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CASE REPORT

A Case Report of a Patient with COQ8B Nephropathy Manifesting Atypical Renal Pathological Changes

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SUMMARY

Background: **COQ8B nephropathy is a hereditary mitochondrial kidney disease. Most cases present with steroid-resistant nephrotic syndrome and focal segmental glomerulosclerosis, whereas this patient exhibited asymptomatic isolated proteinuria and mild renal histopathology.**
Methods: **Appropriate laboratory tests, abdominal ultrasonography, renal biopsy, and whole exome sequencing were performed to explore the cause of the disease.**
Results: **Laboratory results revealed that the patient was asymptomatic. Abdominal ultrasonography confirmed left renal vein nutcracker. Renal histopathology showed mild mesangial proliferation. An unreported splice mutation in the COQ8B (c.893+2T>A) gene was identified by whole exome sequencing.**
Conclusions: **COQ8B nephropathy is an emerging cause of isolated proteinuria, particularly prevalent among adolescents. For nephritis of unknown etiology following renal biopsy, prompt consideration of gene sequencing is advisable.**
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KEYWORDS

isolated proteinuria, child, COQ8B nephropathy, CoQ10

INTRODUCTION

COQ8B nephropathy is an autosomal recessive chronic kidney disease caused by homozygous or compound heterozygous variations in the COQ8B gene (previously known as ADCK4) [1]. The renal manifestation of COQ8B nephropathy is characterized by onset during adolescence, presenting with mild to moderate proteinuria and absence of hematuria or edema in most cases. Due to its insidious onset, patients are often encountered with advanced chronic kidney disease (CKD) at initial diagnosis. Early detection of COQ8B nephropathy was achieved by urine screening for proteinuria [2,3]. The pathognomonic histological feature of COQ8B nephropathy is focal segmental glomerulosclerosis (FSGS), and the incidence of this disease among pediatric patients with steroid-resistant nephrotic syndrome

(SRNS) in China is 6.67% [4-6].
Considering the hidden onset, rapid progression, and poor prognosis of the disease, especially with end-stage renal disease (ESRD) as the outcome, early diagnosis plays an essential role in terminating disease progression by Coenzyme Q10 (CoQ10) supplementation at the early stage [6]. Herein, we report a case of a patient harboring an atypical renal histopathological phenotype associated with a hitherto unreported mutation in the COQ8B gene, specifically a splice site mutation at c.893+2T>A.

CASE PRESENTATION

The patient, a 12-year-old male, was admitted to our hospital in February 2024. Two years prior to this admission, routine physical examinations revealed proteinuria of 1+. One year prior, he presented to the hospital for management of proteinuria upgraded to 2+. A treatment by an angiotensin converting-enzyme inhibitor was started with no improvement of the proteinuria. Upon admission, the patient's anthropometric measurements were as follows: height 140 cm and weight 43.5 kg. Blood pressure was normal, and no edema of the lower extremities, hematuria or fever was observed. Laboratory investigations revealed no hypoalbuminemia (41 g/L), and urine contained nephrotic-range glomerular proteins (proteins/creatinine: 2.68 g/g). All the other biochemical investigations (viral serology and immunological analyses) were normal, and glomerular filtration rate (GFR) measured by creatinine clearance was within the normal range (100 mL/minute/1.73 m^2). Renal ultrasound showed medullary nephrocalcinosis (Figure 1A) and left renal vein nutcracker syndrome (Figure 1B). No hearing loss, ocular defects, seizure, apnea, ataxia, myalgia, exercise intolerance, heart failure, lactic acidosis, or hepatic dysfunction was detected. Renal histopathology under light microscope (LM) showed that two glomerulus showed sclerosis, one glomerulus showed segmental sclerosis while the other twenty two glomeruli exhibited minor glomerular abnormalities (Figure 1C - F). Immunofluorescence was negative. Foot processes were segmentally effaced under electron microscope, but no mitochondrial abnormalities were detected (Figure 1G, H). Besides, electron microscope (EM) observation revealed glomerular basement membrane segmental thinning (thickness < 180 nm about 10 - 15%), thinnest at about 150 nm (Figure 1I, J). We analyzed genomic DNA from her peripheral blood mononuclear cells by whole exome sequencing, which revealed a novel splice mutation c.893+2T>A of COQ8B gene, which led to a definitive diagnosis of mitochondrial disease (Figure 2). ACEI treatment was thus terminated, and oral CoQ10 at 150 mg per day was initiated based on the patient's weight. Three months later, his urinary protein/creatinine ratio was reduced from 2.68 g/g to 1.64 g/g. No adverse events were observed.

DISCUSSION

Asymptomatic children presenting with proteinuria may eventually develop nephrotic syndrome. Approximately 10% of nephrotic syndrome cases are SRNS, and these patients, in particular, are at high risk of developing end-stage renal failure (ESRF). With the rapid development and cost reduction of gene sequencing technology, an increasing number of SRNS caused by genetic mutations are being discovered, for instance, mutations in genes coding transcriptional factors (e.g., WT1), glomerular basement membrane (such as LAMB2), or mitochondrial proteins such as CoQ10 (e.g., COQ genes) [2]. Primary coenzyme Q10 (CoQ10) deficiency of genetic origin is one of a few treatable SRNS [7]. CoQ10 is an effective lipophilic antioxidant, a component of the mitochondrial respiratory chain, and a cofactor for mitochondrial dehydrogenase and pyrimidine nucleotide biosynthesis [8]. At least 17 different genes are involved in the synthesis of CoQ10 in mitochondria [9, 10]. Among them, mutations in 10 genes (PDSS1, PDSS2, COQ2, COQ4, COQ6, COQ7, COQ8A, COQ8B, COQ9, and ADCK2) lead to primary CoQ10 deficiency, which is typically inherited in an autosomal recessive manner [10]. At least four genes are associated with SRNS (COQ2, COQ6, PDSS2, COQ8B) [11,12]. Of four genes, mutation in COQ8B causes selective glomerular phenotype mostly without neurological and myopathic deficits [1]. COQ8B is located on chromosome 19q13.2 and expressed in podocytes, which are located in mitochondria inside the foot process [11]. It has been identified that variants of COQ8B gene can cause CoQ10 deficiency and mitochondrial nephropathy [11,9]. COQ8B mutations cause selective glomerular phenotypes, mostly without extrarenal symptoms [11,12]. Although the mechanism of this selectivity remains unclear, a potential explanation may be the difference in distribution patterns between COQ8B and COQ8A with high sequence similarity [11,12]. COQ8B is highly expressed in podocytes, whereas COQ8A is expressed in most body tissues but not podocytes [11]. COQ8B nephropathy mainly manifests clinically as varying degrees of proteinuria. Typical pathology of COQ8B nephropathy is FSGS. The age of onset of COQ8B nephropathy ranges from 6 to 20 years. The presence of irregularly shaped mitochondria in podocytes and proximal tubules can be observed under an electron microscope [3,11]. Compared to patients with other types of hereditary nephrotic syndrome, the onset age in this case is considerably later. However, currently reported cases have not revealed a definitive genotype-phenotype correlation [11,12].
In this case, we identified a novel pathogenic sequence variant in the COQ8B gene that has not been reported previously. Consistent with previously reported cases of COQ8B nephropathy, this patient presented with isolated proteinuria at age ten, without neurological or myopathic features, which are common in mitochondrial diseases. Unlike the reported cases of SRNS and FSGS,

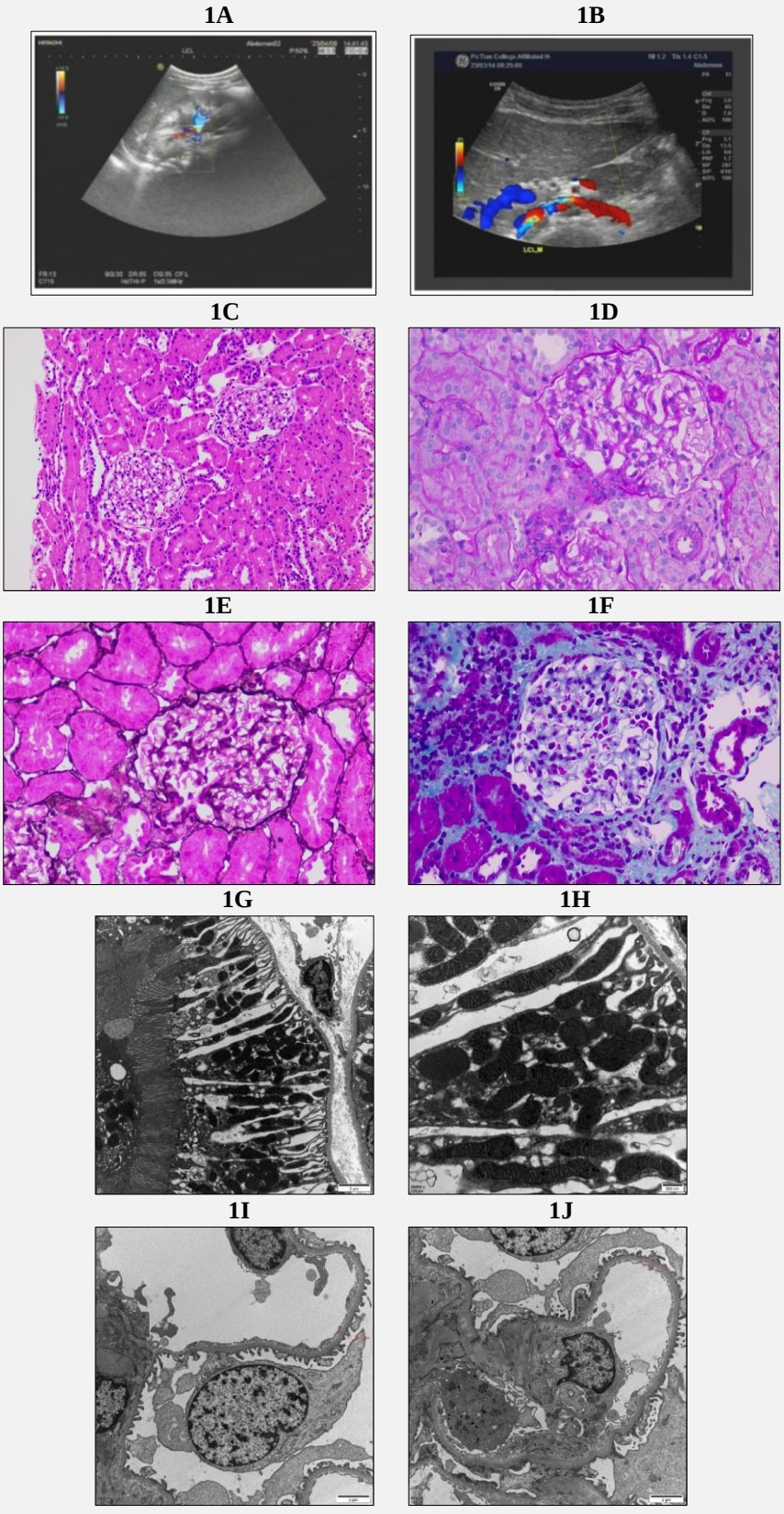

Figure 1. Abdominal ultrasonography (Figure 1A - B). Hematoxylin-eosin (Figure 1C). Periodic Acid-Schiff (Figure 1D). Superior mesenteric venography (Figure 1E). Masson's trichrome (Figure 1F). Electron microscopic images (Figure 1G - J).

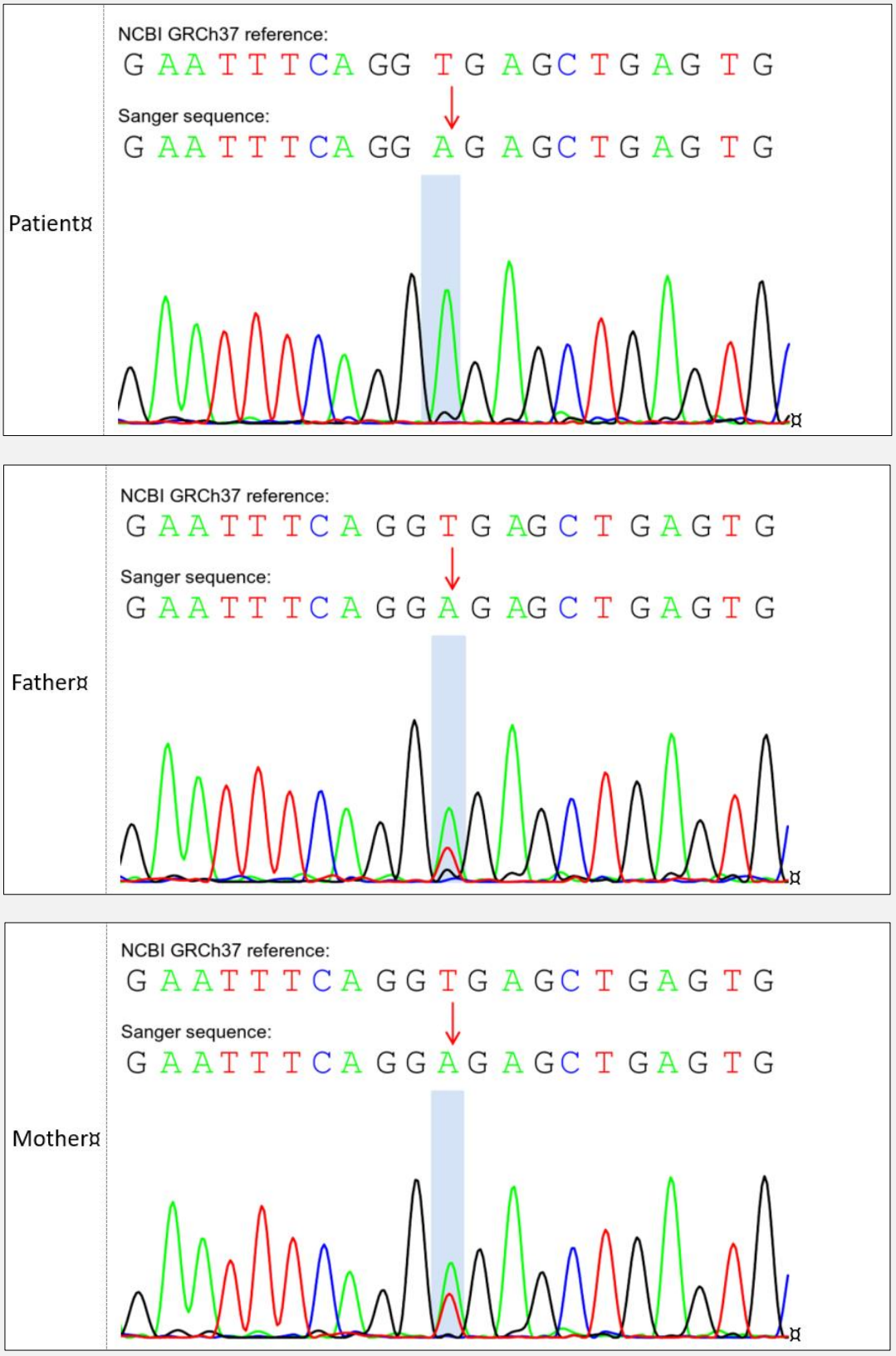

Figure 2. Whole-exome sequencing of the COQ8B gene.

our patient exhibited only mild phenotypic manifestations, and renal histopathology did not progress to FSGS. Under electron microscopy, mitochondria appeared normal, but interestingly, thinning of the glomerular basement membrane was observed, which is not reported in prior studies. Park et al. reported that all six ADCK4-GN patients exhibited renal calcium deposition, which could serve as a useful clinical clue, though the exact pathogenesis remains to be elucidated [3]. In this case, ultrasound imaging also indicated medullary nephrocalcinosis, while the left renal vein nutcracker syndrome is likely unrelated to genetic mutations. After three months of CoQ10 treatment, the patient exhibited a significant reduction in proteinuria. It should be noted that this follow-up period remains relatively short, rendering it insufficient for evaluating the long-term efficacy of the treatment. This constitutes to be one of the limitations of the present study. However, in several case reports and small retrospective studies, it has been proposed that exogenous CoQ10 therapy is advantageous in mitigating proteinuria and preserving GFR [13, 14].

CONCLUSION

In this study, we identified a novel pathogenic mutation underlying COQ8B nephropathy (c.893+2T>A). Notably, the majority of COQ8B nephropathy patients rapidly progress to ESRD, despite the mild phenotypic presentation observed in our case. Nonetheless, renal biopsy and whole-exome sequencing (WES) have significantly advanced early diagnosis, which will assist in identifying pediatric patients who may derive benefit from CoQ10 supplementation. This approach may potentially delay the progression of nephropathy through early initiation of CoQ10 therapy.

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Declaration of Interest:
No conflicts of interest exist in this article.

References:

1. Hildebrandt F. Genetics of Kidney Diseases. Semin Nephrol 2016 Nov;36(6):472-4. (PMID: 27987548)

2. Malaga-Dieguez L, Susztak K. ADCK4 "reenergizes" nephrotic syndrome. J Clin Invest 2013 Dec;123(12):4996-9. (PMID: 24270414)

3. Park E, Kang HG, Choi YH, et al. Focal segmental glomerulosclerosis and medullary nephrocalcinosis in children with ADCK4 mutations. Pediatr Nephrol 2017 Sep;32(9):1547-54. (PMID: 28405841)

4. Wang F, Zhang Y, Mao J, et al. Spectrum of mutations in Chinese children with steroid-resistant nephrotic syndrome. Pediatr Nephrol 2017 Jul;32(7):1181-92. (PMID: 28204945)

5. Rao J, Liu X, Mao J, et al. Genetic spectrum of renal disease for 1001 Chinese children based on a multicenter registration system. Clin Genet 2019 Nov;96(5):402-410. (PMID: 31328266)

6. Zhang H, Wang F, Liu X, Zhong X, Yao Y, Xiao H. Steroid-resistant nephrotic syndrome caused by co-inheritance of mutations at NPHS1 and ADCK4 genes in two Chinese siblings. Intractable Rare Dis Res 2017 Nov;6(4):299-303. (PMID: 29259860)

7. Sadowski CE, Lovric S, Ashraf S, et al. A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome. J Am Soc Nephrol 2015;26(6):1279-89. (PMID: 25349199)

8. Quinzii CM, Lopez LC, Naini A, et al. Human CoQ10 deficiencies. Biofactors 2008;32(1-4):113-8. (PMID: 19096106)

9. Vazquez-Fonseca, L Schaefer J, Navas-Enamorado I, et al. ADCK2 Haploinsufficiency Reduces Mitochondrial Lipid Oxidation and Causes Myopathy Associated with CoQ Deficiency. J Clin Med 2019 Sep 2;8(9):1374. (PMID: 31480808)

10. Vazquez Fonseca L, Doimo M, Calderan C, et al. Mutations in COQ8B (ADCK4) found in patients with steroid-resistant nephrotic syndrome alter COQ8B function. Hum Mutat 2018 Mar; 39(3):406-14. (PMID: 29194833)

11. Ashraf S, Gee HY, Woerner S, et al. ADCK4 mutations promote steroid-resistant nephrotic syndrome through CoQ10 biosynthesis disruption. J Clin Invest 2013 Dec;123(12):5179-89. (PMID: 24270420)

12. Korkmaz E, Lipska-Zietkiewicz BS, Boyer O, et al. ADCK4-Associated Glomerulopathy Causes Adolescence-Onset FSGS. J Am Soc Nephrol 2016 Jan;27(1):63-8. (PMID: 25967120)

13. Song X, Fang X, Tang X, et al. COQ8B nephropathy: Early detection and optimal treatment. Mol Genet Genomic Med 2020 Aug;8(8):e1360. (PMID: 32543055)

14. Atmaca M, Gulhan B, Atayar E, et al. Long-term follow-up results of patients with ADCK4 mutations who have been diagnosed in the asymptomatic period: effects of early initiation of CoQ10 supplementation. Turk J Pediatr 2019;61(5):657-63. (PMID: 32104996)