

Clinical Presentations of Coenzyme Q₁₀ Deficiency Syndrome

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Key Words

Cerebellar ataxia · Coenzyme Q₁₀ deficiency · Encephalomyopathy · Steroid-resistant nephrotic syndrome

Abstract

Coenzyme Q₁₀ (CoQ₁₀) deficiency is a clinically and genetically heterogeneous syndrome which has been associated with 5 major clinical phenotypes: (1) encephalomyopathy, (2) severe infantile multisystemic disease, (3) nephropathy, (4) cerebellar ataxia, and (5) isolated myopathy. Of these phenotypes, cerebellar ataxia and syndromic or isolated nephrotic syndrome are the most common. CoQ₁₀ deficiency predominantly presents in childhood. To date, causative mutations have been identified in a small proportion of patients, making it difficult to identify a phenotype-genotype correlation. Identification of CoQ₁₀ deficiency is important because the disease, in particular muscle symptoms and nephropathy, frequently responds to CoQ₁₀ supplementation.

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Human coenzyme Q₁₀ (CoQ₁₀) deficiency (MIM 607426) is a clinically and genetically heterogeneous syndrome, so far reported in about 100 patients and associated with 5 major clinical phenotypes: encephalomyopathy [Ogasahara et al., 1989; Sobreira et al., 1997; Boitier et al., 1998; Di Giovanni et al., 2001], severe infantile multi-

systemic disease [Rötig et al., 2000; Rahman et al., 2001; Leshinsky-Silver et al., 2003; Salviati et al., 2005; López et al., 2006; Quinzii et al., 2006; Mollet et al., 2007; Duncan et al., 2009; Dinwiddie et al., 2013; Jakobs et al., 2013; Scalais et al., 2013], isolated nephropathy [Diomedici-Cammasei et al., 2007; Ashraf et al., 2013; McCarthy et al., 2013], or associated with sensory hearing loss [Heeringa et al., 2011], cerebellar ataxia [Musumeci et al., 2001; Lamperti et al., 2003; Auré et al., 2004; Gironi et al., 2004; Artuch et al., 2006; Le Ber et al., 2007; D'Arrigo et al., 2008; Lagier-Tourenne et al., 2008; Mollet et al., 2008; Pineda et al., 2010; Castellotti et al., 2011; Horvath et al., 2012; Liu et al., 2013; Mignot et al., 2013], and isolated myopathy [Lalani et al., 2005; Horvath et al., 2006; Gempel et al., 2007]. Primary CoQ₁₀ deficiencies are due to defects in CoQ₁₀ biosynthesis (fig. 1), while secondary deficiencies are due to other causes, including mutations in genes unrelated to ubiquinone biosynthesis. Identification of CoQ₁₀ deficiency is important, because patients frequently respond to treatment [Horvath, 2012].

Encephalomyopathy

Ogasahara et al. [1989] described the first patients with CoQ₁₀ deficiency; 2 sisters who, after normal early development, presented with exercise intolerance and slowly progressive weakness of axial and proximal limb muscles.

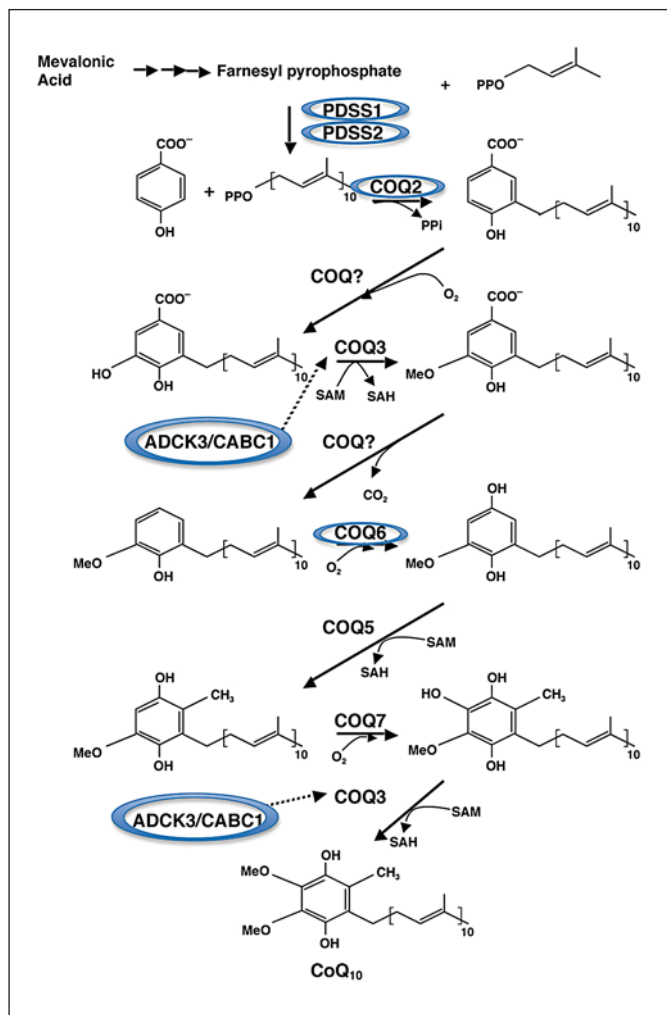


Fig. 1. Biosynthesis of CoQ₁₀. Mutations in CoQ₁₀ biosynthetic genes (indicated by blue ovals) cause primary CoQ₁₀ deficiency.

After 5 years of age, brain involvement manifested with learning disability in both sisters, seizures in one and cerebellar syndrome in the other. In addition, both had episodes of myoglobinuria following seizures or intercurrent infections. Laboratory abnormalities included lactic acidosis and increased serum creatine kinase; EMG showed myopathic features. Muscle biopsies showed ragged-red fibers and excessive accumulation of lipid droplets in type I fibers, decreased activities of mitochondrial respiratory chain complexes I+III and II+III, and markedly decreased concentration of CoQ₁₀ (about 5% of normal); on the contrary, CoQ₁₀ level was normal in serum and cultured fibroblasts [Ogasahara et al., 1989]. Since then, several patients with the same clinical triad of mitochondrial myopathy, recurrent myoglobinuria, and encephalopathy

have been reported [Sobreira et al., 1997; Boitier et al., 1998; Di Giovanni et al., 2001; Auré et al., 2004]. Mutations in *ADCK3* have been found in one patient [Auré et al., 2004; Mollet et al., 2008]. In all these patients, treatment with CoQ₁₀ supplementation mainly improved the muscle symptoms.

Interestingly, Salviati et al. [2012] reported a patient with similar phenotype and haploinsufficiency of *COQ4* caused by a 3.9-Mb deletion of chromosome 9q34.

Severe Infantile Multisystemic Disease

The first patients described were 3 siblings who presented soon after birth with neurological symptoms, including nystagmus, optic atrophy, sensorineural hearing loss, ataxia, dystonia, weakness, rapidly progressive nephropathy, and widespread CoQ₁₀ deficiency [Rötig et al., 2000], associated with mutations in *PDSS2* [Rötig, pers. comm.].

Rahman et al. [2001] reported a newborn with generalized limb hypertonia, reduced truncal tone, lactic acidosis, renal tubulopathy, and left ventricular hypertrophy with global hypokinesia. Brain MRI revealed cerebral and cerebellar atrophy. The boy developed severe seizures and dystonia and died at 2 years of age [Rahman et al., 2001]. Homozygosity mapping and screening of candidate genes revealed a homozygous mutation in *COQ9* [Duncan et al., 2009].

Leshinsky-Silver et al. [2003] 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 activity that was restored by addition of CoQ₁₀ to the liver homogenate, indicating CoQ₁₀ deficiency; however, the CoQ₁₀ level and the causative molecular genetic defect in this patient are unknown.

In 2006, we reported 2 siblings who shared a homozygous missense mutation in the *COQ2* gene encoding para-hydroxybenzoate-polyprenyl transferase [Quinzii et al., 2006]. The first proband was a 33-month-old boy who developed 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, 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. The

sister developed nephrotic syndrome at 12 months of age without any clinical signs of neurological involvement [Salviati et al., 2005; Diomedi-Camassei et al., 2007]. Both siblings improved with CoQ₁₀ supplementation [Diomedi-Camassei et al., 2007; Montini et al., 2008]. Rötig et al. [2000] subsequently reported 2 siblings harboring a homozygous base pair deletion in exon 7 of the *COQ2* gene. The girl had neonatal neurologic distress, nephrotic syndrome, hepatopathy, pancytopenia, diabetes mellitus, seizures, and lactic acidosis, progressing to fatal multiorgan failure at the age of 12 days [Mollet et al., 2007]. The older brother also had anemia, liver failure, renal insufficiency, and died at the age of 1 day.

Recently, mutations in the *COQ2* gene have been described in 4 additional patients with severe infantile multisystemic disease [Dinwiddie et al., 2013; Jakobs et al., 2013; Scalais et al., 2013].

Scalais et al. [2013] described an infant with myoclonic seizures and hypertrophic cardiomyopathy in the first months of life. He subsequently developed nephrotic syndrome due to focal segmental glomerulosclerosis and died at 5 months of age, despite supplementation with CoQ₁₀. This patient harbored a novel homozygous mutation in the *COQ2* gene.

Using whole exome sequencing analysis, Dinwiddie et al. [2013] identified compound heterozygous *COQ2* mutations in an infant with metabolic acidosis, hyperglycemia, and hypertrophic cardiomyopathy who developed encephalopathy, necrotizing colitis, and respiratory insufficiency. The patient died at 2 months of age of multiorgan failure. The molecular defect was identified post-mortem.

A novel homozygous mutation in *COQ2* was reported in dizygotic twins from consanguineous Turkish parents [Jakobs et al., 2013]. The children, born prematurely, presented with respiratory insufficiency, seizures, feeding problems, episodes of apnea, generalized hypotonia, and generalized edema, and died at the ages of 5 and 6 months. As in the case described by Dinwiddie et al. [2013], in these twins there was no evidence of renal involvement.

In 2006, we reported a male infant with nephrotic syndrome and Leigh syndrome [López et al., 2006]. The boy presented with neonatal pneumonia and hypotonia. At the age of 3 months, he developed seizures and subsequently became progressively floppy, had difficulty feeding, severe episodic vomiting, and lactic acidosis, and died at 8 months of age due to status epilepticus. The patient carried mutations in *PDSS2* which encodes 1 of 2 subunits of polyprenyl diphosphate synthase, the first enzyme of the CoQ₁₀ biosynthetic pathway. Interestingly,

Leigh syndrome was previously reported in 2 sisters with CoQ₁₀ deficiency and encephalopathy, growth retardation, infantilism, ataxia, deafness, and lactic acidosis. Although also in these patients the disease had early onset, both clinical and biochemical abnormalities improved remarkably with CoQ₁₀ supplementation; when taking 300 mg CoQ₁₀ per day, the one proband resumed walking, gained weight, underwent puberty, and grew 20 cm, and she was still alive at the age of 31 years [Van Maldergem et al., 2002].

In a consanguineous family, 2 siblings had CoQ₁₀ deficiency due to a homozygous *PDSS1* mutation manifesting as a multisystem disease with early-onset deafness, encephaloneuropathy, obesity, livedo reticularis, and cardiac valvulopathy [Mollet et al., 2007].

CoQ₁₀ deficiency in fibroblasts and early renal involvement seem to be a hallmark of primary infantile multisystemic syndromes [López et al., 2006; Quinzii et al., 2006; Diomedi-Camassei et al., 2007; Mollet et al., 2007; Duncan et al., 2009]. Early supplementation in patients with *COQ2* mutations appears to have alleviated the nephropathy and may prevent the development of neurological signs and symptoms [Montini et al., 2008].

In the patient with a *COQ2* mutation described by Scalais et al. [2013], CoQ₁₀ supplementation at high dose (30 mg/kg daily) was started at 5 months of age, only 2 weeks before the patient died; therefore, late initiation of treatment may account for the lack of response to the therapy. The patients with *PDSS2* and *COQ9* mutations described by López et al. [2006] and Rahman et al. [2001] died despite CoQ₁₀ replacement.

A single patient with cardiofaciocutaneous syndrome due to a *BRAF* gene mutation also had CoQ₁₀ deficiency and improved with CoQ₁₀ supplementation [Aeby et al., 2007].

Nephropathy

As mentioned above, of the first 2 siblings described carrying *COQ2* mutations, the sister developed nephrotic syndrome at 12 months of age without any clinical signs of neurological involvement [Salviati et al., 2005]. In 2007, another 2 patients with early-onset glomerulopathy due to mutations in the *COQ2* gene were described [Diomedi-Camassei et al., 2007]. The first patient presented with steroid-resistant nephrotic syndrome at the age of 18 months as a result of collapsing glomerulopathy, without extra-renal manifestations. The second patient, presenting with oliguria at 5 days of life, had severe extra-

capillary 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 CoQ₁₀ level were decreased in renal cortex as well as in skeletal muscle [Diomedi-Camassei et al., 2007].

An extensive screening of *COQ2* and *PDSS2* mutations performed in 117 European non-Finnish patients with congenital nephrotic syndrome was negative and indicated that mutations in those genes are rare causes of early-onset nephrotic syndrome [Machuca et al., 2010].

More recently, the simultaneous screening of 24 genes associated with steroid-resistant nephrotic syndrome using next-generation sequencing in 36 children with this syndrome led to the identification of 2 mutations in *COQ2* in 1 patient. The patient developed nephropathy and acute renal failure at the age of 2 years, was neurologically normal, and did not develop sensorineural hearing loss [McCarthy et al., 2013].

Mutations in monooxygenase 6 (*COQ6*) have been reported in 13 individuals (7 families) with steroid-resistant nephrotic syndrome and neurosensory deafness. In the 2 patients treated, CoQ₁₀ supplementation improved proteinuria but not the hearing function [Heeringa et al., 2011].

Using a combination of homozygosity mapping and whole exome sequencing, Ashraf et al. [2013] were able to identify mutations in the *aarF* domain-containing kinase 4 (*ADCK4*) gene in 15 individuals with steroid-resistant nephrotic syndrome from 8 unrelated families. *ADCK4* has high sequence similarity with *ADCK3* and is expressed in podocytes and foot processes, localized to mitochondria, and interacts with *COQ6* [Ashraf et al., 2013].

Steroid-resistant nephrotic syndrome, in isolation or in association with other signs and symptoms, may also be a manifestation of secondary CoQ₁₀ deficiency; nephrotic syndrome has been described in 2 sisters with unknown molecular defect(s) and no mutations in any of the genes known to be involved in the CoQ₁₀ biosynthesis pathway [Emmanuele et al., 2012].

Cerebellar Ataxia

The cerebellar phenotype of CoQ₁₀ deficiency is apparently the most common and characterized by cerebellar ataxia and atrophy variably associated with neuropathy, seizures, mental retardation, muscle weakness, hypogonadism, and low levels of CoQ₁₀ in fibroblasts

[Musumeci et al., 2001; Lamperti et al., 2003; Gironi et al., 2004; Artuch et al., 2006; Lagier-Tourenne et al., 2008; Mollet et al., 2008; Pineda et al., 2010; Horvath et al., 2012; Liu et al., 2013; Mignot et al., 2013]. Muscle morphology did not show ragged-red fibers and lipid storage myopathy in the first reports. Some patients carry mutations in *APTX* [Quinzii et al., 2005; Le Ber et al., 2007; D'Arrigo et al., 2008; Castelotti et al., 2011] or in *ADCK3/CABC1* [Lagier-Tourenne et al., 2008; Mollet et al., 2008; Liu et al., 2013; Mignot et al., 2013]. The condition usually begins in childhood or adolescence, except for 2 adult brothers with cerebellar ataxia and hypogonadism described by Gironi et al. [2004] and 2 patients with *ADCK3* mutations with adult-onset and very mild phenotype, recently reported by Horvath et al. [2012]. Interestingly, in muscle from less severely affected patients, CoQ₁₀ levels were normal. Mutations in *ADCK3* have been found in additional patients with cerebellar ataxia, cerebellar atrophy, exercise intolerance, dystonia, and mild cognitive impairment. However, the level of CoQ₁₀ in muscle and fibroblasts in these patients was not mentioned [Gerards et al., 2010]. Disease progression is typically slow.

Supplementation with CoQ₁₀ has been associated with increased strength and energy level and disappearance of seizures in the affected individuals with aprataxin mutations we described [Musumeci et al., 2001; Quinzii et al., 2005], and with mild clinical improvement in patients with cerebellar ataxia associated with mutations in *ADCK3/CABC1* [Lagier-Tourenne et al., 2008; Mollet et al., 2008; Liu et al., 2013; Mignot et al., 2013]. More recently, Pineda et al. [2010] 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.

Isolated Myopathy

Lalani et al. [2005] and Horvath et al. [2006] described a pure myopathic form of CoQ₁₀ deficiency with lipid storage myopathy and respiratory chain dysfunction. Gempel et al. [2007] found mutations in the patients reported by Horvath et al. [2006] in the *ETFDH* gene encoding electron-transferring-flavoprotein dehydrogenase which previously had been associated with glutaric aciduria type II (multiple acyl-CoA dehydrogenase deficiency). In that report, all 7 patients from 5 families presented with exercise intolerance, fatigue, proximal myopathy, and elevated serum creatine kinase. Muscle

histology showed lipid storage and subtle signs of mitochondrial myopathy. All of the patients with pure myopathy showed dramatic improvements after CoQ₁₀ supplementation [Gempel et al., 2007].

In contrast, other studies reported patients with multiple acyl-CoA dehydrogenase deficiency and *ETFDH* mutations who had normal CoQ₁₀ levels in muscle [Liang et al., 2009; Ohkuma et al., 2009].

Conclusions

The phenotypes associated with CoQ₁₀ deficiency are heterogeneous; the association of encephalopathy and steroid-resistant nephrotic syndrome in infants as well as cerebellar ataxia without known molecular defects, especially if inherited as autosomal recessive traits, should lead to measurement of complexes I+III and II+III activities and CoQ₁₀ levels in muscle.

The problem of establishing a molecular diagnosis in patients with CoQ₁₀ deficiency persists, since most of the cases are sporadic, and even in the presence of a positive

family history, the number of affected individuals is too small to perform linkage analysis. However, it is important to diagnose the biochemical defect of CoQ₁₀ because of the potential therapeutic effects of CoQ₁₀ supplementation.

Diagnosis of additional patients, associated with further genetic and functional studies, are needed to better characterize the genotype-phenotype correlation and the pathogenic mechanism of the disease and the variability of the response to the supplementation with CoQ₁₀ and its analogs.

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