RESEARCH ARTICLE OPEN ACCESS

Clinical Features, Biochemistry, Imaging, and Treatment Response in a Single-Center Cohort With Coenzyme Q_{10} Biosynthesis Disorders

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Neurol Genet 2024;10:e200209. doi:10.1212/NXG.0000000000200209

Abstract

Background and Objectives

Disorders of coenzyme Q_{10} (CoQ_{10}) biosynthesis comprise a group of 11 clinically and genetically heterogeneous rare primary mitochondrial diseases. We sought to delineate clinical, biochemical, and neuroimaging features of these disorders, together with outcomes after oral CoQ_{10} supplementation and the utility of peripheral blood mononuclear cell (PBMNC) CoQ_{10} levels in monitoring therapy.

Methods

This was a retrospective cohort study, registered as an audit at a specialist pediatric hospital (Registration Number: 3318) of 14 patients with genetically confirmed CoQ_{10} biosynthesis deficiency, including 13 previously unreported cases.

Results

We show that oral doses of CoQ_{10} up to 70 mg/kg/d were needed to ameliorate neurologic features. Additional idebenone was required to control seizures in some cases, and 3 children with neonatal-onset neurologic disease died in early childhood despite receiving high-dose oral CoQ_{10} from birth. We also demonstrate that early diagnosis and treatment of CoQ_{10} deficiency with oral supplementation (30 mg/kg/d) can reverse renal manifestations and can completely prevent kidney disease over 10 years of follow-up. PBMNC CoQ_{10} levels increased after oral CoQ_{10} supplementation, demonstrating absorption of exogenous CoQ_{10} into the bloodstream.

Discussion

An early genome-wide diagnostic approach is needed for expeditious diagnosis of CoQ_{10} biosynthesis disorder because our study demonstrates that there are no pathognomonic blood, muscle, or imaging biomarkers of these diseases. Our findings indicate that earlier diagnosis and treatment with high-dose CoQ_{10} is key in halting progression of kidney disease or preventing it altogether. This study uses serial PBMNC CoQ_{10} levels to monitor therapy. Patients with genetically confirmed CoQ_{10} biosynthesis disorder should receive high-dose oral CoQ_{10} as soon as possible after presentation, regardless of genetic cause, to prevent disease progression, but parents of children with neonatal or infantile neurologic presentations should be counseled about the poor prognosis.

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Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by UCL.

Glossary

CoQ_{10} = coenzyme Q_{10}; **PBMNC** = peripheral blood mononuclear cell; **SRNS** = steroid-resistant nephrotic syndrome; **VUS** = variants of uncertain significance.

Introduction

Coenzyme Q_{10} (CoQ_{10}), or ubiquinone, is a lipophilic molecule composed of a benzoquinone ring and a polyisoprenoid tail found in the inner mitochondrial membrane.[1] It is an essential component of the mitochondrial respiratory chain where it transfers electrons from respiratory chain complexes I and II and the electron transfer flavoprotein dehydrogenase to complex III. CoQ_{10} thus contributes to the mitochondrial electrochemical gradient that drives energy generation via oxidative phosphorylation. In addition, CoQ_{10} functions as a potent membrane antioxidant, regulator of the mitochondrial permeability transition pore, and in the metabolism of pyrimidines and fatty acids.[2-5]

CoQ_{10} is primarily generated from endogenous de novo synthesis through an intricate pathway within the mitochondria and then distributed to cell membranes.[6] Primary coenzyme Q_{10} deficiency comprises a group of recessively inherited rare mitochondrial disorders that present with heterogeneous clinical features. These disorders are caused by pathogenic variants in 11 genes encoding proteins directly involved in the biosynthesis of CoQ_{10}. To date, variants in *PDSS1*, *PDSS2*, *COQ2*, *COQ4*, *COQ5*, *COQ6*, *COQ7*, *COQ8A*, *COQ8B*, *COQ9*, and *ADCK2* have been reported with involvement of almost every organ system.[7,8] The associated clinical manifestations are highly heterogeneous and mainly affect the central and peripheral nervous system, skeletal muscle, kidney, and heart. This group of diseases is important because it is potentially treatable with exogenous CoQ_{10}. Oral supplementation with CoQ_{10} has been reported in some cases to improve the clinical symptoms in instances of early diagnosis and initiation of therapy.[9]

Hence, it is important to identify CoQ_{10} deficiency rapidly to allow for prompt treatment with exogenous CoQ_{10} to potentially improve outcomes in an otherwise devastating disorder. Previous studies were inconsistent in treatment of patients with CoQ_{10} biosynthesis disorders with variable initiation, duration, dose, and formulation of therapies. Here, we report comprehensive clinical, biochemical, and genetic details and therapeutic response to high-dose CoQ_{10} supplementation in a single-center cohort of patients with a diagnosis of primary CoQ_{10} deficiency disorder.

Methods

Patients

Children with primary CoQ_{10} deficiency who were diagnosed at a specialist pediatric hospital between January 2000 and January 2024 were included. One patient has been reported previously.[10,11] All the others are new cases. General clinical condition, symptoms, laboratory and biochemical values and radiologic findings were collated and, where applicable, compared before and after treatment. All brain images were reviewed by the same experienced neuroradiologist.

Standard Protocol Approvals, Registrations, and Patient Consents

This retrospective cohort study was approved as an audit at a specialist pediatric hospital (Registration Number: 3318). All data contained in this article are de-identified and thus consent-to-disclose is not applicable.

Genetic Variant Detection

Blood samples of the patients were collected for genetic testing after obtaining informed parental consent. Gene variants were detected using the following methods: nephrotic syndrome gene panel (1 proband), ataxia panel (1 patient), research homozygosity mapping and candidate gene sequencing (1 proband), research metabolic panel sequencing (2 patients), research exome sequencing (1 patient), clinical trio exome sequencing (1 patient), and whole-genome sequencing conducted as part of the Genomics England 100,000 Genomes Project (2 patients). Familial variant testing was used to confirm gene variants in 5 relatives of affected individuals, 3 symptomatic (prenatal testing in 1 case) and 1 presymptomatic.

Enzyme Assays and Coenzyme Q_{10} Quantification

Skeletal muscle biopsy specimens (50 mg) were snap frozen immediately and stored at −70°C until analysis. Analysis of the mitochondrial respiratory chain enzyme complexes was conducted as previously described.[12] Muscle CoQ_{10} and white cell (peripheral blood mononuclear cell, PBMNC) CoQ_{10} concentrations were determined by high-performance liquid chromatography as previously described.[13]

Coenzyme Q_{10} Treatment Preparation and Doses

Oral CoQ_{10} therapy consisted of either ubidecarenone in capsules or as a liquid preparation combined with vitamin E (15 international units of vitamin E per 50 mg of CoQ_{10}), aiming for doses of CoQ_{10} ranging from 30–60 mg/kg/d in 3 to 4 divided daily doses. In cases with intractable seizures, the CoQ_{10} analog idebenone was added, aiming for doses ranging from 10–20 mg/kg/d in 2 divided daily doses.

Data Availability

All relevant de-identified qualitative and quantitative data are contained within the article. Where relevant, anonymized data

not published within this article will be made available by request from any qualified investigator.

Results

Clinical Features of the Cohort

Our cohort comprises a total of 14 patients, including 13 previously unreported cases, diagnosed and managed by the Metabolic Department at a specialist pediatric hospital. Clinical and biochemical data are summarized in Tables 1 and 2. The clinical and genetic details of patient 12 have been reported previously.[10,11] Detailed clinical data were not available for 2 neonates who presented and died rapidly in local hospitals. All 14 patients had biallelic pathogenic variants in genes encoding proteins involved in the CoQ_{10} biosynthetic pathway: 2 were found to have variants in *COQ2* encoding 4-hydroxybenzoate polyprenyltransferase, 5 patients had pathogenic variants in *COQ4* encoding an enzyme required for oxidative decarboxylation of the C1 carbon atom of the CoQ_{10} quinone ring,[14] 1 in *COQ6* encoding a flavin-dependent monooxygenase responsible for C5-hydroxylation of the quinone ring,[15] 1 in *COQ8A* and 2 in *COQ8B*, both encoding atypical kinases, and finally 3 in *COQ9* encoding a lipid-binding protein that associates with the COQ7 hydroxylase to form a multimeric protein complex that facilitates CoQ_{10} biosynthesis[16] (Table 1, Figure 1).

The most common feature across all patients at presentation was seizures, with 8 patients being diagnosed with epilepsy. Other neurologic phenotypes observed in members of our cohort included developmental delay, microcephaly, hypotonia, hypertonia, movement disorders, and ophthalmoplegia (Figure 2). Three patients had steroid-resistant nephrotic syndrome (SRNS), including 1 with seizures and 1 with encephalopathy. SRNS was an isolated finding in the third patient. One was the presymptomatic relative of a proband with SRNS leading to end-stage kidney disease. Ten of the 14 patients received CoQ_{10} supplementation. Treatment included ubidecarenone (CoQ_{10}) supplementation, and for some patients, additional idebenone, an analog of CoQ_{10} with a shorter isoprenoid chain.

Neuroimaging Findings

Brain imaging studies were completed for 9 patients (Figure 3, eTable 1). Abnormalities in the thalami were observed in 5 patients, specifically bilateral laminar hyperintensity in 3 and small thalami in 2 of these patients. Within the white matter, deep parietal hyperintensities were present in 3 patients. Bilateral occipital volume loss with underlying white matter gliosis was observed in the cortex of 1 patient and a loss of gyral pattern in another. There was severe atrophy of the cerebrum in 2 patients and moderate-to-severe atrophy in another patient. In 6 patients, there was some degree of cerebellar atrophy, ranging from marginal to severe. Of the 3 patients with severe cerebellar atrophy, the inferior hemisphere was predominantly affected in 2. Magnetic resonance spectroscopy was performed in 1 patient and revealed a large lactate peak.

Laboratory Measurements and Respiratory Chain Enzyme Assay

A high blood lactate level was found in 5 patients in our cohort and a normal lactate level in 7. Six patients had elevated plasma alanine levels (Table 2). Of those with a normal lactate level, 4 had elevated alanine levels, suggesting intermittent hyperlactataemia.

Respiratory chain enzyme assays were performed in muscle biopsies from 6 patients (Table 2). Normal activities for complexes I, II+III, and IV were obtained for 4 patients (1, 5, 7, and 8). For the other 2 individuals, isolated decrease of complex IV activity was observed in patient 4 (0.010, reference range 0.014–0.034) and decreased complex II+III activity (<0.001, reference range 0.04–0.2044) in patient 12.

CoQ_{10} Determination in Cells and Tissues

Muscle CoQ_{10} content was determined from skeletal muscle biopsies of 2 patients and was decreased in both patients (Table 2). Patient 7 and patient 12 had a CoQ_{10} concentration of 107 pmol/mg or 76% of the lower limit and 37 pmol/mg or 26% of the lower limit of the reference range (140–580 pmol/mg), respectively.

To monitor therapeutic response, we measured CoQ_{10} levels in circulating PBMNCs. Longitudinal data were collected for 5 individuals in our cohort: patients 2, 7, 10, 11, and 13. Serial measurements are reported in Figure 4. These laboratory values demonstrate that oral CoQ_{10} supplementation is absorbed into the blood and that levels can even rise to over double initial levels in some cases (up to 216 from 90 pmol/mg; reference range 37–133). Patient 2 was started on high dose CoQ_{10} (30 mg/kg/d) 3 months after initial symptom development and CoQ_{10} levels initially increased by 352% during treatment to normal levels, with values continuing to increase thereafter. CoQ_{10} supplementation resulted in a 146% increase and a subsequent 320% increase in PBMNC CoQ_{10} concentration in patient 7. Serial measurement of PBMNC CoQ_{10} levels for patient 10 was within reference range and very variable with supplementation having minimal effects on CoQ_{10} levels; this patient admitted to noncompliance with CoQ_{10} supplementation and thus it is difficult to interpret the PBMNC CoQ_{10} concentrations. Patient 13 was treated from birth, and serial PBMNC CoQ_{10} concentrations were within normal range with the first (taken 2 days after commencing CoQ_{10} supplementation) being the lowest and the final being 221% higher, approximately 2 years later.

Effect of Oral Supplementation With CoQ_{10}

Responses to CoQ_{10} supplementation across our cohort of patients were variable. Of the 14 patients who were identified with a disorder of CoQ_{10} biosynthesis, 11 received oral supplementation with CoQ_{10} (Table 3). Of patients who did not receive CoQ_{10} supplementation, all had variants in *COQ4*; patients 3, 4, and 5 received a posthumous diagnosis of CoQ_{10} biosynthesis disorder. Table 3 summarizes details regarding dosing of oral CoQ_{10} supplementation, timing with regards to

Table 1 Summary of Clinical Characteristics and Gene Variants in Our Cohort of Patients

Patient Gene	1 *COQ2*	2 *COQ2*	3 *COQ4*	4 *COQ4*	5 *COQ4*	6 *COQ4*	7 *COQ4*	8 *COQ6*	9 *COQ8A*	10 *COQ8B*	11 *COQ8B*	12 *COQ9*	13 *COQ9*	14 *COQ9*
Current clinical status	Died of cardiac arrest	Alive	Died of broncho-pneumonia	Died of aspiration pneumonia	Died	Died of respiratory failure and seizures	Alive	Died of stroke	Alive	Alive	Alive	Died of chest infection	Died of respiratory failure	Died of lactic acidosis and seizures
Variant 1	c.287G>A p.(Ser96Asn)	c.683A>G p.(Asn228Ser)	c.437T>G p. (Phe146Cys)	c.437T>G p. (Phe146Cys)	c.718C>T p.(Arg240Cys)	c.718C>T p.(Arg240Cys)	c.190C>T p.(Pro64Ser)	c.1905-1G>A	c.1805C>G p.(Pro602Arg)	c[1339dupG	c.1339dupG	c.730C>T p.(Arg244*)	c.730C>T p.(Arg244*)	c.730C>T p.(Arg244*)
Variant 2	c.287G>A p.(Ser96Asn)	c.778G>C p.(Gly260Arg)	c.437T>G p. (Phe146Cys)	c.437T>G p. (Phe146Cys)	c.718C>T p.(Arg240Cys)	c.718C>T p.(Arg240Cys)	c.190C>T p.(Pro64Ser)	c.783G>A p.(Pro261 =)	c.1805C>G p.(Pro602Arg)	c.1339dupG	c.1339dupG	c.730C>T p.(Arg244*)	c.730C>T p.(Arg244*)	c.730C>T p.(Arg244*)
Proband	Homozygous	Compound heterozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Compound heterozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous
Genetic diagnosis investigation	Research WES	Nephrotic syndrome panel	Research metabolic exome	Research metabolic exome	Clinical WES	Familial variant testing	100K WGS	100K WGS	Hereditary childhood-onset ataxia panel	Familial variant testing	Familial variant testing	Research homozygosity mapping	Familial variant testing	Familial variant testing
Clinical summary	Congenital lactic acidosis and nephrotic syndrome	Steroid-resistant nephrotic syndrome	Seizures, microcephaly, severe global developmental delay	Seizures, microcephaly	Neonatal encephalopathy	Lactic acidosis and cerebellar hypoplasia	Myopathy, epilepsy	Myoclonic epilepsy, developmental regression, bulbar problems, ophthalmoplegia, possible retinal degeneration	Ataxia, dysphonia, cerebellar atrophy, dysdiadochokinesis, and conjunctival telangiectasia	ESKD, seizures	A/ presymptomatic	Complex multisystem disease	Complex multisystem disease	Complex multisystem disease

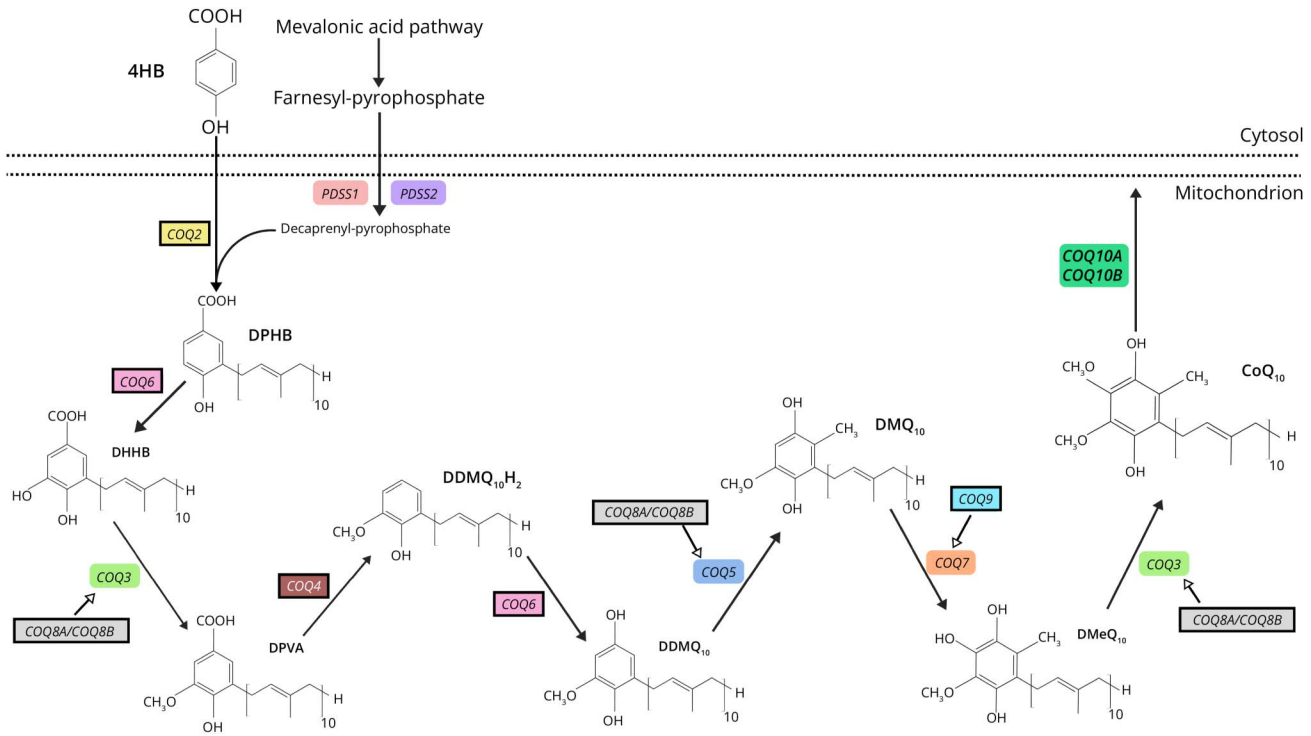
Abbreviations: ESKD = end-stage kidney disease; WES = whole-exome sequencing.

Table 2 Biochemical, Muscle Histology, and Respiratory Chain Enzyme Activity Investigations in Our Cohort of Patients

Patient Gene	1 *COQ2*	2 *COQ2*	3 *COQ4*	4 *COQ4*	5 *COQ4*	6 *COQ4*	7 *COQ4*	8 *COQ6*	9 *COQ8A*	10 *COQ8B*	11 *COQ8B*	12 *COQ9*	13 *COQ9*	14 *COQ9*
Highest lactate (mmol/L) Reference <2.1 mM	Serum: **7.8**	Serum: 2.1	Serum: <2.1	Serum: <2.1	Serum: **7.9**	Blood: **5.9–9.1**	Blood: **6.3**	Blood: 1.6	Serum: <2.1	Serum: 1.8	Serum: 1.4	Serum: **19.4**	Serum: **6.6**	ND
Serum amino acids (<450)	ND	Elevated alanine (566)	Normal	Elevated alanine (546–646)	ND	ND	Elevated alanine (483)	Normal	ND	Elevated alanine	Elevated alanine	ND	Elevated alanine	ND
Muscle histology	A little excess lipid staining for age, no RRF, no ragged blue fibers, no COX-neg fibers	ND	ND	Increased variation in fiber size, slow fiber predominance, prominent lipid staining, no RRF, no ragged blue fibers, no COX-neg fibers		ND	Increased variation in fiber size, no excess lipid staining for age, no RRF, no ragged blue fibers, no COX-neg fibers	ND	ND	ND	ND	Type IIB fiber atrophy, excess lipid, no RRF, no COX-neg fibers	ND	ND
Electron microscopy	Focal areas of increase in mitochondria, glycogen, and lipid	ND	ND	Unremarkable	ND	ND	EM—moderate focal increase in lipid, mitochondrial numbers are not increased and their cristae pattern is normal	EM—patchy increased lipid, increased peripheral mitochondria	ND	ND	ND	ND	ND	ND
Muscle CoQ_{10} (pmol/mg; reference range 140–580)	ND	ND	ND	ND	ND	ND	**107**	ND	ND	ND	ND	**37**	ND	ND
RCEA Summary	Normal	ND	ND	Mildly decreased complex IV	ND	ND	Normal	Normal	ND	ND	ND	Decreased complexes II and III	ND	ND
Complex I (0.104–0.268)	—	—	—	0.153	0.192	—	0.204	0.14	—	—	—	0.163	—	—
Complex II + III (0.040–0.204)	—	—	—	0.045	0.069	—	0.126	0.091	—	—	—	**<0.001**	—	—
Complex II (0.052–0.258)	—	—	—	ND	—	—	ND	ND	—	—	—	0.151	—	—
Complex III (0.008–0.028)	—	—	—	ND	—	—	ND	ND	—	—	—	0.026	—	—
Complex IV (0.014–0.340)	—	—	—	**0.01**	0.032	—	0.019	0.028	—	—	—	0.018	—	—

Abbreviations: ND = no data.

Figure 1 Scheme of CoQ_{10} Biosynthesis



Components of the CoQ_{10} biosynthesis complex and enzymes known to be involved are indicated. Regulatory enzymes such as COQ8 and COQ9 are indicated at the steps in which they are involved. Enzymes outlined in a black box indicate those in which variant(s) in the *COQ* gene(s) are found in our cohort. 4HB = 4-hydroxybenzoate; DPHB = decaprenyl hydroxybenzoic acid; DHHB = 3-hexaprenyl-4,5-dihydroxybenzoic acid; DPVA = decaprenyl-vanillic acid; $DDMQ_{10}H_2$ = demethyl-demethoxy-hydroquinone; $DDMQ_{10}$ = demethoxy-demethyl-coenzyme Q_{10}; DMQ_{10} = demethoxy-coenzyme Q_{10}; $DMeQ_{10}$ = demethyl-coenzyme Q_{10}.

presentation, duration, and outcomes of those in our cohort who received CoQ_{10}.

Both patients with variants in *COQ2* were treated with oral CoQ_{10} supplementation. Patient 1 was treated with 20–50 mg of CoQ_{10} twice a day 1 month after birth and died a few months later from a cardiorespiratory arrest. High-dose CoQ_{10} was not administered as the genetic diagnosis was unknown at the time. Patient 2 (*COQ2*) on presentation with SRNS had a creatinine level of 116uM that rose to 414 uM and was commenced on peritoneal dialysis. He responded well to high-dose CoQ_{10} (30 mg/kg/d) and has come off dialysis with slow recovery of renal function.

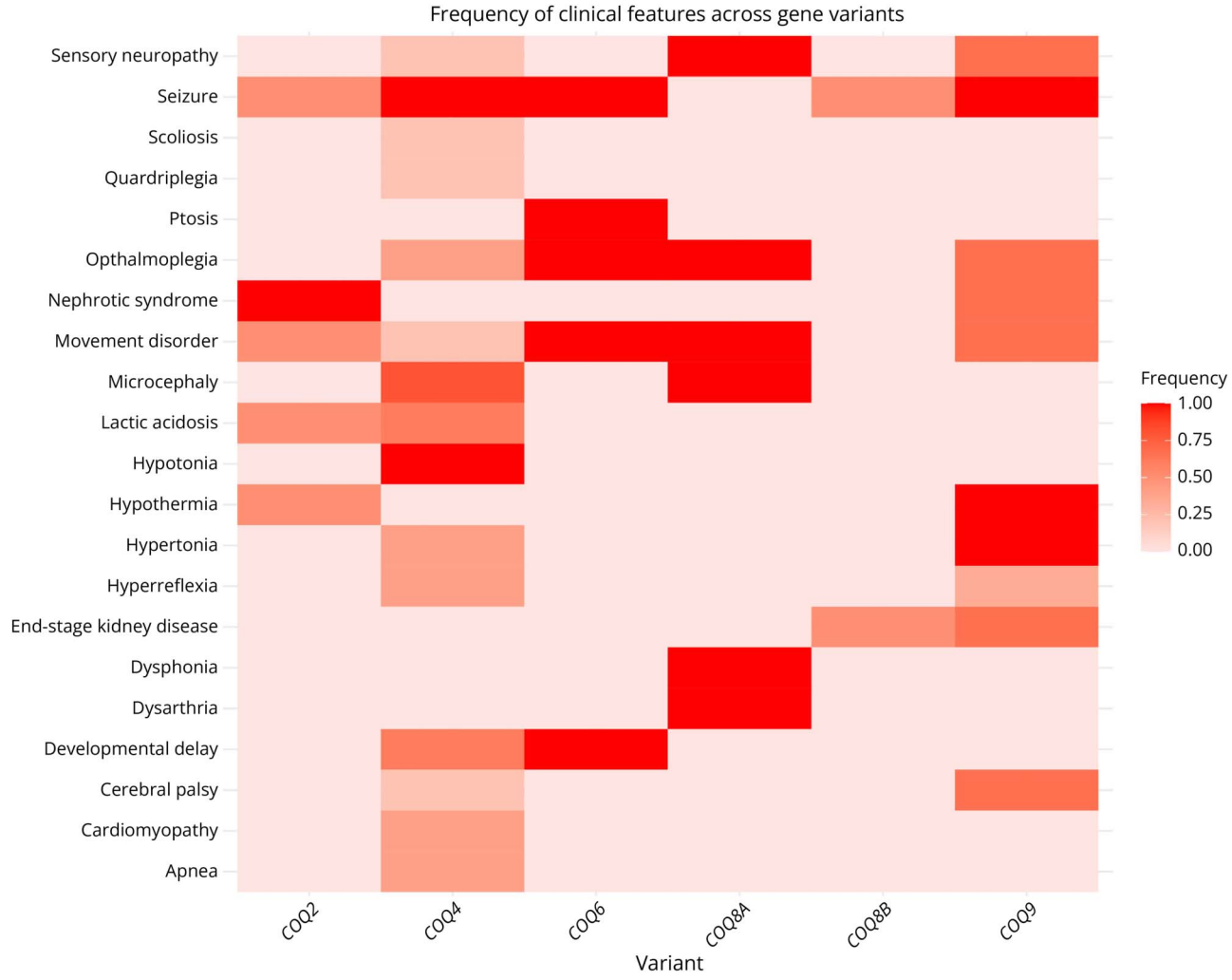
Of the patients with variants in *COQ4*, 2 received oral CoQ_{10} treatment. Patient 6 received very high-dose CoQ_{10} (73 mg/kg/d) and idebenone (10 mg/kg/d) therapy from birth and unfortunately died in less than a month. Patient 7 was started on low-dose CoQ_{10} therapy which was increased to 30 mg/kg/d when the genetic diagnosis was known. Idebenone therapy (20 mg/kg/d) was added more than a year later because seizures had not completely resolved on high-dose CoQ_{10} supplementation.

Patient 8 (*COQ6*) did receive CoQ_{10}, however, at a reduced dose of 300 mg OD and not the high dose of at least 30 mg/kg/d received by the other patients in our cohort. This patient's diagnosis was unknown at the time of their treatment with oral CoQ_{10}, which was continued because the parents had noted a symptomatic benefit from CoQ_{10} supplementation. Very unfortunately, the patient died after deteriorating shortly after stopping CoQ_{10}. Patient 9 (*COQ8A*) was started on CoQ_{10} supplementation in their early teens and reports less fatigue after 1 month of treatment.

Both patients with *COQ8B* variants received CoQ_{10}. Patient 10 presented in end-stage kidney disease and was noncompliant with their medication because of nausea possibly related to their end-stage kidney disease. The patient subsequently received a kidney transplant and remains healthy and stable from a renal perspective. Patient 11 was started on CoQ_{10} (30 mg/kg/d) prophylactically, and to date, this patient has remained stable from a renal perspective with good kidney function and no proteinuria after nearly 10 years of follow-up.

All 3 patients with *COQ9* variants received high-dose CoQ_{10} (30 mg/kg/d) supplementation, but this was not sufficient to prevent fatal outcomes in these individuals. Patient 12 was started on CoQ_{10} (60 mg/kg/d up to 300 mg/d after 6 days) at approximately 1 year of age. The patient's lactate levels decreased (from 7.6 mM to 2. 5 mM) over the course of 4 months; however, the clinical course was not improved, and

Figure 2 Frequency of Clinical Features for Each *COQ* Gene Involved in Our Cohort of Patients With Primary CoQ_{10} Deficiency



In this heatmap, colors indicate the frequency of each symptom in our cohort normalized to the number of patients with variants in 1 of the 6 genes. The most prevalent symptom (deep red) was seizures, observed in 100% of the patients with pathogenic variants in *COQ4* and *COQ9*. Seizures were observed with all gene defects except *COQ8A*.

the patient died approximately 1 year later. Patient 13 (*COQ9*) was started on both CoQ_{10} (up to 60 mg/kg/d) and idebenone (up to 20 mg/kg/d) shortly after birth and died a few years later. Patient 14 was treated with CoQ_{10} (30 mg/kg/d) from birth and died within a week.

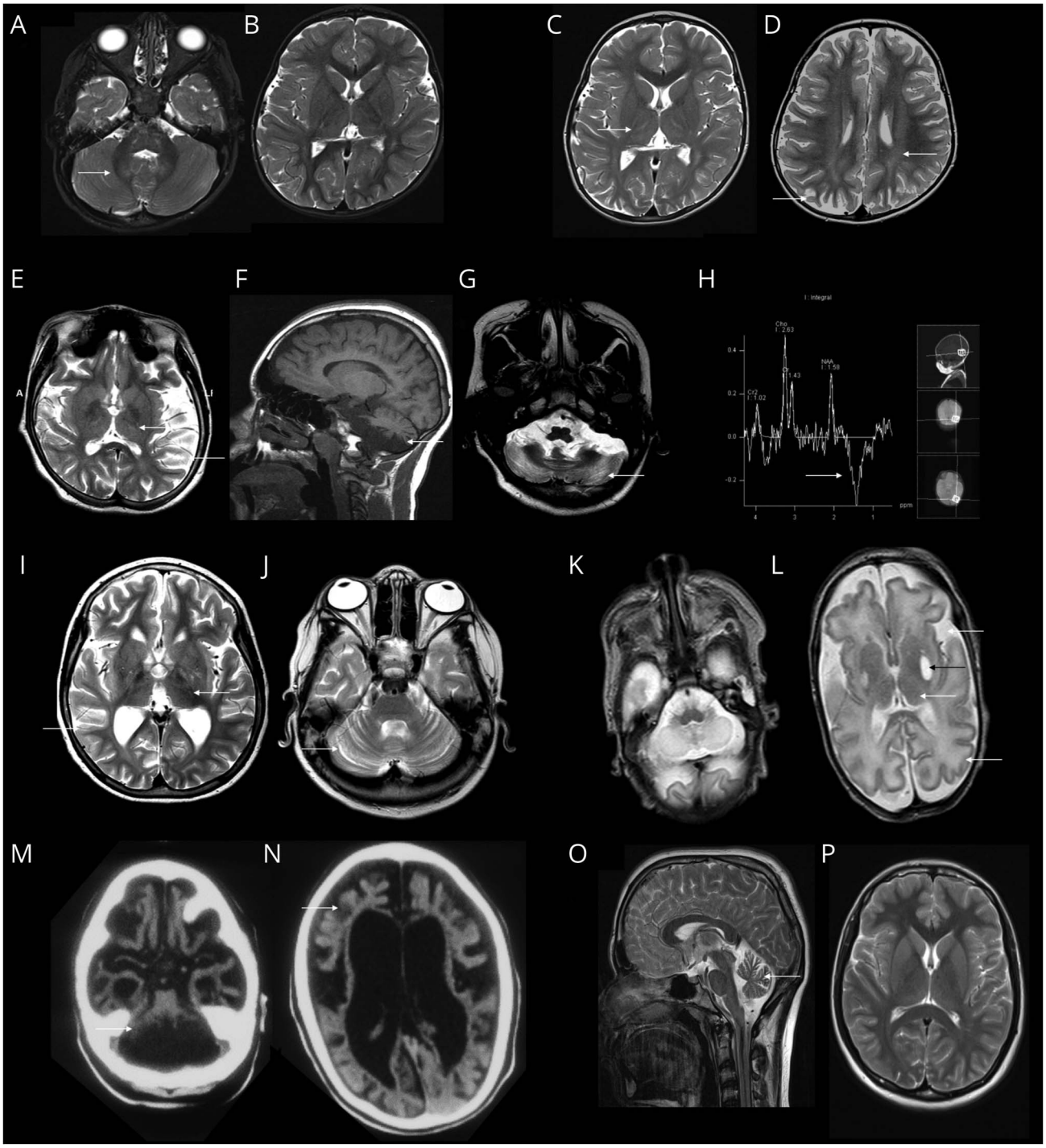
Discussion

In this study, we assessed the efficacy of high-dose oral CoQ_{10} supplementation in a cohort of patients presenting to a specialist pediatric hospital who were diagnosed with disorders of CoQ_{10} biosynthesis. Reports of therapeutic efficacy of CoQ_{10} supplementation in primary CoQ_{10} deficiency are inconsistent. Two large case series of specific phenotypes (renal disease) and/or genotypes (*COQ8A*-related ataxia) reported less than a 50% response to CoQ_{10} supplementation, possibly because of late initiation of treatment and/or inadequate dosing.[17,18] Here, we sought to assess outcomes in children with a range of CoQ_{10}-deficient genotypes and phenotypes treated with a uniform management protocol at a single center.

Of note, we observed a respiratory chain enzyme deficiency pattern (combined deficiencies of complexes II+III) traditionally associated with disorders of CoQ_{10} biosynthesis in only 1 case.[19] Thus, coenzyme CoQ_{10} biosynthesis disorders should be suspected in patients with mitochondrial disease, especially those with steroid-resistant nephrotic syndrome, ataxia, and seizures, especially if complicated with hearing loss, stroke-like episodes, and myopathy.

Peripheral blood leukocyte CoQ_{10} measurements revealed successful uptake of CoQ_{10} into blood with values more than double initial levels in 1 individual. These observations support

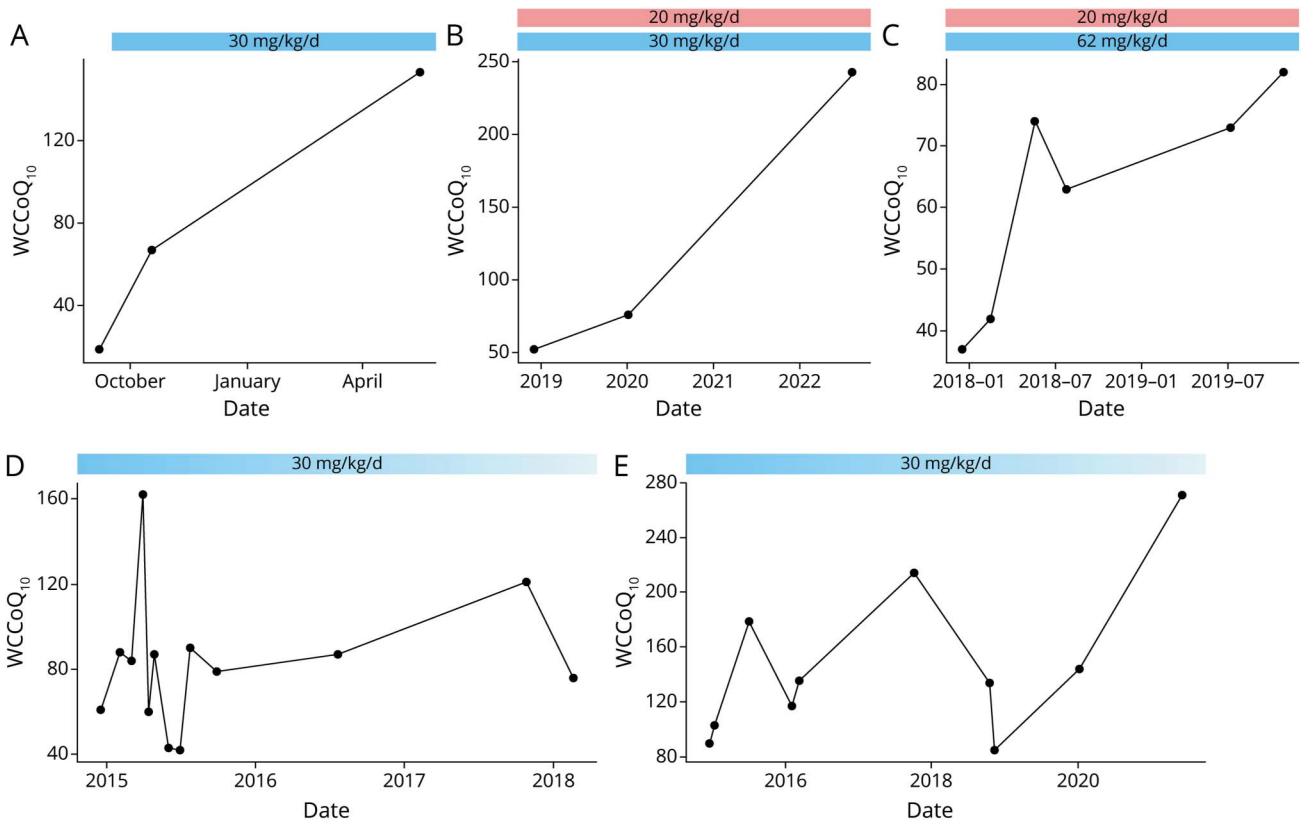
Figure 3 Representative Brain Images of Selected Patients Selected Patients From Our Cohort



MRI images for patient 7 (*COQ4*) at 2 years (A, B) and at 4 years (C, D) show dentate hilus hyperintensity (arrow in A) and thalamic laminar hyperintensity (arrow in C) occipital volume loss and gliosis as well as deep parietal white matter hyperintensity (arrows in D). MRI images for patient 4 (*COQ4*) at 14 years show pronounced cerebral volume loss, small thalamus with laminar hyperintensity (arrows in E), and cerebellar atrophy and parenchymal gliosis with inferior predominance (arrows in F, G). MR spectroscopy for patient 1 (*COQ2*) at 26 days shows intermediate TE showing large inverted lactate peak at 1.3 ppm (arrow in H). MRI images for patient 8 at 9 years shows diffuse cerebral atrophy, small thalamus (arrows in I), as well as diffuse cerebellar atrophy (arrow in J). MRI images for patient 13 (*COQ9*) at 4 weeks show simplified gyral pattern, poor operculization, small thalami (white arrows in L), and cystic foci along striatum (black arrow in L). CT of the brain for patient 12 (*COQ9*) at 12 months shows pronounced cerebellar and cerebral atrophy (arrows in M, N) with ex vacuo ventricular dilatation. MRI of the brain for patient 9 (*COQ8A*) at 14 years shows mild diffuse cerebellar atrophy (arrow in O) and normal supratentorial appearances (P).

the notion that administration of CoQ_{10} can compensate for deficient endogenous synthesis. Elevation of PBMNC CoQ_{10} levels after exogenous supplementation was accompanied by correction of biochemical abnormalities including reduction of elevated plasma lactate and alanine levels. Through serial monitoring of PBMNC CoQ_{10} levels, we observed some level

Figure 4 Serial Peripheral Blood Mononuclear Cell CoQ_{10} Levels in 5 Patients



(A) Patient 2; (B) patient 7; (C) patient 13; (D) patient 10; (E) patient 11. The horizontal blue bar indicates supplementation with oral CoQ_{10} and the red bar indicates idebenone supplementation. Doses are indicated on the bar. The gradient blue bar above D indicates inconsistent supplementation after initial initiation of oral CoQ_{10} because of noncompliance. $WCCoQ_{10}$ = white cell CoQ_{10}. Reference range: 37–133 pmol/mg.

of correlation between CoQ_{10} content in peripheral leukocytes and disease course. Thus, PBMNC CoQ_{10} levels can be used to monitor therapy and compliance.

In our cohort, there appeared to be a better response of renal compared with CNS manifestations of CoQ_{10} deficiency to oral CoQ_{10} supplementation. We observed reversal of focal segmental glomerulosclerosis, allowing cessation of peritoneal dialysis, after CoQ_{10} supplementation in 1 patient with biallelic *COQ2* variants. Prophylactic oral CoQ_{10} supplementation was able to prevent the development of any renal manifestations in a young patient who was diagnosed presymptomatically with a homozygous pathogenic variant in *COQ8B*. The patient remains completely symptom-free with no evidence of microalbuminuria after nearly 10 years of CoQ_{10} supplementation. Our results confirm previous observations of improvement of renal manifestations of CoQ_{10} deficiency disease after oral CoQ_{10} supplementation,[16] but, to our knowledge, we present the first report of prevention of renal involvement through prophylactic treatment with CoQ_{10}. These findings extend the existing literature demonstrating that kidney function can be preserved with CoQ_{10} supplementation.[9,17,20,21]

Responses of other systems to oral CoQ_{10} supplementation were not uniform. Neurologic features including, but not limited to, seizures, developmental delay, and dystonia were the most frequent in our cohort. There was general improvement in clinical condition, especially fatigue, in 1 patient with a homozygous *COQ8A* variant soon after commencing CoQ_{10} treatment. Whether there will be further improvement of the patient's presenting neurologic features (ataxia, tremor, dysarthria, dysphonia, and weakness) at higher treatment doses remains to be seen. Indeed, objective stabilization of ataxia and improvements in ataxia, tremor, dystonia, epilepsy, mental speed, and muscle weakness were reported in only 43% of patients in a multicenter cohort with *COQ8A* variants.[18] Despite supplementation, the clinical courses of some patients were complicated by development of or progression of neurologic disease or development of cardiomyopathy. In our cohort, 1 patient (patient 7) with a variant in *COQ4* who presented with seizures, hypotonia, and developmental delay has been on CoQ_{10} and idebenone, and their clinical features have remained stable with no improvement nor progression of their severe neurologic disease. It is unclear whether the patient with the *COQ6* variant was a responder, given a lack of a genetic diagnosis until around the time of their death. All 3 patients with variants in *COQ9* were treated with CoQ_{10} supplementation, 2 of whom were treated from birth, but unfortunately, this did not prevent fatal outcomes in these cases. These findings suggest that individuals with more

Table 3 Characteristics of and Clinical Response to Oral CoQ_{10} Supplementation

Patient Gene	1 *COQ2*	2 *COQ2*	3 *COQ4*	4 *COQ4*	5 *COQ4*	6 *COQ4*	7 *COQ4*	8 *COQ6*	9 *COQ8A*	10 *COQ8B*	11 *COQ8B*	12 *COQ9*	13 *COQ9*	14 *COQ9*
CoQ_{10} dose	13–20 mg mg/kg/d	30 mg/kg/d	NT	NT	NT	73 mg/kg/d	30 mg/kg/d	17–30 mg/kg/d	16 mg/kg/d	30 mg/kg/d	30 mg/kg/d	60 mgkg/day	62 mg/kg/d	30 mg/kg/d
Idebenone dose	—	—	NT	NT	NT	10 mg/kg/d	20 mg/kg/d	—	—	—	—	—	20 mg/kg/d	10 mg/kg/d
Effect of CoQ_{10} supplementation	Died	Reversal of kidney disease	N/A	N/A	N/A	Died	Seizures controlled after adding idebenone	Died	Self-reported clinical improvement	Alive	Prevention of renal disease	Died	Died	Died

advanced and complex multisystem presentations of primary CoQ_{10} biosynthesis deficiency are especially resistant to therapy.

As with any neurodegeneration, reversal is not possible, and the main goal of treatment is to prevent disease progression. This was evidenced by MRI in a subgroup of our cohort demonstrating cortical atrophy, cerebellar atrophy, bilateral putamina and thalami lesions, and immature gyral folds. One factor underlying poor response is likely the severity of the preexisting neurologic and developmental disturbances in the patients prior to treatment initiation. Indeed, patients in our cohort with severe neonatal-onset disease responded poorly to supplementation. This is further complicated by the fact that many patients with CoQ_{10} deficiency died before diagnosis. Thus, it was not possible to establish the true efficacy of CoQ_{10} treatment across the spectrum of CoQ_{10} biosynthesis deficiency.

The disparate responses to CoQ_{10} supplementation suggest differences in the pathophysiologic mechanisms of the disorders resulting from variants in the different genes. In the future, genome-wide next-generation sequencing will facilitate earlier genetic diagnosis, and this will allow the global community to determine efficacy of CoQ_{10} supplementation in a larger cohort of patients treated prospectively from an earlier age. We would advocate presymptomatic diagnosis by newborn genome sequencing in renal forms of CoQ_{10} deficiency, in view of the excellent outcomes in this subgroup of patients in our study and others.[17] However, the case for newborn screening for neurologic CoQ_{10} deficiency is less clear based on the currently available outcome data.

Nonetheless, the positive responses to high doses of treatment demonstrate that CoQ_{10} supplementation can compensate for deficient endogenous synthesis. Currently it is not possible to predict which patients will respond to oral CoQ_{10} supplementation and thus we suggest that all patients with suspected primary CoQ_{10} deficiency should be started on oral CoQ_{10} immediately and that the dose be titrated to at least 30 mg/kg/d if a genetic diagnosis is confirmed. We suggest that the most effective way to detect these patients is by having a high index of clinical suspicion, together with genetic testing of all patients with compatible clinical features. Here, we have reported a retrospective study of a historical cohort. Reflecting this, testing for gene variants varied during the period in which these patients presented and was performed as relevant to the patients' clinical presentation and changed from research exomes and genomes to NHS gene panels as genetic testing evolved.

Going forward, we would recommend sequencing a clinically relevant gene panel including all genes known to cause primary CoQ_{10} deficiency. In the Genomics England PanelApp,[22] which is used by the NHS Genomic Medicine Service[23] in England and commercial laboratories globally, relevant gene panels include the following: mitochondrial disorders (Version 7.1)—*COQ2, COQ4, COQ6, COQ7, COQ8A, COQ8B, COQ9, PDSS1,*

PDSS2, (*COQ5* currently marked red but will be reviewed); undiagnosed metabolic disorders (Version 1.620)—*COQ2*, *COQ4*, *COQ6*, *COQ7*, *COQ8A*, *COQ8B*, *COQ9*, *PDSS1*, *PDSS2*; early-onset or syndromic epilepsy (Version 6.1)—*COQ2*, *COQ4*, *COQ9*; and unexplained young-onset end-stage renal disease (Version 5.1)—*COQ2*, *COQ6*, *COQ8B*, *PDSS2*. ADCK2 is not yet included in any panels, but so far has been reported only once as a cause of CoQ_{10} deficient myopathy in a single case who had a heterozygous variant in *ADCK2*.[8] Therefore, this gene has not yet achieved a sufficiently strong gene-disease relationship for inclusion in diagnostic gene panels. Alternative diagnostic approaches would be trio exome or genome sequencing, and these would be preferable in a critically unwell child because they take a comprehensive genome-wide approach and are thus potentially more efficient.

The situation for assessment of genetic variants of uncertain significance (VUS) is complicated by the lack of reliable biomarkers for this group of disorders. In this study, we have demonstrated normal lactate levels and muscle respiratory chain enzyme activities in several genetically confirmed cases with CoQ_{10} biosynthesis disorder and that even PBMNC CoQ_{10} levels were normal in a genetically confirmed case of COQ8B deficiency. If the clinical features support pathogenicity of the VUS (e.g., nephrotic syndrome associated with variants in *COQ2*, *COQ6*, or *COQ8B*; ataxia associated with variants in *COQ8A*; seizures associated with variants in *COQ2*, *COQ4*, or *COQ9*), we would recommend a therapeutic trial with high-dose CoQ_{10}; clinical response would provide evidence to support pathogenicity of the VUS, as was the case for patient 2 in our cohort, who had biallelic *COQ2* variants, 1 of which was initially classified as a VUS.

The prevalence of primary CoQ_{10} biosynthesis deficiency is unknown. Based on our experience, we conclude that CoQ_{10} biosynthesis deficiency is a very rare cause of mitochondrial disease, representing less than 2% of our patient population with primary mitochondrial disease. However, our study shows that there are no consistent clinical or biochemical features of CoQ_{10} deficiency disorders, and they are likely underdiagnosed. More accurate prevalence data may be obtained from population wide genomic sequencing, for example in the Genomics England Generation Study which has prioritized genes with variants known to cause CoQ_{10} biosynthesis deficiency for inclusion in this newborn genome sequencing research study.[24]

Formal clinical trials are needed to establish which patients respond to CoQ_{10} supplementation. Given the rarity of CoQ_{10} biosynthesis deficiency as a cause of mitochondrial disease, a prospective study design should ideally be an international multicenter study to be adequately powered. Because CoQ_{10} is not patented and is considered a food supplement, such a study is unlikely to be funded by big pharma and would need research funding support. Another challenge lies in diagnosing patients with primary CoQ_{10} deficiency. A prospective study of patients diagnosed by newborn genomic screening would allow for a larger cohort study and to better understand the impact of CoQ_{10} treatment on disease manifestation in patients with primary CoQ_{10} deficiency. A standardized treatment protocol could be 30 mg/kg/day, doubled to 60 mg/kg/day with or without additional idebenone if there are refractory seizures. Outcome measures could include clinical variables (including seizures, ataxia rating scale, echocardiogram, and renal function), white cell CoQ_{10} levels, and other biochemical parameters.

Further studies are also needed to characterize the pharmacokinetics and bioavailability of CoQ_{10} because this may also account for the disparate responses in our cohort. At present, there are no preparations that are able to penetrate into the brain or the heart and thus the poor response in patients with abnormal neurodevelopment is not surprising. In addition, the absorption of CoQ_{10} can be affected by diet, microbiota, and the intestinal absorption capacity.[25]

Currently, as for other mitochondrial disorders, there are limited treatment options available for patients with CoQ_{10} deficiency. White cell CoQ_{10} levels in our patients demonstrate that intestinal absorption of CoQ_{10} does not appear to be the issue, but that bioavailability and inadequate uptake across the blood-brain barrier and into the heart are likely explanations for the unfavorable treatment response in some patients. Given the variable response, with no obvious correlation between genotype and clinical response, we suggest that high-dose (up to 60–70 mg/kg/d) oral CoQ_{10} should be trialed in all patients with a genetic diagnosis of CoQ_{10} deficiency, with the addition of idebenone when there is severe neurologic disease or there is an antenatal diagnosis with a family history of morbidity and mortality. Furthermore, where possible, monitoring of leukocyte CoQ_{10} levels can serve as a biomarker of uptake of CoQ_{10}. We think primary CoQ_{10} deficiency, the most treatable mitochondrial disorder, is likely underdiagnosed and that many more cases will be identified with the increasing use of next-generation sequencing.

Study Funding

The authors acknowledge grant funding from Great Ormond Street Hospital Children's Charity, the Lily Foundation, and the National Institute of Health Research Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/NG for full disclosures.

Publication History

Received by *Neurology: Genetics* May 2, 2024. Accepted in final form September 9, 2024. Submitted and externally peer reviewed. The handling editor was Associate Editor Alexandra Durr, MD, PhD.

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