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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Congenital nephrotic syndrome may respond to cyclosporine A – A case report and review of literature

Bilsana Mulić[1], Gordana Miloševski-Lomić[2], Dušan Paripović[2], Divna Kruščić[2], Mersudin Mulić[3], Amira Peco-Antić[2]

[1]Novi Pazar General Hospital, Pediatric Department, Novi Pazar, Serbia;
[2]University of Belgrade, University Children's Hospital, Department of Nephrology, Belgrade, Serbia;
[3]State University of Novi Pazar, Novi Pazar, Serbia

SUMMARY

Introduction Congenital nephrotic syndrome (CNF) is manifested at birth or within the first three months of life. The Finnish-type of CNF is caused by the mutation of the NPHS1 gene, which encodes nephrin in the podocyte slit diaphragm. It is a very severe disease, for which immunosuppressive therapy is not advised. Here we describe a patient with CNF who responded to CsA by partial remission.

Case outline A girl aged 2.5 months presented with severe non-syndromic steroid-resistant nephrotic syndrome. She needed aggressive support including daily albumin infusions and diuretics. Substitution of vitamin D, thyroxin, and anticoagulants were regularly administered. She was also treated with angiotensin converting enzyme inhibitor, without clear benefits regarding proteinuria. In addition, she received intravenous gamma-globulin replacement therapy and antibiotics during frequent infections. While waiting for the results of genetic analyses and faced with many problems related to daily albumin infusions, infections, and thromboembolic complications, cyclosporine A (CsA) was introduced as an alternative to early nephrectomy and consequent renal failure. The patient responded by partial remission and CsA treatment continued at home without the albumin infusions. After almost five years since the beginning of the treatment, the patient's renal function remains unreduced.

Conclusion Our case demonstrates that CsA can induce partial remission in patients with genetic forms of steroid-resistant nephrotic syndrome without influencing the glomerular filtration rate. However, its long-term effect and safety should carefully be monitored.

Keywords: NPHS1 gene mutation; nephrin; steroid resistant nephrotic syndrome; children

INTRODUCTION

Congenital nephrotic syndrome (CNS) is manifested at birth, or within the first three months of life. It is mostly an inherited disease caused by an autosomal recessive mutation in the NPHS1 gene, which encodes a transmembrane protein designated as nephrin [1]. Nephrin belongs to immunoglobulin family of cell adhesion molecules. It is a structural protein of the glomerular podocytes slit diaphragm that interacts with two other podocytes proteins – podocin and CD2AP. This explains why nephrin abnormalities cause severe proteinuria [1].

Being the most common in Finland, with an incidence of 1.2 per 10,000 live births, CNS due to the NPHS1 gene mutation is also known as Finnish nephrotic syndrome (CNF) [2]. The causative abnormal gene has been localized to the long arm of chromosome 19 in both Finnish and non-Finnish families [3, 4]. CNF is a very severe disease with prenatal increased proteinuria, premature birth, and early postnatal steroid-resistant nephrotic syndrome (SRNS). Infections, thromboembolism, malnutrition, and psychomotor retardation are common consequences, while terminal renal failure usually occurs at the age of three to eight years [4].

Treatment of CNF is mainly supportive, including daily or every other day albumin infusions, diuretics, replacement of thyroxin and gamma-globulin, a high-protein low-salt diet, and supplements of iron, vitamin D and other vitamins. Prevention of infections and thromboembolic events is also necessary. Angiotensin converting enzyme inhibitors (ACEI) and non-steroidal anti-inflammatory drugs (like indomethacin) are used to decrease proteinuria by reducing intraglomerular pressure. However, some patients need early nephrectomy (even before renal failure develops) due to massive drug-resistant urine protein loss. With known genetic background, immunosuppressive therapy is not advised. However, there are a few reports in literature supporting cyclosporine A (CsA) therapy in hereditary SRNS [5–9]. Here we describe a patient with CNF who responded to CsA by partial remission. Similar experiences from literature are discussed.

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Correspondence to:
Bilsana MULIĆ
Pediatric Department of the Novi Pazar General Hospital
Generala Živkovića 1
36300 Novi Pazar, Serbia
emmulic@mts.rs

CASE REPORT

The patient is a girl born as the fourth child from the third pregnancy. Birth weight and birth length were 3,650 g and 55 cm, respectively. The placenta was enlarged. Early postnatal development was unremarkable.

The first child from a twin pregnancy and the third child were stillborn due to an unknown cause. Consanguinity was not reported.

Nephrotic syndrome was diagnosed at the age of 2.5 months after DiTePer vaccination. C3 and C4 complements were normal, as well as markers for Epstein–Barr, hepatitis B and C viruses infections. The tests for *Toxoplasma gondii* as well as for *Treponema pallidum* were also negative. Glomerular filtration rate was normal, while severe hypoproteinemia (total protein 37 g/l), hypoalbuminemia (9 g/l), hyperlipidemia (cholesterol 6.3 mmol/l, triglyceride 10.7 mmol/l) and nephrotic-range proteinuria (urine protein/creatinine ratio of 28.2 mg/mg) were found. Kidney biopsy showed immature glomeruli with mild degree of mesangial cell hypercellularity and microcystic dilatation of proximal tubules.

The patient needed daily albumin infusions and diuretics (furosemide and spironolactone). Substitution of vitamin D, thyroxin, and iron, as well as anticoagulants, were regularly administered. In addition, she received gamma globulin replacement and antibiotics during frequent infections. Daily albumin infusions were administered via a central venous catheter (Port-a-Cath), which had to be changed four times due to infections. From the third month of life she has been treated by ACEI and from the seventh month of life she received prednisone without any benefit. After four weeks of not responding to steroids and while waiting for the results of genetic analyses, the patient was started on CsA (150 mg/m^2). She responded with partial remission within three months (urine protein/creatinine ratio of 3.6 mg/mg). Blood level of Neoral was in the 75–150 ng/ml range. Regular albumin infusions were no longer required (Table 1). The results of genetic analyses were finished after nearly a year. The documented homozygous missense mutation in exon 9 of the NPHS1 gene designated as Ex9: c.1048T>C p. (Ser350Pro) was found. CsA continued for the next four years.

At the time this manuscript is prepared the patient is 57.7 months old. Her body height is 100 cm (percentile 8.3, Z score -1.4) and body weight is 16 kg (percentile 25.1, Z score -0.67). She is normotensive, with an average casual blood pressure of 90/60 mmHg. Her serum creatinine is 16 µmol/l and her glomerular filtration rate estimated according to the Schwartz's formula is increased (> 120 ml/min./1.73 m^2) [10]. Total protein and albumin are 56gl/l and 19g/l, respectively. Proteinuria is increased (860 mg/l), with protein/creatinine ratio of 3.2 mg/mg.

DISCUSSION

We reported a patient with CNF due to homozygote missense mutation Ser350Pro. This mutation was described previously [11]. To date, more than 140 different NPHS1 mutations have been identified, comprising nonsense, missense, and frameshift insertion/deletion as, well as splice-site mutations [12, 13]. Clinical presentation and histological findings of our patient were typical for CNF. However, clinical course of the disease was modified significantly by the cyclosporine treatment due to which regular albumin infusions could be discontinued without any negative effects on the renal function. Unfortunately, during the last year, due to unfavorable family situation, she received a lower dosage of cyclosporine that could affect her current proteinuria.

CsA is a calcineurin inhibitor and its antiproteinuric properties are attributed to its immunosuppressive effect related to immunomodulatory action on T cells [14, 15]. In addition, it was demonstrated that the antiproteinuric properties of CsA may also result from a direct stabilization of the podocyte actin cytoskeleton by blocking the calcineurin-mediated dephosphorylation of synaptopodin and upregulating the expression of cofilin-1, which is independent of its effect on synaptopodin [16, 17, 18].

Antiproteinuric effect of CsA in patients with hereditary SRNS varies considerably. The clinical experience

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

Age (months)	sCr (µmol/l)	eGFR (ml/min./1.73 m^2)	serum albumin (g/l)	serum protein (g/l)	Urine protein/creatinine (mg/mg)	Daily iv albumin	Captopril (mg/kgBW/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		64	3.1	-	0.9	5.4
57.5	16	306.2	19	56	3.2	-	0.9	4.3

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

is limited to single-center observations demonstrating a partial response to CsA in selected patients [5–9, 16]. Our patient is an additional case supporting the favorable effect of CsA in CNF. However, because of the small number of reported patients and CsA nephrotoxic side effects, it still remains unclear whether the benefit of CsA-induced partial remission improves overall renal survival. In patients reported by Malina et al. [6], Gellermann et al. [7], Caridi et al. [8], and Hinkes et al. [9], the CsA-induced partial remission significantly improves renal outcome. In contrast, data from a German study strongly support the idea not to expose CNS/SRNS patients with inherited defects related to podocyte function to intensified immunosuppression with CsA [19]. They found a partial remission in only 17% of patients with hereditary CNS (two patients affected by a WT1 mutation) [19]. Preservation of renal function was significantly better in children with nongenetic SRNS after a mean follow-up time of 8.6 years (terminal renal failure in 29% vs. 71%) [19].

The decision to introduce CsA therapy to patients with CNS is even more complicated by the fact that not all recorded NPHS1 mutations had a severe clinical course [12]. The clinical variability is apparently influenced by the sex of a patient, as the majority of mildly affected cases are female [12, 13]. The decision on the introduction of CsA in our patient was encouraged by numerous problems concerning daily intravenous albumin infusions, including technical problems with peripheral veins, or catheter, related infections, and thromboembolic complications. In fact, the CsA therapy was the only alternative to early nephrectomy and consequent renal failure. Also, it should be said that if we had beforehand received the results of genetic analysis, we would probably not have chosen the CsA therapy.

Congenital nephrotic syndrome is steroid-resistant due to an underlying genetic abnormality. Our case demonstrates that CsA can induce partial remission in patients with genetic forms of SRNS without influencing the glomerular filtration rate. However, its long-term effect and safety have yet to be investigated.

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Конгенитални нефротски синдром се може лечити циклоспорином А – приказ случаја и преглед литературе

Билсана Мулић[1], Гордана Милошевски-Ломић[2], Душан Париповић[2], Дивна Крушчић[2], Мерсудин Мулић[3], Амира Пецо-Антић[2]

[1]Општа болница Нови Пазар, Педијатријско одељење, Нови Пазар, Србија;
[2]Универзитет у Београду, Универзитетска дечја клиника, Одељење за нефрологију, Београд, Србија;
[3]Државни универзитет у Новом Пазару, Нови Пазар, Србија

САЖЕТАК

Увод Конгенитални нефротски синдром (КНС) испољава се на рођењу или у прва три месеца живота. Фински тип КНС настаје због мутације гена *NPHS1*, који кодира нефрин у подоцитима бубрега. То је врло тешка болест, за коју се не саветује имуносупресивна терапија. Приказујемо болесника са КНС код којег је циклоспорин А (*CsA*) довео до парцијалне ремисије нефротског синдрома.

Приказ болесника Код девојчице од 2,5 месеца испољио се тежак, несиндромски облик стероид-резистентног нефротског синдрома (СРНС). Примењена је агресивна терапија укључујући свакодневне инфузије албумина и диуретике. Добијала је и супституциону терапију тироксина и витамина Д и антикоагулантну терапију, а по потреби, због честих инфекција, гама-глобулине и антибиотике. Лечење инхибиторима ангиотензин конвертујућег ензима није значајно смањило протеинурију. Док смо чекали резултате генетичке анализе, а суочени са бројним проблемима везаним за свакодневне инфузије, честе инфекције и тромбоемболијске компликације, ординирали смо *CsA* као једину алтернативу раној нефректомији и очекиваној бубрежној инсуфицијенцији. Болесник је у току три месеца лечења одговорио парцијалном ремисијом без потребе за инфузијама албумина. После пет година од почетка лечења, њена бубрежна функција још увек није снижена.

Закључак *CsA* може довести до парцијалне ремисије код болесника са генетичким облицима СРНС без негативног ефекта на гломерулску филтрацију. Међутим, дугорочно дејство и сигурност ове терапије треба пажљиво пратити

Кључне речи: мутација гена *NPHS1*; нефрин; стероид-резистентни нефротски синдром; деца