gene encoding \textit{para}-hydroxybenzoate-polyprenyl transferase \cite{2}. The proband was a 33-month-old boy who was noted to have nystagmus at 2 months. At 12 months, he was hospitalized because of a severe nephrotic syndrome and neurological examination showed hypotonia and mild psychomotor delay. At 18 months, he developed frequent vomiting, psychomotor regression, tremor, weakness, hypotonia, and status epilepticus. Brain MRI showed cerebral and cerebellar atrophy and stroke-like lesions. He received a successful renal transplant at 3 years of age. His sister developed nephrotic syndrome at 12 months of age without any clinical signs of neurological involvement \cite{3,13}. Both the siblings improved with CoQ$_{10}$ supplementation \cite{3,14}. Rötig and coworkers subsequently reported two siblings harboring a homozygous base-pair deletion in exon 7 of the \textit{COQ2} gene. The girl had neonatal neurologic distress, nephrotic syndrome, hepatopathy, pancytopenia, diabetes, seizures, and lactic acidosis progressing to fatal multiorgan failure at age 12 days \cite{4}. The older brother also had anemia, liver failure, and renal insufficiency and died at the age of 1 day.

In 2007, other two patients with early-onset glomerulopathy due to mutations in the \textit{COQ2} gene were described \cite{3}. The first patient presented with steroid-resistant nephrotic syndrome at age 18 months as a result of collapsing glomerulopathy, without extra-renal manifestations. The second patient presented at 5 days of life with oliguria had severe extracapillary proliferation on renal biopsy, rapidly developed end-stage renal disease, and died at the age of 6 months after a course complicated by progressive epileptic encephalopathy. Combined complex II + III activity and CoQ$_{10}$ level were decreased in renal cortex as well as in skeletal muscle.

Mutations in \textit{PDSS2} that encodes one of the two subunits of polyprenyl diphosphate synthase, the first enzyme of the CoQ$_{10}$ biosynthetic pathway, have been reported in a male infant with nephrotic syndrome and Leigh syndrome \cite{1}. The boy presented with neonatal pneumonia and hypotonia. At the age of 3 months, he developed seizures and subsequently became progressively floppy, had difficulty in feeding, had severe episodic vomiting and lactic acidosis, and died at age 8 months due to severe refractory focal status epilepticus. In a consanguineous family, two siblings had CoQ$_{10}$ deficiency due to a homozygous \textit{PDSS1} mutation manifesting as a multisystem disease with early-onset deafness, encephaloneuropathy, obesity, livedo reticularis, and cardiac valvulopathy \cite{6}.

In 2009, Duncan et al. reported mutations in another gene, \textit{COQ9}, required for the biosynthesis of CoQ$_{10}$ in a newborn with generalized limb hypertonia, reduced truncal tone, lactic acidosis, renal tubulopathy, and cardiopathy \cite{7}. Brain MRI revealed cerebral and cerebellar atrophy. He developed severe seizures and dystonia and died at 2 years of age.

CoQ$_{10}$ deficiency in fibroblasts and early renal involvement seem to be a hallmark of primary infantile multisystemic syndromes \cite{1–4,7}. Early supplementation in patients with \textit{COQ2} mutations appears to have alleviated the nephropathy and may prevent development of neurological signs and symptoms \cite{14}. In contrast, the patients with \textit{PDSS2} and \textit{COQ9} mutations described by Lopez et al. and Rahman et al. died despite CoQ$_{10}$ replacement.

In 2003, Leshinsky-Silver et al. reported a patient who presented with neonatal liver disease, pancreatic insufficiency, tyrosinemia, hyperammonemia, subsequent sensorineural hearing loss, and Leigh syndrome. Liver biopsy revealed markedly reduced complex I + III and II + III activities that were restored by addition of CoQ$_{10}$ to the liver homogenate indicating ubiquinone deficiency. However, CoQ$_{10}$ level and the molecular defect in this patient are unknown \cite{15}.
In 2001, Musumeci et al. described the most common phenotype associated with CoQ$_{10}$ deficiency in muscle, characterized by childhood-onset cerebellar ataxia and atrophy variably associated with neuropathy, seizures, mental retardation, muscle weakness, hypogonadism, and low levels of CoQ$_{10}$ in fibroblasts [5,6,16–19]. Some patients with juvenile-onset cerebellar ataxia carry mutations in $ADCK3$/$CABC1$ [5,6]. Mutations in this gene have been recently found in additional patients with cerebellar ataxia, cerebellar atrophy, exercise intolerance, dystonia, and mild cognitive impairment. However, the level of CoQ$_{10}$ in muscle and fibroblasts from these patients was not mentioned [20]. Supplementation with CoQ$_{10}$ was associated with mild, subjective, clinical improvement in patients with cerebellar ataxia associated with mutations in $ADCK3$/$CABC1$ [5,6]. More recently, Pineda et al. assessed the clinical outcome in 14 patients with cerebellar ataxia with and without documented CoQ$_{10}$ deficiency in muscle and/or fibroblasts and unknown molecular defect and observed that all patients with CoQ$_{10}$ deficiency responded to the therapy [21].

### 3. Secondary CoQ$_{10}$ deficiencies

In three of the five patients originally described by Musumeci in 2001, secondary CoQ$_{10}$ deficiency has been found to result from a stop codon mutation in the $APTX$ gene encoding aprataxin [16,22,23], a protein involved in double-stranded DNA repair known to cause ataxia-oculomotor-apraxia 1 (AOA1) [24,25]. In these patients, CoQ$_{10}$ deficiency was not correlated with disease duration, severity, or progression or with biologic measures, indicating that CoQ$_{10}$ deficiency is not the primary or the only cause of neurological decline in AOA1. Nevertheless, three patients improved considerably after CoQ$_{10}$ supplementation [22].

Lalani and Horvath described a pure myopathic form of CoQ$_{10}$ deficiency, with lipid storage myopathy and respiratory chain dysfunction [26,27]. In 2007, Gempel and coworkers [28] found that the patients reported by Horvath and colleagues had mutations in the $ETFDH$ gene encoding electron-transferring flavoprotein dehydrogenase, which previously had been associated with glutaric aciduria type II (multiple acyl-CoA dehydrogenase deficiency [MADD]). In that report, all seven patients from five families presented with exercise intolerance, fatigue, proximal myopathy, and high serum creatine kinase (CK). Muscle histology showed lipid storage and subtle signs of mitochondrial myopathy. All of the patients with pure myopathy showed dramatic improvements after CoQ$_{10}$ supplementation [28]. In contrast, other studies reported patients with MADD and $ETFDH$ mutations who had normal CoQ$_{10}$ levels in muscle [29,30].

Secondary CoQ$_{10}$ deficiency with multisystemic infantile presentation has also been described in one patient with cardiofaciocutaneous syndrome due to a $BRAF$ mutation [31].

Secondary CoQ$_{10}$ deficiency in muscle has been reported in patients with a variety of mitochondrial diseases. In 1989, Zierz et al. described a patient with Kearns-Sayre syndrome and reduced CoQ$_{10}$ level in plasma and muscle [32]. In 1991, Matsuoka et al. reported that levels of CoQ$_{10}$ in muscle from 25 patients with mitochondrial encephalomyopathies, mostly carrying mtDNA mutations, were significantly lower than in controls [33]. Montero et al. in 2005 found just one patient with mild decrease in CoQ$_{10}$ level in a group of nine patients with diagnosis of mitochondrial disease [34]. In 2009, the same group reported that a newborn girl with mtDNA depletion and CoQ$_{10}$ deficiency in muscle and fibroblasts, without molecular defect in any gene, was known to be involved in mtDNA depletion syndrome, but mutation screening of genes required for CoQ$_{10}$ biosynthesis was not performed [35]. In 2008, Miles et al. assessed CoQ$_{10}$ muscle level in a large cohort of pediatric patients with possible or probable mitochondrial disease and found significantly
decreased CoQ10 concentration in the probable defect group [36]. The most recent study is a multicenter analysis performed in 76 patients with heterogeneous mitochondrial phenotypes, which showed a high proportion of patients with CoQ10 deficiency, including patients with isolated PEO and PEO associated with myopathy, patients with multisystemic disease and/or encephalomyopathy [37]. Thus, coenzyme Q10 deficiency appears to be a relatively common finding in mitochondrial disorders and is likely to benefit from exogenous supplementation; large-scale randomized clinical trials to evaluate this treatment options are now underway [38].

There is growing evidence of acquired CoQ10 deficiencies; however, in these conditions, CoQ10 level was measured and found low in plasma and/or serum [39]. In contrast, there are few reports of CoQ10 measurement in tissues, but one report showed evidence of low CoQ10 in the muscle of a sub-group of children with food intolerance and allergies [40].

4. In vitro studies of primary CoQ10 deficiencies

The disparate phenotype and responses to CoQ10 supplementation suggest differences in the pathomechanisms of CoQ10 deficiencies or in the pharmacokinetics of CoQ10 supplementation. To address these issues, the consequence of CoQ10 deficiency on mitochondrial bioenergetics, oxidative stress, and antioxidant defenses in tissues and cells from patients with CoQ10 deficiencies and the effects of CoQ10 supplementation have been investigated.

Initial studies of cultured fibroblasts from two siblings with infantile-onset CoQ10 deficiency showed mild respiratory chain defects but no evidence of increased superoxide anions, lipid peroxidation, or apoptosis-mediated cell death [41].

Lopez-Martín et al. showed that COQ2 mutant fibroblasts require uridine to maintain growth and proposed that deficiency of CoQ10 caused a defect in de novo pyrimidine biosynthesis because of the dependence of dihydro-orotate dehydrogenase on ubiquinol [42].

In the same two cell lines carrying COQ2 mutations and in two other cell lines from patients with CoQ10 deficiency with unknown molecular defects, Rodríguez-Hernández et al. observed increased levels of lysosomal markers as well as enhanced expression of transcriptional and translational levels of autophagic genes [43]. Because inhibition of autophagy resulted in apoptotic cell death, the authors suggested that autophagy is a protective mechanism involved in the degradation of dysfunctional mitochondria.

Our initial studies in cultured skin fibroblasts harboring COQ2 and PDSS2 mutations suggested that defects in the first two committed steps of the CoQ10 biosynthetic pathway produce different biochemical alterations. PDSS2 mutant fibroblasts have 12% CoQ10 content and 28% residual CII+III activity relative to control cells with markedly reduced ATP synthesis, but do not show increased ROS production, signs of oxidative stress, or increased antioxidant defense markers. In contrast, COQ2 mutant fibroblasts have 30% CoQ10 content and 48% residual CII+III activity with mild defects of ATP synthesis and show significantly increased ROS production as well as oxidation of lipids and proteins [44]. We extended our studies to other patients’ cell lines, with variable degrees of CoQ10 deficiency due to different molecular defects, including mutations in COQ2 [3], ADCK3/CABC1 [4,5], and COQ9 [7], and we have observed a correlation between levels of CoQ10 and ROS production: 10–15% or >60% residual CoQ10 content is not associated with significant ROS production, whereas 30–50% residual CoQ10 content is associated with maximal increases in ROS production and cell death [45]. These studies confirm that varying degrees of CoQ10 variably impair ATP synthesis and induce oxidative stress. In the same cell lines with mutations in PDSS2, COQ2, and COQ9, we have evaluated the efficacy
of CoQ10 supplementation in normalizing the bioenergetic status and the oxidative balance, comparing it with the efficacies of short-tail ubiquinone analogs (idebenone and CoQ2), which are less lipophilic, and vitamin C, a hydrophilic antioxidant [46]. We observed that after 24 h of 5 μM CoQ10 supplementation (the approximate concentration reached in the plasma of patients treated with high doses of oral supplementation of CoQ10), cellular CoQ10 levels increased dramatically and that all four compounds significantly reduced superoxide anion levels and cell death in mutant fibroblasts with oxidative stress. However, after 24 h of CoQ10 treatment, none of the cell lines showed significant improvement in ATP levels or in ATP/ADP ratios, which are markers of respiratory chain function. In marked contrast to treatment for 24 h of CoQ10, incubation of ubiquinone-deficient fibroblasts for 1 week with 5 μM CoQ10 (but not short-tail ubiquinone analogs and vitamin C) increased ATP levels and ATP/ADP ratios significantly [46]. These results indicate that the pharmacokinetic constraints of CoQ10 in reaching the mitochondrial respiratory chain and the dose of CoQ10 are key limiting factors in determining its efficacy in CoQ10-deficient patients.

5. Conclusions

CoQ10 deficiencies are clinically and genetically heterogeneous diseases that can occur due to defects of ubiquinone biosynthesis (primary deficiencies) or due to other causes (secondary deficiencies). Diagnosis of CoQ10 deficiency is most reliably made by measuring levels in muscle, fibroblasts, or both, but not plasma as circulating levels are influenced by dietary intake. Because both forms may improve with CoQ10 supplementation early diagnosis is important. In vitro studies have revealed that CoQ10 deficiency leads to diverse biochemical consequences that variably contribute to cell death. Future studies are likely to identify new causes and to provide new insights into the pathogenesis and treatment of CoQ10 deficiencies.

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