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Clinical Observations

Response to Early Coenzyme Q10 Supplementation Is not Sustained in CoQ10 Deficiency Caused by *CoQ2* Mutation

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ABSTRACT

BACKGROUND: *COQ2* mutations cause a rare infantile multisystemic disease with heterogeneous clinical features. Promising results have been reported in response to Coenzyme Q10 treatment, especially for kidney involvement, but little is known about the long-term outcomes.
METHODS: We report four new patients from two families with the c.437G→A (p.Ser146Asn) mutation in *COQ2* and the outcomes of two patients after long-term coenzyme Q10 treatment.
RESULTS: Index cases from two families presented with vomiting, nephrotic range proteinuria, and diabetes in early infancy. These patients were diagnosed with coenzyme Q10 deficiency and died shortly after diagnosis. Siblings of the index cases later presented with neonatal diabetes and proteinuria and were diagnosed at the first day of life. Coenzyme Q10 treatment was started immediately. The siblings responded dramatically to coenzyme Q10 treatment with normalized glucose and proteinuria levels, but they developed refractory focal clonic seizures beginning at three months of life that progressed to encephalopathy.
CONCLUSIONS: In our cohort with CoQ10 deficiency, neurological involvement did not improve with oral coenzyme Q10 treatment despite the initial recovery from the diabetes and nephrotic syndrome.

Introduction

Coenzyme Q10 (CoQ10), also named ubiquinone, is a lipophilic, vitamin-like molecule with a quinone group, and a polyisoprenoid tail that has 10 subunits in humans. CoQ10 plays an essential role in the electron transport chain of the mitochondrial oxidative phosphorylation system by shuttling electrons from complex I and complex II to complex III. Its reduced form, ubiquinol, also has antioxidant and antiapoptotic functions and protects mitochondrial membrane proteins

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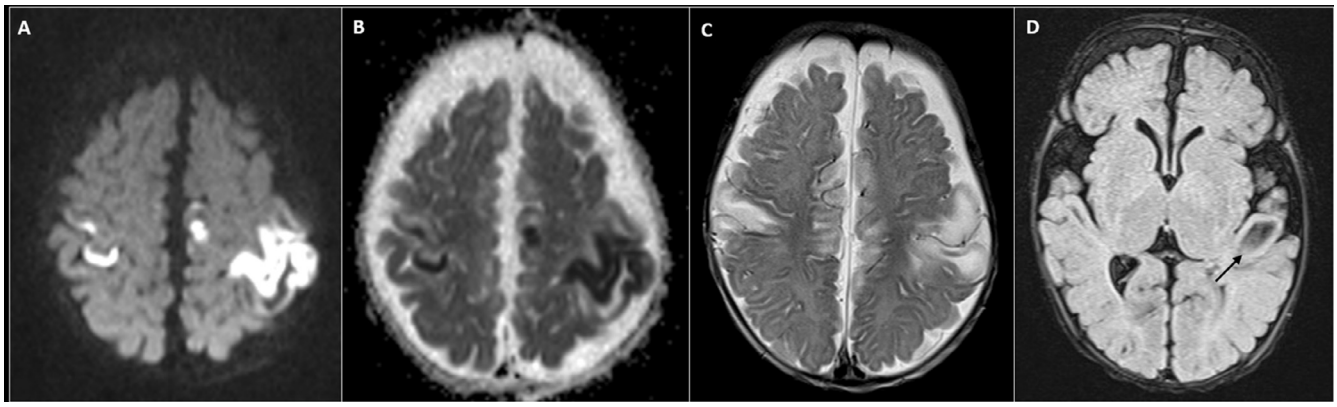

FIGURE 1. Diffusion-weighted imaging (DWI; *b*-factor, 1000 s/mm^2) of Patient 1 shows bilateral asymmetrical restricted diffusion associated with cytotoxic oedema in the perirolandic cortices (trace image, A, and apparent diffusion coefficient map, B). An axial T2-weighted image reveals hyperintense signal changes in the bilateral fronto-parietal cortico-subcortical regions (C). A fluid-attenuated inversion recovery (FLAIR) image demonstrates a subcortical cystic encephalomalacia (arrow) in the left superior temporal gyrus (D).

from oxidative damage induced by reactive oxygen species.[1,2]

CoQ10 is located in the inner mitochondrial membrane and is synthesized endogenously by a multienzyme complex encoded by several human COQ genes.[1] Mutations in these genes have been linked to certain clinical phenotypes that involve the central nervous system (CNS), skeletal muscle, and kidneys.[1] One of the genes involved in CoQ10 synthesis is *COQ2,* which encodes 4-hydroxybenzoate polyprenyltransferase. Primary CoQ10 deficiency due to *COQ2* mutations has been rarely reported in the literature with the few cases described as having heterogeneous clinical features ranging from infantile multisystemic disease associated with neurological symptoms to isolated nephropathy.[3,4] Recently, oral supplementation with CoQ10 has reportedly improved some of these clinical symptoms in instances of early diagnosis, with especially promising results for kidney involvement, but there is little knowledge about the response of these patients to long-term treatment.[1,5]

We report four new patients with CoQ10 deficiency from two unrelated families with a defined homozygous c.437G→A (p.Ser146Asn) mutation in *COQ2* who presented with neonatal diabetes and proteinuria that progressed to refractory seizures and neurological deterioration.[3] The index cases were diagnosed after death; their siblings were diagnosed in the neonatal period and were placed on CoQ10 treatment immediately after diagnosis. One of the patients received CoQ10 treatment for as long as 2.5 years.

Patient descriptions

Patient 1 was born by urgent Caesarean section after 34 weeks of uneventful pregnancy due to oligohydramnios in the third trimester and a nonreactive stress test. The Apgar scores were 9/10/10. He was hospitalized for prematurity follow-up. At the fourth day of life, his blood glucose was 600 mg/dL while on enteral feeding, and he had a concomitant low C peptide level (0.34 ng/mL [0.9–7.1]). Insulin infusion was started, followed by subcutaneous NPH insulin (neutral protamine Hagedorn; an intermediate-acting insulin). The patient tested negative for anti-insulin, anti-islet cell, and anti-GAD antibodies. A genetic evaluation for neonatal diabetes including *KCNJ11, ABCC8, INS*, and *EIF2AK3* was negative. Routine laboratory tests revealed proteinuria (with a urinary protein (mg)/creatinine (mg) ratio [U-PCR] of 4), hyponatremia (Na 129 mEq/L) and low albumin levels (2.9 mg/dL). Urine protein electrophoresis was consistent with glomerular proteinuria. A renal biopsy showed unremarkable changes based on examination with a light microscope. At two months of age, the patient began to have jerky movements in all his extremities. Electroencephalography revealed a bilateral frontal spike and wave discharges. Visual evoked potentials reflected delayed P1 latencies, and electroretinography showed no response. Brain magnetic resonance imaging (MRI) showed acute cytotoxic oedema on diffusion-weighted imaging (Fig 1A).

The patient had also developed severe hyponatremia, hyperkalemia, and metabolic acidosis with increased lactate levels. Liver enzymes gradually increased, and an abdominal MRI showed normal liver parenchyma and an atrophic pancreas. Electron microscopy of the kidney biopsy revealed that the podocyte cell bodies were filled with numerous dysmorphic mitochondria, lacking cristae (Fig 2), suggesting a mitochondrial disease.

Oral CoQ10 (ubiquinol, 30 mg/kg/day, soft-gel capsules, in three doses) was started at three months of age. Despite this treatment, the patient had medically refractory seizures, developed severe encephalopathy, hypotonia, respiratory failure, and eventually died at age 4.5 months. Genetic analysis revealed a homozygous c.437G→A (p.Ser146Asn) mutation in *COQ2*.

Patient 2 was the sister of Patient 1. She was born after thirty-seventh weeks of gestation by urgent Caesarean section due to oligohydramnios and bradycardia. She had an elevated glucose level of 274 mg/dL in the first hours of life with a concomitant low C-peptide level of

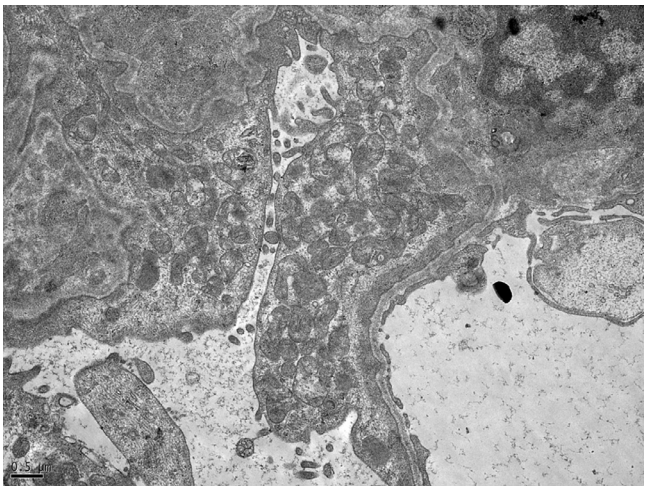

FIGURE 2. Electron microscopy of renal biopsy of Patient 1 showing a marked proliferation of pleomorphic mitochondria and diffuse effacement of foot processes in the podocytes.

0.21 ng/mL (0.9 to 7.1) and insulin of 1.09 mIU/L (1.9 to 2.3). Insulin infusion was commenced with a diagnosis of neonatal diabetes. She had mild metabolic acidosis with increased lactate levels, hyponatremia (125 mEq/L), and proteinuria (U-PCR 8.04 mg/mg). CoQ10 (ubiquinol, 30 mg/kg/day, soft-gel capsules, in three doses) was started immediately based on the diagnosis of the index case (Patient 1). She responded to treatment with recovery of lactic acidosis on the third day. Her blood glucose level normalized by the sixth day, and insulin treatment was discontinued. U-PCR decreased to 0.69 (mg/mg), and she was discharged with oral sodium, captopril, and CoQ10 supplementation. Genetic analysis showed that the patient had the same homozygous mutation (c.437G→A [p.Ser146Asn]) as her brother.

While continuing the oral CoQ2 supplements (soft-gel capsules) at two months of age, she presented with focal clonic seizures and electroencephalography showed right central ictal discharges; brainstem auditory evoked potentials and visual evoked potentials showed no response. A brain MRI revealed lesions that were similar to those of her brother. Her blood glucose, sodium, and urine protein levels were normal. On follow-up, despite antiepileptics and CoQ10 treatments, she showed profound neurological deterioration with encephalopathy and refractory seizures.

At age 18 months, she required mechanical ventilation through a tracheostomy for respiratory difficulties. During times of stress, especially infections, her blood glucose levels increased without a corresponding increase in HbA1C, and she needed temporary low doses of insulin. At 25 months of age, her glucose level rose to 397 mg/dL with a HbA1C level of 8.8% (4 to 6.5). Regular NPH insulin (0.8 U/kg/day) was started regularly. After three months, her HbA1c decreased to 7.6%. Even though she remained on the same dose (30 mg/kg/day) of CoQ10 therapy, by 24 months of age, her urine protein excretion reached a nephrotic range with normal serum albumin and creatinine levels. At 30 months of age, she was hospitalized with pneumonia and acute kidney injury. Her creatinine levels returned to a normal range with supportive therapy, but one month later she was hospitalized with sepsis, required peritoneal dialysis and died from multiorgan failure. At 31 months of age she had microcephaly (head circumference 45 cm; less that third percentile) despite having a normal weight (15 kg, seventy-fifth percentile) and height (90 cm, twenty-fifth percentile).

Patient 3 was a four-month-old girl referred for intractable vomiting, poor weight gain, and marked proteinuria. Laboratory examination revealed nephrotic range proteinuria (139 mg/m^2/h), hypoalbuminemia, and lactic acidosis. A renal biopsy showed a fetal glomerular appearance and visceral epithelial hypertrophy. The tubulointerstitial area was normal with mild oedema. At three months of age, the patient began having refractory seizures and developed kidney failure. Despite supportive treatment that included peritoneal dialysis, she died at six months of age due to respiratory distress and multiorgan failure. Postmortem genetic evaluation revealed a homozygous c.437G→A (p.Ser146Asn) mutation in *COQ2*.

Patient 4, the brother of Patient 3, was born by Caesarean at the thirty-seventh week of gestation due to preterm labour and fetal distress. On his fifth day of life, he was admitted to the hospital due to poor feeding; CoQ10 therapy (ubiquinol, 30 mg/kg/day, soft-gel capsules, in three doses) was instituted immediately based on his sister's diagnosis. A laboratory evaluation showed hyponatremia (124 mEq/L), marked proteinuria (U-PCR 8.9 mg/mg), and hyperglycaemia, which indicated insulin therapy. After a month of CoQ10 supplementation, his proteinuria (U-PCR 0.68 mg/mg) decreased, his albumin levels increased (3.6 g/dL) and insulin was stopped. At 3.5 months of age, he began to have focal clonic seizures. Despite a gradual CoQ10 dose increase to 60 mg/kg/day, the seizures continued, and the patient deteriorated neurologically. A brain MRI showed cortical and subcortical stroke-like lesions in the frontal, insular, and temporal regions with diffuse cerebral atrophy. The disease course was further complicated by infections and resulted in death at 14 months of age.

Discussion

Since most patients with CoQ10 deficiency die before diagnosis, there are limited and conflicting reports on the effects of CoQ10 treatment.[1,2,5,6] Desbats et al.[1] suggested that renal, CNS, and muscular symptoms respond well to treatment, but the clinical response to CoQ10 supplementation has been unclear in most of the CoQ2-deficient patients reported so far.[6] In our patients, at early stages, peripheral tissues like the kidney and pancreas seemed to respond to CoQ10 therapy with a dose of 30 mg/kg/day; however, neurological features impeded the prognosis. In Patient 1, CoQ10 treatment was not started until the late stages of the disease, and his unsatisfactory result may be attributed to irreversible structural changes. In Patients 2 and 4, the CoQ10 treatments were started immediately after birth. These patients remained neurologically stable for two to three months, but they

had the same medically refractory seizures as their siblings at similar age while taking the same formulation (soft-gel capsule) and dose of CoQ10 and while they had normal blood glucose levels and no proteinuria.

There are two marketed formulations of CoQ10, ubiquinone and its reduced form ubiquinol. Both are absorbed in the gastrointestinal tract; ubiquinone is reduced to ubiquinol upon absorption. Unfortunately, there is little information about the bioavailability of CoQ10. The market is supplied by many manufacturers, and the therapeutic level is unknown, especially for CNS disorders.[1,6,7] Some reports have failed to show an increase in total cerebrospinal fluid (CSF) CoQ10 levels with ubiquinone or ubiquinol supplementation,[8] but recently Mitsui et al.[9] showed that ubiquinol supplementation at 840 and 1200 mg/day elevated the total CSF CoQ10 levels in a patient with multiple system atrophy due to a heterozygous *COQ2* mutation.

Another factor in patient response to CoQ10 treatment may be the variability in the progression of damage between tissues. An *in vitro* study has shown that neuronal cells were highly vulnerable to CoQ10 deficiency; even a small deficit in the neuronal cells' CoQ10 status (76% residual CoQ10 levels) resulted in a simultaneous loss of respiratory chain function, increased oxidative stress, and dysfunction of mitochondrial DNA.[10] Under CoQ10 treatment, the damage may take longer in the kidney and pancreas. In Patient 2, during stress conditions, we observed temporary increases in renal function tests and serum glucose levels, but, in the end, that patient developed renal failure and insulin-dependent diabetes (IDDM).

Three of our patients (1, 2, and 4) were diagnosed with IDDM during the neonatal period. IDDM is a relatively rare complication of the CoQ10 deficiency, but it was also reported by Mollet et al.[11] in two siblings with *COQ2* mutation. Our patients needed insulin at the time of diagnosis and insulin treatment was discontinued in Patients 2 and 4 after early CoQ10 supplementation, but, at later stages, both patients required insulin during stress periods and subsequently became insulin dependent. Diabetes is a well-known feature of mitochondrial diseases and includes mitochondrial inherited diabetes and deafness chronic progressive external ophthalmoplegia, Kearns-Sayre syndrome and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke syndrome.[2] Mitochondrial metabolism generates ATP (adenosine triphosphate), which is a key factor in the efficient coupling of glucose recognition to insulin secretion by β cells. Moreover, inhibition of the mitochondrial electron transport chain is a major cause of reactive oxygen species production within cells, which may result in β-cell apoptosis.[12] The abdominal MRI of Patient 1 showed an atrophic pancreas, which could have caused an endocrine dysfunction; however, there was no sign of exocrine pancreatic insufficiency. Patient 2 is the first report of neonatal IDDM secondary to a *COQ2* mutation who responded to CoQ10 supplementation. Unfortunately, this response was not sustained.

In conclusion, in our cohort of CoQ10 deficiency, despite the initial dramatic recovery of the diabetes and nephrotic syndrome, we observed only a temporary response to early CoQ10 treatment. Neurological involvement, which determined the prognosis of the disease, did not improve with oral CoQ10 treatment. Further studies are needed to characterize the pharmacokinetics and bioavailability of CoQ10.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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