Case Report

Diuretic-resistant Edema in a Child With Primary Coenzyme Q10 Deficiency and Nephrotic Syndrome: A Case Report

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ABSTRACT

Background: Managing nephrotic syndrome in infancy can be challenging, especially when resistant to conventional treatments. This study reports a case with diuretic-resistant nephrotic syndrome and primary coenzyme Q10 (CoQ10) deficiency.

Case Presentation: The case was a 22-month-old boy with diuretic-resistant edema, nephrotic syndrome, developmental delay, seizures, and multi-system involvement. Despite intensive interventions, including albumin and diuretic infusions, renin-angiotensin-aldosterone system inhibitors, and peritoneal dialysis, edema persisted. Initial suspicion of methylmalonic acidemia led to the administration of hydroxocobalamin. However, whole-exome sequencing revealed a homozygous pathogenic *PDSS2* mutation, confirming primary CoQ10 deficiency, which led to the continuation of CoQ10 supplementation and discontinuation of methylmalonic acid (MMA) treatment. Unfortunately, the patient succumbed to sepsis before assessing the treatment response.

Conclusions: This case highlights the diagnostic challenge of refractory nephrotic syndrome in infants and emphasizes the value of early genetic testing to identify rare but treatable conditions like CoQ10 deficiency. Timely diagnosis can enable targeted interventions and potentially improve outcomes.

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Introduction

Nephrotic syndrome is a common pediatric kidney disorder characterized by massive proteinuria, hypoalbuminemia, edema, and hyperlipidemia. Genetic mutations affecting podocyte structure and function have been implicated in several forms of nephrotic syndrome, with some leading to progressive kidney failure and end-stage kidney disease [1]. Edema in nephrotic syndrome is usually managed with diuretics and albumin infusions, but some cases remain resistant to treatment. The mechanisms of diuretic-resistant edema are complex and involve factors such as impaired drug absorption due to intestinal edema, the "braking phenomenon" where chronic diuretic use reduces effectiveness, and alterations in renal sodium handling [2].

Congenital nephrotic syndrome (CNS), which manifests within the first three months of life, is often linked to genetic mutations in glomerular filtration barrier proteins such as NPHS1 and NPHS2 [3]. While most genetic forms of CNS are resistant to standard therapies, mitochondrial disorders, including primary coenzyme Q10 (CoQ10) deficiency, should also be considered. These disorders, resulting from defects in oxidative phosphorylation, can affect multiple organ systems, with kidney involvement often presenting as nephrotic syndrome [3].

Primary CoQ10 deficiency, caused by pathogenic variants in genes such as *COQ2*, *COQ6*, and *COQ8B*, is one of the few treatable mitochondrial disorders. Studies have demonstrated that early CoQ10 supplementation can stabilize kidney function and improve clinical outcomes in affected patients [1, 3]. However, due to the clinical heterogeneity of CoQ10 deficiency and symptom overlap with other genetic kidney diseases, many cases remain undiagnosed [3]. Starr et al. described *COQ2* nephropathy as a treatable cause of nephrotic syndrome in children, emphasizing the importance of genetic screening for primary CoQ10 deficiency. Their study highlighted cases where early recognition and intervention with CoQ10 supplementation led to clinical improvement, preventing disease progression [4]. This underscores the need for a high index of suspicion in pediatric nephrotic syndrome, particularly when standard treatments fail [5].

In this case report, we present a 22-month-old boy with diuretic-resistant nephrotic syndrome, developmental delay, and mitochondrial dysfunction, ultimately diagnosed with primary CoQ10 deficiency due to a pathogenic *PDSS2* variant.

Case Presentation

A 22-month-old boy was admitted to the hospital with generalized edema, including scrotal and periorbital swelling, along with persistently elevated blood pressure. His parents reported worsening edema over the past 10 days. On examination, he was alert but exhibited poor eye contact and significant developmental delay. Neurological assessment revealed microcephaly, hypotonia, and an inability to sit or hold his head. Hearing loss was also noted. Genital examination showed micropenis, while cardiovascular and respiratory examinations were unremarkable. His abdomen was soft and non-tender. His vital signs included a pulse rate of 110 beats per minute, a respiratory rate of 43 beats per minute and a blood pressure of 130/100 mm Hg.

The infant was born at 37 weeks of gestation via cesarean section to consanguineous parents (G4P2Ab2). He had a birth weight of 3 kg and a head circumference of 34 cm. He required neonatal intensive care unit admission at birth and was intubated for 12 days due to respiratory distress. At four months of age, he began experiencing recurrent seizures, which were controlled with anticonvulsant therapy by six months. Due to concerns about a possible mitochondrial respiratory chain disorder, he was started on a mitochondrial cocktail, including vitamin B1, biotin, riboflavin, vitamin B6, vitamin E, folic acid, L-carnitine and CoQ10. His medical history was also significant for a cerebrovascular accident and recurrent infections, including pneumonia and mastoiditis.

Laboratory findings were notable for severe hypoalbuminemia (1.7 g/dL), marked proteinuria, hyperlipidemia, and electrolyte abnormalities. His complete blood count showed leukocytosis (WBC: 14,100/mm^3), hemoglobin (13.3 g/dL), and a platelet count of 403,000/mm^3. Renal function tests revealed a blood urea nitrogen (BUN) of 11.6 mg/dL and a creatinine level of 0.27 mg/dL. His electrolyte levels were sodium 138 mEq/L, potassium 4 mEq/L, calcium 7.1 mg/dL, and phosphorus 4.9 mg/dL. His lipid profile revealed a total cholesterol level of 900 mg/dL and triglyceride levels of 461 mg/dL. Urinalysis revealed a specific gravity of 1025, proteinuria (+++), and minimal red and white blood cells. Complement levels were reduced (C3: 32 mg/dL, C4: 10 mg/dL), while autoantibody screening was negative. Immunoglobulin levels showed low IgG (<7 mg/dL), with elevated IgA (54 mg/dL) and IgM (278 mg/dL). D-dimer was elevated at 700 ng/mL, and lactate dehydrogenase (LDH) was 1137 U/L. Blood and urine cultures were negative. Abdominal ultrasound

showed increased echogenicity of both kidneys, bilateral pleural effusion, and free peritoneal fluid. Computed tomography scan of the brain revealed encephalopathic changes in the bilateral occipital lobes, mastoid opacity, and scalp soft tissue edema.

The patient was started on intravenous diuretic and albumin infusions due to severe hypoalbuminemia and generalized edema. Given the suspicion of CNS as the underlying etiology, oral captopril was initiated. Genetic testing and TORCH screening were administered. Over the next few days, albumin infusions and intravenous diuretics were increased in frequency, and indomethacin was started. His metabolic tests revealed increased blood amino acid levels, including alanine, glutamine, and arginine. The acylcarnitine profile was normal, while the organic acid profile in the urine showed elevated methylmalonic acid (MMA). The patient's lactate level was 44.3 (normal; <20), and MMA level was 32.7 (normal; <12), leading to an initial suspicion of methylmalonic acidemia. Therefore, hydroxocobalamin was administered while awaiting genetic testing results.

Despite these interventions, the patient's edema remained refractory to treatment, and he developed signs of fluid overload and respiratory distress. He was transferred to the ICU, where peritoneal dialysis was initiated as an ultrafiltration method. However, there was no significant improvement in his condition. Given the concern for diuretic-resistant edema, tolvaptan, a vasopressin receptor antagonist, was introduced to aid in fluid management. Meanwhile, intravenous immunoglobulin was administered due to persistent concerns about immunodeficiency. Genetic testing confirmed a homozygous pathogenic variant in the *PDSS2* gene (*c.1063G>C*; *p. Gly355Arg*), establishing the diagnosis of primary *CoQ10* deficiency. Therefore, hydroxocobalamin and other treatments for methylmalonic acidemia were discontinued, leaving only CoQ10 supplementation (100 mg daily). Unfortunately, despite aggressive management, the patient's condition deteriorated further. He developed septicemia with positive blood and peritoneal fluid cultures. His clinical status continued to decline, and he ultimately succumbed to severe sepsis before the potential effectiveness of CoQ10 and tolvaptan could be evaluated.

Discussion

Diuretic resistance occurs when maximal doses of diuretics fail to produce the desired reduction in edema [6]. Multiple factors contribute to this phenomenon in nephrotic syndrome. One key mechanism is the presence of intestinal mucosal edema, which impairs the absorption of oral diuretics, thereby reducing their bioavailability and effectiveness [7]. Additionally, loop diuretics like furosemide are highly protein-bound, and in the setting of hypoalbuminemia, their transport to the kidney tubules is significantly reduced [6]. When serum albumin levels fall, a greater proportion of furosemide remains unbound and diffuses into peripheral tissues instead of reaching the renal tubules, thereby decreasing its therapeutic efficacy [8, 9]. Furthermore, during prolonged diuretic therapy, a phenomenon known as the "braking phenomenon" occurs, leading to a progressive decline in sodium and water excretion. This is often accompanied by post-diuretic sodium retention, mediated by the activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system [10]. While combining albumin with furosemide has been shown to enhance diuretic delivery to the renal tubules and increase urine output [11], its effects tend to be transient, necessitating careful patient selection for optimal benefit.

Managing edema in diuretic-resistant nephrotic syndrome remains a major clinical challenge, particularly when standard therapies such as diuretics and albumin infusions fail to achieve adequate fluid removal. In our case, despite intensive treatment with diuretics and albumin infusions, the patient's edema persisted, necessitating consideration of alternative strategies. Peritoneal dialysis (PD) is frequently utilized as an ultrafiltration method in cases of fluid overload, particularly in children with nephrotic syndrome. Barman et al. described a child with diuretic-resistant nephrotic edema who responded well to acute peritoneal dialysis, demonstrating that ultrafiltration can be effective when conventional methods fail [12]. However, our patient did not improve with PD, suggesting that the response to ultrafiltration may depend on disease severity and underlying pathology.

Tolvaptan, a selective vasopressin V2 receptor antagonist, has emerged as a promising option for fluid management in nephrotic syndrome. By promoting free water excretion without significantly affecting sodium and potassium balance, it is particularly beneficial in cases resistant to standard diuretics. Saimiya et al. reported successful fluid management with tolvaptan in a patient with refractory nephrotic syndrome, demonstrating significant reduction in edema and improved urine output [13]. Similarly, Shimizu et al. highlighted the effectiveness of tolvaptan in pediatric nephrotic syndrome, supporting its use as an adjunctive therapy for severe edema [14]. In our case, tolvaptan was initiated, but due

to the patient's rapid deterioration from sepsis, its effectiveness could not be evaluated. The detection of elevated urine MMA in our patient posed a significant diagnostic challenge. While MMA accumulation is typically linked to methylmalonic acidemia caused by defects in methylmalonyl-CoA mutase (MMUT) or its cofactor, cobalamin [15, 16], mitochondrial dysfunction has also been implicated in secondary MMA elevations. Studies suggest that disruptions in mitochondrial energy metabolism, particularly within the electron transport chain, can lead to the accumulation of metabolic intermediates such as MMA. This occurs due to impaired activity of enzymes and transporters involved in cellular metabolism, a process further exacerbated by oxidative stress and mitochondrial energy deficits [17, 18].

CoQ10 is integral to mitochondrial oxidative phosphorylation, serving as a crucial component of the electron transport chain. Deficiency in CoQ10 impairs mitochondrial function, resulting in metabolic disruptions that contribute to MMA accumulation. This highlights the importance of mitochondria in maintaining normal metabolic processes and suggests that in cases where MMA elevation is detected without classic features of methylmalonic acidemia, mitochondrial dysfunction should be considered as an alternative explanation [19]. Genetic testing plays a crucial role in diagnosing treatable forms of nephrotic syndrome, particularly in infants with atypical presentations. Mitochondrial cytopathies, including primary CoQ10 deficiency, are recognized causes of hereditary nephrotic syndrome, often resulting from mutations in genes such as *COQ2*, *COQ6*, and *COQ8B*, which disrupt oxidative phosphorylation and lead to podocyte injury. Schijvens et al. reviewed cases of mitochondrial nephropathies, emphasizing the need for early CoQ10 supplementation to prevent kidney deterioration [3]. Similarly, Drovandi et al. demonstrated improved renal function preservation in patients with genetically confirmed CoQ10 deficiencies who received early supplementation [1].

PDSS2 encodes the prenyl-diphosphate synthase subunit 2, a key regulatory enzyme in the CoQ10 biosynthesis pathway. Compared to *PDSS1*, *PDSS2* deficiency is more frequently associated with steroid-resistant nephrotic syndrome (SRNS) and multisystem involvement, including neurological abnormalities [20]. Sadowski et al. identified two patients with *PDSS2* mutations; one presented with SRNS at birth, while the other developed nephrotic syndrome at 23 months along with cerebral palsy and intellectual disability [21]. Iványi et al. reported a 7-month-old case with SRNS, hypertrophic cardiomyopathy, and retinitis pigmentosa due to compound heterozygous *PDSS2* mutations. Despite early CoQ10 therapy, the patient showed no improvement and passed away at 8 months [22]. The clinical presentation of CoQ10 deficiency varies widely, ranging from isolated nephrotic syndrome to multi-system disease involving neurological and muscular impairments. Herebian et al. emphasized that while biochemical markers such as serum CoQ10 levels may help in diagnosis, genetic confirmation remains the gold standard for identifying patients who may benefit from targeted therapy [23].

Conclusion

This case report highlights the diagnostic and therapeutic complexities associated with CoQ10 deficiency, particularly when patients present with severe multisystem involvement. Despite the availability of disease-modifying treatments, late-stage complications such as infections, intestinal edema, and sepsis may limit the potential benefits of therapy.

Ethical Considerations

Compliance with ethical guidelines

This case report was approved by the Research Ethics Committee of the Research Institute of Children Health, Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.RICH.REC.1404.003), and conducted in accordance with the guidelines in the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the patient's legal guardian for publication of this case report

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Authors contributions

Conceptualization, investigation, and writing the original draft: Neda Ghorbani-khosroshahi and Shiva Fatollahierad; Investigation: Masoumeh Mohkam, Mohammadreza Alaei and Maryam Alemzadeh; Review and editing, and final approval: All authors; Supervision: Masoumeh Mohkam.

Conflicts of interest

The authors declared no conflict of interest.

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