Clinical Presentations of Coenzyme Q$_{10}$ Deficiency Syndrome

Catarina M. Quinzii    Valentina Emmanuele    Michio Hirano

Department of Neurology, H. Houston Merritt Clinical Research Center, Columbia University Medical Center, New York, N.Y., USA

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 [Diomedi-Camascei 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; Llamperti 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 CoQ$_{10}$ deficiencies are due to defects in CoQ$_{10}$ biosynthesis (fig. 1), while secondary deficiencies are due to other causes, including mutations in genes unrelated to ubiquinone biosynthesis. Identification of CoQ$_{10}$ deficiency is important, because patients frequently respond to CoQ$_{10}$ supplementation.

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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, Salviani 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]. Röttig 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 multi-organ 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 polypropyl 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-Camascei 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 monoxygenase 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; Lalani et al., 2005; Gempel et al., 2007] 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 CoQ_{10} supplementation [Gempel et al., 2007].

In contrast, other studies reported patients with multiple acyl-CoA dehydrogenase deficiency and ETFDH mutations who had normal CoQ_{10} levels in muscle [Liang et al., 2009; Ohkuma et al., 2009].

Conclusions

The phenotypes associated with CoQ_{10} 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 CoQ_{10} levels in muscle.

The problem of establishing a molecular diagnosis in patients with CoQ_{10} 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 CoQ_{10} because of the potential therapeutic effects of CoQ_{10} 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 CoQ_{10} and its analogs.

Acknowledgements

This work was supported by 1R01HD057543 (M.H.) and K23HD065871 (C.M.Q.) from the Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD) and the Office of Dietary Supplements (ODS). M.H. is supported by NIH grants R01HD056103, U54 NS078059, and P01 HD032062; a Muscular Dystrophy Association grant; and by the Marriott Mitochondrial Disorder Clinical Research Fund (MMDCRF).

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