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Congenital Nephrotic Syndrome: An Atypical Presentation

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Abstract

We report the case of a 15-year-old boy diagnosed with congenital nephrotic syndrome (CNS) at one month of age. The genetic testing with exome sequencing identified 2 mutations in the NPHS2 gene. He started treatment with an ACE inhibitor at 9 months. Kidney biopsy conducted at the age of 5 revealed no glomerulosclerosis. He has maintained clinical stability with controlled proteinuria (significant but non-nephrotic range), and no impairment of kidney function.

This case shows an atypical evolution of CNS. Considering the identified mutation it would be expected a poor prognosis with early kidney failure and need of kidney replacement therapy. However, this boy, currently 15 years old, has shown a favorable evolution under treatment with an ACE inhibitor.

Introduction

Congenital nephrotic syndrome (CNS) is a rare disease characterized by nephrotic-range proteinuria and oedema that manifest in utero or during the first 3 months of life. It can be caused by congenital infections or maternal allo-immune disease, but most cases have genetic origin, associated with mutations in the *NPHS1*, *NPHS2*, *NPHS3*, *WT1*, or *LAMB2* genes. *NPHS1* is the most affected gene, followed by *NPHS2*, both accounting for approximately 95% of cases [1]. *NPHS2* encodes an integral membrane protein, podocin, which is found exclusively in glomerular podocytes and is crucial for the formation of slit diaphragm in podocytes. Abnormalities in this protein usually lead to steroid-resistant nephrotic syndrome, with severe proteinuria and, most often, a fast progression to kidney failure [2].

Genetic testing is the first-line diagnostic approach in CNS allowing early diagnosis, prognostic assessment, and avoidance of unnecessary immunosuppressive therapy.

CNS is generally associated with a poor prognosis, with most affected children progressing to kidney failure during early childhood.

Treatment is mainly supportive and aims to control the consequences of persistent proteinuria, including edema, hypoalbuminemia, dyslipidemia, infections, and thromboembolic complications. Therapeutic strategies may include albumin infusions, diuretics, nutritional support, and antiproteinuric therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB). Immunosuppressive therapy is usually ineffective in genetically determined forms of CNS. In severe cases, with an uncontrolled proteinuria, bilateral nephrectomy followed by renal replacement therapy and kidney transplantation may be required [3]. However, recurrence of the disease after kidney transplant has been described [4, 5].

Case Presentation

A 1-month-old infant was brought to the Emergency Department of our Hospital due to irritability and feeding difficulties. He was born well, at 36 weeks of gestation, after an uncomplicated, supervised

pregnancy. The parents were second degree cousins, with no family history of kidney disease except for the mother's urolithiasis.

He had no fever or other symptoms. The physical examination showed no abnormalities, namely edema. His urine had no macroscopic alterations. Given the suspicion of urinary infection, an urinalysis was conducted, showing no indicators of infection, but significant proteinuria, with a protein-to-creatinine ratio of 2481 mg/mmol. Blood tests revealed a creatinine of 0.32 mg/dl, blood urea nitrogen 10 mg/dl, albumin 2.45 g/dl, normal electrolytes and lipid profile. A kidney ultrasound showed kidneys of preserved size and no other morphologic changes.

The infant was admitted for monitoring and etiological investigation. Urine protein level was quantified: 90,7 mg/m^2/h. Infectious causes of CNS were excluded (namely syphilis, herpes virus, cytomegalovirus, Epstein Barr virus, toxoplasma and hepatitis B infections) and genetic testing revealed a homozygous variant c.506T > C (p.Leu169Pro) in *NPHS2* gene.

At 9 months old he initiated treatment with enalapril with tolerance and later switched to ramipril.

A kidney biopsy was performed, after 5 years of follow-up. It revealed a preserved morphology, with mild congestion and slight widening of some capillary loops. There was a segmental distribution of mild mesangial hypercellularity in the glomeruli, accompanied by mild mesangial expansion, also with a segmental distribution. There was no thickening of glomerular capillary walls and no signs of sclerosis were observed. The tubules had preserved morphology, although with mild luminal dilatation in some of the proximal ones.

During follow-up, the patient remained clinically stable, with minimal or no edema, and controlled blood pressure. He continued to present with proteinuria, rarely in the nephrotic range, and without impairment of kidney function, along without hypoalbuminemia, mild dyslipidemia, with no need for pharmacological treatment. Thyroid function was normal.

In the most recent laboratory evaluation, at 15 years of age, while receiving ramipril 10mg/day he had a creatinine level of 0.6 mg/dl (eGFR ~ 120ml/min/1.73m2), blood urea nitrogen of 11.78 mg/dl, albumin 4.1 g/dl, total cholesterol 196 mg/dl, and a urine protein-to-creatinine ratio of 87 mg/mmol.

Discussion

CNS when caused by genetic variants is generally associated with an unfavorable prognosis, characterized by progressive kidney dysfunction and the early need for kidney replacement therapy.

CNS caused by *NPHS2* mutations is typically inherited in an autosomal recessive manner and results from defects in podocin, an integral membrane protein expressed almost exclusively in glomerular podocytes. Podocin is a key component of the slit diaphragm, interacting with nephrin, CD2-associated protein (CD2AP), and other structural proteins to preserve the integrity of the glomerular filtration barrier.

Consequently, pathogenic variants in *NPHS2* lead to disruption of podocyte function and the development of steroid-resistant nephrotic syndrome. The most reported histological finding in *NPHS2*-associated disease is focal segmental glomerulosclerosis (FSGS), reflecting progressive podocyte injury and nephron loss. Clinically, patients carrying homozygous or compound heterozygous *NPHS2* variants usually present proteinuria during early childhood, often before six years of age, and frequently experience progressive deterioration of kidney function leading to kidney failure. The disease is also characteristically resistant to corticosteroids and other immunosuppressive therapies.

The patient described in this report presented at one month of age with severe proteinuria and hypoalbuminemia, fulfilling the diagnostic criteria for CNS. Genetic testing identified a homozygous NPHS2 c.506T > C (p.Leu169Pro) variant, supporting monogenic etiology. The presence of parental consanguinity further reinforces the likelihood of autosomal recessive inheritance.

Despite the early presentation, the subsequent clinical course was favorable. Following initiation of angiotensin-converting enzyme inhibitor therapy, the patient remained clinically and biochemically stable throughout childhood and into early adolescence. Over a follow-up period of 15 years, he maintained normal kidney function and did not develop the progressive decline in kidney function that characterizes many forms of *NPHS2*-associated disease. Proteinuria persisted throughout follow-up but generally remained below the nephrotic range, while hypoalbuminemia and dyslipidemia gradually improved without the need for intensive supportive measures.

This clinical course represents an unusually mild phenotype compared with that typically reported in patients with *NPHS2*-associated CNS. Some sources state progression to kidney failure in the first or second decade of life, particularly for earlier-onset cases. Nevertheless, increasing evidence suggests that the phenotypic spectrum of *NPHS2*-related disease is broader than initially recognized, ranging from severe congenital forms to milder presentations and even adult-onset disease. The favorable long-term outcome observed in our patient further illustrates the marked genotype–phenotype heterogeneity that characterizes *NPHS2*-associated disease. One might also question the benefit of early ACE inhibitor use on the course of this case. The kidney biopsy findings are also noteworthy. Although FSGS is the lesion most frequently associated with *NPHS2* mutations, in some cases initially there is minimal change disease that evolves to FSGS. In our case, histological examination performed five years after diagnosis demonstrated only mild mesangial changes and no evidence of segmental sclerosis or significant chronic damage. These findings correlate well with the preserved renal function and overall mild disease course observed throughout follow-up.

This case highlights the importance of early genetic testing in infants presenting with nephrotic-range proteinuria and raises the question of whether early initiation of angiotensin-converting enzyme (ACE) inhibitor may have contributed to the favorable clinical course. Establishing a molecular diagnosis not only prevents unnecessary exposure to potentially ineffective immunosuppressive therapies, but also provides valuable prognostic information, facilitates genetic counselling, and may influence future decisions regarding family screening and the suitability of relatives as potential kidney donors.

Furthermore, reports of atypical or milder phenotypes contribute to a better understanding of the clinical spectrum of *NPHS2*-related disease and may improve future genotype–phenotype correlations.

In conclusion, we report a patient with CNS associated with a homozygous *NPHS2* c.506T > C (p.Leu169Pro) variant who demonstrated an unusually mild clinical course, with preserved kidney function throughout childhood and early adolescence. This case expands the phenotypic spectrum of *NPHS2*-associated CNS and highlights the substantial clinical heterogeneity of the disease, emphasizing the importance of individualized prognostic assessment based on molecular diagnosis.

Summary - what is new
● Case of a 15 year-old-boy diagnosed with congenital nephrotic syndrome who, against all odds, has maintained controlled proteinuria and stable kidney function under treatment with an ACE inhibitor.

Declarations

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Competing interests:

The authors have no relevant financial or non-financial interests to disclose.

Consent

Written informed consent for publication was obtained from the patient´s parents.

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