Congenital Nephrotic Syndrome of Finnish Type. A Report of Two Cases

Sindrom nefrotic congenital de tip finlandez – Prezentarea a două cazuri

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Abstract

Congenital nephrotic syndrome of the Finnish type (CNSF) is a rare autosomal recessive disease with high infant mortality without aggressive treatment. CNSF is characterized by massive in utero proteinuria and nephrosis at birth. The majority of cases are caused by genetic defects in the components of the glomerular filtration barrier, especially nephrin and podocin. Congenital nephrotic syndrome (CNS) may also be a part of a more generalized syndrome or caused by a perinatal infection. Immunosuppressive medication is not helpful in the genetic forms of CNS, and kidney transplantation is the only curative therapy. This paper describes the clinical features and outcome of the last 2 patients from 6 with CNSF who have been admitted to Pediatric Clinics from Târgu Mures in the last 15 years.

Keywords: *congenital nephrotic syndrome, proteinuria*

Rezumat

Sindromul nefrotic congenital tip finlandez este o boală rară, cu transmitere autozomal recesivă având o mortalitate infantilă ridicată fară un tratament agresiv. Se caracterizează prin proteinurie masivă „in utero" şi sindrom nefrotic prezent de la naştere. Majoritatea cazurilor sunt determinate de un defect genetic la nivelul componentelor membranei bazale glomerulare, nefrina şi podocina. Sindromul nefrotic congenital poate fi partea unui sindrom generalizat sau cauzat de o infecţie perinatală. Tratamentul imunosupresiv nu este eficient în formele genetice de sindrom nefrotic, transplantul renal constituind singura opţiune terapeutică în aceste cazuri. În această lucrare descriem ultimele 2 cazuri cu CNSF din cele 6 care au fost internate în clinicile de pediatrie din Târgu Mureş în ultimii 15 ani.

Cuvinte cheie: *sindrom nefrotic congenital, proteinurie*

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Introduction

CNSF is the most frequent of all types of CNS. It was described for the first time in 1959 by Hallman and Hjelt (1). CNSF is inherited as an autosomal recessive trait. The proportion of affected children in sibships is close to 25% (2). CNSF is the commonest form of the disease and occurs with an incidence of 1.2/ 10 000 live births in Finland (3, 4). The disease is not exclusive to Finland and has been described throughout the world.

CNSF is characterized by massive proteinuria, a large placenta (over 25% of the child's birth weight) and nephrotic syndrome from birth (3, 5). The definition is sometimes extended to children who develop these features within the first 3 months of life (3, 6). The differential diagnosis includes Drash syndrome, which consists of the triad of Wilms' tumor, male pseudohermaphroditism, and progressive renal failure secondary to diffuse mesangial sclerosis; nail-patella syndrome; Lowe syndrome. Congenital infection with Treponema Pallidum, Toxoplasma gondii, Cytomegalovirus or Human Immunodeficiency Virus can also present with CNS (3, 6-8).

Diagnosis of CNSF in our cases was based on massive proteinuria, manifestation of nephrotic syndrome soon after birth, exclusion of other types of CNS and typical findings in renal histology. These cases are reported to create awareness about this clinical entity in this part of the world especially among preterm infants.

Patients and clinical features

Since 1995, there have been 6 children with congenital nephrotic syndrome diagnosed at Pediatric Departments from Târgu Mures.

We reviewed the medical records and pathologic specimens of the last two patients (1 male- B.R. and 1 female- G.T.) in whom the onset consisted of edema, hypoalbuminemia, hyperlipidemia, and significant proteinuria within the first month of life. Clinical features, family history, and laboratory data at the time of presentation and during the evolution of the disease were assessed in each child. Renal tissue from these patients, obtained by autopsy, was reviewed and light microscopy findings were evaluated by the same pathologist. The management of each infant was supervised by a pediatric nephrologist, and included careful historical and laboratory evaluation at presentation and during hospital stays. There was no evidence of consanguinity or Finnish ancestry in any of these families. Infants with CNSF were diagnosed within the first 5 weeks of life.

Details of pregnancy were available in both cases, with a normal evolution in both, and spontaneous labour. The gestational age was 38 weeks in the first patient with a birth weight of 3,3 kg, while in the 2nd patient the gestational age was 33 weeks and the birth weight was 1,3 kg. Placental weight was available in both cases and in each there was no evidence of placentomegaly. Mothers denied any history of renal disease in their family.

Edema was the commonest presenting feature. Both infants had similar clinical features: poor general state, pallor, hyporeactivity, generalized edema, bulky abdomen, hepatomegaly, hydrocele (B.R.), umbilical hernia, anterior fontanella widely opened, dehiscent sutures, decreased urine output, high blood pressure.

Proteinuria was higly selective (> 85% albumin) and heavy in both infants, up to 5 g/24 hours. Renal function was impaired at presentation. Respiratory tract infection was a common problem in both cases. None of our patients had evidence of a congenitally acquired infection after testing for specific immunoglobulin antibodies against *Cytomegalovirus, Rubella, Herpes Simplex Virus, and Toxoplasma* (*Table 1*).

In both cases echocardiography revealed an atrial septal defect; G.T. had also patent ductus arteriosus. Abdominal ultrasonography showed renomegaly, loss of corticomedullary differentiation with increased

Table 1. Laboratory investigation at presentation

	B.R.	**G.T.**
Blood Count Values		
Hemoglobin (g/dl)	14	17
Leucocyte / mm^3	27000	17900
Trombocyte / mm^3	189000	170000
Erytrocyte sedimentation rate (ESR) (mm/h)	2	5
Serum Chemistry Value		
Serum creatinine (mg/dl)	2,44	0,8
Blood urea (mg/dl)	94,4	80,9
Total protein (mg/dl)	4,32	3,5
Albumin (mg/dl)	2,07	2,5
Gamma globulin (%)	3,9	4,2
Cholesterol (mg/dl)	238	260
Triglyceride (mg/dl)	401	424
Na^+ (mEq/l)	121	132
K^+ (mEq/l)	5,2	5,5
HCO_3^- (mmol/L)	12	-
BE (mmol/L)	-18,3	-
Serology for TORCH	Negativ	Negativ
Karyotype	46, XY	46,XX
Urine analysis		
Protein (mg/dl)	>500	>300
Erytrocytes/ high power field	100	150
pH	5,5	5
SG	1010	1015

parenchymal echogenity, without any evidence of obstructive pathology.

Management in both cases included a high-energy and low-sodium diet; thiazide diuretics were given daily to reduce edema, Albumin was given as a 20% solution in a dose of 1-2 g/kg day I.V. divided into one or two doses, together with I.V. Furosemide (1 mg/kg). Captopril (0,5 mg/kg/day in two divided doses) was prescribed to both infants, but there was no decline in the degree of proteinuria or the need for albumin transfusion. Additional treatment with Spironolactone was used in both infants. Both patients had arterial hypertension (blood pressure 110-120/70 mmHg) (> 99th percentile), and both of them died despite aggressive medical treatment because of bronchopneumonia and quick evolution to end-stage renal disease.

Autopsy findings:

The other major systems were normal except for the respiratory system which showed edematous lungs. The kidneys were slightly edematous. Cut surface of the kidneys was pale with some hemorrhagic spots at the cortico-medullary junction. The cortex had normal thickness, the medulla and thepelvi-calyceal system were normal. Ureters and bladder were macroscopically normal.

Histology report of the kidneys: Renal biopsies were examined for glomerular, tubular, interstitial, and blood vessel changes. The glomeruli were assessed for cellularity, sclerosis, and periglomerular fibrosis. The tubules were assessed for the presence of atrophy, dilatation or microcyst formation. The interstitium was examined for fibrosis and inflammatory cell infiltrate. Light microscopy revealed irregular pseudocystic dilatation of proximal tubules with proteic content, a

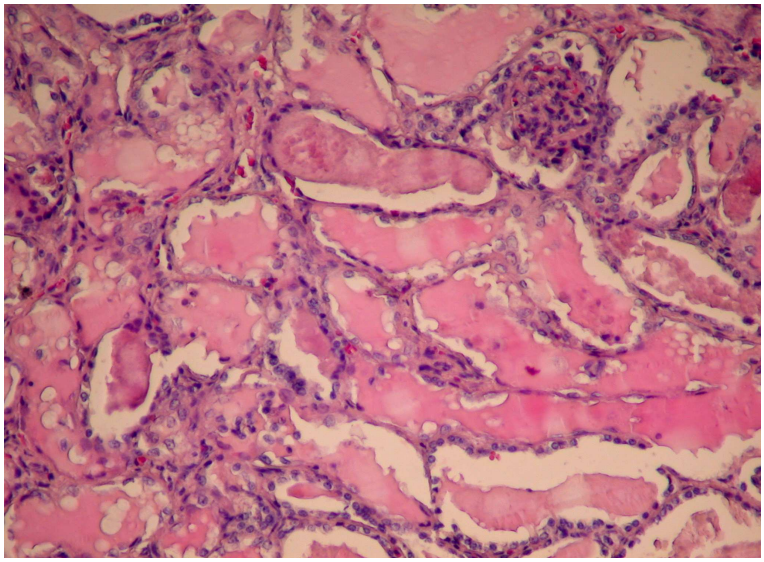

Figure 1. Light microscopy reveales irregular pseudocystic dilatation of proximal tubules with proteic content, a great number of glomeruli have a fetal appearance, mild proliferation of mesangial cells. 400X, Hematoxylin Eosin stain.

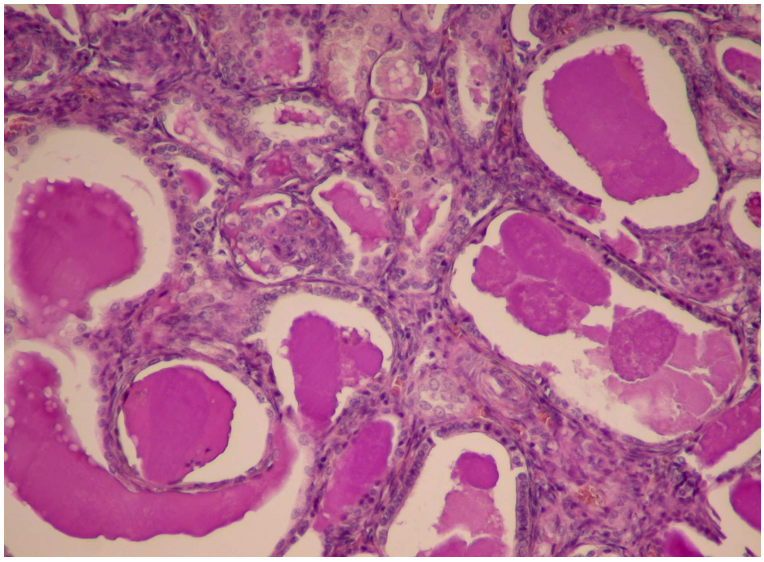

Figure 2. Light microscopy suggest tubular casts. 400X, Periodic Acid Schiff (PAS) hematoxylin stain.

great number of glomeruli had a fetal appearance, mild proliferation of mesangial cells (*Figure 1*). Periodic Acid Schiff (PAS) stain suggested tubular casts *(Figure 2).*

Discussions

Although CNSF occurs most often in Finland and Scandinavia, typical cases of CNSF have been reported all over the world (1:50000 newborns in North America), including our country (5, 7, 9, 10). The incidence of CNSF in Romania is unknown as it is an exceptionally rare disease.

Although uncommon, CNSF continues to be a diagnostic and therapeutic challenge for the pediatrician.

In 1998 Kestila et al identified in the chromosomal region 19q13.1 the gene on which different mutations segregate with the disease (11). This gene NPHS1 (nephrin gene) encodes a protein called nephrin which is expressed only in visceral epithelial cells of the glomeruli and was found to be defective in CNSF. This supports the hypothesis that a mutation of the NPHS1 is responsible for both typical and atypical CNSF in non-Finnish patients. NPHS1 encodes a podocyte-specific type 1 membrane protein, nephrin, which belongs to the large immunoglobulin (Ig)-like superfamily. The protein has 1241 amino acid residues, and extracellular part consisting of 8 Ig motifs followed by a fibronectin type III domain, a short transmembrane region and a cytoplasmic C-terminal part (5). The nephrin is a cell adhesion molecule specifically localized at the slit diaphragm of the glomerular basement membrane (7, 12). This emphasizes the role of NPHS 1 in maintaining proper glomerular filtration.

In our cases there was no evidence of consanguinity as is described in the study made

by Hamed et al where most patients (80%) had parents who were consanguineous (12).

We did not find placentomegaly, which is the most important early sign of the disease as described in other papers (8, 9), in any of the cases (mean placental/fetal weight ratio 1/6).

The proteinuria was marked and highly selective in both cases, as described in the literature. According to Niuadet hematuria is uncommon, fact that reflects the lack of inflammation in the glomeruli (3). In our study both cases presented microscopic hematuria.

Fluid and electrolyte disturbance were present in both cases.

The urinary protein losses were accompanied by profound hypoalbuminemia and severe hypogamaglobulinemia.

Congenital heart disease has also been rarely reported in few cases of CNS. Cardiac lesions described in these children were pulmonary stenosis and subaortic stenosis (13, 14). However, atrial septal defect and patent ductus arterioasus have been reported in just one case (7).

Infectious and thromboembolic complications are particularly dangerous (12, 15). None of our patients presented thromboembolic complications, but both cases developed recurrent respiratory infections, prompting us to start aggressive therapy with 3rd generation cephalosporins.

Since CNSF is not an immune disease, it is resistant to corticosteroids and immunosuppressive drugs, so we did not used these drugs in treating our patients. Furthermore, these drugs may be harmful due to already high susceptibility to infection, as confirmed by a retrospective study made by Ljungberg et al (16).

Aggressive treatment with albumin infusions, diuretics, antibiotics, supplemental thyroid preparations and, sometimes, proteinuria-reducing drugs as Indomethacin and angiotensin-converting enzyme inhibitor (ACEI) improve the clinical evolution of the affected infants. Furthermore early bilateral nephrectomy and renal transplantation allow a longer life span (7). The reduction in mortality secondary to CNSF is related to the introduction of aggressive interventional treatment in the past decade (20).

A possible medical alternative to nephrectomy has been described in two children. The combination of an ACEI and Indomethacin therapy, both of them lowering intraglomerular pressure, markedly reduce proteinuria and led to significant improvement of nutritional status and growth (17).

Pomeranz et al (18) described two infants with CNS who responded to treatment with Captopril (5 mg/kg) and Indomethacin (4 mg/kg) (18). Subsequently, Heaton et al have also reported similar success (19). ACEI and prostaglandin inhibitors have been shown to reduce proteinuria (18, 20). Prostaglandin inhibitors are most effective within 1-3 days, while ACEI show an optimal effect after 4-8 weeks of treatment. A combination of these drugs was successfully used by Pomeranz et al and Kovacevic et al in their studies to reduce proteinuria in children with CNS (18, 20).

In addition, contrary to the reportedly successful clinical control of CNS by ACEI and non-steroidal anti-inflammatory drugs (prostaglandin synthetase inhibitors) (17, 18, 20), we did not obtain any substantial response in our patients when these drugs were used alone (Captopril) similar with the results observed by Hamed et al (12). In both cases hyperkalemia was demonstrated at presentation in our department; that was the reason we used ACEI only and not a combination with indomethacin.

The goals of therapy during the first months are to control edema and possible uremia, prevent and treat complications such as infections and thromboses, and provide optimal nutrition so that the child grows and develops as normally as possible. In most cases, kidney transplantation is the only curative treatment (8, 15). This progressive disease leads to death in the first two years of life; the only curative therapy is bilateral nephrectomy followed by renal transplantation. Renal transplantation after bilateral nephrectomy is a successful long-term

treatment option. Nephrotic proteinuria may recur after transplantation as a result of alloimmunization against normal nephrin in the kidney graft, requiring increased immunosuppression and plasma exchanges (6).

Kovacevic et al obtained good results in CNS patients using early treatment with Captopril and indomethacin therapy in combination with unilateral nephrectomy. With this treatment the second nephrectomy, dialysis and transplantation could be delayed until the 3rd year of life (20).

The typical histological findings of Finnish congenital nephrosis kidneys are dilated proximal tubules, mesangial hypercellularity, and glomerular fibrosis and sclerosis (4, 15), similar with histology kidney reports of our cases.

Because of rapid progression to end-stage renal failure in our cases, we had to make a differential diagnosis between CNSF and DMS (diffuse mesangial sclerosis). A review of the literature shows that DMS has some features in common with CNSF: early onset, familial occurrence with autosomal recessive transmission and tubular ectasia on renal biopsy, but DMS is not associated with premature birth, low birth weight or placental enlargement and has a characteristic pattern of involving the glomeruli (2).

CNSF is an extremely severe disease of early childhood and prenatal diagnosis should be performed in families who previously had an affected child.

Prenatal diagnosis of CNSF has previously been based on the quantization of alpha-fetoprotein (AFP) in the amniotic fluid and maternal serum during the second trimester, but an increased AFP is not specific for the disease (7, 15, 21). AFP values can be elevated also in other fetal structural abnormalities, such as neural tube defects and abdominal wall defects (6, 21). If the AFP concentration in amniotic fluid is very high and the ultrasound examination does not reveal fetal anencephaly or other malformations, CNSF is a probable diagnosis.

Prenatal diagnosis is a problem especially in families with no CNSF history. Improved prenatal diagnosis of CNSF, based on DNA analysis of chorionic villus tissue, is now possible in developed countries. Genetic analysis is the method of choice for precise CNSF diagnosis (6, 15, 21). The knowledge of etiology helps in assessing management and prognosis, in follow-up for possible associated symptoms, and in genetic counseling of the family. Prenatal diagnosis in families with a known risk for CNS should be based on genetic testing whenever possible (6).

Conclusion

The management of children with CNSF in the developing countries is different from that in the developed countries because of the considerable cost of care, severe complications and the poor outcome. The early diagnosis of CNSF is important for proper clinical management of the patients, prognosis and genetic counseling of the families.

In case of cardiovascular disease (cardiac heart defect) in a patient with CNS, differential diagnosis must rule out a CNS secondary to intrauterine infection.

Complications of cardiac heart defect like cardiac failure or infective endocarditis might affect the outcome, so associated anomalies should be looked for in a child with CNSF.

If pregnancy occurs in families of our patients prenatal diagnosis should be done.

We can conclude that in all infants, even if apparently healthy, urinalysis must be performed soon after birth, to evaluate the presence of CNSF, especially those born from pregnancies with placentomegalia and increased maternal serum AFP levels, when other causes have been excluded.

Abbreviation list

ACEI = angiotensin-converting enzyme inhibitor
BP = blood pressure

CNS = congenital nephrotic syndrome
CNSF = congenital nephrotic syndrome of Finnish-type
DMS = diffuse mesangial sclerosis
IV = intravenous
NPHS1 = nephrin gene

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