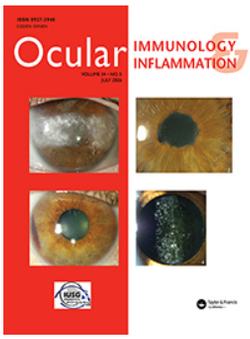

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BRIEF REPORT

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Atypical COQ2-Related Retinopathy in Identical Twins with Nephropathy Mimicking Intermediate Uveitis

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ABSTRACT

Purpose: To describe an atypical presentation of COQ2-related retinopathy in identical twins with nephropathy, mimicking intermediate uveitis with cystoid macular oedema (CMO).

Methods: Retrospective case report.

Results: A 33-year-old man presented with bilateral vision worsening and suspected intermediate uveitis. Examination revealed vitreous cells, CMO, retinal microangiopathy, and severely abnormal electrooculography (EOG) with only borderline full-field electroretinography (ERG) changes. CMO worsened with topical corticosteroids but improved bilaterally after a single unilateral intravitreal bevacizumab injection, suggesting a systemic therapeutic effect. His identical twin exhibited very similar retinal and systemic findings. Whole-exome sequencing identified a homozygous likely pathogenic COQ2 variant (c.683A > G), confirming primary coenzyme Q10 (CoQ10) deficiency type 1. Both twins also had nephropathy consistent with focal segmental glomerulosclerosis (FSGS) but no neurological involvement.

Conclusions: This report expands the phenotypic spectrum of COQ2-related retinopathy, characterized by retinal microangiopathy, CMO, and primary retinal pigment epithelium (RPE) dysfunction with preserved rod function, in contrast to the typical retinitis pigmentosa–like phenotype. Recognition of this presentation is critical, as early CoQ10 supplementation may stabilize disease progression and prevent systemic complications. Genetic testing should be considered in young patients with CMO resembling intermediate uveitis, particularly when associated with nephropathy.

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Coenzyme Q10 deficiency; COQ2; intermediate uveitis; nephropathy; retinopathy

Coenzyme Q10 (CoQ10), or ubiquinone, is a lipid-soluble molecule produced in the inner mitochondrial membrane of all tissues, with particularly high levels in organs with heavy energy demands—such as the liver, heart, kidneys, skeletal muscle, and eyes.[1] Primary CoQ10 deficiency is an inherited condition affecting the mitochondrial respiratory chain. Clinical manifestations include retinitis pigmentosa (RP), optic atrophy, sensorineural hearing loss, renal failure, hypertension, cardiomyopathy, and skeletal myopathy.[2] Ocular phenotypes have been reported due to pathogenic variants in CoQ10 biosynthesis genes such as *PDSS1*, *COQ2*, *COQ4*, and *COQ5*.[1] Inheritance is autosomal recessive, with disease resulting from biallelic pathogenic variants in CoQ10 biosynthesis genes. Clinically, *COQ2*-related disease most often presents with steroid-resistant nephrotic syndrome, encephalomyopathy, and/or an RP-like phenotype.[1,3,4] *COQ2*-related ocular phenotype presented with optic nerve atrophy and RP-like phenotype.[1,3,5,6] However, there is growing evidence of substantial phenotypic variability, including isolated renal or retinal involvement without neurological manifestations.[7] Here, we report identical twins harbouring a homozygous pathogenic *COQ2* variant who presented with vitreous inflammation, retinal vasculopathy, and cystoid macular oedema (CMO) in the absence of RP features, expanding the recognised phenotypic spectrum of *COQ2*-related retinopathy.

Case report

A 33-year-old male engineer was referred to a tertiary eye centre due to bilateral visual worsening and suspected intermediate uveitis. At presentation, the patient described progressive, slow bilateral vision decline that had gradually worsened over the past three years. Medical history was significant for nephropathy and well-controlled arterial hypertension; both diagnosed at age 13 and treated with perindopril. His identical twin had a similar medical history and was being monitored for presumed central serous chorioretinopathy by a community ophthalmologist. There was no known consanguinity, nor was there a family history of hereditary ocular or systemic disease.

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At presentation, best-corrected visual acuity (BCVA, Snellen) was 0.7 in the right eye and 0.8 in the left. The anterior segment examination was unremarkable, and both eyes presented with 1+ vitreous cells. Fundus examination revealed subtle macular oedema and retinal vascular attenuation with irregular telangiectatic capillaries. Fundus autofluorescence showed mild irregularities linked to the macular oedema, along with subtle, patchy, concentric relative hypo- and hyperautofluorescence with hypoautofluorescent lesions nasally (Figure 1). Indocyanine green angiography (ICGA) revealed normal choroidal vasculature, while fluorescein angiography (FA) demonstrated irregular capillary networks with peripheral dropout and diffuse late leakage (Figure 1). Goldmann perimetry revealed no significant visual field defect. Macular

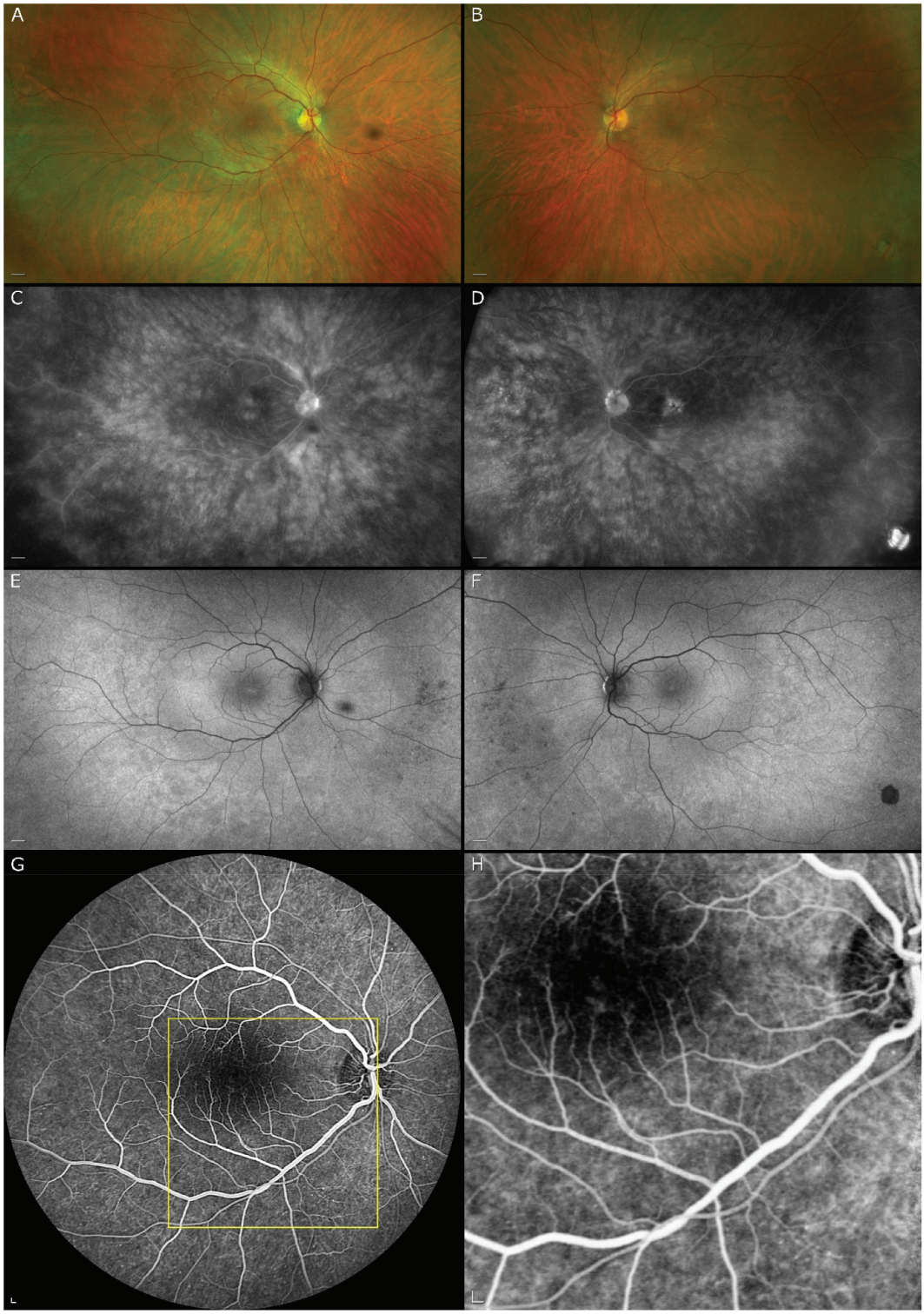

Figure 1. A, B: Fundus examination revealed subtle macular oedema, with no signs of optic atrophy or bone-spicule pigmentation; **c, D**: Fluorescein angiography (FA) showed mild diffuse late leakage. **e, F**: Fundus autofluorescence demonstrated concentric areas of relative hypo- and hyperautofluorescence, as well as hypoautofluorescent lesions nasally without significant rod–cone dystrophy changes. **g, H**: FA demonstrated irregular capillary networks.

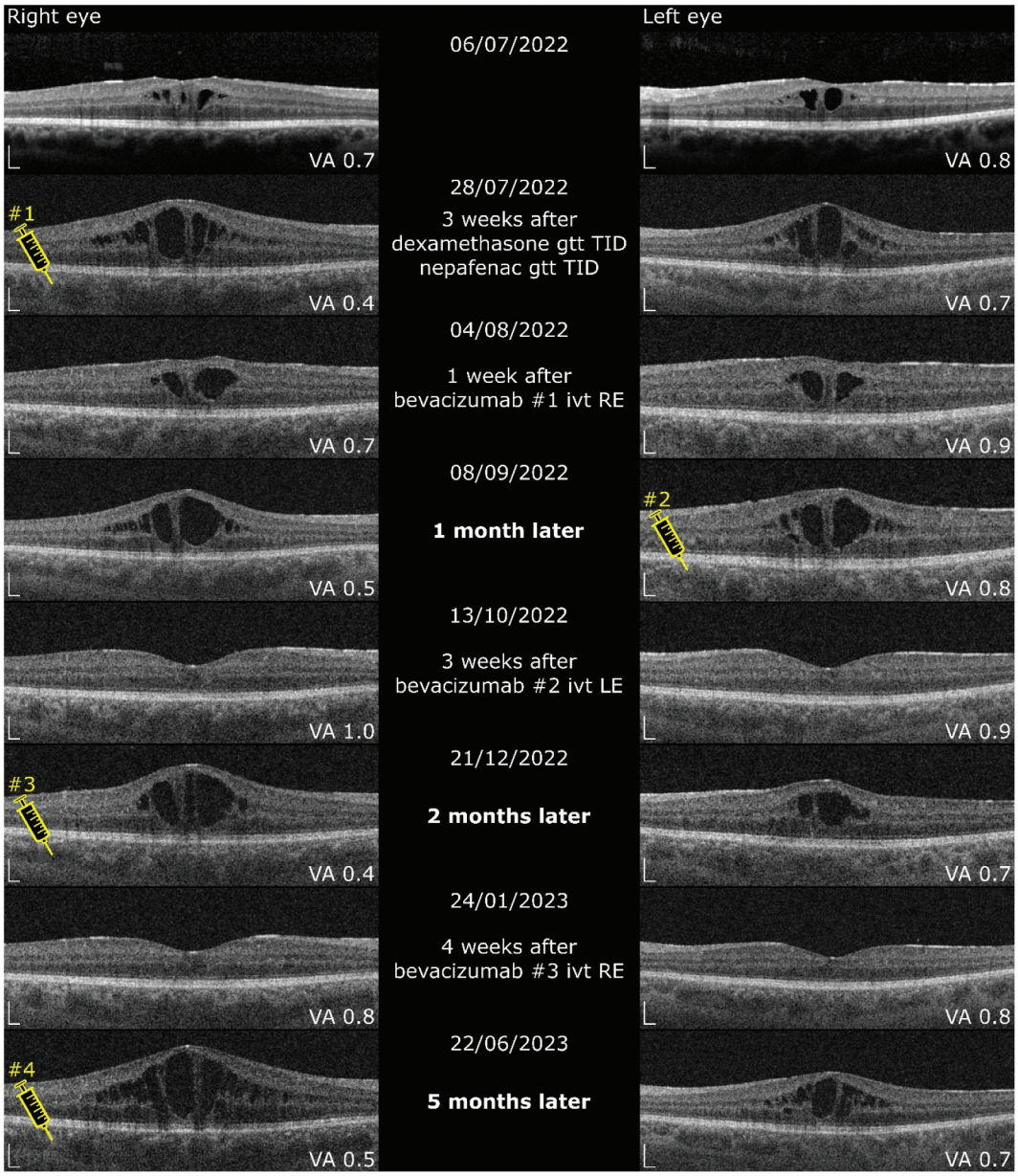

Figure 2. Changes and treatment of cystoid macular oedema during the follow-up period.

optical coherence tomography (OCT) demonstrated bilateral CMO with preserved outer retinal layers (Figure 2).

CMO was initially treated bilaterally with topical steroids and nonsteroidal anti-inflammatory drugs (NSAIDs); however, it worsened after three weeks, prompting discontinuation of the treatment. Unilateral intravitreal bevacizumab was subsequently administered, producing significant bilateral CMO reduction. Upon recurrence, contralateral injection resulted in complete bilateral CMO resolution. Treatment was continued on a *pro re nata* basis with intravitreal bevacizumab, followed by the addition of dorzolamide eye drops and later oral acetazolamide. However, the therapeutic efficacy of carbonic anhydrase inhibitors declined over time (Figure 2).

Electrophysiological assessment revealed findings consistent with predominant retinal pigment epithelium (RPE) dysfunction. Specifically, results included borderline reduced a-wave amplitudes in dark- and light-adapted full-field electroretinography (ERG), a normal pattern ERG, and a severely abnormal electro-oculogram (EOG) (Figure 3, Supplementary Table 1).

Due to unexplained nephropathy, the patient underwent kidney biopsy, which showed focal segmental glomerulosclerosis (FSGS) with 40% podocyte foot process effacement and swelling, pointing towards podocyte injury, but without true podocytopathy. There were signs of hypertensive nephrosclerosis due to known arterial hypertension as well. No signs of tubulointerstitial nephritis were present, excluding a uveitis-related mechanism.

Ophthalmic evaluation of the twin brother, including multimodal imaging and electrophysiology, yielded very similar clinical findings, ruling out the previous diagnosis of central serous chorioretinopathy. Whole-exome sequencing identified a homozygous variant in the *COQ2* (NM_015697.8: c.683A > G;

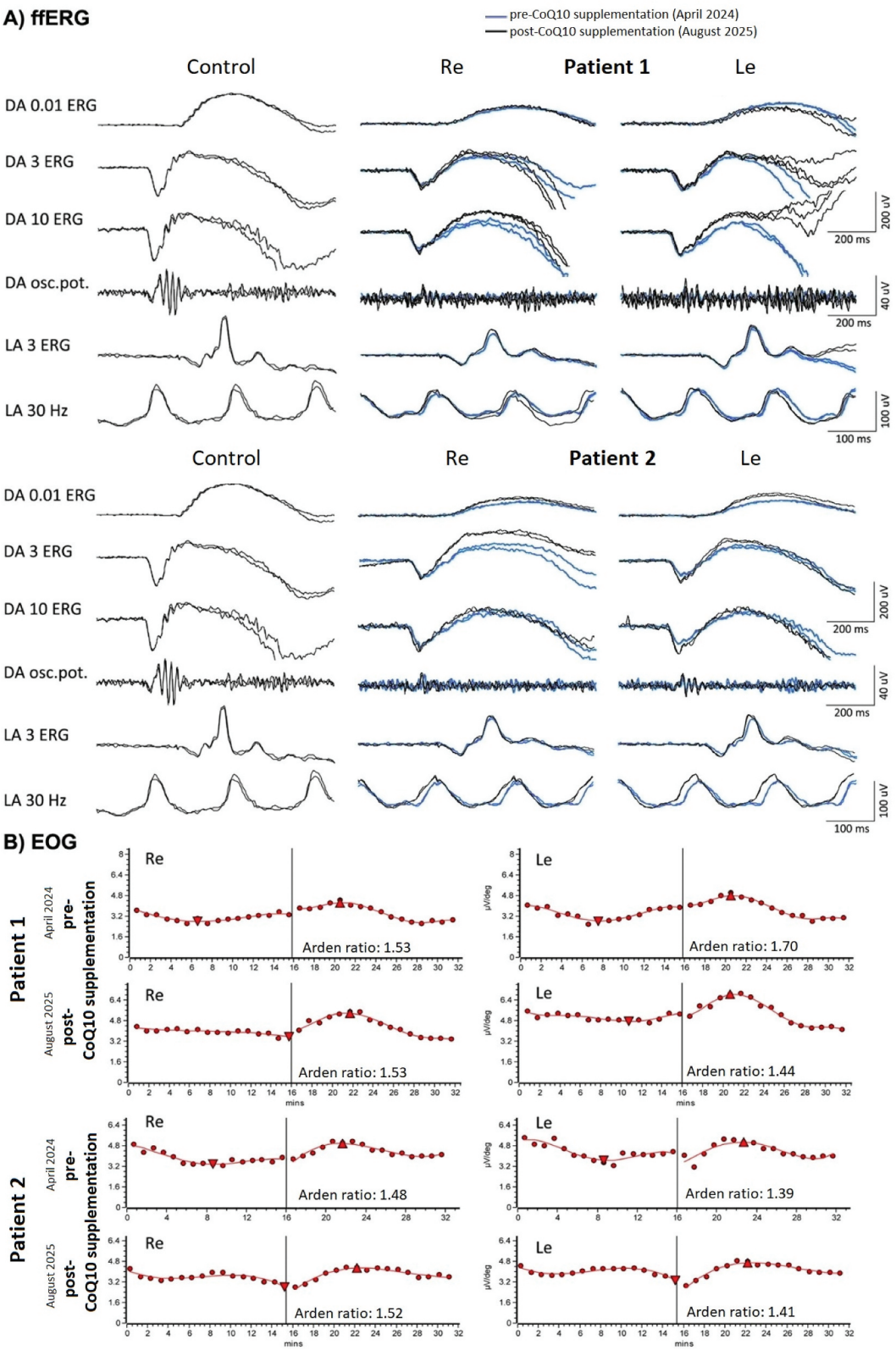

Figure 3. Changes of the full-field erg (a) and EOG (b) during the 16 months follow-up period.

p.Asn228Ser; OMIM 607 426) consistent with primary CoQ10 deficiency type 1. According to ACMG/AMP criteria, the variant is classified as likely pathogenic (PM3_STR, PS3_SUP, PM2, PP4).

Following neurological consultation, both twins underwent extensive systemic workup, including electromyography (EMG), MR spectroscopy, cardiac ultrasound, and electroencephalography (EEG), all of which were unremarkable. Serum CoQ10 levels were decreased in the proband (0.68 mg/L; reference range 0.8–1.4 mg/L) and within the low-normal range in his twin. Both patients were commenced on oral Coenzyme Q10 supplementation. Initially, the patient received treatment

for six months at a dosage of 10 mg/kg/day, resulting in an increase of the serum CoQ10 concentration to 8.37 mg/L. Thereafter, therapy was continued at a maintenance dose of 5 mg/kg/day. After one year of treatment, electrophysiological follow-up demonstrated in general similar findings, but with a slight possibility of improvement in EOG and full-field ERG parameters, with slightly better defined EOG light-rise (but still abnormal LP:DT ratio) and slightly higher amplitudes and shorter peak times of the ERG responses compared to baseline (Figure 3).

Discussion

Several aspects of this case significantly broaden the established phenotypic spectrum of *COQ2*-related retinopathy and provide important insights into its pathophysiology and management. Unlike most reported cases of CoQ10 pathway–related disorders—which typically present with an RP-like phenotype characterized by nyctalopia, peripheral field loss, and advanced photoreceptor degeneration[1,3] or optic atrophy[6]—our patient presented primarily with vitreous inflammation, CMO, and preserved visual fields. While structural and electrophysiologic phenotypes of COQ10 pathway–related disorders have been described, our report provides the first detailed characterization of angiographic findings in this context. Furthermore, we formally document the presence of vitreous cells, a feature not previously reported in COQ10 pathway–related disorders. It is increasingly recognized that vitreous cells can be present in up to 32% of pediatric rod–cone dystrophies, often representing a "pseudo-inflammatory" marker of an active degenerative phase rather than a primary uveitic process. In our patients, these cells, alongside the macular oedema and vascular leakage seen on imaging, initially led to a misdiagnosis of intermediate uveitis. Recognizing this "uveitis masquerade" is critical, as it highlights that metabolic distress and rapid neuroretinal degeneration in CoQ10 deficiency can trigger secondary inflammatory signs.

Furthermore, the electrophysiological findings, specifically the severely abnormal EOG and only mildly reduced rod ERG responses—strongly indicate predominant RPE dysfunction. Notably, EOG abnormalities have not been previously reported in CoQ10 pathway–related disorders, and in our patients, these abnormalities were more pronounced than the ffERG findings. This suggests that the RPE may be the primary site of metabolic failure in CoQ10 pathway–related disorders, with photoreceptor loss occurring as a secondary consequence.

After one year of CoQ10 supplementation, follow-up electrophysiology demonstrated a possibility of slightly improved function of the retinal layers (Supplementary Table 1). Specifically, the light-rise of the EOG was slightly better defined and ERG amplitudes and peak times were slightly improved compared with baseline. However, the improvement was mostly within an expected intra-individual test-retest variability (reported to be approximately 25–40% for ERG amplitudes[8] and around 10% for EOG parameters[9]), so further follow-up will be needed to support early initiation of CoQ10 supplementation as a potentially disease-modifying approach in *COQ2*-related retinopathy.

The presence of recurrent macular oedema in our patients is likely attributable to retinal endothelial and glial cell dysfunction. Cells essential for maintaining ionic gradients, fluid homeostasis, and vascular integrity—particularly Müller cells, astrocytes, and pericytes—are highly dependent on mitochondrial ATP production. CoQ10 deficiency impairs oxidative phosphorylation, resulting in increased reactive oxygen species (ROS) generation and reduced antioxidant capacity.[10] This cascade leads to cellular stress, apoptosis, and disruption of the blood–retinal barrier, promoting chronic vascular leakage and impaired fluid resorption. The inability of Müller cells and pericytes to maintain homeostasis under oxidative stress further exacerbates oedema and contributes to progressive neurodegeneration.[11] Interestingly, the worsening of CMO following topical corticosteroid treatment is consistent with the mitochondrial hypothesis. Corticosteroids primarily suppress inflammation but do not address the underlying mitochondrial defect. Moreover, they may aggravate the condition by increasing oxidative stress, mitochondrial dysfunction, and vascular dysregulation,[12] which may explain the worsening of CMO after corticosteroid therapy in our patient.

The resolution of macular oedema following anti-VEGF therapy in our patients suggests that while the primary pathology is mitochondrial, a secondary upregulation of VEGF or pro-permeability cytokines may occur. An additional consideration is the underlying microangiopathy associated with COQ10 deficiency. Given the central role of CoQ10 in ATP production, tissues with high metabolic demand—including retinal and renal podocytes—may be particularly vulnerable to energy deficits. This mechanism may mirror aspects of diabetic vasculopathy, where metabolic distress leads to blood-retinal barrier breakdown, potentially explaining why *COQ2*-related retinopathy exhibits a VEGF-dependent component.

However, we must emphasize that anti-VEGF therapy is generally not considered first-line treatment for IRD-associated "pseudo-oedema," where oral or topical carbonic anhydrase inhibitors are more commonly favoured. Furthermore, the response to anti-VEGF agents in inherited retinal disorders is typically less pronounced than in primary vascular pathologies, such as diabetic macular edema or retinal vein occlusion, and recurrence or incomplete resolution is frequently observed.[13]

The observation of a significant bilateral reduction in CMO following a single unilateral intravitreal bevacizumab injection is noteworthy. While spontaneous fluctuations cannot be excluded, the consistent bilateral improvement observed strongly suggests a systemic effect (Figure 2). A contralateral response after unilateral bevacizumab administration has been reported previously, possibly due to systemic absorption.[14] Matsuyama *et al.* documented a reduction in VEGF levels in the fellow eye of patients with proliferative diabetic retinopathy, supporting this mechanism.[14] Given that the *COQ2* mutation is associated with increased vascular permeability, systemic exposure to bevacizumab may be more pronounced in our cases, thereby explaining the marked bilateral therapeutic effect. Finally, the selective involvement of the retina and kidney in *COQ2*-related CoQ10 deficiency is best explained by

tissue-specific vulnerability to mitochondrial dysfunction. Tissues with high metabolic demands, such as the retina and renal podocytes, are particularly susceptible to defects in mitochondrial energy metabolism. Podocytes and proximal tubular cells are densely populated with mitochondria, making them prone to energy depletion and structural damage, which can manifest as FSGS, as observed in our patients.[15] This tissue-specific vulnerability may precede, or occur independently of, skeletal muscle or central nervous system involvement.

In conclusion, we report a distinctive presentation of *COQ2*-related retinopathy in identical twins complicated by nephropathy. The atypical ocular features—characterized by retinal microangiopathy, CMO, and primary RPE dysfunction—broaden the known phenotypic spectrum of this inherited disorder. Prompt recognition is crucial, as early initiation of CoQ10 supplementation has the potential to stabilize or even reverse disease progression and prevent further systemic complications. Clinicians should consider genetic testing in young patients presenting with CMO resembling intermediate uveitis, particularly when accompanied by nephropathy or other systemic conditions. Ultimately, this case highlights the retina's role as a sentinel organ for early diagnosis and genetically guided therapeutic intervention in systemic disease.

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GAU performed the conceptualization, investigation, methodology, and drafted the original manuscript. KN, VM, OD, MA, ŠHM, KP, and JMP were involved in the clinical management and contributed to the critical review and editing of the manuscript. All authors have read and approved the final manuscript.

Author contributions

CRediT: **Ana Ursula Gavric MD, PhD, FEBO:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing; **Marija Volk MD, PhD:** Investigation; **Nika Kojc MD, PhD:** Writing – review & editing; **Damjan Osredkar MD, PhD:** Writing – review & editing; **Andrej Meglič PhD:** Writing – review & editing; **Maja Sustar Habjan PhD:** Writing – review & editing; **Peter Kiraly MD, PhD:** Writing – review & editing; **Polonca Jaki Mekjavic MD, PhD:** Writing – review & editing.

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Data availability statement

The raw data of this article are available from the corresponding author upon reasonable request.

Informed consent

Both patients provided written consent to publish this case report.

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