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A rare cause of steroid-resistant nephrotic syndrome – a case report

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Abstract

Steroid resistance is a common condition occurring in children with nephrotic syndrome. Until now, over 50 genes involved in steroid-resistant nephrotic syndrome (SRNS) pathogenesis have been identified, among which the most prevalent are NPHS1, NPHS2, CD2AP, and PTPRO. The patterns of inheritance of SRNS are autosomal recessive, autosomal dominant, or mitochondrial, and tissues of those patients show focal segmental glomerulosclerosis (FSGS) signs in histopathological image analysis.

We present a case of a 6-year-old girl who was admitted to the pediatric nephrology department due to nephrotic range proteinuria and edema of the lower leg.

We started therapy with prednisone at a dose of 45 mg (60 mg/m^2), enalapril as a nephroprotection, and antihistamines as an additional treatment. During in-patient treatment, we detected increased blood pressure. Due to persistent proteinuria in spite of 6-week treatment with steroids at the maximal dose, we confirmed disease resistance to steroids. Additionally, FSGS signs were confirmed in kidney biopsy samples. After genetic screening for SRNS and detection of the rare gene mutation NUP93 we reduced prednisone but maintained nephroprotective treatment and administered cyclosporin A. The girl remains currently under the care of nephrologists with normal arterial blood pressure, trace proteinuria in follow-up examination, and normal kidney function.

NUP93 mutation is extremely rare; therefore few cases have been described to date. The onset of the symptoms in all pediatric patients appeared before the age of 8 and they developed end stage kidney disease (ESKD). They might manifest symptoms from the other systems.

Key words: *steroid-resistant nephrotic syndrome, steroid resistance, children, rare mutation.*

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Introduction

The incidence of steroid resistance in children with nephrotic syndrome is between 35% and 92% according to the statistics [1, 2]. Mutation of a gene responsible for podocyte building was detected in one out of three patients. Most prevalent are *NPHS1*, *NPHS2*, *CD2AP*, and *PTPRO*, which take part in cell-cell signaling at the podocyte slit membrane, *ACTN4*, and *INF2*, which are involved in the foot process actin network, and *LAMB2* and *ITGA3*, which play an important role in foot process-glomerular basement membrane interaction. The patterns of inheritance of steroid-resistant nephrotic syndrome (SRNS) are autosomal recessive, autosomal dominant, and mitochondrial. Until now, over 50 genes involved in SRNS pathogenesis have been identified, and tissues of those patients show focal segmental glomerulosclerosis (FSGS) signs in histopathological image analysis [1].

In the following case, we confirmed the rare gene mutation NUP93. This mutation can manifest as SRNS, also known as NPH12. It shows an autosomal recessive inheritance pattern [3]. To understand the mechanism of the disease, further exploration of NUP93 function should be made [3]. NUP93 is a nucleoprotein with a molecular weight of 90 kDa and an essential subunit of the nuclear pore complex (NPC), involved in active transport of molecules between the nucleus and the cytoplasm [4]. It builds scaffolds of neural progenitor cells (NPCs) along with NUP188 and NUP205 proteins [5]. High expression of NUP93 protein was detected in the central nervous system, esophagus, urinary bladder, and testicle tissues. A medium level of expression was observed in the gastrointestinal, respiratory, and lymphatic systems, and kidneys. We have no proof of expression in the liver, spleen, or adipose tissue [6].

NUP93 protein regulates migration and proliferation of the podocytes during kidney development *via*

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SMAD 4 [7]. After BMP7 stimulation, NUP93 and IPO7 protein join the nuclear ring structure at various stages of glomerular development and in podocyte precursor cells at an early stage of the capillary loop. NUP93 also interacts with the activated protein SMAD1/5, affects the expression of NUP205 in the nuclear pores, and has a protective function against oxidative stress [8]. NUP93 participation in the remodeling of the actin cytoskeleton leads to an increase in invasiveness and progression of triple-negative breast cancer [9] and cervical cancer [10]. Moreover, a colon cancer cell investigation showed that NUP93 regulates HOXA gene expression during cell differentiation [11]. The occurrence of an autosomal recessive form of non-progressive cerebellar ataxia is related to the prevalence of this protein mutation according to some studies [12].

Case report

A 6-year-old girl with streptococcal pharyngitis diagnosed in the outpatient department underwent laboratory examination on the fifth day of treatment with amoxicillin. Due to proteinuria > 500 mg/dl and increased antistreptolysin O level (ASO – 685 IU/ml) the girl was admitted to the pediatric department.

Hitherto she had remained disease-free. Frequent upper respiratory infections, requiring the administration of antibiotics, had been repeatedly appearing in the period prior to hospitalization. She was hospitalized at the age of 4 due to hand and foot edema with skin lesions. At that time proteinuria (102 mg/dl) was detected in the urinalysis. Extended examination and controlled urinalysis were not conducted.

Full-term delivery with an uneventful first pregnancy was reported. The girl was given an Apgar score of 10. The adaptation period and postnatal development remained within normal limits. She had no evidence of dysmorphia or urinary tract anomalies.

The examination in the pediatric clinic revealed only edema of the lower leg. Blood specimens were obtained for laboratory analysis. Creatinine was 0.3 mg/dl, urea 20 mg/dl, glomerular filtration rate (GFR), albumins and total protein were normal, total blood cholesterol was 210 mg/dl, and ASO was 685 IU/ml. A 24-hour urine collection revealed proteinuria of 60 mg/kg/24 h.

Abdominal ultrasound revealed a slightly bilateral hyperechogenicity of the kidney. Treatment with clemastine and third-generation cephalosporins was started after diagnosis of acute post-streptococcal glomerulonephritis as a continuation of pharyngitis therapy. Upon persistent proteinuria, the girl was transferred to the center providing a higher level of medical care.

We broadened the assessment criteria of nephrotic syndrome due to suspicion of its first presentation. Blood specimens were obtained for laboratory analysis. Blood count, renal and liver function parameters (creatinine 0.3 mg/dl, urea 20 mg/dl), GFR, glucose, ions (Na, K, Ca, Mg), albumins, and total protein remained normal. Increased levels of $\alpha 1$ and $\alpha 2$ globulins (6.7% and 14.6% respectively) were detected in protein electrophoresis. The other globulin levels remained within normal limits, as was the coagulation profile. Acute-phase protein was slightly elevated (CRP 1.1 mg/dl, N < 1). The lipoprotein profile showed total cholesterol of 203 mg/dl and triglycerides of 148 mg/dl. Leukocyturia and erythrocyturia were not confirmed, proteinuria was increased up to 648 mg/dl and 24-hour urine collection confirmed persistent nephrotic-range proteinuria – 64 mg/kg/24 h. The glomerulonephritis screening revealed ASO levels of up to 660 IU/ml and borderline titer of ANA antibodies (1 : 160), while ANCA antibodies were not detected. Complement components 3 and 4, immunoglobulin (IgG, IgM, IgA) titers as well as the rheumatoid factor were normal. Screening for latent diseases (CMV, EBV, TBC, HBV, HCV, HAV, HIV) was negative. Celiac syndrome was excluded. Bronchial provocation test for allergy revealed reaction to house dust mite, orchard grass, birch, sweet vernal grass, and rye pollen. Screening for food allergens was negative. No abnormalities were found in the chest X-ray and abdominal ultrasound.

We started therapy with prednisone at a dose of 45 mg (60 mg/m^2), enalapril for nephroprotection, and antihistamines as an additional treatment. During in-patient treatment, we detected increased blood pressure. Due to persistent proteinuria in spite of 6-week treatment with steroids at the maximal dose, we confirmed disease resistance to steroids. We performed a kidney biopsy and found in optical microscope images 13 glomeruli with slightly increased mesangial hypercellularity and without any changes in the glomerular interstitium. Direct immunofluorescence microscopy tissues showed no reaction to IgM, IgG, and IgA antibodies, C1q and C3 complements, F, K, and L. Electron microscopic findings were as follows: the majority of glomerular capillaries with a wide cross-sectional area, walls collapsed in singular capillaries; in the lumen, endothelial cell swelling and single erythrocytes were observed; basal membranes of the correct thickness; slight depletion of the mesangium matrix in singular glomerular capillaries. Podocyte foot processes were preserved on most of the basal membranes, merged in some segments, and detached from the basal membranes – the onset of FSGS is plausible.

Due to continuing proteinuria, we administered 2 doses of methylprednisolone. A pulsatile treatment was terminated on account of increasing loss of protein (up to 366 mg/dl) and elevated glucose (up to 118 mg%).

We suspected a genetic origin of the disease. Therefore, we performed genetic screening for steroid-resistant nephrotic syndrome and confirmed the genetic origin of the disorder: the rare gene mutation NUP93, c1772G>T (p.Gly591Val) homozygous variant. We reduced prednisone but maintained nephroprotective treatment and administered cyclosporin A.

Table 1. Study group: genetic diagnosis, detected variants, mutations and clinical characteristics

Variant	Mutation	Sex	Region	Age of onset	Kidney biopsy results	Treatment	Effecti-veness	Age of ESKD onset	Tx	Relapse of SRNS	Extrarenal manifestations
Bezdíčka *et al.* [14]											
c.1772G>T/c.1916T>C	p.Gly591Val/p.Leu639Pro	M	Czech Republic/Slovakia	1 3/4	FSGS	CsA	?	2 5/6	+	+	
c.1772G>T/c.1537+1G>A	p.Gly591Val/?	F	Czech Republic/Slovakia	3	MCD	?	?	3 5/12	+	–	
c.1772G>T/c.1298delA	p.Gly591Val/p.D433Afs*23	F	Czech Republic/Slovakia	3 11/12	FSGS	CsA	?	5 1/12	+	–	
c.1772G>T/c.1772G>T	p.Gly591Val/p.Gly591Val	M	Czech Republic/Slovakia	7	FSGS	CsA	partial remission	3	–	–	
Braun *et al.* [8]											
c.1772G>T/c.1162C>T	p.Gly591Val/p.Arg388Trp	F	Serbia	6	FSGS	RTX	?	6	12	?	
c.1326delG/c.1772G>T	p.Lys442Asnfs14/p.Gly591Val	F	Germany	3	FSGS	CsA	partial responce	3	6	?	
c.1537+1G>A/c.1772G>T	Delex13/p.Gly591Val	F	Germany	3	FSGS	CsA, RTX	?	4	4	?	hematuria, Marcus-Gunn syndrome
c.1772G>T	p.Gly591Val	M	Turkey	3	FSGS	ACE-I	?	11	–	–	
c.1772G>T	p.Gly591Val	F	Turkey	6	–	ACE-I	?	–	–	–	
c.1886A>G	p.Tyr629Cys	M	Turkey	1	DMS/FSGS	RTX	?	1	3	?	
c.1886A>G	p.Tyr629Cys	M	Turkey	1	–	?	?	–	–	–	
Bierzynska *et al.* [18]											
c.2084T>C/c.2267T>C	p.Leu695Ser/p.Leu756Ser	F	Europe	6 1/12	FSGS	?	?	12	+	–	
Bierzynska *et al.* [19]											
c.1909A>G	p.Lys637Glu	M	South Asia	2	FSGS, IF, TA	Plasma exchange					
c.1473T>G/c.1538-6A>G	p.His491Gln	M	Caucasian	8	FSGS, IF, TA	?					
Rossanti *et al.* [16]											
c.727A>T/c.2137-18G>A	p.Lys243 – exon 8/intron 19	M	Russian Federation	2	FSGS	?	?	–	–	–	
Sandokji *et al.* [15]											
c.A575G/c.C1605G	p.Tyr192Cys/p.Tyr535Ter	M	Africa/America/Spain	5	?	?	?	5	+	–	developmental retardation, below-average growth
Zhao [19]											
c.1655A>G/c.1732C>T	p.T192C/p.Tyr535Ter	M	People's Republic of China	6/12	FSGS	?	?	2/3	–	–	death
Hashimoto [7]											
c.1573C>T/c.1886A>G	p.Arg525Trp/p.Tyr629Cys	F	Japan	4 11/12	FSGS	?	?	6	15	–	
Our case study											
c.1772G>T	p.Gly591Val	F	Poland	6	FSGS	CsA, ACE- I	remission	–	–	–	–

? – not firmly established, FSGS – focal segmental glomerulosclerosis, MCD – minimal change disease, DMS – diffuse mesangial sclerosis, IT – interstitial fibrosis, TA – tubular atrophy, CsA – cyclosporin A, RTX – rituximab, ACE-I – angiotensin-converting enzyme (ACE) inhibitors CKD – chronic kidney disease, Tx – kidney transplantation, ESKD – end stage kidney disease

The girl remains currently under the care of nephrologists with normal arterial blood pressure and trace proteinuria in follow-up examination. Kidney function remains within normal limits.

Discussion

The major effect of the NUP93 mutation with nephrological manifestations, as it happened in the mentioned case, is the disruption of the BMP7-dependent SMAD signaling. The BMP7 protein plays a key role in kidney development and is active in podocytes and collecting duct cells. It is a significant mediator of the kidney's response to injury and it has a protective function, proved in numerous models of acute and chronic kidney damage. In addition, BMP7 balances the profibrotic effect of transforming growth factor β (TGF-β) inhibits apoptosis and promotes podocyte survival in experimental models of diabetic nephropathy [8]. *In vitro* testing of human immortalized podocyte lines showed that NUP93 protein mutation impairs and reduces the rate of podocyte migration, induces apoptosis in response to oxidative stress, and reduces the level of the NUP205 protein, but without affecting interaction with it [8].

The NUP93 mutation is extremely rare; therefore few cases have been described to date (Table 1 [8, 13-19]). The onset of symptoms in all children appeared before the age of 8 and they developed end stage kidney disease (ESKD) within 1.5 years or up to 7 years in the case of the homozygous G591V mutation [6, 14, 15]. Kidney biopsies showed FSGS, minimal change disease (MCD), or diffuse mesangial sclerosis (DMS). Furthermore, dilation of the proximal tubules with urinary casts and infiltration of interstitial cells was reported in several children [8, 14]. Partial confluence of the foot podocyte processes was found in the electron microscope images. Calcineurin inhibitors, cyclosporine and tacrolimus, along with prednisolone, are recommended for the treatment of children with SRNS, especially when no genetic mutation was detected. According to several scientific studies, the administration of mycophenolate mofetil, rituximab, or cyclophosphamide did not show any significant changes. Furthermore, the optimal duration of treatment is not exactly known; however, the Guidelines from Kidney Disease Improving Global Outcomes recommend not less than 12 months. If a genetic test detects a mutation, discontinuation of calcineurin inhibitors should be considered. In this case, due to the higher risk of ESKD, additional tests should be conducted, e.g. monitoring the levels of albumin, cholesterol, or triglycerides, screening for proteinuria and blood clots. Also vitamin D supplementation ought to be prescribed [1]. The renoprotective treatment of patients with the homozygous mutation G591V appears to be sufficient but cyclosporin A implementation leads to partial remission. Children with heterozygous G591V and homozygous Tyr629Cys mutations do not respond to cyclosporin A treatment and the only available therapy is organ transplantation [8, 14]. Moreover, one child with the heterozygous mutation c.1772G>T; c.1916T>C presented recurrence of the disease after kidney transplantation [20]. Children with mutations of European and Turkish origin did not present extrarenal manifestations [8, 14]. Nevertheless, heart failure was diagnosed in a child with an African-type mutation. The echocardiography showed systolic and diastolic dysfunction of the heart (ejection fraction up to 35%) and features of dilated cardiomyopathy. After kidney transplantation, the ejection fraction increased to 60%, and echocardiography did not show abnormalities in the structure of the heart cavities [15]. According to the literature, the ten-year ESKD-free survival rate with SRNS was 43%, while for children with partial remission it was 72% and with complete remission 94%. The 5-year ESKD-free survival rate with diffuse mesangial sclerosis was 21%. This research suggested that the response to initial steroid therapy and the detection of hereditary abnormalities in podocyte structure are prognostic indicators of good and poor long-term prognosis of SRNS, respectively [21].

Clinical symptoms of NUP93 mutation have been evaluated by several researchers. Braun *et al*. analyzed genomes of more than 1900 families from around the world [8] and Bezdíčka studied the occurrence of nephrological manifestations in relation to specific variants of the NUP93 gene mutation in a population of 70 Czech and Slovak families. In this group, Bezdíčka detected in 6 patients of European origin the heterozygous mutation G591VAL, which represents the European founder allele (c.1772G>T) and other mutations: (p.Arg388Trp (c.1162C>T); p.Lys442Asn fs*14 (c.1326delG); del ex13 (c.1537+1G>A); p.Leu639Pro (c.1916T>C); D433Afs*23 (c.1298delA)) [14]. In the medical literature, we can also find cases with a homozygous mutation. One of those children was of Turkish origin and the parents were biologically related [8, 14]. In two Turkish patients, whose parents were relatives, the homozygous mutation TYR 629CYS was detected. It represented the Turkish founder allele (c.1886A>G) [8]. Heterozygous mutations TYR 629CYS (c.1886A>G) and Arg525Trp (c.1573C>T) were found in a girl of Japanese origin [13]. Moreover, heterozygous mutations Tyr192Cys (c.575A>G) and Tyr535Ter, observed in the African population (c. 1605C>G), were detected in a girl of Afro-Latino origin [15]. Rini Rossanti *et al*. found an intronic variant of the mutation NUP93 – c.2137-18G>A in intron 19 of a 9-year-old boy with FSGS confirmed in bioptic samples [16].

Although our patient presented only nephrological symptoms, patients with the same or similar mutation variants might also manifest symptoms from other systems [15].

The authors declare no conflict of interest.

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