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Case Report
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A Case with Congenital Nephrotic Syndrome having E117K Mutation: Is this a Polymorphism? or Mutation?

Ebru Yılmaz[1*], Nida Dinçel[2], Gözde Gözüolu[3], Kadriye Özdemir[4], Afig Berdeli[4] and Sevgi Mir[4]

[1]*Behcet Uz Children Disease and Surgery Training and Research Hospital, Izmir, Turkey*

[2]*Ankara Children Health and Research Hematology Oncology Education Research Hospital, Ankara, Turkey*

[3]*Department of Pediatrics, Faculty of Medicine, Ege University, Turkey*

[4]*Department of Pediatric Nephrology, Faculty of Medicine, Ege University, Turkey*

[*]**Corresponding author:** Ebru Yılmaz, Behcet Uz Children Disease and Surgery Training and Research Hospital, Izmir, Turkey, Tel: +90 532 3361214; E-mail: ebruylmz@yahoo.com

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Introduction

Congenital nephrotic syndrome (CNS) is a rare disease has been defined as the occurrence of nephrotic syndrome (NS) within the first three months of life. CNS might be primary or secondary. Primary CNS arises from genetic causes, whereas secondary CNS is the major complication of intrauterine infections. CNS of the Finnish type (CNF), an autosomal recessive disorder, is the most common type of CNS and is characterized by massive proteinuria, which may even start in utero, a large placenta, marked edema, and characteristic radial dilatations of the proximal tubules. The course of CNF is progressive and most of infants with primary CNS do not benefit from specific therapies. CNS often leads to end-stage renal disease within two to three years of age [1,2].

Congenital nephrotic syndrome is clinically and genetically heterogeneous disease caused by mutation in the genes NPHS1, NPHS2 and WT1. It may be inherited, sporadic, acquired or as part of a general malformation syndrome. The NPHS1 gene identified as the major gene involved in CNS, has been localized to chromosome 19q13.1, which codes for the nephrin protein, an essential component of the slit diaphragm [1]. Mutations of the NPHS1 gene lead to disruption of the filtration barrier. The mutation rate of NPHS1 approaches 98% in Finnish cases, while 39-80% in non-Finnish ones [2-6].

While the mutation rate was showed as 39% in Europeans [5], the mutation detection rate was reported 80% in a group of 35 CNS patients from North America, Europe and North Africa [4]. A homozygous mutation was identified in the NPHS1 gene in the proband in Japanese familial CNS [7]. A composite heterozygous mutations of the NPHS1 gene was also detected in the proband of a Chinese familial CNS [8]. Recently two novel NPHS1 mutations have identified in the proband of another Chinese familial CNS [9].

This case is reported to make attention to a homozygous mutation of E117K in the 3rd exon, which is reported as polymorphism in literature, but showed a disease course like reported disease causing mutations.

Case Report

A boy was admitted to the Department of Pediatrics, Ege University Hospital, for evaluation of generalized edema that occurred 35 days after birth. He was a full term normal delivery with a birth weight of 3.2 kg (50th percentile) and length of 51 cm (50th percentile) with uneventful prenatal course. The weight of the placenta was unknown. He had an unremarkable family history and healthy unrelated parents (maternal age was 23 years and paternal age was 29 years).

Generalized edema, abdominal distension, and ascites were noted on admission at physical examination. His blood pressure was 50/30 mmHg and other vital signs were all in normal ranges. There was no evidence of congenital infections. Urine analysis showed +3 protein and morning urine sample protein/creatinine ratio was 127 mg/mg. Urinary glucose was not detected. Laboratory studies revealed normal complete blood count, normal serum electrolytes, 0.3 mg/dL serum creatinine, 1.2 mg/dL total serum protein, 0.6 mg/dL albumin and 351 mg/dL serum cholesterol. Screening of serum excluded the presence of antibodies for syphilis, rubella, toxoplasmosis, herpes simplex, cytomegalovirus, hepatitis B and chlamydia trachomatis were excluded. Serum complement 3 and 4 were normal and antinuclear antibodies were negative. The patient urine output was 2.1 cc/kg/hour. Echocardiographic evaluation and abdominal ultrasonography were not showed any accompanying abnormality. Hyperechoic kidneys with normal size were seen in renal ultrasonography.

He underwent renal biopsy showed 9 glomeruli. Two glomerulus had mesengial proliferation and 3 glomerulus showed immaturity. The kidney had ectatic and microcysticaly dilated proximal tubules in the light microscopy. There were no staining for Ig G, Ig A, Ig M, C1q or C3, C4 at immunofluorescent microscopy. The pathological diagnosis was compatible with congenital nephrotic syndrome.

With the informed consent of parents, sample of blood was obtained for genetic analysis of WT1, NPHS1 and NPHS2 genes. There were no any mutations in WT1 gene or NPHS2 gene. The primers for amplifying NPHS1 exons 1-29 were synthesized according to published information regarding intron-exon boundaries [4]. A homozygous mutation in exon 3 of NPHS1, E117K was identified, depicts protein amino acid change. Further mutational analysis of the NPHS1 gene of the parents showed both heterozygous single nucleotide mutation of E117K.

Treatment with albumin infusions and diuretics was started. The albumin infusions started with the dose of 1 g/kg/day divided in two doses and this was progressively increased to the dose of 2 g/kg/day according to the clinical needs. At the first week of admission, patient received angiotensin-converting enzyme inhibitor (ramipril 6 mg/m^2/day) to minimize proteinuria. Caloric intake of 120-130 cal/kg/day with 3 to 4 g/kg/day of protein were adjusted. After 12 days of therapy, albumin infusion requirement was discontinued. Kidney function was remained stable with a serum creatinine of 0.4 mg/dL. The proteinuria was decreased to the level of 12 mg/mg (protein/creatinine ratio). An

infant showed catch up growth at 6 months later. The serum protein and albumin gradually increased and returned to 3.5 g/dL total serum protein, 1.7 g/dL albumin and renal function tests were normal. At 8 months of age, he had oliguria. Laboratory evaluation revealed 151 mg/dL serum urea, 4 mg/dL creatinine, 15 mg/dL uric acid. The glomerular filtration rate was 6 mL/min./1.73m^2 and continuous peritoneal dialysis was started.

Discussion

The most common causes of congenital nephrotic syndrome were mutations in NPHS1 gene. The NPHS1 gene mutation detection rate differs among ethnic groups. The NPHS1 mutation detection rate approaches 98% in Finland [1] and is 39-80% outside Finland [2-6]. This mutation rate was found as 39% in Europeans [5] in another study. It was reported as 80% in a group of 35 CNS patients from North America, Europe and North Africa at 1999 [4].

The Lenkerri et al. reported the E117K as a single nucleotide polymorphism in 1999 in congenital nephrotic syndrome cohort and from now on it has been accepted as polymorphism [10]. Our case had a homozygous E117K mutation in exon 3 of the NPHS1 gene admitted with generalized edema on the first month after birth, heavy proteinuria and marked hypoalbuminemia, this severe mutation caused a severe clinical phenotype.

Nephrin, directly participates in the structural basis of the slit diaphragm is a 1241-residue transmembrane adhesion protein consisting of eight extracellular Ig-like domains, one fibronectin type III motif and a cytosolic C-terminal tail [11]. Missense mutations of NPHS1 lead to abnormal retention of nephrin in the endoplasmic reticulum, and therefore it fails to traffic out to the cell surface [12]. Severe and early-onset phenotypes could be explained by functional disability of nephrin, mostly due to NPHS1 mutations of especially truncated and missense kinds. Most of missense mutations are composed of more than 50% of extracellular domain mutations and 66% of them occur in Ig domains thus leading to hot mutations. Koziell et al. at 2002 reported that most mutations causing CNF with a serious clinical phenotype were in Ig2, Ig4 and Ig7 of nephrin [13]. This data was supported our thought that E117K mutation in exon 3 of the NPHS1 must be reevaluated to answer the question if it is polymorphism or not? Severe clinic with rapidly progression to ESRD, early onset and partial response to antiproteinuric treatment were seen in our case which was similar to other accepted mutations.

The most of the missense mutations affect extracellular domain associated with Ig domains thus leading to hot mutations. E117K mutation is also a missense mutation [12]. Koziell et al. showed the diminished nephrin expression in podocyte cell cultures of patients having missense NPHS1 mutation [13]. The most commonly found mutation of R1160X is a truncating mutation, leads to mild disease progression in females, whereas severe course in males. At the beginning of disease patients were normotensive and renal functions reserved with pathological findings of micro cystic dilatation, and foot process fusion on electron microscopy. Antiproteinuric treatment at early stages of disease onset was effective but on the long term follow up survival was similar. Gender, laboratory findings, clinical course, pathology and disease progression of our patient was resembling to patients with truncating mutation of R1160X.

CNF may be genetically heterogeneous by detection of NPHS2 mutations in some CNF patients in whom NPHS1 mutations were not found. An overlap in the NPHS1/NPHS2 mutation spectrum with the characterization of a unique di-genic inheritance of NPHS1 and NPHS2 mutations, which results in a 'tri-allelic' hit and appears to modify the phenotype from CNF to one of congenital focal segmental glomerulosclerosis (FSGS) [13]. But there were no mutation in the analysis of NPHS2 gene of our patient.

We suggest that E117K missense mutation can occur in patients with sporadic CNS and results in the same disease progress with other known accepted disease causing mutations. It makes us to think E117K mutation is one of the hot mutations.

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