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Case Report

COQ6 mutation in Patients with Nephrotic Syndrome, Sensorineural Deafness, and Optic Atrophy

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Abbreviations ACE: Angiotensin-Converting Enzyme; ADCK4: Aarf Domain Containing Kinase 4; COQ2: Coenzyme Q2 4-hydroxybenzoate polyprenyl transferase; COQ6: Coenzyme Q 10 biosynthesis monooxygenase 6; COQ9: Ubiquinone bisynthesis protein coenzyme Q9; CoQ10: coenzyme Q10; DMS: Diffuse Mesangial Sclerosis; ESRF: End-Stage Renal Failure; FSGS: Focal Segmental Glomerulosclerosis; NS: Nephrotic Syndrome; OCT: Optical Coherence Tomography; PDSS2: Prenyl (Decaprenyl) Diphosphate Synthase Subunit 2; SRNS: Steroid-Resistant Nephrotic Syndrome; VA: Visual Acuity

Abstract

Introduction: Primary coenzyme Q10 (CoQ10) deficiencies are a group of mitochondrial disorders that has proven responsiveness to replacement therapy. Mutations in enzymes involved in the biosynthesis of CoQ10 genes are associated with these deficits. The clinical presentation of this rare autosomal recessive disorder is heterogeneous and depends on the gene involved. Mutations in the COQ2, COQ6, PDSS2, and ADCK4 genes are responsible for Steroid-Resistant Nephrotic Syndrome (SRNS), which is associated with extra-renal symptoms. Previous studies have reported COQ6 mutations in 11 patients from five different families presenting with SRNS and sensorineural deafness.

Case reports: Our study reports the cases of two brothers of Turkish origin with renal failure and sensorineural deafness associated with COQ6 mutations responsible of CoQ10 deficiency. Ocular symptoms were present in the eldest that improved with coenzyme Q10 therapy.

Conclusion/Discussion: For the first time, COQ6 mutation with ocular involvement is associated with renal and hearing impairment. Although the response to replacement CoQ10 therapy was difficult to evaluate, we think that this treatment was able to stop the disease progression in both patients, and even to prevent the occurrence/development of ocular and neurological impairment in the younger brother. Mitochondrial dysfunction secondary to CoQ10 deficiency should always be suspected in patients with SRNS and extra-renal symptoms. Early recognition of this genetic SRNS is mandatory since SRNS can be avoided by adequate treatment based on CoQ10 supplement. All cases of primary CoQ10 deficiency should be treated at an early stage to limit the progression of lesions and prevent the emergence of new symptoms.

Introduction

Nephrotic Syndrome (NS), a chronic kidney disease, manifests with significant proteinuria, hypoalbuminemia, and edema. Approximately 20% of children with NS are typically resistant to steroids and other immunosuppressive therapy methods [1]. Steroid-resistant NS (SRNS) is a frequent cause of End-Stage Renal Failure (ESRF). SRNS is a glomerular disease caused by numerous different etiologies, all of which lead to similar patterns of glomerular damage. In the majority of children with SRNS, light microscopy reveals focal segmental glomerulosclerosis (FSGS). Now that the single-gene causes of SRNS have been identified, we have a deeper understanding of this disease's pathogenesis.

Ubiquinone, also called coenzyme Q10 or CoQ10, is a lipid-soluble component of virtually all cell membranes and has multiple metabolic functions. Deficiency of CoQ10 (MIM 607426) has been associated with different clinical presentations including glomerular diseases that suggest genetic heterogeneity. Patients with all forms of CoQ10 deficiency have shown clinical improvements after initiating oral CoQ10 supplementation [2]. Primary CoQ10 deficiency is a rare but significant causative element in SRNS owing to it being the only treatable mitochondrial disorder. CoQ10deficiency involves various mutations in different genes. Mutations in several genes including PDSS1, PDSS2, COQ2, COQ4, COQ6, ADCK3, ADCK4, and COQ9 have been associated with CoQ10 deficiency. Onset can be at any age, but pediatric forms are more common. Symptoms include those typical of respiratory chain disorders (encephalomyopathy, ataxia, lactic acidosis, deafness, retinitis pigmentosa, hypertrophic cardiomyopathy), but some (such as steroid-resistant nephrotic syndrome) are peculiar to this condition [3].

Heeringa et al. reported ubiquinone deficiency related to COQ6 mutations in five Turkish and Lebanese families with SRNS and sensorineural deafness [4].

This paper reports the case of two Turkish siblings with renal impairment, sensorineural deafness, and optic atrophy exhibiting COQ6 mutation. We sought to assess the efficacy of oral ubiquinone therapy in these patients.

Case Reports

Patient 1

Patient 1 was the second child of a consanguineous Turkish couple, a boy born after a term pregnancy with normal delivery. No significant events were found in the family history. ESRF was diagnosed when the patient presented with asthenia, vomiting, and high blood pressure at 5 years old. Renal ultrasonography revealed normal-sized kidneys with hyperechogenic cortex and normal renal Doppler imaging results. Renal biopsy detected lesions of pan nephritis with generalized glomerular fibrosis and skin biopsy revealed normal expression of the type IV collagen alpha chain. The patient started peritoneal dialysis immediately following diagnosis and underwent successful renal transplantation at 6 years old. He received immunosuppressive treatment with corticosteroids, azathioprine, and cyclosporine following anti-lymphocyte serum administration. The short-term evolution of transplantation was characterized by a primary cytomegalovirus infection. The long-term outcome was good, with no rejection. In addition, this child presented with bilateral sensorineural deafness, diagnosed at 6 years old on account of his delay in language acquisition. Audiogram revealed a severe perception deficit in the high frequencies. Ocular examination, by means of slit lamp, visual acuity, and fund us tests, was normal. The patient additionally exhibited normal psycho motor development.

At the age of 17, he complained of sudden visual loss. Ocular examination revealed bilateral papilledema and a visual acuity (VA) of 20/200for the right eye and 20/50for the left (Figure 1). Optical Coherence Tomography (OCT), associated with an analysis of the Retinal Nerve Fiber Layer (RNFL) thickness, confirmed the existence of a bilateral papilledema. Inflammatory and infectious etiologies were all ruled out. We conducted Magnetic Resonance Imaging (MRI) of the brain and visual pathways, along with cerebral scan angiography, both coming back as negative for vasculitis lesions. Given the patient's severe ocular involvement, and pending results, steroid therapy was initiated. The patient received four intravenous boluses of methyl prednisolone (1g/1.73m^2) then replaced with oral corticosteroids at 1mg/kg/day for 10 days. Despite a slight decrease in papilledema, bilateral VA showed no improvement. The poor response to steroid treatment led us to suspect Leber's hereditary optic neuropathy. No mutation was found in the mitochondrial DNA. Exploration of the mitochondrial respiratory chain on the muscular biopsy was normal, including the combined activities of complexes I+III and II+III. Because of the ethnical background and the association of renal and sensorineural symptoms we asked for molecular study of COQ6 gene. Genetical analysis detected a missense mutation in the homozygous state in exon 9 of the COQ6 gene (c.1058 C>A [pA353D]), the same mutation that was described by Heeringa et al. in three patients from two Turkish families [4].

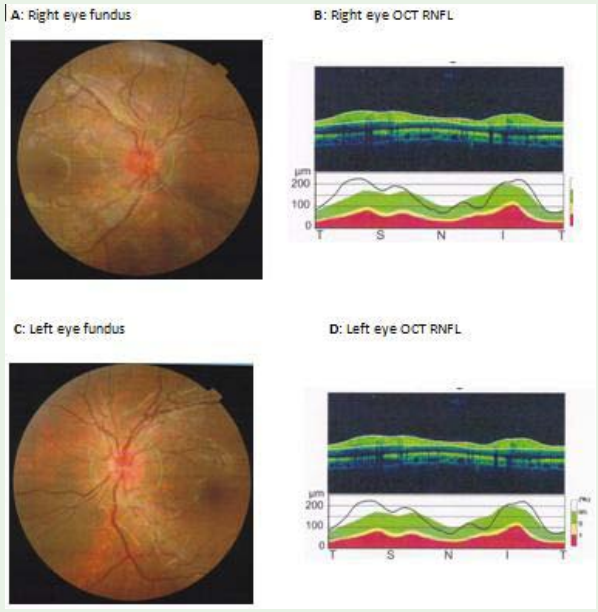

Figure 1: Ocular examination in patient 1 before COQ 10 supplementation. (A and C) Eye fundus. (B and D) Ocular Coherence Tomography (OCT) associated with an analysis of the Retinal Nerve Fiber Layer (RNFL). Bilateral papilledema.

Supplement treatment with Idebenone (Coenzyme Q10) was started 3 months after the onset of ocular symptoms. We administered 15mg/kg/day in three divided doses. Prior to initiating Ibedenone, the VA was still unchanged, recorded at 20/100for the right eye and 20/50for the left. Ocular examination revealed a persistent slight papilledema without optic atrophy. Goldmann visual field examination revealed a central scotoma. After 2 months of treatment, we observed an improvement in the VA, increasing to 20/32for the right eye and 20/32 for the left. Optical examination revealed the papilledema to have disappeared, with onset of optic atrophy (Figure 2). This optic atrophy was the result of the initial optic nerve fiber impairment. The central scotoma was still present in the visual field. After 13 months of treatment, when the patient was 18 years old, the ocular examination was stable. The patient did not recover normal vision, still exhibiting a bilateral VA of 20/32 and persistent optic atrophy. Goldmann visual field exam revealed the central scotoma to have disappeared and a new manifestation of small paracentral scotomas. Ocular examination performed after two years of treatment demonstrated an improved VA at 20/20 for the right eye and 20/25 +for the left. And after three years of treatment the VA was stable at 20/25 + for both eyes with mild optic atrophy (Figure 3). The deafness status had not changed since treatment initiation. Renal function

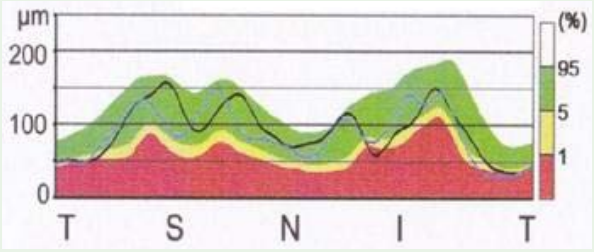

Figure 2: Ocular examination in patient 1 after 2 months of COQ 10 supplementation. Ocular Coherence Tomography (OCT) associated with an analysis of the retinal nerve fiber layer (RNFL), right eye. Papilledema disappeared with onset of optic atrophy.

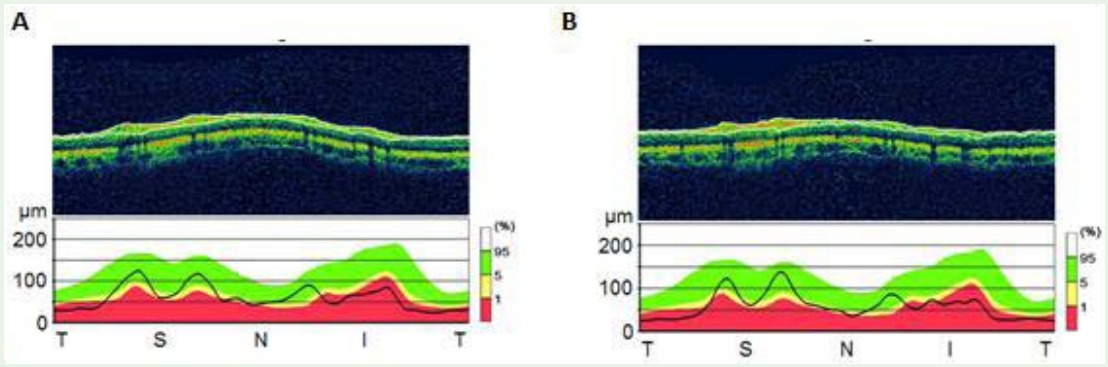

Figure 3: Ocular examination in patient 1 after 36 months of COQ 10 supplementation. Ocular coherence tomography (OCT) associated with an analysis of the Retinal Nerve Fiber Layer (RNFL). (A) Right eye. (B) Left eye. Minimal optic atrophy.

remained stable and the neurological examination was still normal. No treatment side effects were observed. At the time of writing, the patient was looking for employment.

Patient 2

Patient 2, the little brother of patient 1, was born after a term pregnancy and normal delivery. Psychomotor development and growth were normal. Bilateral sensorineural deafness was diagnosed at the age of 4, requiring specific equipment at 6.Given the patient's development of deafness and family history, his renal function was closely monitored. Non-nephrotic glomerular proteinuria revealed at 5 years old justifying initiation of Angiotensin-Converting Enzyme (ACE) inhibitor treatment (Enalapril). Although treatment compliance was good, proteinuria reached a nephrotic range. His NS was resistant to steroids, indicating a course of prednisone. Renal biopsy revealed FSGS, and skin biopsy was normal. The anti-proteinuric treatment, enhanced by increasing the Enalapril associated with angiotensin receptor antagonists (Losartan) and diuretics (hydrochlorothiazide), resulted in complete remission of the NS. At the time of publishing, the anti-proteinuric treatment relies on Enalapril and Losartan. The patient exhibits normal psychomotor development and follows a normal school curriculum. Genetic analysis of patient 1 revealed primary Coenzyme Q10 deficiency caused by a COQ6 mutation. Resulting from this finding, the genetic analysis found the same homozygous mutation in patient 2. COQ6mutation was present in the patients' healthy parents and sister in the heterozygous state. Following this, anocular examination was performed in the patients' healthy parents and sister, revealing no abnormalities. The patient was started on Idebenone treatment at 10mg/kg/day at 7 years old. After 13 months of treatment, hearing loss was unchanged. Renal involvement remained stable and, proteinuria was negative. He presented no new symptoms, notably neither ophthalmological nor neurological.

Discussion

In this study, we report on the cases of two brothers from a consanguineous Turkish couple who both presented a primary CoQ10 deficiency caused by a COQ6 mutation. They presented with SRNS, bilateral sensorineural deafness, and ocular involvement, consisting of optic neuropathy in patient 1. CoQ10 supplement appeared to be effective in resolving ocular impairment.

CoQ10, also known as ubiquinone, is an essential component of the mitochondrial electron transport chain and one of the most potent lipophilic antioxidants. CoQ10 operates as a redox carrier in the mitochondrial respiratory chain, shuttling electrons from respiratory chain complexes I (NADPH dehydrogenase) and II (succinate dehydrogenase) to complex III (ubiquinol cytochrome-c reductase). CoQ10 has also been implicated in the inhibition of apoptosis by its prevention of inner mitochondrial membrane collapse [5,6].

The biochemical pathway of CoQ10 biosynthesis is complex and has yet to be fully elucidated, though we know that it requires at least 13 genes. Mutations in these genes cause primary CoQ10 deficiency, with ubiquinone biosynthetic gene mutations not only causing CoQ10 deficiency but also having been implicated in monogenic mitochondriopathy [5-7].

CoQ10 deficiency is a biochemical occurrence that was first described in 1989 and has since been associated with a wide variety of clinical phenotypes [8]. Primary deficiencies are highly heterogeneous, both clinically and genetically, and are usually transmitted as autosomal recessive traits. Primary CoQ10 deficiency is generally characterized by clinical symptoms involving the central nervous system, skeletal muscle, and peripheral nerves [9-11], with renal impairment being the primary complication in certain subtypes. COQ2, COQ6, PDSS2, and ADCK4 mutations are responsible for SRNS, associated with different extra-renal disorders depending on the gene mutated [4,6,9-16] (Table 1). COQ9 mutations are responsible for renal tubulopathy with extra renal manifestations [7]. Some cases of isolated SRNS have been described in patients with COQ2 and ADCK4 mutations [6,10,11,13,16]. The link between CoQ10 and renal disease was first established in 2000 by Rotig et al. when three siblings were diagnosed with a complex clinical syndrome characterized by progressive encephalomyopathy and SRNS. At this time, the mutation was unknown [17].

COQ2mutation-related nephropathy was the first to be described, reported in 2005. Individuals with COQ2 mutations presented with phenotypes ranging from isolated NS to neonatal multisystem disorder with encephalomyopathy and renal involvement, as well as a recently described case of multiple-system atrophy. Most affected individuals exhibit seizures, motor or mental retardation or hypotonia, optic atrophy, and SRNS. To date, COQ2 mutations have been identified in 14 patients from nine different families. Five underwent kidney

biopsy, which revealed focal segmental glomerulosclerosis for three and a collapsing glomerulopathy for the remaining two [6,10-14,18-20] (Table 1).

In addition, PDSS2 mutations have also been implicated in monogenic SRNS. The patients described in 2000 by Rotig et al. were affected by a PDSS2 mutation [17,21]. Moreover, Lopez et al. reported a child with PDSS2 mutation who developed Leigh syndrome with drug-resistant seizures, SRNS, and cortical blindness [15].

In 2009, Duncan et al. reported in a young boy, mutations of another gene, CoQ9, required for the biosynthesis of CoQ10. He presented with cardiomyopathy, renal tubulopathy, and neurological symptoms, later developing severe seizures and dying at two years old [7].

Furthermore, autosomal recessive COQ6 mutations have recently been identified in 11 individuals from five Lebanese and Turkish families [4]. This gene encodes monooxygenase-6. Coenzyme Q10 monooxygenase 6 (COQ6) is required for the biosynthesis of Coenzyme Q10 and is thought to catalyze one or more ring hydroxylation steps. All 11 affected individuals presented with SRNS. They each exhibited proteinuria at a median age of 1.2 years (range: 0.2-6.4 years) and had all progressed to ESRF by a median age of 1.7 years (range: 0.4-9.3 years), with five dying in early childhood (median age: 5.0 years). Renal biopsy revealed FSGS in seven cases and diffuses mesangial sclerosis in one. One patient presented with seizures, another exhibited white matter abnormalities and seizures and died of multi-organ failure in sepsis, and two other individuals exhibited ataxia and facial dimorphisms. Nine of the 11 patients had sensorineural deafness. The COQ6 mutations carried by our patients had already been described by Heeringa et al. in Turkish families, and the renal presentation and deafness we observed were similar to those of that study. However, our study's two brothers had still not developed neurological involvement at the ages of 18 and8 years, respectively. Also, unlike our patient, none of the patients of the Heeringa cohort presented with optic atrophy. The ophthalmic symptoms of our patient appeared late, however; ten years after the deafness and ESRF, and the Heeringa study involved only short-term follow up. Our study therefore illustrates the clinical heterogeneity of primary CoQ10 deficiency.

In a more recent study conducted in 2013, Ashraf et al. identified recessive mutations in ADCK4 that cause primary Coenzyme Q10 deficiency. This is a novel single-gene cause of SRNS. All 15 affected individuals of the eight families studied exhibited SRNS. All manifested with proteinuria at a median age of 16 years (range: <1-21 years) and progressed to ESRF by a median age of 15.3 years (range: 7-23 years). Renal biopsy revealed FSGS in most cases and one patient manifested neurological involvement with psychomotor retardation [16].

Table 1: Renal, extra-renal involvement and response after treatment in primary coenzyme Q10 deficiency in literature.

Gene	Cases(family)	Clinical symptoms	Renal histology	Outcome after or without CoQ10 treatment	Ref
PDSS2	3 (1)	NS,encephalopathy,optic atrophy,sensorineural deafness, hypertrophic cardiomyopathy	ND	2 patients treated with neurological and ophthalmic improvement 1 patient died without treatment at 8 months	[15]
PDSS2	1 (1)	NS,seizures,hypotonia	ND	Treated, died at 8 months	[13]
COQ2	2 (1)	Isolated SRNS for the sister SRNS, mild psychomotor delay, optic atrophy for the brother	FSGS	2 patients treated with recovery of renal function, decreased of proteinuriafor the sister; neurological improvement but renal transplant at 3 years for the brother	8-Sep
COQ2	2 (2)	Isolated SRNS for the first patient NS, encephalopathy, respiratory failure for the second	Collapsing glomerulopathy	First patient was treated and remained stable Second patient died without treatment at 6 months	[11]
COQ2	2 (1)	NS,liver failure,seizures,pancytopenia, insulin-dependent diabetes	ND	Died at 1 and 12 days without treatment	[10]
COQ2	2 (1)	Respiratory failure seizures,hypotonia	ND	Died at 5 and 6 months without treatment	[16]
COQ2	4 (2)	Multiple-system atrophy,retinitis Pigmentosa	ND	2 patients alive without treatment, 2 patients died without treatment	[17]
COQ2	1 (1)	NS, Myoclonic epilepsy, hypertrophic cardiomyopathy	FSGS	Treated, died at 5 months	[12]
COQ2	1(1)	Hypertrophic cardiomyopathy, encephalopathy,respiratory failure	ND	Died at 2 months without treatment	[18]
COQ9	1 (1)	Renal tubulopathy, cardiomyopathy, neurological impairment	ND	Treated, died at 2 years	5[]
ADCK4	15 (8)	SRNS , developmental delay for one patient	FSGS	1 patient treated with decreased of proteinuria	[14]
COQ6	11 (5)	SRNS, sensorineural deafness, neurological impairment	FSGS, DMS	3 patients treated with decreased of proteinuria or deafness improvement	[2]
COQ6	2 (1)	SRNS, sensorineural deafness and optic atrophy for one patient	FSGS	Both treated, ophthalmic improvement	Our Case reports

ADCK4: aarF domain containing kinase 4; COQ2: coenzyme Q2 4-hydroxybenzoate polyprenyltransferase; COQ9: Ubiquinone bisynthesis protein coenzyme Q9; COQ6: coenzyme Q 10 biosynthesis monooxygenase 6; DMS: diffuse mesangialsclerosis; FSGS: focal segmental glomerulosclerosis; ND: no data available; NS: néphrotic syndrome; PDSS2: prenyl (decaprenyl) diphosphate synthase subunit 2; Ref: references; SRNS: steroid resistan nephrotic syndrome.

While most forms of monogenic childhood NS are characterized by a lack of response to therapy, some symptoms of primary CoQ10 deficiencies can respond to specific therapy. No evidence-based study regarding dosage has yet been performed, however, and most patients receive empirical doses of CoQ10 ranging from 5 to 30mg/kg per day [6,9,22-24]. Furthermore, no information on the pharmacokinetics of CoQ10 in CoQ10-deficient patients is currently available.

Response to replacement therapy is variable in primary CoQ10 deficiency. Many patients with encephalomyopathy have been shown to respond to CoQ10 supplement, demonstrating significant improvement in neurological symptoms [9,23,25,26]. Response to CoQ10 therapy in patients with SRNS is, however, highly variable (Table 1).

Some studies have reported no positive change in symptoms following oral CoQ10 supplementation. Scalais et al. described a patient with COQ2 mutation who presented with hypertrophic cardiomyopathy, epilepsy and nephrotic syndrome. Despite receiving Coenzyme Q10 supplement, administered at 30/mg/kg/day, the patient passed away at 5 months old (14). One patient with PDSS2 mutation-related deficiency with SRNS and drug-resistant seizures received oral CoQ10 supplement and died at 8 months old [15]. The individual with COQ9 mutation was treated with CoQ10 supplement at 300mg/day and died at two years of age [7].

Rotig et al. were the first to report a family in which CoQ10 deficiency caused by PDSS2 mutation responded to CoQ10 supplement, their study involving three affected siblings [17,21]. Two siblings developed bilateral sensorineural deafness, ocular and neurological symptoms, and NS resulting in terminal renal failure and required transplantation. The third sibling had a more severe disease course and died at 8 years old following rapid neurological deterioration. The two surviving children were treated with oral CoQ10 5mg/kg per day, which resulted in substantial improvement in their neurological and ophthalmic conditions. The treatment did not, however, improve their renal function, perhaps owing to the patients already having advanced kidney disease.

In 2005, Salvati et al. described another family with CoQ10 deficiency caused by COQ2 mutation, presenting with infantile encephalomyopathy and nephropathy. The boy exhibited encephalomyopathy, optic atrophy, and SRNS. After receiving CoQ10 supplement at 22 months old, the child's neurological manifestations improved dramatically, though there was no change in renal function owing to an already-advanced chronic renal failure. He underwent renal transplantation at 3 years old. His sister presented with SRNS without neurological symptoms. After three weeks of CoQ10 supplement at 30mg/kg per day, her proteinuria levels were reduced and renal function recovered. No neurological impairment appeared. Early administration of CoQ10 was a crucial factor in the resolution of renal symptoms and preventing neurological damage in this patient [10,11].

Diomedi-Camassei et al. reported the case of an 18-month-old boy with severe SRNS resulting in terminal renal failure. His neurological examination remained completely normal when receiving CoQ10 supplement (30mg/kg/day) for 8 months of follow up [13].

Only one individual with ADCK4 mutation, presenting with renal and neurological impairment, has been treated with oral CoQ10 (15mg/kg/day) for over 4 years. This treatment resulted in significantly decreased proteinuria [16].

Regarding the patients with COQ6 mutation in Heeringa et al. cohort, three received oral CoQ10 replacement therapy. The first patient was treated at 2 months old with CoQ10 at 30mg/kg/day, associated with ACE inhibitors, while exhibiting non-nephrotic proteinuria. After 13 months of treatment, we noted a decrease in proteinuria and return to normal renal function, yet an onset of deafness at 10 months old. For the second patient, his sister, who presented with bilateral deafness and ESRF, CoQ10 treatment consisting of 100mg per day resulted in a substantial improvement of her deafness. The third patient exhibited bilateral deafness and SRNS, with cyclosporin a treatment inducing partial remission. After two months of treatment with CoQ10, his proteinuria levels decreased but hearing was not improved [4].

Given the previous reports of successful CoQ10 treatment, we administered CoQ10 in both of our patients. CoQ10 supplement was given at 15mg/kg/day in patient 1, resulting in an improvement in his ophthalmic impairment. After 2 months of CoQ10 replacement therapy, his VA improved, though ocular examination revealed a bilateral optic atrophy probably caused by bilateral papilledema. After 13 months of supplement, ocular results remained stable, and after 36 months VA was found to have improved, with minimal optic atrophy. CoQ10 supplement did not, however, improve the hearing loss. Renal function remained stable and the neurological findings were unchanged throughout. Patient 2 had received CoQ10 supplement since 24 months. No change in hearing loss was observed, the proteinuria was still negative, and the renal function remained stable. Replacement therapy could potentially prevent optic nerve and renal disease in this patient, along with other symptoms in both patients, such as neurological disorders.

Conclusion

In conclusion, CoQ10 deficiency caused by COQ6 mutations is a rare cause of SRNS with variable neurological, renal, hearing, and ocular impairment. CoQ10 deficiencies are clinically and genetically heterogeneous diseases. Mitochondrial dysfunction secondary to CoQ10 deficiency should always be suspected and investigated in patients with SRNS and extra-renal symptoms. Early recognition of this genetic entity of SRNS is a crucial diagnostic tool, as this rare disorder can be successfully treated by CoQ10 supplement. All cases of primary CoQ10 deficiency should be treated at an early stage to limit the progression of lesions and prevent the emergence of new symptoms.

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