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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Genotype/phenotype relationship in mild congenital nephrotic syndrome

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SUMMARY

Introduction Congenital nephrotic syndrome (CNS) is a severe disease complicated by hemodynamic instability, infections, thrombosis, growth disorder and progressive renal failure leading to end-stage kidney disease within a few years. The mutations of *NPHS1* encoding nephrin is the most common cause of the CNS.

The aim of this paper was to present a patient with *NPHS1* homozygous Ser350Pro missense mutation that unexpectedly caused a mild clinical course of CNS.

Case outline We present a female patient who was diagnosed with severe nephrotic syndrome at 2.5 months of age. While waiting for the result of the genetic analysis, she was treated unsuccessfully with corticosteroids and angiotensin converting inhibitor (ACEI) four weeks, and then under Cyclosporine A (CsA) and ACEI she achieved partial remission within three months. Initially, the milder clinical course was explained by the positive effect of CsA, but as partial remission persisted even after the discontinuation of this drug, it remains unclear what influenced the improvement of the clinical course of the disease. At the time of writing this paper, the patient was 10.9 years old with normal serum creatinine, normal blood pressure and non-nephrotic proteinuria.

Conclusion *NPHS1* homozygous Ser350Pro missense mutation may be presented by a mild clinical course of CNS. Further studies are needed to clarify a more predictive CNS genotype/phenotype relationship.

Keywords: *NPHS1* gene; nephrin; hereditary nephrotic syndrome; infant

INTRODUCTION

Congenital nephrotic syndrome (CNS) is a heterogeneous group of disorder characterized by massive, nephrotic proteinuria, hypoalbuminemia, and edema, manifested in utero or during the first three months of life. CNS consequences are numerous including hemodynamic instability, infections, thrombosis, growth disorder and progressive renal failure leading to end-stage renal disease (ESRD) usually in the early childhood [1].

In most cases the CNS is caused primarily by the underlying genetic abnormality related to structural and regulatory proteins of the glomerular filtration barrier [2, 3]. However, it can rarely be secondary, caused by congenital infections (syphilis, cytomegalovirus infection, toxoplasma, rubella, pertussis, immunodeficiency virus infection, malaria, hepatitis B) or due to immune disease of the mother [3–6].

Nowadays, genetic diagnosis of hereditary CNS is possible in 85% of cases. More than 80% of genetic causes of CNS include mutations of the genes *NPHS1, NPHS2, WT1, PLCE1* and *LAMB2*, while other less commonly mutated genes account for an additional ~5% of CNS diagnoses [2]. The mutations of *NPHS1* or *NPHS2* are the most common causes of the CNS [2, 7]. An established genetic diagnosis of the CNS has a great influence on its management and prognosis. Since CNS is almost always a serious disease that is resistant to immunosuppressive therapy, management is very challenging and may require daily albumin infusions and intensive symptomatic treatments, but when optimal conservative measures are not successful to avoid complications, early unilateral or bilateral nephrectomy may be indicated [4]. Therefore, most children require renal replacement therapy in early childhood and the mortality rate is high [1, 4, 8]. However, although patients with CNS often have an inevitable rapid progression to ESRD, extremely rare milder cases of the disease indicate that genetic diagnosis is not always reliable for predicting the clinical course of CNS [9, 10].

The aim of this report was to present our patient with *NPHS1* homozygote Ser350Pro missense mutation that unexpectedly manifested a mild clinical course. This way, we wanted to point out the possible variations of the CNS genotype–phenotype relationship.

CASE REPORT

We present a female who was diagnosed with severe nephrotic syndrome at 2.5 months of age (Table 1). It had been noticed that her placenta was enlarged. Parents denied consanguinity. An infectious or immunological etiology of the

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Table 1. Trends of renal function, serum protein, proteinuria and therapy over time

Age (months)	sCr (μmol/l)	eGFR (ml/min./1.73 m2)	Serum albumin (g/l)	Serum protein (g/l)	Urine protein/creatinine (mg/mg)	Daily iv albumin	Captopril (mg/kg BW/day)	CsA** (mg/kgBW/day)
2.5	15	134.7	9	37	28.2	-	-	-
7.3	25	100.8	37	62	32.8	12 g / 24 h	0.4	-
9	28	95	26	55	33	12 g / 24 h	0.4	6.2*
10.5	35–40	76.6	31	60	3.6	12 g / 24 h	0.6	5.8
12	33–83	84.8	31	63	5	-	0.9	4.5
18	26	139.4	23	55	3.6	-	0.7	4.6
20.5	25–40	148	18	53	4.9	-	0.9	7.2
24	21	184.3	18	51	4.9	-	1.2	6.6
30	27	153.3	18	54	4	-	1.2	6.6
42	43–45	103.7	-	-	-	-	5.4	
57.5	16	306.2	19	56	3.2	-	0.9	4.3
Lost to follow-up								
9 years	45	136	33	65	1.5	-	0.5	?
10.5 years	39.9	180	30	63	1.5	-	0.3	-
10.9 years	31	197	32	66	1.45	-	0.3	-

sCr – serum creatinine; eGFR – estimated glomerular filtration rate; iv – intravenous; BW – body weight; CsA – cyclosporine A; **therapy started at the age of eight months

CNS was ruled out by appropriate investigations. A kidney biopsy was performed, which showed immature glomeruli with a mild degree of mesangial cell hypercellularity and microcystic dilatation of proximal tubules. A genetic analysis was requested abroad and homozygous *NPHS1* (NM_004646.4) c.1048T>C (p. Ser350Pro) missense mutation was reported. Due to hemodynamic instability caused by severe hypoalbuminemia, the patient required daily albumin infusions through a central venous catheter, which was changed several times due to infections. In addition, the patient received diuretics, vitamin D, thyroxin, and iron, as well as anticoagulants, gamma globulin replacement and antibiotics during frequent infections. Angiotensin-converting enzyme inhibitor (ACEI) was introduced into therapy in the third month of life, and corticosteroids from the seventh month for four weeks, without improvement of the disease. Cyclosporine A (CsA) treatment was then initiated with continuing ACEI, and partial remission was achieved within three months, together with resolving the need for albumin infusion. CsA and ACEI continued for the next four years. From the fourth to the ninth year of life, the girl was lost from medical follow-up because the situation in the family worsened due to the mother's illness (severe depression that required long-term hospital treatment), which most likely caused her not to receive regular medication, including CsA. During the most recent check-up, after the improvement of the mother's illness, the girl was 10.9 years old, body height was 125 cm (-2.85 z), body weight 28.5 kg (-1.36 z), body mass index was 18.2 kg/m2 (0.37 z). Her short stature may not only be the result of a chronic disease, but also the influence of genetics, as both parents are short. She was normotensive, without edema. Her serum creatinine was normal as well as serum protein, and her proteinuria was in non-nephrotic range (416.8 mg / 24 hours) (Table 1).

Ethical approval was granted by the local Ethics Committee of the Novi Pazar General Hospital. The number of the ethical approval is 3498/2023. A signed, informed parental consent was taken for this publication.

DISCUSSION

It is very well known that an established genetic diagnosis of CNS has great influence of its management and prognosis; in genetic forms of CNS the use of immunosuppressive drugs should be avoided and renal biopsy is not necessary [4, 6]. However, the genetic diagnosis is not always able to reliably indicate the severity of the disease, which has a great impact on the treatment of the disease and its acceptance by the patient and parents or caregivers. Variable disease penetrance can be a function of the specific mutation(s) involved or of allele dosage as well as the modulating influence of additional genetic variants but may also reflect the action of unlinked modifier genes, epigenetic changes or environmental factors [11].

While waiting for the genetic diagnosis, we tried treatment with corticosteroids without success, and then with CsA, during which a partial remission occurred and the need for albumin infusions ceased. The decision to introduce CsA in our patient was motivated by numerous problems in our patient related to daily intravenous albumin infusions, as well as reports on the favorable effect of CsA in hereditary nephrotic syndrome, which is explained by its ability to stabilize the actin cytoskeleton beyond its immunosuppressive effects [12, 13, 14]. In the previous report [15], the favorable course of the disease was mainly attributed to the effects of ACEI and CsA. However, since the patient was under very low and irregular doses of CsA for the next six years, its influence on the course of the disease is not entirely clear. The antiproteinuric effect of ACEI cannot be underestimated but our patient received the drug in a small dose and probably irregularly. When everything is taken into consideration, it seems most likely

Table 2. Clinical and genetic characteristics of the *NPHS1* patients with mild congenital nephrotic syndrome course

Study	Age at onset	Mutation in *NPHS1*	Clinical course	Treatment
Bérody et al. [8]	No data	c.2131C > A(p.Arg711ser) homozygous missense mutation	Renal survival of 30 years	No data
Kestilä et al. [16]	After birth	Fin-major mutation in one gene and a missense mutation (a change of arginine-743 to cysteine in the extracellular Ig-5 domain) in the other one.	Partial remission	Indomethacin and Enalapril started at three months of age
Lenkkeri et al. [18]	11 days	Compound heterozygous for two different sequence variants in exons 9 and 27 (NM_004646.4:c.1048T>C:p.Ser350Pro; M_004646.4:c.3478C>T:p.Arg1160Ter)	Remission at six months	Supportive
Espinosa et al. [19]	No data	c.3478 C > T in exon 27 homozygous missense mutation	Remission at 11 years of age	No data
Li et al. [20]	50 days	c.3312-23C > T intron 25 c.2207T > C exon 16 c.928G > A in exon 8	Remission	Glucocorticoids
Our case	2.5 months	Ex9: c.1048T > C p. (Ser350Pro)	Partial remission at 12 months	CsA + ACEI during four years

CsA – Cyclosporine A; ACEI – angiotensin converting inhibitor

that the *NPHS1* genetic disorder had the primary and decisive influence on the milder course of the disease in our patient. *NPHS1* gene is localized to chromosome 19q13.1 and encodes for nephrin protein, which is a fundamental constituent of the slit diaphragm, and plays a crucial role in cell signaling [16]. Patrakka et al. [17] found that most *NPHS1* patients have the negative nephrin expression as well as the lack of slit diaphragm in kidneys that strongly indicate the total lack of functional nephrin in these patients causing massive proteinuria. Only one out of 46 patients with CNS had some nephrin expression retained in the kidneys associated with a mild CNS clinical course (Table 2). The authors suggested nephrin expression to be predictive for the favorable course of *NPHS1* disease [17]. This way of predicting the clinical course of the disease is generally not applied in clinical practice, and the findings of genetic analysis are mainly used. Table 2 presents other patients reported in the literature with a mild CNS clinical course. The homozygous missense mutation in exon 9 of the *NPHS1* gene designated as Ex9: c.1048T>C p. (Ser350Pro) was demonstrated in our patient. This mutation was first reported by Lenkkeri et al. [18] in 1999. To our knowledge, this homozygous mutation is not known to cause benign CNS except in our patient. Espinosa et al. [19] reported a patient who had spontaneous CNS remission at six months of age with an *NPHS* mutation identical to our patient (c.1048T>C (p. Ser350Pro) in exon 9) in one gene and different one in the other gene (c.3478C>T(p. Arg1160Ter) in exon 27). Wong et al. [9] performed *NPHS1* mutation analysis in 19 patients, five Caucasian patients and 14 Maori patients with a highly variable and protracted timeline to ESRD with median renal survival of 30 years versus 0.7 years in Caucasian patients. A Chinese study described complete remission of CNS under corticosteroid therapy in a girl who had heterozygous *NPHS1*mutation [20]. In a Turkish study no association between the *NPHS1* mutation type (protein truncating or missense) and survival or age at diagnosis was found, but the patients with mutations affecting transmembrane or intracellular domains of nephrin in ≥ 1 alleles had a significantly longer survival time than patients with mutations affecting the extracellular domain in both alleles [7].

It can be concluded that *NPHS1* homozygous Ser350Pro missense mutation may be presented by a mild clinical course of CNS. More data are needed before the question of phenotype/genotype correlations in CNS can be addressed.

Conflict of interest: Not declared.

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Однос између генотипа и фенотипа у благом конгениталном нефротском синдрому

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САЖЕТАК

Увод Конгенитални нефротски синдром је тешка болест компликована хемодинамском нестабилношћу, инфекцијама, тромбозом, поремећајем раста и прогресијом бубрежне инсуфицијенције до терминалног стадијума у року од неколико година. Мутације гена *NPHS1* који кодирају нефрин су најчешћи узрок конгениталног нефротског синдрома. Циљ овог рада је да опишемо болесницу са хомозиготном *NPHS1 Ser350Pro missense* мутацијом која је неочекивано изазвала благи клинички ток конгениталног нефротског синдрома.

Приказ болесника Приказан је случај девојчице којој је са два и по месеца дијагностикован тешки нефротски синдром. Док је чекала резултат генетичке анализе, девојчица је четири недеље безуспешно лечена кортикостероидима и инхибитором ензима који конвертује ангиотензин, а затим је под циклоспорином А и инхибитором ензима који конвертује ангиотензин постигла делимичну ремисију у року од три месеца. У почетку се блажи клинички ток објашњавао позитивним дејством циклоспорина А, али како је делимична ремисија трајала и после укидања овог лека, остаје нејасно шта је утицало на побољшање клиничког тока болести. У време писања овог рада болесница је имала 10,9 година, нормалан креатинин серума, нормалан крвни притисак и ненефротску протеинурију.

Закључак *NPHS1* хомозиготна *Ser350Pro missense* мутација се може испољити благим клиничким током конгениталног нефротског синдрома. Потребне су даље студије да би се разјаснио предиктивни однос између генотипа и фенотипа у конгениталном нефротском синдрому.

Кључне речи: ген *NPHS1*; нефрин; хередитарни нефротски синдром; одојче