

## CASE REPORT

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# Congenital Nephrotic Syndrome – Finish Type

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## ABSTRACT

**Introduction:** Identification of the NPHS1 gene, which encodes nephrin, was followed by many studies demonstrating its mutation as a frequent cause of congenital nephrotic syndrome (CNS). While this gene is found in 98% of Finnish children with this syndrome, non-Finnish cases have lower level of incidence ranging from 39 to 80%. **Case report:** This report describes the clinical presentation of a two-week-old neonate who presented with periorbital and lower extremities edema, abdominal distention, heavy proteinuria, serum hypoproteinemia and failure to thrive. Genetic analysis revealed NPHS1 gene mutation leading to CNS-Finnish type diagnosis. **Conclusion:** Through this case we want to create awareness about diagnosis and treatment challenges in developing countries for rare congenital diseases.

**Key words:** Congenital Nephrotic Syndrome, CNS, Congenital Nephrotic Syndrome-Finnish Type, NPHS1.

## 1. INTRODUCTION

Congenital nephrotic syndrome (CNS) is a very rare form of nephrotic syndrome. Its usual onset is within the first days of life and always before three months of age. Infants with CNS have a uniform clinical course characterized by failure to thrive, frequent infections and declining renal function. Recently, molecular genetics research has improved identification of mutant genes in many renal disorders. Accordingly, NPHS1 and NPHS2 mutations account for about 75% of CNS cases (1).

The prognosis in CNS is poor as the majority of cases die within six months of life. However, intravenous albumin supplementation, nutritional management, treatment of complications, dialysis and renal transplantation have been shown to improve the growth and development of affected children (2).

Here, we report an infant with CNS who is the first case confirmed by genetic study in our country.

## 2. CASE REPORT

A two-week-old male baby was admitted in the department of Neonatology because of periorbital and

lower extremities edema, abdominal distension, high temperature and failure to thrive.

He was born on 34<sup>th</sup> week of gestation. His birth weight was 2300 g, height 43 cm and head circumference 30 cm. Apgar score was 7 and 8 in the 1st and 5th minute, respectively. Prenatal course has been uneventful and family history was unremarkable. No information about the weight of placenta was recorded.

In admission, his weight was 2300 g and right inguinal hernia was noticed. Urinalysis revealed massive proteinuria (4+). Urinary sediment showed 15-20 RBC and 10-12 WBC per HPF. Laboratory studies demonstrated RBC count  $4.4 \times 10^{12}/\text{mm}^3$ , WBC count  $20900/\text{mm}^3$ , Hgb 11.5 g/dL, PLT  $155000/\text{mm}^3$ , total serum proteins 34 g/L, albumins 17 g/L, creatinine 101.4  $\mu\text{mol}/\text{L}$ , urea 11.4 mmol/L, cholesterol 7.29 mmol/L, CRP 120 mg/L and PCT 1.03 ng/ml. TORCH test resulted negative. Lumbar puncture found mass of leukocytes and liquor culture resulted positive on *Klebsiella pneumoniae*, which has been treated for 21 days based on antibiogram results. Abdominal ultrasound showed enlarged hyperechogenic kidneys with

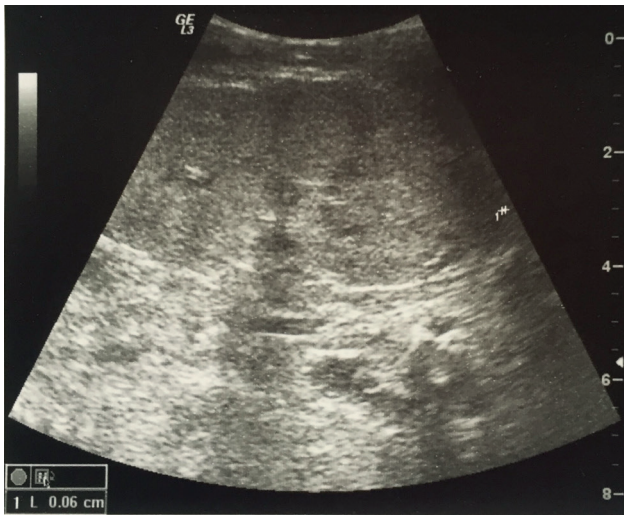


Figure 1. The ultrasound image of right kidney

abnormal cortico-medullary differentiation (Figure 1). CNS ultrasound found no pathological changes. Genetic examination demonstrated two heterozygous pathogenic variants of NPHS1 gene: I. c.248 dupA (protein. Tyr 83\*) in exon 2 and II. c.1048 T.C (protein: Ser 350Pro) in exon 9. Not any pathogenic variant were detected in other gene of the panel by sequencing (ACTN4, CD2AP, INF2, NPHS2, TRPC6, WT1). Hence, diagnosis of congenital nephrotic syndrome - Finnish type was made. Renal biopsy was not done as parents refused consent.

Albumin infusions and diuretic drugs were immediately started. Despite continuous treatment, the health condition of patient was still poor with edema, proteinuria, hypoproteinemia, high blood triglycerides and failing to thrive. Hence, Captopril and Indomethacin were added.

At the age of 4 months he developed pneumonia, confirmed with bilateral changes on chest x-ray. By that time he weighted 3600 g. Laboratory tests revealed leukocytosis  $21500/\text{mm}^3$  and high ESR 140 mmHg. Antibiotherapy for the next 14 days were started. In addition, other laboratory tests were as follows: urea 10.5 mmol/L, creatinine 58  $\mu\text{mol/L}$ , total proteins 28 g/L, albumins 12 g/L, triglycerides 15.8 mmol/L, cholesterol 5.60 mmol/L, iron 7.1  $\mu\text{mol/L}$ ; capillary blood gas analysis: Ph 7.4, Na 140 mEq/L, K 4.2 mEq/L, Ca 1.66 mmol/L. Massive proteinuria (4+) and numerous RBC were found in urinalysis and urinary sediment, respectively. Urine protein to urine creatinine ratio was 112 mg/mg. Urinoculture was sterile. Thyroid hormone profile showed hypothyroidism: TSH: 16.3 (normal values: 0.4-4.2 mU/l), FT4: 9.4 pmol (normal values: 10.3-35 pmol/L) FT3: 9.4 (normal values: 1.54-3.8 nmol/L). Anti TPO antibodies were normal at 24.7 IU/ml (normal values: <50 IU/ml). Thyroxine supplements were started.

Despite substitution and supportive therapy, the patient is failing to thrive. Now the baby is six months old and weights only 4000 g. Since dialysis for infants is not possible in our country, we are planning to transfer him to a more specialized center outside the country for dialysis and renal transplantation.

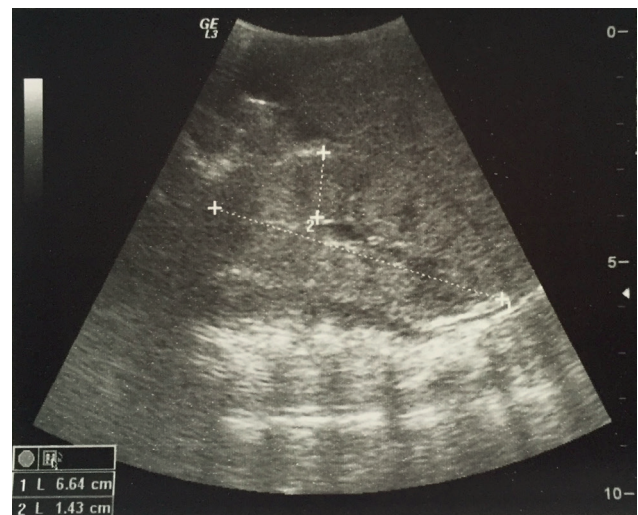


Figure 2. The ultrasound image of left kidney

### 3. DISCUSSION

We have reported a patient with CNS, who presented with edema, failure to thrive and abdominal distention at two weeks of age. The clinical course of the patient was typical of CNS. Genetic study identified two mutations in NPHS1 gene: I. c.248 dupA (protein. Tyr 83) in exon 2, a nonsense variant which has previously been described as disease cause for CNS finish type (3) and II. c.1048 T.C (protein: Ser 350Pro) in exon 9 a missense change which previously has been described as disease causative also for CNS finish type (4). The NPHS1 gene has 26 kb size and 29 exons. It codes a transmembrane protein named “nephrin”. This gene mutation detection rate varies among different ethnic groups. It approaches 98% in Finish children with CNS (5), but is lower outside Finland. Lenkkeri et al. reported that 80% of patients with CNS from North America, Europe and North Africa have mutations of the NPHS1 gene (4). Furthermore, in another study the frequency of Finish type in the Europe only, was reported to be 39% (1).

The treatment of CNS is very challenging. Intensive therapy with frequent albumin infusions, nutritional and vitamin supplementation, together with early bilateral nephrectomy, followed by dialysis, and transplantation, has been considered the standard treatment (2). Hypothyroidism develops secondary to loss of thyroid binding globulin, thyroid hormone and iodine, thus, thyroxine supplements are needed (6).

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II type-1 receptor blockers (ARB) showed to delay the progression of chronic renal diseases (7). Furthermore, children with nephrotic syndrome and other glomerular diseases showed decreased urinary protein excretion when treated with ACEi or ARB (8, 9) Indeed, Kovacevic et al. (10) reported a successful management of CNS with Captopril and Indomethacin in combination with unilateral nephrectomy, which might serve as an alternative medicine, allowing a delay for transplantation until the third year of life or longer. However, lack of possibility for dialysis in infants in our country overcomes the risk of undergoing nephrectomy and obligates

us to transfer him in a more specialized Centre outside the country.

This case is reported to highlight the diagnostic and therapeutic difficulties in developing countries when facing rare congenital problems as well as, to call attention to clinicians considering prenatal diagnosis through elevated maternal serum alpha fetoprotein and large placental size (11).

- The authors have no conflict of interest to disclose.

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