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CLINICAL INSIGHTS

Familial thrombotic microangiopathy in a child with coenzyme Q10 deficiency-associated glomerulopathy

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Abstract

We report a child with biallelic *COQ6* variants presenting with familial thrombotic microangiopathy (TMA). A Chinese boy presented with steroid-resistant nephrotic syndrome at 8 months old and went into kidney failure requiring peritoneal dialysis at 15 months old. He presented with hypertensive encephalopathy with the triad of microangiopathic haemolytic anaemia, thrombocytopenia, and acute on chronic kidney injury at 25 months old following a viral illness. Kidney biopsy showed features of chronic TMA. He was managed with supportive therapy and plasma exchanges and maintained on eculizumab. However, he had another TMA relapse despite complement inhibition a year later. Eculizumab was withdrawn, and supportive therapies, including ubiquinol (50 mg/kg/day) and vitamins, were optimized. He remained relapse-free since then for 4 years. Of note, his elder sister succumbed to multiple organ failure with histological evidence of chronic TMA at the age of 4. Retrospective genetic analysis revealed the same compound heterozygous variants in the *COQ6* gene.

Keywords *COQ6* gene · CoQ10 deficiency · Thrombotic microangiopathy · Eculizumab · Ubiquinol

Case report

An 8-month-old Chinese infant of non-consanguineous parents was referred to our unit with steroid-resistant nephrotic syndrome. He failed to attain remission despite treatment with full-dose prednisolone for 6 weeks and calcineurin inhibitors. Kidney biopsy was declined initially. Whole exome sequencing (WES) report was available 2 months later, revealing compound heterozygous variants in *COQ6* (NM_182476.3) gene c.427G > A p.(Val143Met) and c.1335G > T p.(Arg445Ser), which was verified by Sanger sequencing and parental testing. At that time, both variants were classified as variants of uncertain significance (VUS) based on the American College of Medical Genetics (ACMG) guideline. His diagnosis was suspected to be coenzyme Q10 deficiency-associated glomerulopathy. Immunosuppressants were withdrawn, while oral coenzyme Q10 supplementation (ubiquinol 30 mg/kg/day) and angiotensin-converting enzyme (ACE) inhibitor were commenced. Despite treatment, he progressed to kidney failure at 15 months and was put on peritoneal dialysis (PD) with good blood pressure control.

Ten months later, the patient returned with fever, respiratory distress, and hypertensive encephalopathy

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following a parainfluenza infection. His blood pressure was 200/110 mmHg on admission. He was transferred to intensive care unit for respiratory support and blood pressure control. Blood tests revealed microangiopathic haemolytic anaemia (MAHA) (haemoglobin 7.1 g/dL, normal 11.0–14.0 g/dL; moderate amount of schistocytes; raised lactate dehydrogenase 2376 IU/L, normal 198–327 IU/L; low haptoglobin < 0.04 g/L, normal 0.07–1.63 g/L; and negative direct Coomb's test), thrombocytopenia (platelet 84×10^9/L, normal $200–490 \times 10^9$/L), and acute on chronic kidney injury as evidenced by anuria, surge of serum creatinine (from 280 to 616 µmol/L, normal 15–31 µmol/L), and rise in urine spot protein/creatinine ratio (from 2 to 26 mg/mg). He also had multiple organ dysfunction with deranged liver function (ALT 5372 IU/L, normal 11–30 IU/L) and raised cardiac enzymes (high sensitivity troponin I 23,976 ng/L, normal ≤ 21). Lactate was elevated (3.5 mmol/L, normal 0.5–2.2 mmol/L), and urine organic acid showed moderate hyper-excretion of 3-methyglutaric acid and 3-methylglutaconic acids; mitochondrial dysfunction was likely in view of these results [S1]. Additional microbiological, metabolic, and immunological workups were negative. Kidney biopsy revealed features of chronic TMA and abnormal mitochondria (Fig. 1). Further workup of TMA showed slightly reduced ADAMTS13 activity (44%, normal 70–160%). Evidence of complement pathway activation including hypocomplementemia (C3 0.43 g/L, normal 0.83–1.52 g/L; C4 0.07 g/L, normal 0.13–0.37 g/L) and unquantifiable CH50 and AH50 was present. He was tested negative for anti-Factor H antibody, and levels of Factor H, I, and B were normal. Genetic panel was repeated, and none of the common variants associated with TMA, including complement and non-complement variants, was identified.

In view of the severe presentation of TMA with evidence of complement activation, the patient was empirically started on plasma exchange as C5 inhibitors were not available. He

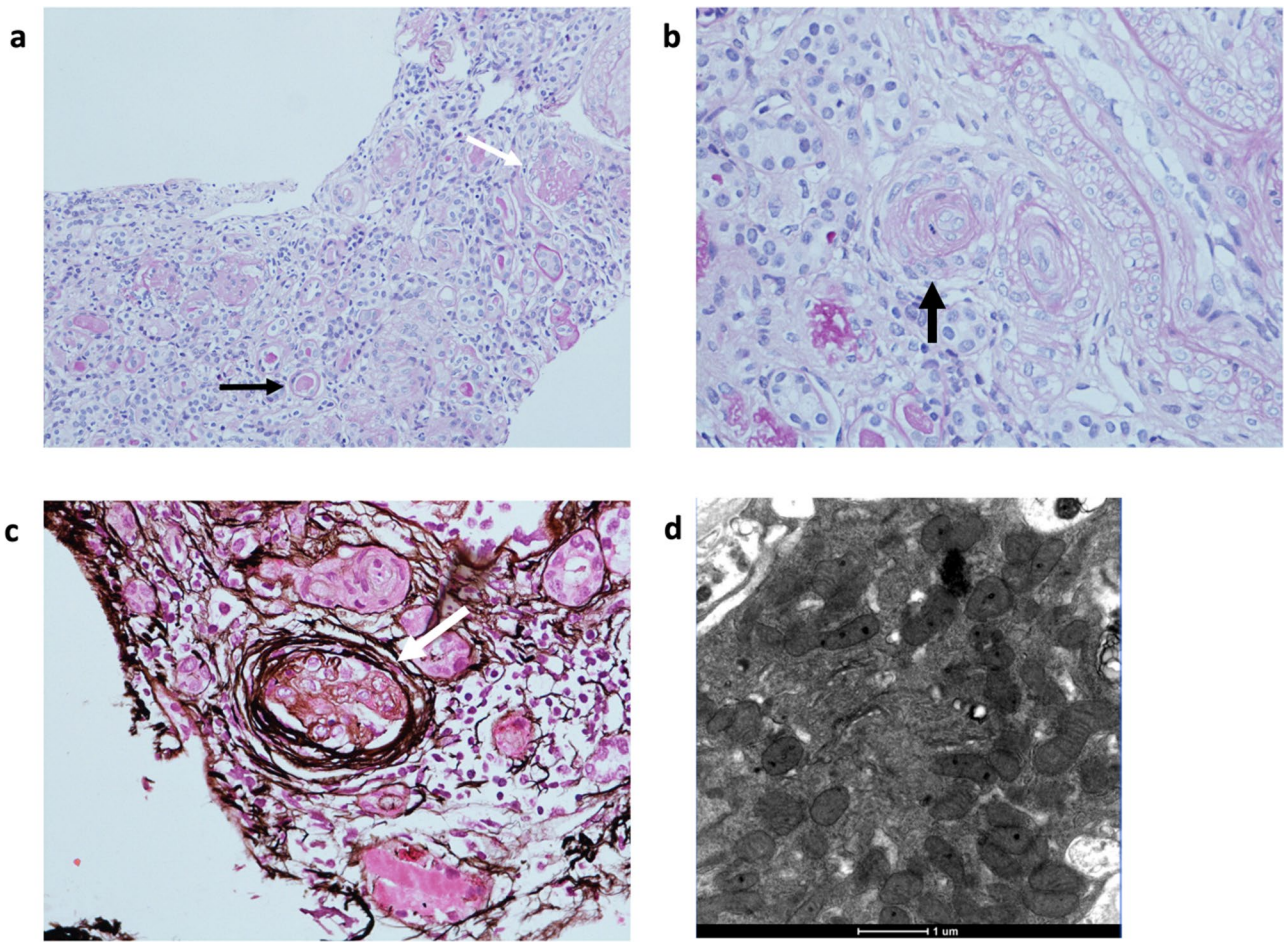

Fig. 1 **a** PAS stain showing chronic changes with global glomerulosclerosis (white arrow) and marked tubular atrophy (black arrow) (periodic acid-Schiff, ×200). **b** Arteriolar narrowing with swollen endothelial cells and lamination (black arrow) (periodic acid-Schiff, ×400). **c** Silver stain shows segmental tramlines and an arteriole with edematous wall and swollen endothelial cells (white arrow) (Jones silver stain, ×400). **d** Electron micrograph showing a few dense core materials in mitochondria (transmission electron microscopy, ×18,500)

responded to supportive treatment with normalization of haematological indices, ALT (5372 to 30 IU/L) and lactate (3.5 to 0.7 mmol/L) the following week. He was discharged from PICU with full recovery of liver and cardiac functions, although he remained PD dependent. C5 inhibitors were started 4 weeks after the acute presentation as maintenance therapy. He was clinically stable with good blood pressure control. One year later, he was admitted again for a mild relapse of TMA following a mild viral illness despite full complement function suppression by C5 inhibitors. He presented with hypertensive urgency and MAHA, with raised creatinine from 300 to 489 µmol/L and elevated lactate level to 3.5 mmol/L (Supplementary Table 2). The patient responded to supportive treatment including optimization of ubiquinol (50 mg/kg/day), supplementation of mitochondrial vitamin cocktails (levocarnitine, riboflavin, and thiamine), and blood pressure control. Skin fibroblast analysis (Supplementary Table 1) confirmed coenzyme Q10 deficiency, and the detected *COQ6* variants were upgraded to likely pathogenic according to the ACMG guideline. C5 inhibitors were discontinued and he remained relapse-free for over 4 years to date.

Of note, the patient's elder sister who enjoyed good past health died suddenly of multi-organ failure at the age of 4 following a viral illness. She did not have hypertension on presentation. Post-mortem studies surprisingly revealed features of chronic TMA in her kidneys and liver. Genetic evaluation of the deceased sister identified the same compound heterozygous variants in the *COQ6* gene.

Discussion

We report an unusual family of TMA cases with variants at the *COQ6* gene. Both children developed severe TMA, one deceased soon after presentation and the other first had steroid-resistant glomerulopathy and then C5 inhibitors-resistant TMA. Primary coenzyme Q10 deficiency represents a group of heterogeneous diseases with variable phenotypes, ranging from multi-organ involvement to isolated kidney or neurological disease [1]. The *COQ6* gene is one of the 16 genes involved in coenzyme Q10 biosynthesis [1]. Homozygous or compound heterozygous variants of the *COQ6* gene are associated with infantile steroid-resistant nephrotic syndrome and sensorineural hearing loss. Drovandi et al. evaluated 251 patients with primary coenzyme Q10 deficiency due to variants in *COQ2*, *COQ6*, and *COQ8B*. Kidney involvement, mainly nephrotic-range proteinuria, was observed in 98% of patients. Two-thirds of patients progressed to kidney failure. Of note, TMA was not observed in any of these patients, highlighting the novelty and importance of our patients [2]. Early supplementation of coenzyme Q10 (5 to 50 mg/kg/day) reduces proteinuria and the rate of progression to kidney failure [1, 3]. Its effect is particularly prominent in *COQ6*-related diseases [3]. Nonetheless, our patient progressed to kidney failure despite the supplementation, since advanced chronic kidney disease was already established at the time of genetic diagnosis.

Our patient presented with TMA, severe hypertension, and multi-organ failure following a viral infection. While the cause of the TMA phenotype could be related to severe hypertension or infection, the relationship between TMA and the underlying *COQ*6 mutation remains intriguing. Severe hypertension in this case could be related to multiple factors, including acute TMA, mitochondrial dysfunction, and fluid overload/sympathetic overactivity in this child with kidney failure. However, the unexpected histological finding of chronic TMA in the index patient and his deceased sister could imply that a chronic disease process, rather than an acute event, has resulted in chronic TMA. Reports concerning the potential association of mitochondrial disorder and TMA are extremely scarce [S2-4]. On the other hand, TMA was not infrequently reported in children with steroid-resistant nephrotic syndrome; a variety of mechanisms have been proposed, including hypertension and drugs [4]. However, our patient was free from drugs with the potential to cause TMA, and he had good blood pressure control while on dialysis and coenzyme replacement. Severe liver function derangement was also an uncommon presentation of TMA secondary to hypertension [5]. We postulate that the TMA phenotype in our patient could be triggered by an infection, which resulted in acute medical distress in the setting of mitochondrial dysfunction, hence energy deprivation and endothelial cell injury. Severe hypertension would in turn result in further endothelial stress, secondary complement activation, and organ damage. Further studies are required to delineate the pathogenesis relating TMA and mitochondrial disease in more detail.

In conclusion, we report a pair of siblings with proven biallelic *COQ6* variants and coenzyme Q10 deficiency-associated glomerulopathy with devastating TMA. While the pathogenesis of their familial TMA remains to be elucidated, clinicians should be aware of the heterogeneity of TMA phenotypes across the globe and individualize patient management accordingly. Organ support, blood pressure control, and multi-team involvements would be vital to care for these critically ill patients. Future research should hopefully shed light on the exact disease mechanism and solve the mystery.

Summary

What is new?

• We report the rare presentation of thrombotic microangiopathy in siblings with mitochondrial disease.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00467-024-06496-1.

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Declarations

Consent to participate The authors declare that they have obtained consent from the patient discussed in the report.

Conflict of interest All the authors declared no competing interests.

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