



Proteinuria and progressive kidney failure due to an inborn error of metabolism: Answers

Özlem Ünal Uzun¹ · Nurcan Cengiz² · Büşra Çavdarlı³ · Umut Bayrakçı⁴ · Saba Kiremitçi⁵ · Aynur Küçükçongar Yavaş⁴

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Answers

1. What would be the next diagnostics for the diagnosis?

A. *Kidney biopsy*: Kidney biopsy showed diffuse and severe vacuolization of glomerular and tubular epithelial cells. Light microscopic examination of kidney biopsy revealed 19 glomeruli showing either segmental sclerosis or global sclerosis. In nonsclerotic loops of the glomeruli, swollen podocytes with cytoplasmic vacuolization were remarkable. Most of the tubules were dilated and the lumens were filled with swollen tubular epithelial cells showing cytoplasmic enlargement and foamy appearance. Oil Red O stain, applied to the frozen section of the biopsy, showed diffuse lipid deposits in tubular epithelial cells. Immunofluorescence examination showed no deposits of immune complexes (Fig. 1a, b, c, d).

B. *Molecular genetic analysis*: A lysosomal storage disorder was suspected in the patient; however, whole exome sequencing (WES) was performed due to the lack of specific pre-diagnosis. Analysis of the data revealed that the patient had two heterozygous pathogenic variants (c.1109A>G (p.Tyr370Cys)/c.689G>A (p.Cys230Tyr)) of the *NEUI* gene that explained the clinical findings with a diagnosis of nephrosialidosis. Mutations were proven to be in trans position by confirming that each parent was a carrier for one allele via Sanger sequencing (Fig. 2).

2. What is your diagnosis?

Nephrosialidosis: Inborn errors of metabolism (IEMs) may involve almost all organs and systems, either as a part of a systemic clinical picture or individually. The kidney is one of the target organs for inherited metabolic disorders and a variety of IEMs present with different types of kidney disorders. Fanconi syndrome, proteinuria, renal tubular acidosis, nephrolithiasis, kidney cysts, acute kidney injury, and chronic kidney disease can be clinical manifestations of IEMs. Specific patterns of kidney involvement could be indicative of an underlying IEM. Kidney failure is a well-defined severe morbidity in Fabry disease, primary hyperoxaluria, cystinosis, and methylmalonic acidemia. Nephrosialidosis is a very rare subgroup of the lysosomal storage disorders leading to proteinuria and kidney failure [1].

3. The patient has a life-limiting inherited metabolic disease and kidney failure due to this disorder. Genetic counseling and information about the condition should be given to the parents. To date, the age of symptom onset in all cases is under 2 years of age, and most patients have died under age 10. Our patient became dialysis-dependent at 8 years of age. In comparison with other cases reported

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✉ Özlem Ünal Uzun
unalozlem@gmail.com

¹ Kocaeli University, Pediatric Metabolism, Umuttepe Yerleşkesi, İzmit, Kocaeli, Turkey

² Muğla Sıtkı Koçman University, Pediatric Nephrology, Muğla, Turkey

³ Ankara City Hospital, Medical Genetics, Ankara, Turkey

⁴ Ankara City Hospital, Pediatric Nephrology, Pediatric Metabolism, Ankara, Turkey

⁵ Ankara University, Pathology, Ankara, Turkey

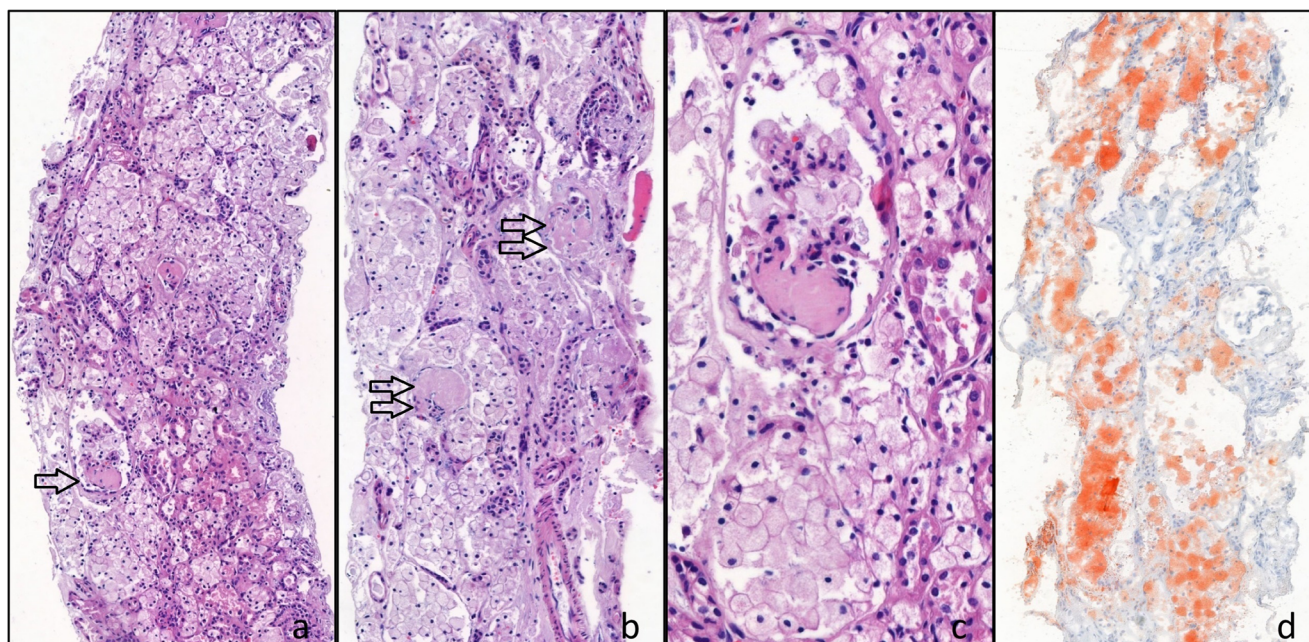


Fig. 1 a–d Diffuse cytoplasmic vacuolization of tubular epithelial cells and glomerular sclerosis are seen. Segmental sclerosis (single arrow) and global sclerosis (double arrow). Hematoxylin & Eosin $\times 143$. c Higher magnification of a segmental sclerotic glomerulus shows swollen

podocytes having vacuolated foamy cytoplasm. H&E $\times 403$. e Extensive red oil droplets are seen in tubular epithelial cells by Oil Red O stain in a frozen section of the biopsy. Oil Red O $\times 129$

before, the mild clinical phenotype in our patient may be associated with compound heterozygosity. It is difficult to say anything definite about the prognosis in this case.

Discussion

Sialidosis is a rare lysosomal storage disorder characterized by neuraminidase deficiency. It is caused by mutations in the *NEU1* gene on chromosome 6p21 [2]. Neuraminidase deficiency affects glycoprotein degradation and leads to abnormal accumulation of sialyl oligosaccharides and glycoproteins. Sialidosis is divided into two groups: type 1 and type 2. Clinical severity is heterogeneous depending on the residual enzyme activity. Type 1 sialidosis is the milder form and usually presents in the second decade with neurological findings. Type 2 presents with earlier onset and mucopolysaccharide-like phenotype with dysostosis multiplex and organomegaly. Rarely, type 2 may affect the kidney and lead to proteinuria progressing to nephrotic syndrome and chronic kidney disease.

Maroteaux et al. proposed the term ‘nephrosialidosis’ for patients with sialidosis and kidney involvement [3]. Firstly, in 1977, Kelly and Graetz reported an 8-month-old female with neuraminidase deficiency [4]. Roth et al. presented a follow-up on the patient, with the fulminant nature of nephrotic syndrome an unusual

feature of the disease. Pathological examination of the kidneys revealed kidney epithelial cell damage, most marked in the membranes of the glomeruli and proximal tubules [5]. Since these first reports on patients with sialidosis and kidney involvement, only 16 patients have been described in the literature before our patient, and two of these have been genetically confirmed [1].

Chen et al. reported a 2-year-old boy with nephrosialidosis who had steroid-resistant nephrotic syndrome. Kidney biopsy showed diffuse and severe vacuolization of glomerular and tubular epithelial cells [6]. Kidney pathology was described in 11 patients with nephrosialidosis, and vacuolated cells and appearance of focal segmental glomerulosclerosis were common findings, as in our patient [1]. Because treatment success has not been reported in the literature, we did not initiate steroid therapy in our patient.

Recently, Maroofian et al. reviewed the literature on 16 patients with nephrosialidosis and reported an Iranian female infant who presented with nephrotic syndrome at 9 months old. The patient was diagnosed with nephrosialidosis with parental WES analysis after the patient’s death. Her parents were heterozygous for c.1109A>G mutation [1]. Molecular genetic analysis of our patient revealed compound heterozygosity and he was also found carrying this same mutation in one allele.

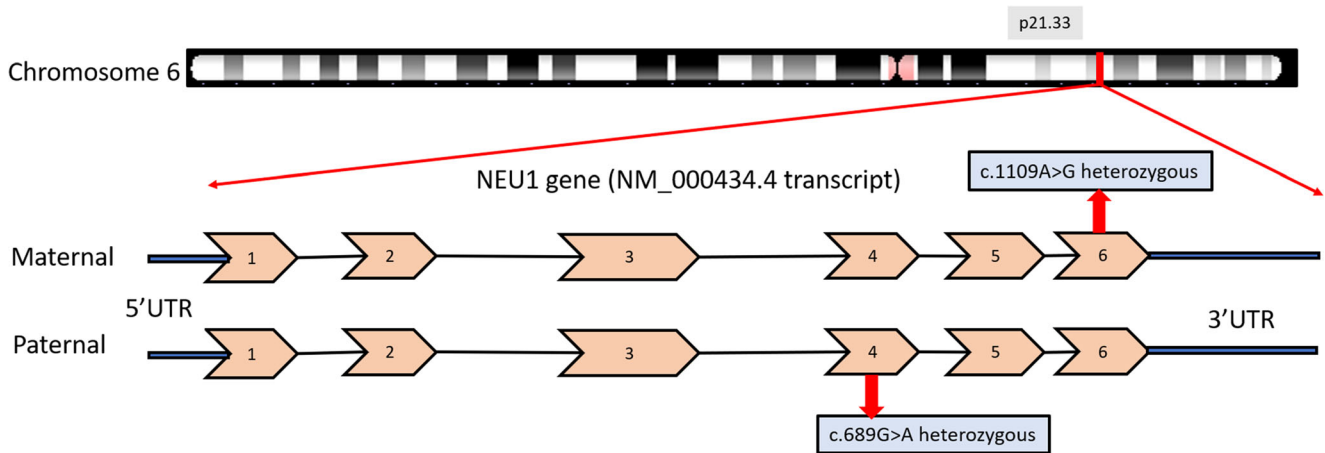


Fig. 2 Demonstration of the two variants in the *NEU1* gene. The c.1109A>G variant was in exon 6 of the maternal allele of the *NEU1* gene while the c.689G>A variant was in exon 4 of the paternal allele

Applying the criteria of the American College of Medical Genetics and Genomics (moderate pathogenic criteria: PM1-6, supporting pathogenic criteria: PP1-5) [7], these two variants were classified as likely pathogenic variants that describe the clinical findings of the patient. The variants are demonstrated in Fig. 2. The c.1109A>G (rs1310267862) variant is located in the “helical” transmembrane region of the gene that is known to be a functional domain (PM1) and its frequency is very low in the healthy population (PM2). The rate of benign missense variants in the *NEU1* gene is very low, and the missense variants formed in this gene are responsible for the disease mechanism (PP2). In silico analyses predict a pathogenic effect of the variant in terms of evolutionary conservation, effects on the protein level, and coding dysfunctions (PP3). And finally, the variant was reported as causal for nephrosialidosis in the literature before (PP5). In our patient, the other variant, c.689G>A, was also a rare (PM2), missense variant (PP2) with pathogenic predictions (PP3) and it was determined to be in trans position with the other likely pathogenic variant (c.1109A>G) (PP3).

The clinical findings of our patient were milder and progression rate was slower compared with most of the patients reported in the literature. The other molecular genetically confirmed patient was reported by Caciotti et al. nearly 10 years ago. She was found to carry a homozygous c.807+1G>A splicing defect and exhibited the congenital lethal form of the disease. Fourteen of the 16 previously reported cases were no longer alive at the time of the literature review conducted by Maroofian et al. 2 years ago. Hepatomegaly was present in nearly all cases, whereas corneal clouding and cherry-red spot was observed in only 50% of cases. In our patient, ophthalmologic evaluation was initially normal, but cherry-red spot was observed 6 months after

first examination. This finding shows that clinical features may become prominent in the follow-up period, and long-term follow-up and investigating the clinical course of older patients is very important for these very rare and often lethal disorders.

Until now, the age of onset of symptoms in all patients was under 2 years of age, and most patients died aged under 10. In our patient, mild coarse face, organomegaly, and proteinuria were noticed incidentally during an infectious disease at 6 years old, and he became dialysis dependent at 8 years. In comparison with other patients reported before, mild clinical phenotype in our patient may be associated with compound heterozygosity.

In conclusion, here we report the clinical features of a Turkish boy who presented with proteinuria and rapidly progressed to kidney failure at the age of 7. Consideration of nephrosialidosis and evaluation for lysosomal storage findings are important in the differential diagnosis of proteinuria and kidney failure.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent statement Informed consent was obtained from the parents of the patient.

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