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## Case Report / Приказ случаја

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

Конгенитални нефротски синдром се може лечити циклоспорином А –  
Приказ болесника и преглед литературе

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

### Конгенитални нефротски синдром се може лечити циклоспорином А – Приказ болесника и преглед литературе

#### SUMMARY

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

**Case Outline** A girl aged 2.5 months presented with severe non syndromatic steroid resistant nephrotic syndrome. She needed aggressive support including every day albumin infusions and diuretics. Substitution of vitamin D, thyroxin, and anticoagulants were regularly administered. She has been also treated by angiotensin converting enzyme inhibitor, without clear benefit on 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 every day 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 continued with CsA treatment at home without albumin infusions. After almost five years since the beginning of the treatment, her renal function has not yet been reduced.

**Conclusion** 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 should carefully be monitored.

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

#### Сажетак

**Увод** Конгенитални нефротски синдром (КНС) се испољава на рођењу или у прва три месеца живота. Фински-тип КНС настаје због мутације *NPHS1* гена, 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 (ЦсА) 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 3 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 у болесника са генетичким облицима СРНС без негативног ефекта на гломерулску филтрацију. Међутим, дугорочно дејство и сигурност ове терапије треба пажљиво пратити.

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

#### INTRODUCTION

Congenital nephrotic syndrome (CNS) is manifested at birth, or within the first three months of life. It is mostly inherited disease caused by autosomal recessive mutation in *NPHS1* gene which encodes a transmembrane protein designated as nephrin [1]. Nephrin belongs to immunoglobuline family of cell adhesion molecules. It is structural protein of 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 of live births, CNS due to NPHS1 gene mutation is known also 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 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 (TRF) usually occurs at age of 3 to 8 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 are 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 by partial remission on CsA. Similar experiences from literature are discussed.

### **CASE REPORT**

A patient is a girl born as fourth child from the third pregnancy. Birth weight and birth length were 3650 g and 55 cm, respectively. The placenta was enlarged. Early postnatal development was normal.

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

Nephrotic syndrome was diagnosed at 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. Tests for Toxoplasma Gondii as well as for Treponema pallidum were also negative. Glomerular filtration rate (GFR) was normal, while severe hypoproteinemia (total protein 37 g/l), hypoalbuminemia (9 g/l), hyperlipidemia (cholesterol 6.3 mmol/l, trygliceride 10.7 mmol/l) and nephrotic range proteinuria (urine protein/creatinine ratio 28,2 mg/mg) were found. Kidney biopsy showed immature glomeruli with mild degree of mesangial cell hypercellularity and micro cystic dilatation of proximal tubules.

The patient needed every day albumin infusions and diuretics (furosemide and spironolactone). Substitution of vitamin D, thyroxin, and iron, and anticoagulants were regularly administered. In addition, she received gamma globulin replacement and antibiotics during frequent infections. Every day albumin infusions were administered via a central venous catheter (Port -A- Cut) which had to be

changed four times due to infections. From the 3<sup>rd</sup> month of life she has been treated by ACEI and from the 7<sup>th</sup> month of life she received prednisone without any benefit. After 4 weeks not responding on steroids and while waiting for the results of genetic analyses, Neoral (CyA) has been started (150 mg/m<sup>2</sup>). She responded with partial remission within 3 months (urine protein/creatinine ratio 3.6 mg/mg). A blood level of Neoral ranged 75-150 ng/ml. Regular albumin infusions were not further required (Table 1). The results of genetic analyses were finished after nearly a year. The documented homozygous missense mutation in exon 9 of NPHS1 gene designed as Ex9: c.1048T>C p. (Ser350Pro) was found. Cyclosporine A has been continued during the next 4 years.

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

Age (mo)	s Cr (μmol/l)	eGFR (ml/min/1.73m <sup>2</sup> )	Serum albumin (g/l)	Serum protein (g/l)	Urine protein/creatinine (mg/mg)	Every day iv albumine	Captopril (mg/kgB W/day)	Neoral (mg/kgB W/day)
2.5	15	134.7	9	37	28.2	-	-	-
7.3	25	100.8	37	62	32.8	12 g/24h	0.4	-
9.0	28	95.0	26	55	33.0	12 g/24 h	0.4	6.2*
10.5	35-40	76.6	31	60	3.6	12 g/24h	0.6	5.8
12.0	33-83	84.8	31	63	5.0	-	0.9	4.5
18.0	26	139.4	23	55	3.6	-	0.7	4.6
20.5	25-40	148.0	18	53	4.9	-	0.9	7.2
24.0	21	184.3	18	51	4.9	-	1.2	6.6
30.0	27	153.3	18	54	4.0	-	1.2	6.6
42.0	43-45	103.7	64	64	3.1	-	0.9	5.4
57.5	16	306.2	19	56	3.2	-	0.9	4.3

Mo- months; sCr-serum creatinine; eGFR- estimated glomerular filtration rate; iv-intravenous; BW- body weight; \*therapy started at 8 months of age

At the time this manuscript was 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 glomerular filtration rate (GFR) estimated according to the Schwartz's formula [10] is increased (>120 ml/min/1.73m<sup>2</sup>). Total protein and albumin are 56g/l and 19g/l, retrospectively. Proteinuria is increased (860 mg/l) with protein creatinine ratio 3.2 mg/mg.

## DISCUSSION

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

Cyclosporine A 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 [16, 17] and up regulating expression of cofilin-1, which is independent of its effect on synaptopodin [18].

Antiproteinuric effect of CsA in patients with hereditary SRNS varies considerably. The clinical experience 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 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., Gellermann et al., Hinkes et al., and Caridi et al. [6-9], the CsA-induced partial remission significantly improve renal outcome. On the contrary, data from 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 the 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 (TRF in 29% versus 71%) [19].

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

## CONCLUSION

Congenital nephrotic syndrome is steroid resistant due to 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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