Published in final edited form as:
Arch Neurol. 2012 August ; 69(8): 978–983. doi:10.1001/archneurol.2012.206.

Heterogeneity of coenzyme Q_{10} deficiency: Patient Study and Literature Review

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Abstract

CoQ_{10} deficiency has been associated with five 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. Review of 149 cases, including our cohort of 76 patients, confirms that CoQ_{10} deficiency is a clinically and genetically heterogeneous syndrome that predominantly begins in childhood and predominantly manifests as cerebellar ataxia. CoQ_{10} measurement in muscle is the gold standard for diagnosis. Identification of CoQ_{10} deficiency is important because it frequently responds to treatment. Causative mutations have been identified in a small proportion of patients.

INTRODUCTION

Coenzyme Q_{10} (CoQ_{10} or ubiquinone) deficiency in human 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 (CUMC), New York, NY, USA under CUMC Institutional Review Board protocols. CoQ_{10} levels were measured in muscle, cultured fibroblasts, and/or lymphoblasts.[2,3] CoQ_{10} levels reduced more than 2 SD below mean control values were considered deficient. Patients with

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Author Contributions: All authors contributed to this manuscript. *Study concept and design:* Emmanuele, DiMauro, Quinzii, and Hirano. *Acquisition of data:* Emmanuele, López, Berardo, Naini, Tadesse, Wen, D'Agostino, Solomon, Quinzii, and Hirano. *Analysis and interpretation of data:* Emmanuele, López, Berardo, DiMauro, Quinzii, and Hirano. *Drafting of the manuscript:* Emmanuele, López, Solomon, Quinzii, and Hirano. Critical revision of the manuscript for important intellectual content: Emmanuele, Berardo, Naini, Tadesse, Wen, D'Agostino, DiMauro, Quinzii, and Hirano. *Statistical analysis:* Emmanuele and Solomon. *Obtained funding:* Quinzii and Hirano. *Administrative, technical, and material support:* Emmanuele, López, Naini, Tadesse, Wen, and Hirano. *Study supervision:* Emmanuele, DiMauro, and Quinzii.

Financial Disclosure: None reported.

CoQ_{10} level decreased in one 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, *PSAP* encoding saposin B, a cytosolic protein that binds and transfers CoQ_{10}, and *POLG* were sequenced (eTable 1).

CLINICAL FEATURES

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

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

The **encephalomyopathic** form of CoQ_{10} deficiency manifesting as a triad of mitochondrial myopathy, recurrent myoglobinuria, and encephalopathy, has been reported in 4 patients (eTable 2).[4-6] Neurological features included cerebellar ataxia, seizures, mental retardation, delayed motor development; progressive external ophthalmoplegia and ptosis.

The **myopathic** form of CoQ_{10} deficiency presents with muscle weakness, myoglobinuria, exercise intolerance, cramps, myalgia, and elevated CK. This condition has been described in 10 patients.[6-9] We have 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).[2,10-16] Neurological manifestations are: 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.[15,17] In addition, liver, cardiac and pancreatic involvement, and obesity have been described in literature and in our cohort.[10,12,18] 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** (SRNS), due to collapsing glomerulopathy and focal segmental glomerulosclerosis (FSGS), has been reported in 2 patients.[14] Moreover, the association between SRNS with sensorineural hearing loss has been described in patients with mutations in the CoQ_{10} biosynthetic gene, *COQ6*; however, CoQ_{10} level was not measured in these patients (eTable 5).[16]

Cerebellar ataxia is the most common phenotype, with 94 patients (including 23 new patients) (eTable 6).[3,19-33] 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, hypoalbuminemia, and hypercholesterolemia.

Among the patients classified as “atypical cases”, there are two adult sisters with childhood onset Leigh-syndrome, growth retardation, infantilism, ataxia, deafness, and lactic acidosis, [34] a 4-year-old Moroccan girl with cardiofaciocutaneous syndrome (CFC),[35] two unrelated patients with neonatal hypotonia and infantile spasm (one reported)[36], two Portuguese 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 is the father of a child with cerebellar ataxia (P119 in eTable 6), with mild CK elevation, but normal examination and brain MRI.

DIAGNOSIS

Initial biochemical evaluation of patients with suspected CoQ_{10} deficiency should include blood lactate measurement, although normal values do not exclude ubiquinone deficiency. Muscle biopsies occasionally show mitochondrial proliferation or lipid droplets, but can be normal or show only non-specific changes.

Reduced biochemical activities of respiratory chain complexes, in particular, complexes I +III (NADH:cytochrome *c* oxidoreductase) and II+III (succinate:cytochrome *c* oxidoreductase) in muscle suggest CoQ_{10} deficiency, although activities of these enzymes may be normal particularly when the deficiency is mild. Reduction of these enzyme activities and deficiency of CoQ_{10} in skin fibroblasts can be an important confirmation of ubiquinone deficiency; however normal levels do not exclude deficiency in muscle. Direct measurement of CoQ_{10} 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 CoQ_{10} in peripheral blood mononuclear cells (MNC) has detected deficiency in a small number of patients; however, correlations with muscle CoQ_{10} measurements in a larger cohort of patients will be necessary to assess clinical utility of MNC ubiquinone levels.

Morphological 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 (RRF or excessive SDH histochemical activity) and lipid accumulation as well as reduced biochemical activities of respiratory chain enzyme complexes I+III and II+III while all muscle samples showed decreased CoQ_{10} levels. In contrast, fibroblast CoQ_{10} levels have varied and was normal in one patient with encephalomyopathy, but low in 1/2 with the myopathic form and 7/8 with the infantile multisystemic form.

In two patients with **isolated nephropathy,** CoQ_{10} levels and respiratory chain enzyme activities were reduced in either fibroblasts or muscle. RRF-like were observed in the only patient who underwent muscle biopsy.[14]

In patients with the **ataxic form**, muscle biopsies revealed mitochondrial proliferation, COX-negative fibers, or lipid accumulation in 15/49, and reduced respiratory chain enzyme activities in 27/51. Levels of CoQ_{10} were low in muscle, but reduced in 18/30 fibroblasts.

GENETICS

Primary CoQ_{10} deficiency is due to mutations in genes involved in CoQ_{10} biosynthesis (Figure 1). Secondary deficiencies include diseases caused by mutations in genes unrelated

to ubiquinone biosynthesis, for example aprataxin (*APTX*) gene, causing ataxia and oculomotor apraxia,[21,27,28,30] electron-transferring-flavoprotein dehydrogenase gene (*ETFDH*), causing isolated myopathy,[9] and *BRAF* gene, causing CFC syndrome.[35] Moreover, CoQ_{10} 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. Except for the patients reported by Gempel in 2007,[9] we did not find other mutations in *ETFDH* in our cohort of patients with **isolated myopathy**, indicating that other genes can be responsible for this phenotype.

Most patients with the **infantile-onset multisystemic variant** have genetically confirmed primary CoQ_{10} deficiency. Mutations have been described in *COQ2* (3 patients)[13,14,18], *PDSS2* (1 patient)[2], *COQ9* (1 patient)[11], *PDSS1* (2 patients)[18], and *COQ6* (3 patients)[16]. Interestingly, two patients with isolated nephrotic syndrome have *COQ2* mutations.[13,14] Thus, patients with *COQ2* mutations have presented with either infantile multisystemic syndrome or isolated nephropathy. There are three potential explanations for the divergent phenotypes. First, variations in the phenotypes may be due to genetic or environmental modifiers. Second, patients with isolated nephropathies may develop multisystemic disease later in life. Third, CoQ_{10} treatment may have altered the clinical course of the disease by preventing neurological complications in both patients with only renal disease. In contrast, in 9 patients, mutations in *COQ6* gene have been associated with kidney involvement (nephrotic syndrome, and nephrolithiasis) and sensorineural hearing loss.[16] A subgroup of patients with **juvenile-onset cerebellar ataxia** have primary CoQ_{10} deficiency due to mutations in the *ADCK3* gene (22 patients).[3,25,29,31-33] Secondary forms have been described in association with mutations in the *APTX* gene (12 patients) including four affected members of one family that we studied.[21,27,28,30] The majority of patients with cerebellar ataxia and CoQ_{10} deficiency still lack molecular diagnosis.

THERAPY

Patients with CoQ_{10} deficiency showed variable responses to CoQ_{10} treatment (Table 3). We recommend oral supplementation doses up to 2,400 mg daily in adult patients and up to 30mg/kg daily in pediatric patients, divided into three doses per day.

In patients with **encephalomyopath**y, muscle symptoms improved after therapy.[4-6] In one of our patients, muscle symptoms and seizures resolved, CK and lactic acid normalized, and a muscle biopsy showed CoQ_{10} level normalization.[6] In contrast, another patient, developed cerebellar ataxia.[5]

Six patients with **pure myopathy**[6-9] (including one unreported) improved after CoQ_{10} supplementation, while 2 patients with *ETFDH* mutations improved only after addition of riboflavin (100 mg/day).[9]

In some patients with the **infantile multisystemic form**, CoQ_{10} supplementation has halted progression of the encephalopathy and improved the myopathy.[17] One patient with a homozygous *COQ2* mutation, on therapy showed neurological but not renal improvement, and underwent kidney transplant, but his sister, with **isolated nephropathy**, received coenzyme Q_{10} and has had progressive recovery of renal function, reduced proteinuria and no neurological manifestations.[13-15] In contrast, a patient with a homozygous *COQ9* mutation, on therapy, had reduction of blood lactate, but neurological and cardiac

worsening, and died at age 2 years.[11] Similarly, despite treatment, a patient with *PDSS2* mutations developed intractable seizures and died at age 8 months[2] 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 *COQ6* gene noted decreased proteinuria in both patients after CoQ_{10} treatment, but hearing improved only in one patient.[16]

Response to CoQ_{10} supplementation in patients with **cerebellar ataxia** is also variable. Three patients with mutations in *ADCK3* gene showed mild clinical improvement after treatment,[3,31,32] but 7 patients carrying mutations in the same gene did not improve,[25,33] and another patient, despite dramatic muscle improvement, developed tremor, myoclonic jerks, and cerebellar atrophy.[24,25] In 3 siblings with mutations in *APTX* gene, CoQ_{10} supplementation was associated with clear improved ambulation, and resolution of seizures in one patient.[21] Nevertheless, another patient with *APTX* mutations did not improve after therapy.[28] Improvement in muscle but not neurological signs and symptoms has been noted in one new and 2 reported patients.[19,20] A reduction in ICARS score in 9 patients with unknown genetic defect and in one patient with *ADCK3* gene mutations has been documented.[23,26,31] Eleven patients with undefined molecular defect did not respond to therapy.[22,32]

Among the clinically atypical cases of CoQ_{10} deficiency, two sisters with Leigh syndrome and one patient with CFC syndrome improved after CoQ_{10} supplementation.[34,35] One patient with neonatal hypotonia and infantile spasm showed no improvement.[36]

CONCLUSIONS

It is important to identify CoQ_{10} deficiency as this condition often responds to supplementation. The diagnosis can be made by direct measurement of CoQ_{10} 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 CoQ_{10} deficiency. Our observations not only highlight the clinical heterogeneity of CoQ_{10} 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 CoQ_{10} deficiencies. Clinical improvement after CoQ_{10} 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 CoQ_{10} deficiencies may help us develop a more accurate molecular classification of this syndrome, while additional studies of the pathogenesis of CoQ_{10} deficiency may lead to more effective therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to all of the patients and relatives for their collaboration. We thank all of the clinicians who referred us the patients and samples The project described was supported by K23HD065871 (CMQ) and 1R01HD057543 (MH) from the Eunice Kennedy Shriver National Institute Of Child Health & Human Development. MH is supported by NIH grants R01HD056103 and 1RC1NS070232, a Muscular Dystrophy Association grant, and by the Marriott Mitochondrial Disorder Clinical Research Fund (MMDCRF).

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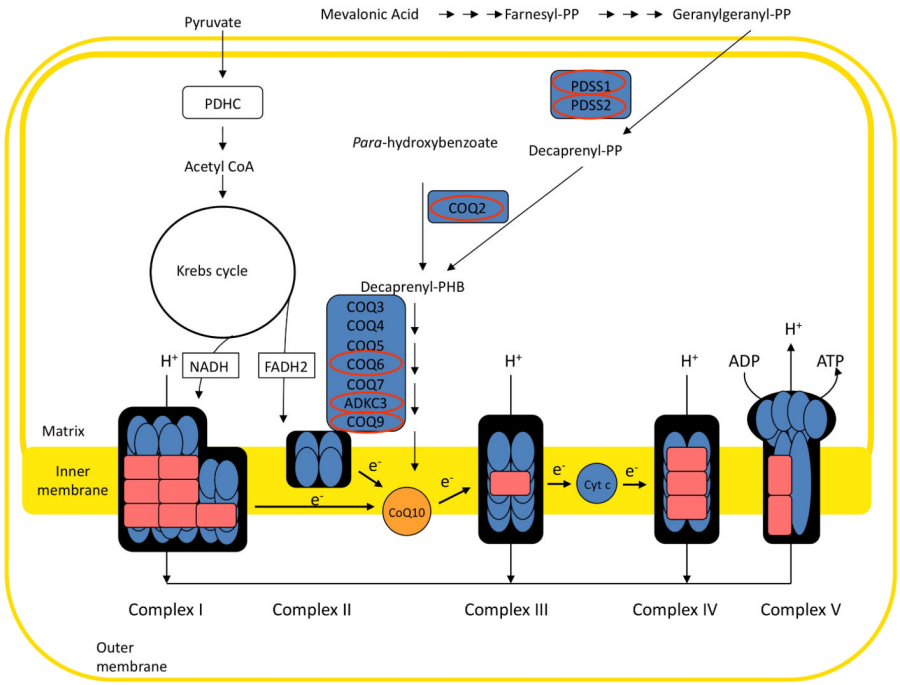

Figure 1.

Biosynthesis of coenzyme Q_{10} (CoQ_{10}). Mutations in CoQ_{10} biosynthetic genes (indicated by red ovals) cause primary CoQ_{10} deficiency. CoQ_{10} transport electrons from mitochondrial respiratory chain complexes I and II to complex III.

Table 1

Clinical features of major forms of CoQ_{10} deficiency

Syndrome	Number of cases (new cases)	Clinical features	Natural history	Responsible genes (numbers of patients/families)	References
Encephalomyopathy	4	Juvenile-onset mitochondrial myopathy, recurrent myoglobinuria, and encephalopathy	Slow progression of weakness	None known	4-6
Isolated myopathy	14 (4)	Juvenile or adult-onset muscle weakness, myoglobinuria, exercise intolerance, cramps, myalgias, elevated CK	Slow progression of weakness	*ETFDH* (7/5)	6-9
Nephropathy	11	Infantile or early childhood-onset steroid-resistant nephrotic syndrome.	May progress to renal failure. Encephalopathy may develop.	*COQ2* (2/2),	2,10-19
		Infantile or juvenile-onset steroid-resistant nephrotic syndrome typically with congenital or juvenile-onset sensorineural deafness	Nephropathy typically progresses to renal failure. Seizures and ataxia may develop. May be fatal (2/8=25%)	*COQ6* (8/4)	
Infantile multisystemic disease	17 (2)	Infantile-onset psychomotor regression, encephalopathy, optic atrophy, retinopathy, hearing loss, renal dysfunction (mainly nephrotic syndrome). Less common: liver, cardiac, and pancreatic dysfunction and obesity.	Typically progresses rapidly with high mortality (11/17=65%)	*COQ2* (4/3?), *PDSS2* (1/1), *COQ9* (1/1) *PDSS1* (1/1), *COQ6* (3/?)	14-18
Cerebellar ataxia	94 (23)	Typically juvenile-onset cerebellar ataxia. Multiple additional neurological and non-neurological manifestations may occur.	Slow or minimal progression of ataxia.	*ADCK3* (22/13?), *APTX* (12/8?)	3,20-34
Atypical presentations	9 (5)	Adults with childhood-onset Leigh syndrome	Subacute progression.	None known	35-37
		Cardiofaciocutaneous syndrome	Uncertain.	BRAF (1/1)	
		Neonatal hypotonia, infantile spasms	?	None known	
		Adult-onset cerebellar ataxia and nephrotic syndrome	?	None known	
		Childhood-onset encephalomyopathy, short stature, hearing loss and retinopathy	?	None known	

Table 2

Laboratory features of major forms of CoQ_{10} deficiency

Syndrome	Blood lactate	Serum CK	Muscle Histology	Mitochondrial respiratory chain enzyme activities	CoQ10 levels
Encephalomyopathy					
Isolated myopathy					
Isolated nephropathy					
Infantile multisystemic disease					
Cerebellar ataxia					
Atypical presentations					

Table 3

Clinical response to CoQ10 supplementation in major forms of CoQ_{10} deficiency

Syndrome	CoQ_{10} doses and duration	Response to therapy
Encephalomyopathy		
Isolated myopathy		
Isolated nephropathy		
Infantile multisystemic disease		
Cerebellar ataxia		
Atypical presentations		