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CASE REPORT / *OLGU SUNUMU*

A Case Series of 4 Patients with Congenital Nephrotic Syndrome

Konjenital Nefrotik Sendrom: 4 Vaka Sunumu

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ABSTRACT

Congenital nephrotic syndrome (CNS) is a rare hereditary kidney disease that begins at birth or within the first three months of life. CNS is characterized by severe proteinuria, hypoalbuminemia, edema, and hyperlipidemia. It is primarily caused by gene mutations that result in damage to the glomerular filtration barrier. We wanted to present the clinical course of our four patients, one of whom was in spontaneous remission. In this study, we wanted to draw attention to the different clinical courses of patients with nephrin mutations.

Keywords: Children, Congenital Nephrotic Syndrome, Nephrin

ÖZ

Konjenital nefrotik sendrom (CNS), doğumda veya yaşamın ilk üç ayında başlayan, nadir görülen kalıtsal bir böbrek hastalığıdır. CNS, şiddetli proteinüri, hipoalbüminemi, ödem ve hiperlipidemi ile karakterizedir. CNS'ye esas olarak glomerüler filtrasyon bariyerinde hasarla sonuçlanan gen mutasyonları neden olur. Biri spontan remisyonda olan dört hastamızın klinik seyrini sunmak istedik. Bu çalışmada nefrin mutasyonları olan hastaların farklı klinik seyirlerine dikkat çekmek istedik.

Anahtar Kelimeler: Çocuk, Konjenital Nefrotik Sendrom, Nefrin

INTRODUCTION

Congenital nephrotic syndrome (CNS) is a rare hereditary kidney disease that begins at birth or within the first three months of life (1). CNS is characterized by severe proteinuria, hypoalbuminemia, edema, and hyperlipidemia. CNS usually occurs within a few days after birth (2). CNS is caused by gene mutations that cause damage to the glomerular filtration barrier, especially podocyte components (2). The mutations in genes encoding for components of the glomerular filtration barrier are the most common cause of the primary CNS (1). Mutations in the *NPHS1, NPHS2, WT1, LAMB2,* and *PLCe1* genes cause 80% of CNS (3). The *NPHS1* gene, which encodes nephrin, can cause 40%-80% of primary CNS. Nephrin is a transmembrane protein responsible for podocyte function (4). Up to now, over 200 mutations in the NPHS1 gene have been detected (5). In this article, we report four patients with *NPHS1* mutations and highlight the clinical variability of this disease. Written informed consent was obtained from all patients.

OBSERVATION

Patient #1.

A 3-day-old girl was admitted to the neonatal intensive care unit with edema. She was born at 36 weeks of gestation with a birth weight of 2.6 kg. She was the second child of non-consanguineous parents. Antenatal and family histories were unremarkable **(Table 1).** Her physical examination revealed edema without extrarenal findings. Biochemical analysis revealed hypoalbuminemia, proteinuria, and hyperlipidemia. She was diagnosed with congenital nephrotic syndrome. Secondary causes were excluded by laboratory analysis. Urinary system ultrasound was normal. Echocardiography showed a patent foramen ovale. Genetic analysis uncovered a

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homozygous frameshift mutation on *NPHS1* (i.e NM_004646.3: c.3356_3357dup (p.Thr1120fs)). Edema regressed via the replacement of albumin. The other supportive treatments (enalapril, indomethacin, dipyridamole, acetylsalicylic acid, magnesium oxide, and calcidiol) were also started. The patient was discharged on the 13th day of hospitalization. Initially, the patient needed albumin infusions twice a week. Due to the decreased glomerular filtration rate, the albumin infusion requirement decreased over time. Currently, she is 6 years old. Peritoneal dialysis was started one month ago. Laboratory data of the patient were given in **Table 2.**

Patient #2.

A 4-day-old girl was admitted to the neonatal intensive care unit with edema. She was born at 35 weeks with a birth weight of 2.4 kg. Antenatal history was unremarkable. She was the fifth child of consanguineous (second-degree cousins) parents. She had two healthy siblings and a history of two siblings who died in the first month of life due to CNS. Her physical examination revealed edema without extrarenal findings. Biochemical analysis revealed hypoalbuminemia, proteinuria, and hyperlipidemia. The patient was diagnosed as congenital nephrotic syndrome. Secondary causes were excluded. Urinary system ultrasound was normal. Mutation analysis of *NPHS1* uncovered a homozygous nonsense mutation (i.e. c.3478C>T (p.Arg1160*)) Edema regressed with albumin replacement. The other supportive treatments (enalapril, calcidiol) were also started. The patient was discharged on the 10th day of hospitalization. Currently, the patient is 15 months old, and requirement of albumin infusions are continuing once a week. Laboratory data of the patient were given in **Table 2.**

Patient #3.

A 2-day-old girl was admitted to the neonatal intensive care unit with edema. She was born at 37 weeks with a birth weight of 4 kg. Antenatal history was unremarkable. She was the third child of consanguineous (first-degree cousins) parents. She had two healthy siblings. Her physical examination revealed edema without extrarenal findings. Biochemical analysis revealed hypoalbuminemia, proteinuria, and hyperlipidemia. The patient was diagnosed as congenital nephrotic syndrome. Secondary causes were excluded. Urinary system ultrasound was normal. Echocardiography showed secundum atrial septal defect. Due to hypoalbuminemia, proteinuria, and hyperlipidemia, we performed a genetic analysis that unveiled a novel homozygous frameshift mutation on *NPHS1* (i.e. c.3523_3524delTT (p.Leu1175fs)). Edema regressed with albumin replacement. The other supportive treatments (enalapril, indomethacin, and calcidiol) were also started. The patient was discharged on the 8th day of hospitalization. Albumin infusions were given twice day a week. Proteinuria decreased over time and disappeared in the fourth month of the follow-up period. The patient who had spontaneous remission did not need further albumin infusion. At present, the patient is 19 months old, and she is still in remission. Laboratory data of the patient were given in **Table 2.**

Patient #4.

A 1-day-old boy was admitted to the neonatal intensive care unit with edema and dyspnea. She was born at 27 weeks with a birth weight of 1.4 kg. Antenatal history was unremarkable. She was the 6th child of consanguineous (first-degree cousins) parents. She had 5 healthy siblings. Her physical examination revealed edema and dyspnea. Biochemical analysis revealed hypoalbuminemia, proteinuria, and hyperlipidemia. The patient was diagnosed as congenital nephrotic syndrome. Secondary causes were excluded. Urinary system ultrasound revealed hyperechogenic kidneys. Due to hypoalbuminemia, proteinuria, and hyperlipidemia, we performed genetic analysis for CNS. A homozygous missense mutation on *NPHS1* was found (i.e. c.1250G>T (p.Cys417Phe)). Edema regressed with albumin replacement. The other supportive treatments (enalapril, indomethacin, calcidiol, and thyroxine) were also started. Respiratory problems resolved over time. The patient was discharged on the 42nd day of hospitalization. Albumin infusions continued twice a day weekly. At 6 months of age, the patient died of sepsis. Laboratory data of the patient were given in **Table 2.**

DISCUSSION

The defect of the glomerular filtration barrier leads to severe proteinuria and edema (6). Three patients were female, and

Table 1: Demographic data of the patients

	Patient 1	Patient 2	Patient 3	Patient 4
Consanguinity	(-)	(+)	(+)	(+)
Presence of CNS in family	(-)	(+)	(-)	(-)
Gestational week	36 weeks	35 weeks	37 weeks	27 weeks
Birth weight/percentile	2630 gr	2400 gr	3100 gr	1435 gr
Age of diagnosis	3 days	4 days	2 days	1 day
Current age	6 years	1 year 3 months	1 year 7 months	6 months
Current weight/percentile	14 kg (<3p)	7.5 kg (<3p)	9 kg (3-10 p)	3.1kg (<3p)
Current height/percentile	101 cm (<3p)	73 cm (3-10p)	78 cm (3-10p)	52 cm (<3p)

*__CNS:__ Congenital Nephrotic Syndrome

Table 2: Laboratory data of the patients

	Patient 1		Patient 2		Patient 3		Patient 4	
	Time at diagnosis	Last visit	Time at diagnosis	Last visit	Time at diagnosis	Last visit	Time at diagnosis	Last visit
WBC (x10^9/L)	12.4	17.2	15.7	11.2	11.4	7.1	6.8	8.1
HB (mg/dL)	14.7	9.8	15.6	12.1	11.4	10.4	9.6	8.7
PLT (x10^9/L)	615	439	514	566	883	556	529	643
Urea (mg/dL)	15	116	24	28	22	26	7	30
Creatinine (mg/dL)	0.24	4.8	0.26	0.4	0.24	0.20	0.21	0.2
Albumin (g/L)	1.2	2.3	1.2	0.8	1.3	4.2	1.2	1.8
Calcium (corrected) (mg/dL)	8.5	7.6	8.1	8.4	8.1	10.1	9.2	9.5
Magnesium (mg/dL)	1.5	1.8	1.8	1.7	1.9	2	1.5	2
Triglycerides (mg/dL)	258	210	181	170	176	192	182	165
LDL (mg/dL)	163	120	123	110	80	75	74	83
25-OH vit. D (ng/mL)	10	25	2.5	21	3	19	16	24
TSH (mU/L)	3.8	4.1	4.2	4.4	2.05	4.2	13.5	4.2
Free T4 (ng/dl)	0.81	0.72	0.86	0.82	0.9	0.8	0.55	0.8
Protein/creatinine ratio	44	10	40.5	32	41	0.1	40.4	36
Microscopic hematuria	(+)	(+)	(+)	(-)	(+)	(-)	(+)	(+)
eGFR (ml/dk/1.73m2)	93	11.5	86.5	82	96	98	112	110
Nephrin mutation status	c.3356_3357dup (p.Thr1120fs) homozygous frameshift		c.3478C>T (p.Arg1160*) homozygous nonsense		c.3523_3524delTT (p.Leu1175fs) homozygous frameshift		c.1250G>T (p.Cys417Phe) homozygous missense	

***WBC:** White Blood Cell **HB:** Hemoglobin **PLT:** Platelet **LDL:** Low-Density Lipoprotein **TSH:** Thyroid-Stimulating Hormone

one patient was male. The age at diagnosis for all mutations was similar (within the first week of life). Prematurity has been detected in 80% of patients with primary CNS. Three of our patients were born at <37 weeks of gestational age (7). None of the patients had extrarenal abnormalities. Central nervous system and cardiac abnormalities may accompany CNS (8). Minor cardiac abnormalities were detected in two of our patients.

At the time of diagnosis, blood albumin level and urine protein/creatinine ratio were similar (in the range of 40 to 45). Intravenous albumin and diuretics were administered for severe edema. Antiproteinuric agents such as ACE inhibitors and indomethacin were also given to the patients. Due to the protein losses, the patients have low levels of vitamin D, calcium, magnesium, and free t4 (9). The patients often require vitamin D and thyroxin supplements. All the patients used vitamin D supplements, and three of them used thyroxin. A high-energy (130 kcal/kg/day) and high-protein (3-4 g/kg/day) diet were administered to all the patients. Despite this, all the patients except the third patient had growth retardation. Urinary protein losses contribute to hypercoagulability. (10). Thus, one patient who had severe thrombocytosis needed aspirin and dipyridamole. None of the patients had thrombotic episodes. Urinary losses of gamma globulin and complement factors contribute to bacterial infections. The first patient had two sepsis attacks throughout the follow-up period. The fourth patient died of sepsis. The NPHS1 mutations can cause kidney enlargement and cortical echogenicity in ultrasound (11). One patient had cortical echogenicity in ultrasound examination. Immunosuppressive treatment was not administered in any of our patients. We did not discover any significant correlation between the mutations in the NPHS1 gene, with the age of diagnosis, clinical course, renal survival, or family history. Genotype–phenotype correlation for NPHS1 mutation is not very well-defined yet. To our best knowledge, there is no proven genotype-phenotype correlation for NPHS1 mutation in the literature (12,13).

Spontaneous remission has been reported previously in patients with NPHS1 mutations. For now, there is no proven predictive factor for spontaneous remission (14).

In this study, whole-exome sequencing has been performed on the patients with Twist Human Core Exome Kit (Twist Bioscience, CA) on the Illumina NextSeq 500 system (Illumina Inc., San Diego, CA, USA). The data were analyzed on the Sophia DDM v4 software (Sophia Genetics, Saint-Sulp). Visualization of the data was performed with IGV 2.7.2 (Broad Institute) software. The molecular analysis confirmed the presence of four variations in the NPHS1 gene of the patients. The mutations belong to evolutionary highly conserved regions and in silico tools (MutationTaster, PolyPhen, SIFT) showed that the mutations were caused by the disease. All

the mutations are homozygous, and the mutation detected in patient three has never been reported before.

CONCLUSION

In conclusion, we wanted to draw attention to the different clinical courses of patients with nephrin mutations.

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