Case Series

CoQ10 supplementation: a new treatment modality in steroid-resistant nephrotic syndrome with unknown molecular etiology

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ABSTRACT

Background: Steroid-resistant nephrotic syndrome (SRNS) is a common problem in paediatric nephrology practice which tends to progress to end-stage renal disease. SRNS-causing genes are expressed in the glomerular podocyte which is a specialized cell type. However, there are more than 80% of SRNS cases with unknown molecular etiology. Coenzyme Q10 (CoQ10) has an important role in the mitochondrial electron-transport chain. Synthesis of CoQ10 is a complex pathway, involving enzymes from various genomes; termed from CoQ1 to CoQ10. Due to sequenced reactions of synthesis, enzymes and regulatory proteins are needed in obligation. So any dysfunction here; affects the biosynthesis of CoQ10. **Aim:** We here described quinone-responsive six patients having CoQ2 mutations, presented with steroid-resistant NS. **Findings:** CoQ 10 deficiency is strongly related with CoQ2 deficiency and/or any mutation of encoding genes. Among the 5 types of CoQ 10 deficiency, infantile form can be presented only with renal involvement, nephrotic syndrome. Also in other forms, renal involvement is not rare besides the neurological pathologies. All 6 cases of us with CoQ2 mutation responded to CoQ 10 treatment. **Conclusions:** In conclusion, early recognition of CoQ2 nephropathy is crucial. CoQ10 supplementation improves the clinical symptoms and prevents neurologic complications. Long-term follow-up is important to define the prognosis of these patients.

Key words: CoQ 10, CoQ2 nephropathy, SRNS, quinone, children, mutation

INTRODUCTION

Steroid-resistant nephrotic syndrome (SRNS) is a malfunction of the glomerular filter, a common problem in paediatric nephrology practice which tends to progress to end-stage renal disease (ESRD).[1-9] SRNS-causing genes are expressed in a specialized cell type, the

glomerular podocyte.[10] Approximately, 33% of infantile and 10%–28% of all childhood SRNS cases are caused by single-gene mutations of one of 4 genes encoding the podocyte proteins; NPHS1, NPHS2, LAMB2, and WT1.[11-16] However, there are more than 80% of SRNS cases with unknown molecular etiology.[11,13]

Coenzyme Q10 (CoQ10) is a type of endogenous ubiquinone, found in human cells. It is mostly synthesized by a cascade pathway in the inner membrane of the mitochondria.[17] A small proportion is taken by diet.[18] It has an important role in the mitochondrial electron-transport chain, transfers electrons from complex I and II to complex III.[19]

Besides its major role in mitochondrial electron transport, it has several different functions which include protection of membrane phospholipids and serum lipoproteins from lipid peroxidation, and role in endothelial and membrane functions by preventing the mitochondrial membrane proteins from reactive oxygen species leading to oxidative damage.[20,21]

Synthesis of CoQ10 is a complex pathway that has not been explained exactly. It involves at least 10 different enzymes, isolated from various genomes and is termed from COQ1 to COQ10.[22,23] As shown in figure 1, on the first step, from mevalonate pathway; geranylgeranyl diphosphate is produced and formstwo substances. One is decaprenyl diphosphate; the other is para-hydroxybenzoate (PHB), derived from tyrosine or phenylalanine. PHB goes to prenylation with PHB-polyprenyltransferase. This enzyme is encoded by CoQ2.[19] Following this step, multiple reactions (catalyze condensation, methylation, decarboxylation, and hydroxylation) take place to form coenzyme Q10. CoQ 3-8 encodes the enzymes having role in these multiple reactions.[24] Due to the fact that, sequenced reactions involved in synthesis process, an obligatory need of enzymes and regulatory proteins in all steps is unleavable. Any dysfunction of regulatory proteins and/or enzymes or pathogenic mutations of encoding genes affect the biosynthesis of CoQ10.[25] Primary CoQ10 deficiency is an autosomal recessive disorder.[26] Five major phenotypes have been described. In almost all types,

findings of central nervous system, skeletal muscle and peripheral nerve involvement are seen.[23,27-31]

Oral supplementation with CoQ10 has been shown to improve clinical symptoms.[32-34] Thus early diagnosis has a crucial role in follow-up. Here, we described quinone-responsive six patients having CoQ2 mutations and presented with steroid-resistant NS.

METHODOLOGY

This is a case series. Six children with steroid resistant nephrotic syndrome followed in Ege University Paediatric Nephrology Department, having no mutation detected in NPHS1, NPHS2 and WT1 genes; evaluated for CoQ2 mutation and found as having a homozygous mutation on CoQ2 in the Molecular Genetic Research Laboratory of Ege University Medical Faculty, were reviewed. The presence of homozygous mutation on CoQ2 led us to give them oral CoQ10 (quinone) treatment. We summarised the clinical and diagnostic features of these six cases by reporting the outcome after CoQ10 supplement, in the light of literature review. The study was approved by Ethical Committee of the institution, and informed consent was obtained from each patient or patient's relative.

CASES

CASE 1
He was 20 months old, delivered after a healthy pregnancy of unconsangious marriage. He had a 10 years old brother without any disease. Parents were healthy; his uncle (brother of mother) was transplanted for chronic renal failure with unknown etiology at the age of 16. At 14 months of age, he was admitted to our clinic with the findings of nephrotic syndrome and acute renal failure. Serology for hepatitis B and C, HIV, Epstein-Barr virus, and parvovirus B19 was negative. Acute treatment was begun, but rapidly progressed to end stage renal disease (on the second months of disease onset). The renal pathology revealed sclerosis in 33% of glomerules, global sclerosis in 25% of glomerules and interstitial fibrosis, tubuler atrophy. He began haemodialysis after unsuccesful peritoneal dialysis attempts. There were no signs of neuromuscular involvement and dilated cardiomyopathy.

Table 1: Features of five different forms

Form	Component	References
Encephalomyopathic Form	• Exercise intolerance • Mitochondrial myopathy • Seizure • Cognitive impairment • Cerebellar symptoms	30,33,42,43
InfantileEncephalopathic Form	• Encephalopathy (hypotonia, seizures, stroke-like episodes, cerebellar and cerebral atrophy) • Optic nerve atrophy • Retinitis pigmentosa • Bilateral sensorineuronal deafness • Nephrotic syndrome progression to renal failure • Renal tubulopathy • Progressive ataxia • Cardiomyopathy (ventricular hypertrophy) • Metabolic disturbances (hypothermia, lactic acidosis) • Developmental delay	29,31,44,45
Cerebellar Form	• Epilepsy (most common) • Cerebellarathrophy, ataxia • Pyramidal signs • Mental retardation • Myopathic weakness • Delayed motor development • Hypogonadism (only in 2 cases) *No ragged-red fibers and lipid storage myopathy on muscle biopsy*	46-49 *There are 21 patients reported in literatüre, the most common form*
Leighsendrome	• Growth retardation • Deafness • Ataxia	50
Variant Isolated Myopathy	• Exercise intolerance (subacute onset) • Proximal limb weakness *Lipid storage and ragged-red fibers in all muscle specimens, increased serum lactate and creatine kinase*	24,28 *There are 4 patients reported in literature*
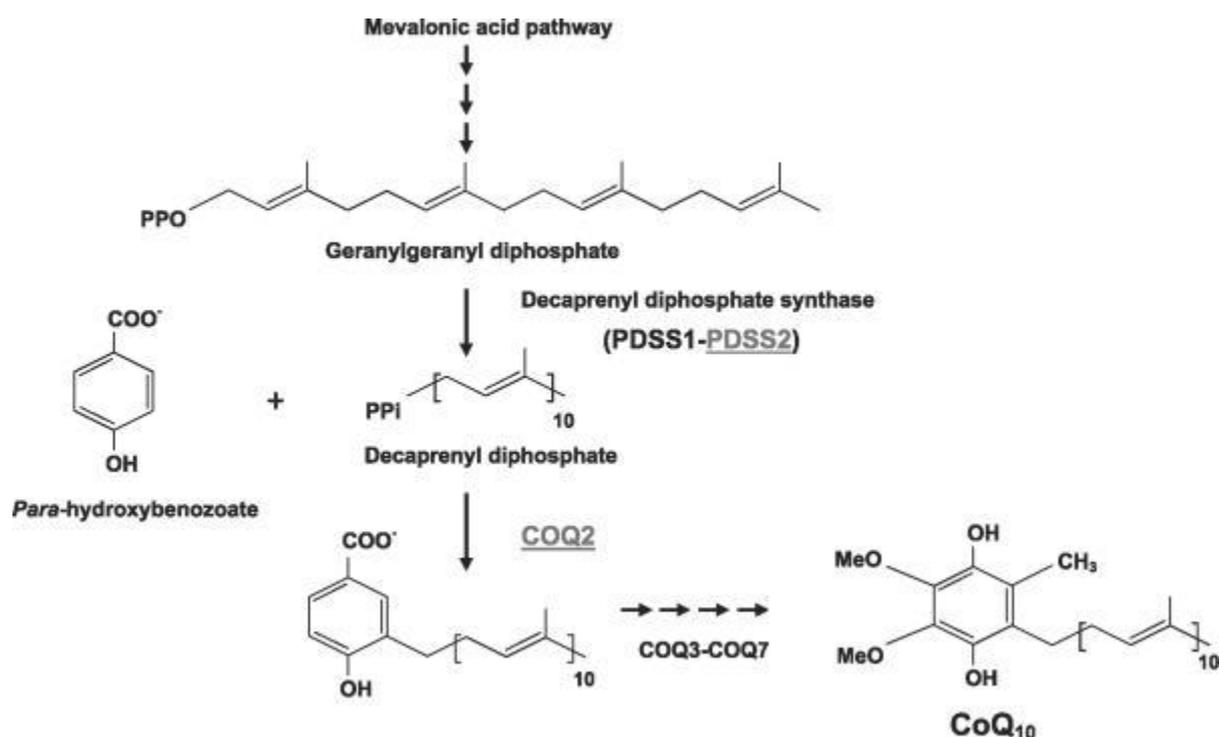
Figure 1: CoQ$_{10}$ biosynthetic pathway. Mevalonic acid pathway generates geranylgeranyl diphosphate. Decaprenyl diphosphate is synthesized from geranylgeranyl diphosphate by decaprenyl diphosphate synthase enzyme. Para-hydroxybenozoate (PHB) is derived from the amino acids tyrosine or phenylalanine. After PHB and decaprenyl diphosphate are produced, at least seven enzymes catalyze condensation, methylation, decarboxylation, and hydroxylation reactions to synthesize CoQ $_{10}$.[30,54,55]

As there were no mutation in NPHS1, NPHS2 and WT1 genes, CoQ2 gene was examined with the result of V66L homozygous mutation. There was V66L heterozygous mutation of CoQ2 in his mother, and no mutation was detected in his father. Since then, the patient has been on oral supplementation of CoQ10 (30 mg/kg per day). He has been on our follow up with a well functioning graft from his mother for 2 years.

CASE 2
An eight years old boy, having SRNS since he was 11 months. Pregnancy and delivery were not adversely eventful, and there was no associated family history. He had moderate motor-mental retardation and severe hearing loss. Mutations in NPHS1, NPHS2 and WT1 genes were negative except CoQ2 (V66L homozygous). His parents had no mutation. In his renal histology, there were 20% global sclerosis and focal fibrosis in interstitial region, tubulary athrophy. After CoQ10 administration for a year, any nephrotic syndrome attacks experienced with well renal functions.

CASE 3
The patient was 19 months old when he had NS. NS was not responsive to steroid and cyclophosphamid therapy. On the third months of disease onset, ESRD was seen. He was born after a normal pregnancy with consangious marriage. He, his mother and father had heterozygous mutation about Canavan disease. He had a brother who died from Canavan disease at the age of 1 year. He had no pathology in other systems apart from kidneys. He went for renal biopsy when he was 20months of age. Pathologic findings were global sclerosis in more than half glomerules, interstitial fibrosis, and tubulary athrophy.While NPHS1 and NPHS2 mutations revealed no mutation, CoQ2 had V66L nucleotid change. He is on haemodialysis programe now, preparing for transplantation with administration of CoQ10.

CASE 4
Patient was a 5-year old boy. He was born on the 27th weeks of pregnancy, and had NS when he was 17 months old. There were no important features in his family history. Hearing loss and SRNS was the

main pathologies. Almost in all glomerules (27 in 30) global sclerosis, focal microcalcification, fibrosis, tubulary dilatation were noted in the renal biopsy. He responded to cyclosporin and CoQ10.

CASE 5
He was 13-years oldwith an infantile type of SRNS (age of onset: 12months). He had NS attacks more than 5 times, and his attacks were resistant to cyclophoshamid. Renal histology was evaluated as FSGS (more than half glomerules were globally sclerotic). Myopathy was the only sign of neurologic component of his disease. No mutation detected in NPHS1, NPHS2 and WT1 genes. Homozygous V66L mutation was found in CoQ2. He had no attacks after CoQ10 administration since 2 years.

CASE 6
This was an 8-year old girl was from unrelated parents, the proband. Disease onset was 11 months; with histology suggestive of FSGS. She was responsive to cyclosporin treatment. She had V66L heterozygous mutation on CoQ2. She was the only patient that presented with isolated renal involvement.

All the 6 patients were responsive to CoQ10 treatment.

DISCUSSION

Renal dysfunction associated with mitochondriopathies is generally a rare event.[35] These days, number of mitochondriopathies presenting with isolated renal involvement are increasing. This study reports on the identification of mutations in COQ2genes ofubiquinone (CoQ10) synthesis pathway, in 6 unrelated patients. The genome scan analysis identified mutation in the COQ2(PDSS1) gene encoding prenyldiphosphate synthase, one of the key enzymes of the ubiquinone biosynthesis pathway.[34,36] The absence of these mutation in control DNA samples of healthy children is a pointer to the pathogenicity..

There are few reported cases with CoQ 10 deficiency via mutations on CoQ2 gene. Three cases that presented with central-peripheral nervous system involvement and nephrotic syndrome in the first decade of life were previously reported in the literature.[34] Ogasahara *et al.* described first patients with CoQ10 deficiency in

1989.[37] Two sisters developed exercise intolerance, slowly developed progressive weakness of axial and proximal limb muscles, myoglobinuria and brain involvement by learning disability.[37] Exact diagnosis was reached by the assesment of markedly decreased CoQ10 concentrations (about 5% of normal) in muscle biopsies.[37] In a study done by DiGiovanni *et al.* on patients with the same clinical triad (mitochondrial myopathy, recurrent myoglobinuria, and CNS signs) and muscle CoQ10 deficiency appeared 8 and 11 years later.[33] Notably, all patients improved remarkably with oral CoQ10 supplementation. In 2000, Rotig *et al.* described the first infantile-onset cases in three siblings.[34] Soon after birth with neurological symptoms, including nystagmus, optic atrophy, sensorineural hearing loss, ataxia, dystonia, weakness, and rapidly progressive nephropathy were seen in all siblings in whom any causative mutations has been reported.[34]

Primary CoQ10 deficiencies have been recognized since the late 1980s, but no mutation had been described in CoQ10 synthesis genes until the first decade of 21th century.[22,30] In 2006, Quinzii *et al.* reported the first mutation responsible for CoQ10 deficiency in a proband with infantile-onset multisystemic disease and his younger sister, who shared a homozygous missense mutation in the CoQ2 gene.[22] The elder sibling was a 33-month-old boy having nystagmus, severe nephrotic syndrome and psychomotor delay, at the age of 2, 12, and 18 months, respectively.[22] He went on successful renal transplant at 3 years of age. The sister developed nephrotic syndrome at 12 months of age without any clinical signs of neurological involvement.[22] Both siblings improved with CoQ10 supplementation.[22] Rotig *et al.* reported a girl with neonatal neurological distress, nephrotic syndrome, hepatopathy, pancytopenia, diabetes, seizures, and lactic acidosis progressing to fatal multiorgan failure at age 12 days.[34] Rotig *et al.* also reported quinone-responsive mitochondrial encephalomyopathy in two siblings with coenzyme Q10 deficiency.[34] The older brother also had anemia, liver failure, and renal insufficiency and died at the age of 1 day.[34] Both siblings had a homozygous base-pair deletion in exon 7 of the CoQ2 gene.[34] Three patients among 4 reported by Diomedi *et al.* presented with isolated

renal symptoms.[35] Although these cases were diagnosed as CoQ2 nephropathy, a group of mitochondrial cytopathy, they had isolated renal involvement, without any neuropathologic findings. Diomedi *et al.* called this entity as CoQ2 nephropathy.[35] Similar to the literature, our 1st and 6th patientshad only nephropathy, and the 5th patient had only myopathy and physicomotor developmental retardation 6 months following the renal findings. This can be explained by three reasons. First, ubiquitously expression of CoQ10 and high CoQ10 content in kidneys can be affected.[38] Second, residual enzyme activity may have prevented cell damage in other organs.[35] Lastly, enough dietary intake of CoQ10 cured the impaired CoQ10 synthesis in some tissues.

CoQ2 nephropathy has a heterogeneous pattern of glomerular lesions.[35] Wharram *et al.* reported that podocyte damage secondary to inherited mitochondrial dysfunction may cause visceral cell depletion, accumulation of extracellular matrix, and ultimately sclerosis of the glomerular tuft.[39] Findings documented by Lee *et al.* also support that of Wharrams' study. They explain that mitochondrial diseases trigger epithelial cell proliferation (particularly podocytes), associated with GBM collapse.[40] FSGS pathogenesis is based on the increased apoptosis of podocyte cells in mitochondrial cytopathies.[40] The result that injured podocytes leads to proliferative lesions is stil unclear.[40,41]

An autoimmune response involves both the tubular interstitium and glomeruli, causing the death of glomerular podocytes were demostrated by ultrastructural analysis in mitochondria of mutant mice.[42,43]

Our biopsy findings included mostly sclerotic glomerules and tubulointerstisyel changes, similar to literatue. Also, similar findings were reported in a murine model, in which animals spontaneously develop proteinuria and renal disease associated with the presence of numerous dysmorphic mitochondria in all cell types, and histologically collapsing glomerulopathy.[44] In this model, a mutation in the gene encoding for a mitochondrial protein, involved in the CoQ10 synthesis pathway is the trigger factor of mitochondrial dysfunction.[41,44]

Among the biopsy findings, presence of extracapillary proliferation indicates that there was pathology also in parietal epithelial cells besides to podocytes. All patients responded to CoQ 10 treatment, similar to other papers.[1,35] CoQ 10 deficiency is strongly related with CoQ2 deficiency and/or any mutation of encoding genes.[1,35] Among the 5 types of CoQ 10 deficiency, infantile form can be presented only with renal involvement, nephrotic syndrome.[45] Also in other forms, renal involvement is not rare besides the neurological pathologies.[35]

In conclusion, it is important to emphasize on the clinical findings of CoQ10 deficiency, related with CoQ2 nephropathy; as it can only begins with renal involvement, may cause the time wasting by doing molecular analysis of other genes; such as NPHS1, NPHS2 anf WT1. It should be put in mind that CoQ2 nephropathy and/or CoQ10 deficiency should be on the top list of differential diagnosis. This makes early recognition of CoQ2 nephropathy possible. CoQ10 supplementation improves the clinical symptoms and prevents neurologic complications. Long-term follow-up is important to define the prognosis of these patients.

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