Heterogeneity of Coenzyme Q$_{10}$ Deficiency

Patient Study and Literature Review

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Coenzyme Q$_{10}$ (CoQ$_{10}$) deficiency has been associated with 5 major clinical phenotypes: encephalomyopathy, severe infantile multisystemic disease, nephropathy, cerebellar ataxia, and isolated myopathy. Primary CoQ$_{10}$ deficiency is due to defects in CoQ$_{10}$ biosynthesis, while secondary forms are due to other causes. A review of 149 cases, including our cohort of 76 patients, confirms that CoQ$_{10}$ deficiency is a clinically and genetically heterogeneous syndrome that mainly begins in childhood and predominantly manifests as cerebellar ataxia. Coenzyme Q$_{10}$ measurement in muscle is the gold standard for diagnosis. Identification of CoQ$_{10}$ deficiency is important because the condition frequently responds to treatment. Causative mutations have been identified in a small proportion of patients.


Coenzyme Q$_{10}$ (CoQ$_{10}$ or ubiquinone) deficiency in humans is associated with clinically heterogeneous diseases.¹ Five major phenotypes have been described: (1) encephalomyopathy, (2) cerebellar ataxia, (3) infantile multisystemic form, (4) nephropathy, and (5) isolated myopathy (Table 1).

METHODS

Seventy-six patients with CoQ$_{10}$ deficiency (36 previously unreported) were studied at the H. Houston Merritt Clinical Research Center, Columbia University Medical Center, New York, New York, under the center’s institutional review board’s protocols. Coenzyme Q$_{10}$ levels were measured in muscle, cultured fibroblasts, and/or lymphoblasts. Coenzyme Q$_{10}$ levels reduced more than 2 standard deviations below mean control values were considered deficient. Patients with CoQ$_{10}$ levels decreased in 1 member of the family with similar phenotype and/or genetic mutation were considered to have CoQ$_{10}$ deficiency.

Dideoxy sequencing was performed on all exons and flanking intronic regions of genes involved in CoQ$_{10}$ biosynthesis, associated with secondary CoQ$_{10}$ deficiencies, or encoding proteins with similar function, structure, or both as proteins associated with CoQ$_{10}$ deficiency. In addition, we sequenced PSAP-encoding saposin B, a cytosolic protein that binds and transfers CoQ$_{10}$, and POLG (eTable 1, http://www.archneurol.com).

CLINICAL FEATURES

Since the first description of human ubiquinone deficiency, 113 patients have been reported (Tables 1, 2, and 3). Of 455 patients referred to our center for possible CoQ$_{10}$ deficiency from 1997 to 2010, 76 patients (64 families) had CoQ$_{10}$ deficiency, 40 of which were previously described. The reported patients and our 36 new patients composed 149 cases: 4 patients with encephalomyopathy, 14 with isolated myopathy, 17 with infantile-onset multisystemic disease, 11 with nephropathy (with or without sensorineu-
ral hearing loss), 94 with cerebellar ataxia, and 9 with atypical presentations.

Onset was predominantly in childhood (82% were aged <13 years) including 23% in infancy (aged <12 months). Onset during adolescence (7% were aged 13-18 years) and adulthood (11% were aged >18 years) were uncommon. The mortality rate was low (8%) and mainly seen in the infantile multisystemic and renal forms.

The encephalomyopathic form of CoQ10 deficiency, manifesting as a triad of mitochondrial myopathy, recurrent myoglobinuria, and encephalopathy, has been reported in 4 patients (eTable 2).2-4 Neurologic features included cerebellar ataxia, seizures, mental retardation, delayed motor development, progressive external ophthalmoplegia, and ptosis.

The myopathic form of CoQ10 deficiency presents with muscle weakness, myoglobinuria, exercise intolerance, cramps, myalgias, and elevated creatine kinase. This condition has been described in 10 patients.4-7 We identified 4 additional patients (eTable 3).

Among the 17 patients (including 2 new patients) with the infantile multisystemic form, the combination of encephalopathy and nephropathy has been the most common presentation (eTable 4).6,13-15 Neurologic manifestations include psychomotor regression, ataxia, hypotonia, seizures, pyramidal syndrome, optic atrophy and retinopathy, deafness, and Leigh syndrome. The renal involvement is mainly nephrotic syndrome but occasionally tubulopathy. Three patients required kidney transplantation.13,15 In addition, liver, cardiac, and pancreatic involvement, as well as obesity have been described in literature and in our cohort.10,16,33 Eleven patients (65%) died in early infancy, and causes of death were opportunistic infections, kidney failure, encephalopathy, or multi-organ failure.

Early-onset isolated steroid-resistant nephrotic syndrome owing to collapsing glomerulopathy and focal segmental glomerulosclerosis has been reported in 2 patients.12 Moreover, the association between steroid-resistant nephrotic syndrome with sensorineural hearing loss has been described in patients with mutations in the CoQ10 biosynthetic gene, COQ6; however, CoQ10 level was not measured in these patients (eTable 5).14

Cerebellar ataxia is the most common phenotype, with 94 patients (including 23 new patients) (eTable 6).17-32 Other manifestations include neuropathy, seizures, mental retardation, migraine, psychiatric disorders, muscle weakness and exercise intolerance, congenital hypotonia, upper motor neuron signs, dystonia and chorea, ptosis and ophthalmoplegia, retinitis pigmentosa, optic atrophy, oculomotor apraxia, deafness, lipomas, Dandy-Walker syndrome, agenesis of corpus callosum, hypogonadism and other endocrinological problems, hypalbuminemia, and hypercholesterolemia.

Among the patients classified as atypical cases, there were 2 adult sisters with childhood-onset Leigh syndrome, growth retardation, infantilism, ataxia, deaf-
ness, and lactic acidosis, a 4-year-old girl with cardio-facio-cutaneous syndrome, 2 unrelated patients with neonatal hypotonia and infantile spasm (1 reported), 2 sisters with adult-onset cerebellar ataxia and nephrotic syndrome, and a 16-year-old girl with onset at age 4 years of exercise intolerance, fatigue, recurrent headaches, short stature, deafness, retinopathy, and mental retardation. One new patient was the father of a child with cerebellar ataxia (P119 in eTable 6) who had mild creatine kinase elevation but normal examination and brain magnetic resonance imaging results.

Table 2. Laboratory Features of Major Forms of CoQ10 Deficiency

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Blood Lactate</th>
<th>Serum Creatine Kinase</th>
<th>Muscle Histology</th>
<th>Mitochondrial Respiratory Chain Enzyme Activities&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CoQ10 Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalomyopathy</td>
<td>Elevated in 3/3 patients</td>
<td>Increased in 4/4 patients (2- to 37-fold elevation)</td>
<td>Mitochondrial changes in 4/4 patients</td>
<td>↓ I+III, II+III in 4/4 patients</td>
<td>3.7%-39% of normal in muscle, normal in fibroblasts in 1 patient</td>
</tr>
<tr>
<td>Isolated myopathy</td>
<td>Elevated in 5/10 patients</td>
<td>1.5- to 150-fold elevation</td>
<td>Mitochondrial changes in 8/11 patients</td>
<td>↓ II+III ± other complexes 8/10 patients</td>
<td>12.4%-49% of normal in muscle, normal in fibroblasts in 1 patient</td>
</tr>
<tr>
<td>Isolated nephropathy</td>
<td>Elevated in 1/2 patients</td>
<td>NA</td>
<td>Mitochondrial changes in 1 patient</td>
<td>↓ I+III, II+III in fibroblasts in 1 patient; ↓ II+III in muscle in 1 patient</td>
<td>38% of normal in muscle in 1 patient, 17% of normal in fibroblasts in 1 patient</td>
</tr>
<tr>
<td>Infantile multisystemic disease</td>
<td>Elevated in 8/9 patients</td>
<td>NA</td>
<td>Mitochondrial changes in 4/8 patients</td>
<td>↓ II+III ± other complexes in muscle in 4/7 patients; ↓ II+III fibroblast in 1; ↓ II+III ± other complexes in liver in 2</td>
<td>2.5%-37% of normal in muscle, reduced in fibroblasts in 10/11 patients</td>
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<tr>
<td>Cerebellar ataxia</td>
<td>Elevated in 11/34 patients</td>
<td>20- to 23-fold elevation in 2 patients, normal in 1 patient</td>
<td>Mitochondrial changes in 15/49 patients</td>
<td>Reduced in 27/51 patients in muscle</td>
<td>4%-66% of normal in muscle, reduced in fibroblasts in 18/30 patients</td>
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Abbreviations: CoQ10, coenzyme Q10; NA, not available.
<sup>a</sup>Mitochondrial changes included ragged-red fibers, cytochrome c oxidase–negative fibers, and lipid accumulation.

Table 3. Clinical Response to CoQ10 Supplementation in Major Forms of CoQ10 Deficiency

<table>
<thead>
<tr>
<th>Syndrome (No. of Patients)</th>
<th>CoQ10 Doses; Duration</th>
<th>Response to Therapy</th>
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<tbody>
<tr>
<td>Encephalomyopathy (4)</td>
<td>150 mg/d; 3-8 mo</td>
<td>Improvement of muscle symptoms in 4/4 and encephalopathy in 1 patient</td>
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<tr>
<td>Isolated myopathy (8)</td>
<td>150-500 mg/d; 4-12 mo</td>
<td>Improvement in 6 patients</td>
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<tr>
<td>Isolated nephropathy (4)</td>
<td>30 mg/kg/d-100 mg/d; 2-50 mo</td>
<td>Reduced proteinuria in 3 patients; hearing improvement in 1/2 patients; no follow-up data in 1 patient</td>
</tr>
<tr>
<td>Infantile multisystemic disease (4)</td>
<td>30 mg/kg/d-300 mg/d; 5-36 mo</td>
<td>Improvement of myopathic symptoms and stabilization of encephalopathy in 1 patient; neurological, but not renal improvement in 1 patient</td>
</tr>
<tr>
<td>Cerebellar ataxia (54)</td>
<td>5 mg/kg/d-3000 mg/d; 1 mo-12 y</td>
<td>Improvement of muscle symptoms in 13/20 patients; seizures in 3/14 patients; ataxia in 25/54 patients.</td>
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Abbreviation: CoQ10, coenzyme Q10.

Initial biochemical evaluation of patients with suspected CoQ10 deficiency should include blood lactate measurement, although normal values do not exclude ubiquinone deficiency. Muscle biopsies occasionally show mitochondrial proliferation or lipid droplets, but they can be normal or show only nonspecific changes.

Reduced biochemical activities of respiratory chain complexes, in particular complexes I + III (nicotinamide adenine dinucleotide–cytochrome c oxidoreductase) and complexes II + III (succinate–cytochrome c oxidoreductase) in muscle, suggest CoQ10 deficiency, although activities of these enzymes may be normal particularly when the deficiency is mild. Reduction of these enzyme activities and deficiency of CoQ10 in skin fibroblasts can be an important confirmation of ubiquinone deficiency; however, normal levels do not exclude deficiency in muscle. Direct measurement of CoQ10 in skeletal muscle by high-performance liquid chromatography is the most reliable test for the diagnosis. In contrast, plasma concentrations of ubiquinone are significantly influenced by dietary uptake, therefore not reliable. Measurements of CoQ10 in peripheral blood mononuclear cells
has detected deficiency in a small number of patients; however, correlations with muscle CoQ₁₀ measurements in a larger cohort of patients will be necessary to assess clinical use of mononuclear cell ubiquinone levels.

Morphologic and biochemical findings differ in the various clinical forms. In patients with the encephalomyopathic, myopathic, or infantile multisystemic forms, muscle biopsies have typically revealed abnormal mitochondrial proliferation (ragged-red fibers or excessive succinate dehydrogenase histochemical activity) and lipid accumulation as well as reduced biochemical activities of respiratory chain enzyme complexes I/II and II/III, while all muscle samples showed decreased CoQ₁₀ levels. In contrast, fibroblast CoQ₁₀ levels have varied and were normal in 1 patient with encephalomyopathy but low in 1 of 2 patients with the myopathic form and in 7 of 8 patients with the infantile multisystemic form.

In 2 patients with isolated nephropathy, CoQ₁₀ levels and respiratory chain enzyme activities were reduced in either fibroblasts or muscle. Ragged-red–like fibers were observed in the only patient who underwent muscle biopsy.¹¹

Muscle biopsies revealed mitochondrial proliferation, cytochrome c oxidase–negative fibers, or lipid accumulation in 15 of 49 patients and reduced respiratory chain enzyme activities in 27 of 51 patients with the ataxic form. Levels of CoQ₁₀ were low in muscle but reduced in 18 of 30 fibroblasts.

Primary CoQ₁₀ deficiency is due to mutations in genes involved in CoQ₁₀ biosynthesis (Figure). Secondary deficiencies include diseases caused by mutations in genes unrelated to ubiquinone biosynthesis, for example, the aprataxin (APTX) gene causing ataxia and oculomotor apraxia,²⁰,²⁷,²⁹ the electron-transferring-flavoprotein dehydrogenase gene (ETFDH) causing isolated myopathy,⁷ and the BRAF gene causing cardiofaciocutaneous syndrome.³⁵ Moreover, CoQ₁₀ deficiency has been reported in association with mitochondrial DNA mutations.¹

In most cases, family history suggests autosomal recessive inheritance. Pathogenic mutations have been reported in 63 patients (Table 1).

No mutations have been described among the encephalomyopathic patients.

**GENETICS**

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Figure. Biosynthesis of coenzyme Q (CoQ₁₀). Mutations in CoQ₁₀ biosynthetic genes (red ovals) cause primary CoQ₁₀ deficiency. Coenzyme Q₁₀ transports electrons from mitochondrial respiratory chain complexes I and II to complex III. ADP indicates adenosine diphosphate; ATP, adenosine triphosphate; CoA, coenzyme A; Cyt c, cytochrome c; e, electron; FADH, flavin adenine dinucleotide; H, hydrogen; NADH, nicotinamide adenine dinucleotide; PDHC, pyruvate dehydrogenase complex; PHB, para-hydroxybenzoate; and PP, pyrophosphate.
Mutations have been described in mutations in the 2 patients with CoQ10 level normalization.4 In contrast, another patient tic acid levels normalized, and a muscle biopsy showed complications in both patients with only renal disease. In contrast, in 9 patients, mutations in the COQ6 gene have been associated with kidney involvement (nephrotic syndrome and nephrolithiasis) and sensorineural hearing loss.14

A subgroup of patients with juvenile-onset cerebellar ataxia have primary CoQ10 deficiency owing to mutations in the ADCK3 gene (22 patients).17,24,30-32 Secondary forms have been described in association with mutations in the APTX gene (12 patients) including 4 affected members of 1 family that we studied.20,27,29 Most patients with cerebellar ataxia and CoQ10 deficiency still lack molecular diagnosis.

Patients with CoQ10 deficiency showed variable responses to CoQ10 treatment (Table 3). We recommend oral supplementation doses up to 2400 mg daily in adult patients and up to 30 mg/kg daily in pediatric patients, divided into 3 doses per day.

In patients with encephalomyopathy, muscle symptoms improved after therapy.2,4 In 1 of our patients, muscle symptoms and seizures resolved, creatine kinase and lactate acid levels normalized, and a muscle biopsy showed CoQ10 level normalization.4 In contrast, another patient developed cerebellar ataxia.3

Six patients with pure myopathy4-7 (including 1 unreported) improved after CoQ10 supplementation, while 2 patients with ETFDH mutations improved only after addition of treatment with riboflavin, 100 mg daily.7

In some patients with the infantile multisystemic form, CoQ10 supplementation has halted progression of the encephalopathy and improved the myopathy.15 One patient with a homozygous COQ2 mutation during therapy showed neurologic but not renal improvement and underwent kidney transplant; however, his sister with isolated nephropathy received CoQ10 and has had progressive recovery of renal function, reduced proteinuria, and no neurologic manifestations.11,13 In contrast, a patient with a homozygous COQ9 mutation during therapy had a reduction of blood lactate but neurologic and cardiac worsening and died at age 2 years.2 Similarly, despite treatment, a patient with PDSS2 mutations developed intractable seizures and died at age 8 months,8 and a patient with infantile-onset Leigh syndrome, hepatopathy, and hypertrophic cardiomyopathy after initial clinical improvement died at age 3 years. Published data for 2 patients with mutations in the COQ6 gene noted decreased proteinuria in both patients after CoQ10 treatment, but hearing improved in only 1 patient.14

Response to CoQ10 supplementation in patients with cerebellar ataxia is also variable. Three patients with mutations in the ADCK3 gene showed mild clinical improvement after treatment,17,30,31 but 7 patients carrying mutations in the same gene did not improve24,32 and another patient, despite dramatic muscle improvement, developed tremor, myoclonic jerks, and cerebellar atrophy.23,24 In 3 siblings with mutations in the APTX gene, CoQ10 supplementation was associated with clear improved ambulation as well as resolution of seizures in 1 patient.50 Nevertheless, another patient with APTX mutations did not improve after therapy.27 Improvement in muscle but not neurologic signs and symptoms has been noted in 1 new and 2 reported patients.18,50 Reductions in International Cooperative Rating Scale scores in 9 patients with an unknown genetic defect and in 1 patient with ADCK3 gene mutations have been documented.31 Eleven patients with undefined molecular defect did not respond to therapy.21,31

Among the clinically atypical cases of CoQ10 deficiency, 2 sisters with Leigh syndrome and 1 patient with cardiofaciocutaneous syndrome improved after CoQ10 supplementation.39,35 One patient with neonatal hypotonia and infantile spasm showed no improvement.30

It is important to identify CoQ10 deficiency as this condition often responds to supplementation. The diagnosis can be made by direct measurement of CoQ10 in muscle and reinforced by the presence of reduced biochemical activities of respiratory chain complexes, in particular complexes I + III and II + III. Molecular genetic testing has revealed causative mutations in a small proportion of patients, indicating that screening for DNA mutations is not yet effective for diagnosing CoQ10 deficiency. Our observations not only highlight the clinical heterogeneity of CoQ10 deficiency but also the genetic heterogeneity that is likely related to the large number of proteins involved in ubiquinone biosynthesis and regulation and of secondary CoQ10 deficiencies. Clinical improvement after CoQ10 supplementation was documented in many patients, but treatment protocols have not been standardized and results have not been uniform. Progress in our knowledge of the genetic bases of CoQ10 deficiencies may help researchers develop a more accurate molecular classification of this syndrome, while additional studies of the pathogenesis of CoQ10 deficiency may lead to more effective therapies.

Accepted for Publication: February 6, 2012.
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Financial Disclosure: None reported.

Funding/Support: This study was supported by grants K23HD065871 (Dr Quinzii) and R01HD057543 (Dr Hirano) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Dr Hirano’s work is supported by grants R01HD056103 and 1RC1NS070232 from the National Institutes of Health, as well as grants from the Muscular Dystrophy Association and the Marriott Mitochondrial Disorder Clinical Research Fund.


Additional Contributions: We are grateful to all of the patients and relatives for their participation. We thank all of the clinicians who referred patients and samples to us.

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