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Retinopathy and Optic Atrophy in a Case of *COQ2*-related Primary Coenzyme Q10 Deficiency

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Abstract

Purpose: To describe a case of primary coenzyme Q_{10} deficiency in a child manifesting as early-onset renal failure, retinal dystrophy, and optic atrophy leading to progressive vision loss.

Methods: Clinical presentation and workup including visual fields, electroretinogram, and optical coherence tomography are presented. Genetic testing was performed.

Results: An eight-year-old female with nephropathy requiring renal transplantation subsequently developed progressive cone-rod dystrophy and optic atrophy. The patient had negative results on a targeted next-generation sequencing retinal dystrophy panel but whole-exome sequencing revealed two variants in *COQ2* (likely biallelic), consistent with a diagnosis of primary coenzyme Q_{10} deficiency.

Conclusions: Primary coenzyme Q_{10} deficiency is a rare disorder with variable systemic and ocular findings; there is also genetic heterogeneity. Genetic testing aids in the diagnosis of this condition, and variants in the *COQ2* and *PDSS1* genes appear to have the strongest association with ocular manifestations. Oral supplementation of coenzyme Q_{10} may slow progression of disease. This case highlights the utility of whole-exome sequencing in the diagnosis of a rare syndromic form of ocular disease and reports a novel phenotypic association for this condition.

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Patient Consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

Keywords

Primary coenzyme Q_{10} deficiency; Cone-rod retinal dystrophy; Optic atrophy; Whole-exome genetic sequencing

Introduction

Primary coenzyme Q_{10} (CoQ_{10}) deficiency is a genetic disorder of the mitochondrial respiratory chain inherited in an autosomal recessive fashion.[1] The systemic manifestations are widespread and involve neurologic, renal, and cardiac findings, reflecting the ubiquity of oxidative phosphorylation. The condition is also genetically heterogeneous with pathogenic variants in nine genes identified to date.[1] There are no formal diagnostic criteria and, as such, diagnosis generally relies on a high index of suspicion and subsequent genetic testing. Patients with primary CoQ_{10} deficiency may also present with retinal dystrophy and, occasionally, optic atrophy, although reports of these are limited in number.[2–7] We report a case of a child with progressive vision loss due to cone-rod retinal dystrophy and optic atrophy of both eyes confirmed to have primary CoQ_{10} deficiency on whole-exome sequencing.

Case Report

An eight-year-old female with best-corrected visual acuity (BCVA) of 20/40 in both eyes (OU) one year prior to presentation developed decreased vision in both eyes over six months. The patient was born healthy after an uncomplicated full-term pregnancy but developed focal segmental glomerulonephritis at age two thought to be due to minimal change disease and C1q nephropathy. She subsequently developed renal failure, requiring kidney transplantation at age three. Past medical history was additionally significant for attention deficit hyperactivity disorder, dyslexia, and short stature. Family history was noncontributory.

BCVA was 20/250 in the right eye (OD) and 20/150 in the left eye (OS) with normal intraocular pressures and no relative afferent pupillary defect. The patient identified 3 of 14 Ishihara color plates OD and 2 of 14 OS. Confrontation visual fields were full, but Goldmann visual fields showed an incomplete midperipheral scotoma OS; there was asymmetric constriction to the I4e target with enlargement of the physiological blind spot in each eye (Figure 1). Slit lamp examination was unremarkable, but dilated fundus examination revealed moderate optic nerve pallor and vascular attenuation OU with a subtle bull’s eye pattern of retinal pigmentary changes (Figure 2A–B).

Macular optical coherence tomography (OCT) revealed parafoveal intraretinal cysts overlying ellipsoid zone loss in a bull’s eye pattern OU (Figure 3A), while optic nerve OCT scans showed diffuse retinal nerve fiber layer thinning, worse OD than OS (Figure 3B). An awake electroretinogram was performed (according to International Society for Clinical Electrophysiology of Vision standard using Burian-Allen bipolar contact lens electrodes), which showed moderate cone greater than rod dysfunction bilaterally (Figure 4A–B). Magnetic resonance imaging of the brain and orbits, performed at an outside facility,

was normal by report. Next-generation sequencing was performed with a targeted 285-gene retinal dystrophy panel (Blueprint Genetics, Espoo, Finland, through the My Retina Tracker Institutional Review Board-approved protocol) and was non-diagnostic.

Over the course of 20 months, the patient's BCVA progressively declined to 20/400 OD. BCVA OS remained stable. She additionally exhibited progressive optic nerve atrophy on exam and OCT. Whole-exome sequencing was performed as a clinical test approximately 1.5 years after initial presentation and uncovered two variants in *COQ2* (NCBI Ref Seq ID: NM_015697.7, OMIM: 609825). The first variant, c.683A>G, was a maternally-inherited, rare (gnomAD allele frequency: 0.01%)[8] missense substitution (p.Asn228Ser) that has multiple lines of evidence supporting pathogenicity.[9–12] As a result, it was classified as likely pathogenic by the reference laboratory (see ClinVar Entry: VCV000001439.5 for additional details).[13] The second variant detected, c.518 G>A, was a similarly rare (gnomAD allele frequency: 0.01%)[8] missense substitution (p.Arg173His) with some evidence supporting pathogenicity.[14, 15] However, it was classified as a variant of unknown significance by the testing laboratory given that it has never been definitively detected in *trans* with a pathogenic variant. The c.518 G>A variant was not detected in the patient's mother, but the father was unavailable for testing. Given that the variant segregates in the general population,[8] it was most likely inherited from the patient's father rather than occurring *de novo*. This indicates that the patient is likely compound heterozygous for two rare, missense variants in *COQ2*.

Given these genetic findings coupled with strong phenotypic overlap, the patient was diagnosed with primary CoQ_{10} deficiency. Additional diagnostic testing was considered, specifically muscle biopsy and measurement of CoQ_{10} concentration plus mitochondrial respiratory chain activity levels.[16, 17] However, the patient's biochemical screening labs (serum lactate, acylcarnitine profile, plasma amino acids, and urine organic acids) were normal, and she lacked systemic findings typical for a mitochondrial myopathy. As a result, the sensitivity of this invasive testing was uncertain, and a negative/inconclusive result was unlikely to change clinical management. Therefore, muscle biopsy was deferred for now. Of note, serum CoQ_{10} levels are not reflective of intracellular concentrations and thus have very limited utility in diagnosing primary CoQ_{10} deficiency (our patient's serum CoQ_{10} was normal).[16] Given the presumed diagnosis, oral supplementation with CoQ_{10} was initiated, with stability of ocular findings over the following six months. The patient was evaluated by neurology and cardiac specialists and found to have no additional systemic pathology.

Discussion

We report a case of primary CoQ10 deficiency characterized by nephropathy, progressive cone-rod dystrophy, and optic atrophy associated with biallelic variants in the *COQ2* gene (c.683A>G, c.518G>A).

CoQ_{10} plays a key role in the oxidative phosphorylation pathway of the mitochondrial respiratory chain, primarily acting to transfer reducing equivalents but also serving as a transmembrane hydrogen carrier and antioxidant.[1] The *CoQ2* gene encodes the enzyme involved in the second step of CoQ10 biosynthesis.[3, 18] To date, pathogenic variants in

the genes *COQ2–9* and *PDSS1–2*, all of which encode proteins involved in the direct biosynthesis of CoQ_{10}, have been identified as a cause for primary CoQ_{10} deficiency.[1]

Primary CoQ_{10} deficiency is associated with a wide range of clinical phenotypes. The systemic hallmark is steroid-resistant nephrotic syndrome presenting with proteinuria in early childhood; left untreated, this condition usually progresses to end-stage renal disease requiring kidney transplantation.[7] Neurologic findings are common but vary widely and range from severe encephalomyopathy (similar to multiple-systemic atrophy) to mild intellectual disability.[6] Other systemic manifestations, reported to occur on a more variable basis, include hypertrophic cardiomyopathy, muscle weakness, and sensorineural hearing loss.[1]

Few reports of eye findings in primary CoQ_{10} deficiency describe retinopathy and optic atrophy as the primary ocular manifestations (Supplementary Table 1). Retinopathy is more commonly reported, and often appears similar to retinitis pigmentosa with abnormal rod greater than cone function.[4, 5, 19] In a case report of primary CoQ_{10} deficiency caused by variants in the *COQ2* gene, all three affected siblings demonstrated extensive intraretinal pigment migration in the periphery and encircling the posterior poles with rod-cone dysfunction and undetectable scotopic responses.[7] All cases of retinopathy in primary CoQ_{10} deficiency have been reported in the setting of mutations in the *COQ2* gene, although none of these reported cases were associated with the pathogenic variants identified in the current case.[5–7] In general, reports of *COQ2*-related CoQ_{10} deficiency are rare; of these, only a handful of patients have been reported to have associated retinopathy since *COQ2* was identified as the first gene associated with primary CoQ_{10} deficiency in 2006.[5–7, 18, 20]

Optic atrophy may occur in conjunction with the retinopathy associated with biallelic variants in *COQ2*,[6, 7] as described in our present case, or it may occur in the absence of retinal pathology, such as in cases of primary CoQ_{10} deficiency due to variants in *PDSS1*.[2, 3] However, because precise molecular diagnosis is a relatively recent development, older case reports do not describe the exact genetic cause. Note, onset of vision loss is variable and reported to range from infancy, presenting as nystagmus, to young adulthood.[5, 6]

While the c.683A>G variant has strong evidence supporting pathogenicity, its implication in cases with ophthalmic manifestations is more rare.[9–12] Diomedi-Camassei et al. report a case of a child with the c.683A>G variant but do not report the presence of retinal disease or optic atrophy.[9] The second variant implicated in the current case, c.518G>A, was recently reported in a case of isolated adult-onset retinitis pigmentosa with Leber hereditary optic neuropathy; notably, the patient lacked any systemic findings consistent with primary CoQ_{10} deficiency.[15] A patient with childhood onset nephropathy was reported to carry both the c.683A>G and c.518G>A variants identified in the current case; despite the same genotype, however, the patient was not reported to have any ocular pathology (although the patient was only two years old at the time of the report).[14] As such, this is the first report to implicate these two variants associated with retinal and optic nerve disease in the setting of primary CoQ10 deficiency with systemic findings.

The diagnosis of primary CoQ_{10} deficiency was historically established by enzymatic assessment of tissue: a reduction in CoQ_{10} concentration and mitochondrial respiratory chain activity levels have been documented.[3, 6] That said, the sensitivity and specificity of such testing is uncertain [PMID: 29781757], particularly in patients that lack systemic findings consistent with severe mitochondrial dysfunction.[17] Therefore, the advent of genetic testing has greatly improved ease and accessibility of diagnosis. Whole-exome sequencing, in particular, facilitates the diagnosis of this rare condition that is not routinely assessed on targeted gene sequencing panels. Early diagnosis is important, as supplementation with oral CoQ_{10} has been reported to improve encephalomyopathy and rarely nephropathy, with the suggestion that earlier treatment may be of greater benefit.[4, 6, 21] In the previously mentioned case report by Abdelhakim and colleagues, treatment with CoQ_{10} over six months did not improve ERG findings in all three siblings; however, BCVA and areas of retinal atrophy remained stable, suggesting treatment may aid in slowing progression of ocular disease.[7]

The differential diagnosis for child presenting with steroid-resistant nephropathy, retinopathy, and optic atrophy includes AVIL-related nephrotic syndrome although optic atrophy has not been reported in this condition.[22] Additionally, Pierson syndrome may be considered although in addition to retinal changes, the ocular phenotype encompasses significant anterior segmental abnormalities of the cornea, lens, and ciliary body.[23] Given the limited understanding of the phenotypic diversity of these conditions, whole exome or genome sequencing ultimately provides timely and definitive diagnosis and improved characterization of disease.

Conclusions

We present a case of primary CoQ_{10} deficiency likely caused by biallelic variants in the *COQ2* gene. The patient's phenotype is characterized by steroid-resistant nephropathy, cone-rod retinal dystrophy, and optic atrophy with normal neurologic function. Primary CoQ_{10} deficiency should be considered in cases of retinal degeneration or optic nerve atrophy associated with classic systemic findings. The increased affordability and availability of whole-exome sequencing will facilitate this diagnosis and lead to prompt treatment of this rare condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Goldmann visual fields showed moderate constriction to the I4e isopter in the right eye and a paracentral scotoma to the I4b isopter in the left eye with enlargement of the physiological blind spot in each eye.

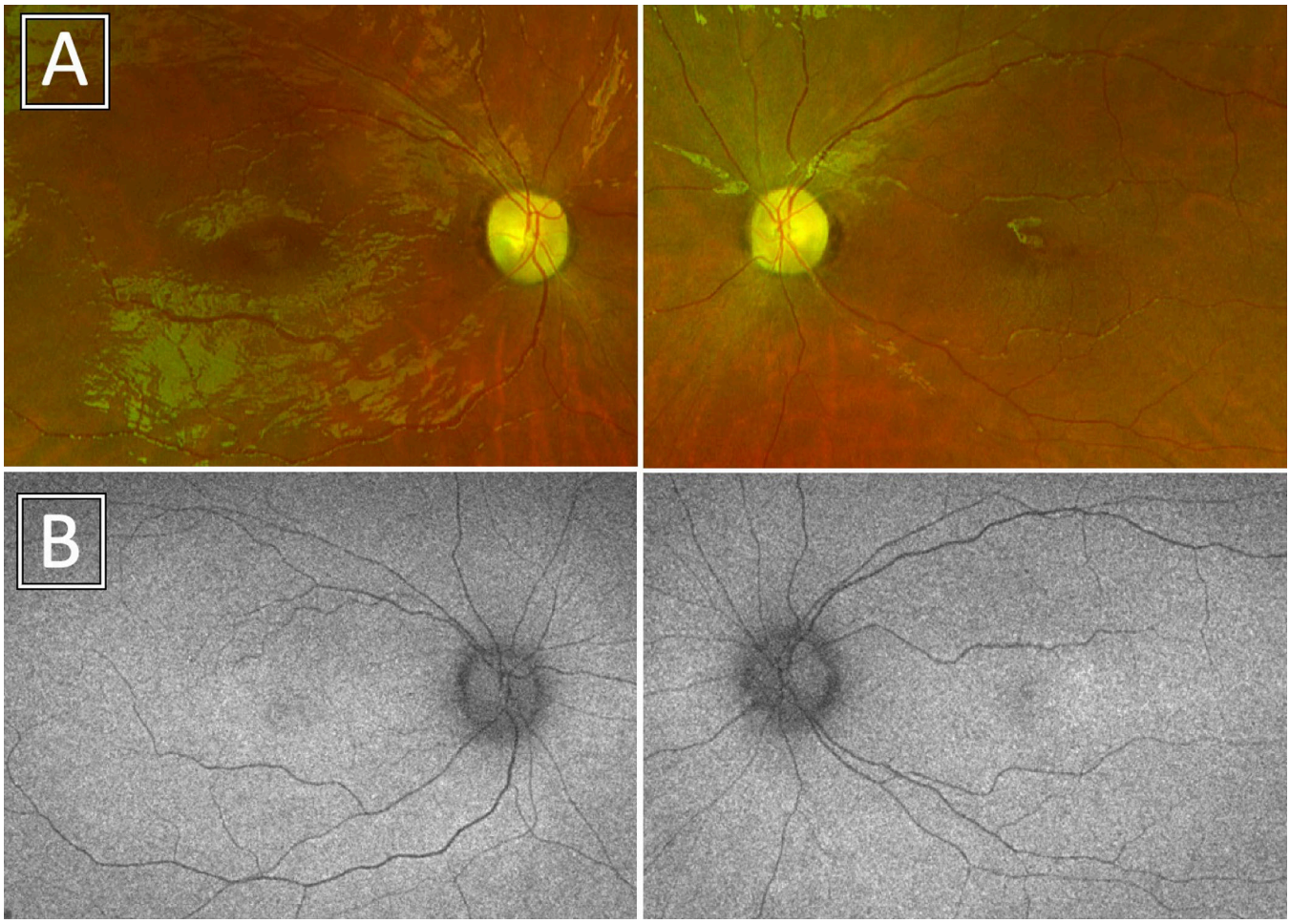

Figure 2A-B.

Ultrawidefield color (**A**) and fundus autofluorescence (**B**) photos demonstrated optic nerve pallor and vascular attenuation with a bull's eye maculopathy pattern in each eye.

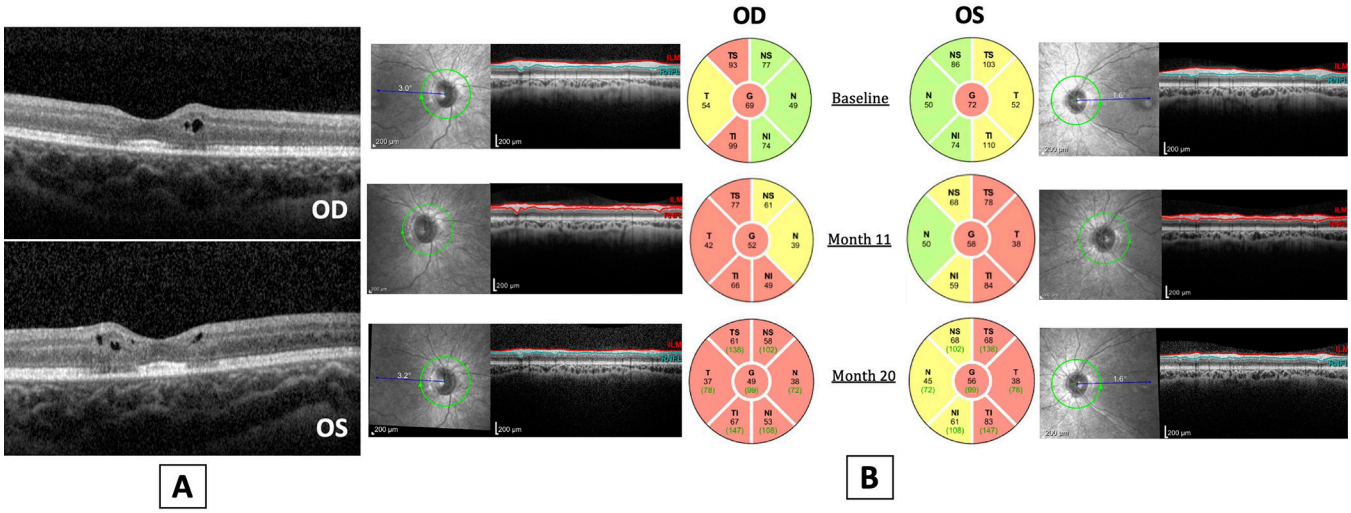

Figure 3.

A. Optical coherence tomography of the macula showed parafoveal intraretinal cysts overlying reduced reflectivity of the ellipsoid zone in a bull's eye pattern. **B.** OCT of the retinal nerve fiber layer over 20 months demonstrated progressive nerve fiber layer thinning, worse in the right eye than the left eye.

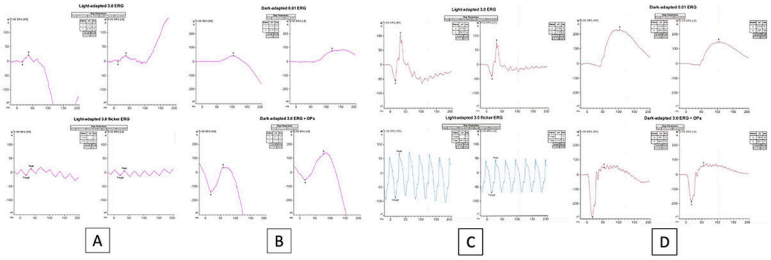

Figure 4A-D.

Full-field electroretinogram traces showed photopic (**4A**) greater than scotopic (**4B**) dysfunction, although blink artifact contaminated the scotopic responses making it impossible to assess scotopic function reliably in each eye. Photopic, cone-mediated responses were reduced by about 60% below the lower limits of normal in amplitude and delayed in timing in both eyes. A normal full-field electroretinogram is displayed in panels **4C** and **4D** for comparison.