Pediatr Pol 2025; 100 (2): 199-202
DOI: https://doi.org/10.5114/polp.2025.152552
Submitted: 13.02.2025, Accepted: 05.05.2025, Published: 04.07.2025

PEDIATRIA Polska
PISMO POLSKIEGO TOWARZYSTWA PEDIATRYCZNEGO
Polish Journal of PAEDIATRICS
OFFICIAL JOURNAL OF POLISH SOCIETY OF PAEDIATRICS

CASE REPORT

Mutation of the *NOP10* gene as a cause of steroid-resistant nephrotic syndrome coexisting with cataract, hearing loss, and enterocolitis

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ABSTRACT

Nephrotic syndrome comprises a set of symptoms caused by proteinuria exceeding the compensatory capabilities of the body. Based on treatment response, it is classified as either steroid-sensitive or steroid-resistant nephrotic syndrome (SRNS). Steroid resistance is an indication for kidney biopsy and genetic testing. In our case, SRNS in a 6-year-old boy was accompanied by bilateral cataracts, sensorineural hearing loss, and enterocolitis. Genetic testing revealed a previously unreported homozygous mutation in the *NOP10* gene. The nucleolar protein NOP10 belongs to a family of ribonucleoproteins that play a crucial role in maintaining proper telomere function and RNA maturation through pseudouridylation. Limited literature reports describe a family with a phenotype similar to that of our patient, in which *NOP10* gene mutations led to reduced pseudouridylation and ribosome dysfunction. Considering these findings, it seems likely that defective pseudouridylation represents a novel pathogenic mechanism linking kidney, eye, ear, and intestinal abnormalities in our case.

KEY WORDS:
steroid-resistant nephrotic syndrome, *NOP10* gene mutation, pseudouridylation.

INTRODUCTION

Nephrotic syndrome (NS) comprises a set of symptoms caused by proteinuria exceeding the body's compensatory capabilities, i.e. 50 mg/kg body weight/24 hours or more than 2 mg/mg creatinine in a urine sample, along with its consequences such as oedema, hypoalbuminaemia, and hypercholesterolaemia [1, 2].

From the perspective of treatment response, NS is classified as steroid-sensitive (80% of children) or steroid-resistant (20%). Steroid-resistant nephrotic syndrome (SRNS) is defined as the failure to achieve remission during 4 weeks of daily steroid treatment (prednisone or prednisolone). The occurrence of steroid resistance is an indication for kidney biopsy and genetic testing for the most common gene mutations, especially those encoding podocyte-related proteins [3].

The diagnosis and treatment of SRNS pose a significant challenge due to its heterogeneous aetiology, frequent lack of remission despite further immunosuppressive therapy, and severe complications, including the development of end-stage kidney disease and recurrence after transplantation.

The onset of proteinuria in the first months of life, a family history of NS, resistance to standard treatments, and the coexistence of symptoms affecting other organs or systems suggest a genetic background of the disease. Currently, more than 50 genes are known to have potential significance in causing proteinuria. These genes primarily encode proteins located in various parts of the podocyte: in the slit diaphragm, cytoskeletal components, glomerular basement membrane, nucleus, mitochondria, lysosomes, or other intracellular structures. Genetic testing is an important component of SRNS diagnostics, allowing

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for prognosis determination, treatment selection, and assessment of the risk of disease recurrence after kidney transplantation [4].

Genetically determined NS can manifest as an isolated condition or as part of a syndrome, in which NS is accompanied by symptoms affecting other organs and systems.

CASE REPORT

A boy, born from the first pregnancy at 38 weeks of gestation via spontaneous labour, with a birth weight of 2750 g and an Apgar score of 9 points. Perinatal and family history were unremarkable, and both parents and siblings were healthy.

At the age of 8 months, the boy was diagnosed with bilateral profound sensorineural hearing loss and qualified for cochlear implantation (right ear at 21 months, left ear at 3.5 years).

At 17 months, an ophthalmologic examination revealed visual impairment with only light perception, due to bilateral congenital cataracts. Further ophthalmologic management included cataract removal with artificial intraocular lens implantation.

In subsequent years, the child presented poor appetite and inadequate weight gain. The patient's intellectual development progressed normally. Due to persistent chronic diarrhoea with mucus (approximately 5 times per day), a gastroenterological consultation was performed at the age of 6 years, ruling out celiac disease and inflammatory bowel diseases. However, during hospitalisation, laboratory tests revealed daily proteinuria of 392.5 mg/kg, a urine protein-to-creatinine ratio of 63 mg/mg, hypoalbuminaemia (19.6 g/l), hypoproteinaemia (45.8 g/l), signs of haemoconcentration in the blood morphology, slightly elevated total cholesterol (5.39 mmol/l), significantly increased triglycerides (4 mmol/l), an erythrocyte sedimentation rate of 77 mm/h, and an estimated glomerular filtration rate (eGFR) according to Schwartz's formula within normal limits (113.17 ml/min/1.73 m^2).

Immunological studies showed decreased IgG levels, slightly elevated levels of other immunoglobulins and complement component C3, normal C4 levels, and negative antinuclear and ANCA antibodies.

Viral serology for CMV, EBV, HCV, HIV, and SARS-CoV-2 showed no signs of active infection.

There was no peripheral oedema on physical examination. The child had an asthenic body build, cochlear implants, corrective eyeglasses, hypertelorism, protruding ears with asymmetric auricular rims, and mild clinodactyly of the fifth fingers.

Abdominal ultrasound revealed mild asymmetry in kidney length (right kidney: 7.5 cm, left kidney: 8.4 cm) but was otherwise unremarkable.

Based on laboratory findings, NS was diagnosed. Treatment was initiated with standard-dose prednisone (2 mg/kg). Initially, proteinuria showed a decreasing trend but later increased, along with persistent biochemical features of NS. After 4 weeks, due to the steroid-resistant course of the disease and high probability of a genetic background of the symptoms, cyclosporine was introduced, with dose adjustments based on serum drug levels. Prednisone tapering was planned with the intention of discontinuation. Given his elevated blood pressure, antihypertensive and nephroprotective therapy was initiated.

Further nephrological evaluation included a kidney biopsy, which revealed focal segmental glomerulosclerosis.

Whole-exome sequencing identified a novel, previously unreported homozygous variant in the *NOP10* gene – p.Arg13Gln.

Following this diagnosis and due to worsening renal parameters and cyclosporine resistance (proteinuria up to 4 g/l), cyclosporine therapy was discontinued after 9 months. However, after discontinuation, proteinuria increased (up to 15 g/l) with worsening hypoalbuminaemia, leading to the reintroduction of cyclosporine in a dose of 3 mg/kg of body weight, utilising its non-immunological mechanisms. Additionally, the patient currently receives nephroprotective treatment with ramipril and antihypertensive therapy with a β-blocker.

At the most recent nephrological follow-up in November 2024, after 2.5 years of observation, serum creatinine was 80 μmol/l (eGFR 60 ml/min/1.73 m^2). Urine tests showed persistent proteinuria of variable severity (maximum 4.3 g/l) without accompanying oedema. The patient reported feeling well. Home blood pressure measurements ranged from 89/56 to 111/76 mm Hg. The patient's height is at the 1st percentile, and BMI at the 4th percentile.

DISCUSSION

In the presented case, SRNS in a 6-year-old boy was accompanied by bilateral cataracts, profound sensorineural hearing loss, and enterocolitis. Steroid-resistant nephrotic syndrome can occur as an isolated symptom or in a syndromic form, with symptoms affecting other organs and systems, such as in genetically determined syndromes like: Alport syndrome (NS, abnormalities of the anterior segment of the eye, hearing impairment), Denys-Drash syndrome (congenital malformations involving the kidneys and gonads), nail-patella syndrome (nail and patellar abnormalities with accompanying NS), Epstein syndrome (thrombocytopenia, large platelets, NS, and deafness), Schimke dysplasia (vertebral-metaphyseal dysplasia, NS, T-cell immunodeficiencies, growth deficiency, skin pigmentation), familial SRNS with sensory-neural deafness, seizures, ataxia, and dysmorphic features (caused by coenzyme Q10 deficiency), and many other syndromes that should be considered in differential diagnosis. However, none of these syndromes describe the simultaneous

occurrence of SRNS, bilateral cataract, profound sensory-neural hearing loss, and enteritis.

Genetic testing revealed a previously unreported homozygous mutation in the *NOP10* gene in our patient. The nucleolar protein NOP10 belongs to the family of ribonucleoproteins (RNP) that play a crucial role in maintaining proper telomeres and RNA maturation through pseudouridylation. Limited literature reports describe families with a phenotype similar to that of our patient, in which *NOP10* gene mutations were associated with reduced pseudouridylation and ribosomal dysfunction. Given these findings, it is likely that defective pseudouridylation represents a novel mechanism underlying the co-occurrence of kidney, eye, ear, and intestinal disorders in our case.

The ribonucleoprotein complex H/ACA RNP family, including the nucleolar protein NOP10, plays a crucial role in maintaining normal telomeres. Telomeres protect chromosomes from shortening, and telomerase, a multi-protein complex, repairs them after mitosis. This complex consists of a reverse transcriptase subunit (TERT), an internal RNA template (TERC), and members of the H/ACA RNP family: dyskerin (DKC1), RNP NHP2, nucleolar protein 10 (NOP10), and GAR1. NOP10, along with DKC1, NHP2, and GAR1, is essential for TERC stability and telomere maintenance [5].

Telomeres were first linked to human diseases when *DKC1* mutations were identified in dyskeratosis congenita (DC). Most genes associated with short telomere syndromes, such as *TERT, TERC, DKC1, TINF2, NHP2,* and *NOP10*, were identified in patients with DC [6].

Telomerase mutations are also linked to pulmonary and liver fibrosis [7]. Additionally, the telomerase-encoding gene locus is associated with cancer risk, and short telomeres may contribute to cardiovascular diseases.

The *DKC1, NHP2,* and *NOP10* genes also have extratelomeric functions related to the maturation of rRNA, tRNA, and snoRNA through pseudouridylation [8]. Therefore, mutations in H/ACA proteins may impair not only telomere maintenance but also ribosome biogenesis, affecting ribosome and spliceosome function, classifying these diseases as ribosomopathies [9].

RNA modifications play a fundamental role in cellular function. The most common RNA modification, pseudouridylation, involves the isomerisation of uridine to pseudouridine, catalysed by the same small H/ACA RNP complexes (snoRNP) consisting of dyskerin (DKC1), NOP10, NHP2, and GAR1.

To date, 2 families have been described with a phenotype including steroid-resistant NS, cataracts (prior to steroid treatment), sensorineural hearing loss, and enterocolitis, with disease onset in early childhood [10]. All males with the *DKC1* p.Glu206Lys mutation (X-linked inheritance) in one family and 2 children with a homozygous *NOP10* p.Thr16Met mutation (autosomal recessive inheritance) in another family had early mortality (up to 7.5 years of age).

Both mutations affect the dyskerin-NOP10 binding interface in a region distinct from those associated with DC, impairing dyskerin-NOP10 interaction and disrupting the catalytic pseudouridylation site. The cited study identified reduced pseudouridine levels in patients' ribosomal RNA (rRNA), demonstrating decreased pseudouridylation, ribosomal dysregulation, and cell cycle defects. The authors proposed that these abnormalities were due to defective snoRNP pseudouridylation and ribosome dysfunction rather than telomere attrition.

We suggest that defective pseudouridylation represents a novel mechanism linking kidney, eye, and ear dysfunction, expanding our understanding of RNA processing as a disease mechanism.

The previously described family with a phenotype similar to that of our patient carried a different homozygous *NOP10* variant – p.Thr16Met. However, according to UniProt data, both variants are located in close proximity within the same 8-amino-acid motif forming a β-sheet secondary structure. Given these circumstances and the phenotypic similarities, it is plausible that the syndromic NS in our case is caused by a genetic mechanism related to pseudouridylation, the most common RNA modification.

There is growing evidence supporting the pathogenicity of defective RNA processing in disease manifestations [11]. Mutations in the KEOPS complex (kinase, endopeptidase, and other small proteins), involved in transfer RNA modification, have recently been identified in steroid-resistant NS and Galloway-Mowat syndrome (characterised by microcephaly, hiatal hernia, and early-onset steroid-resistant NS) [12].

CONCLUSIONS

The findings presented here suggest that defective pseudouridylation is a novel mechanism underlying kidney, eye, ear, and intestinal abnormalities. However, due to limited data on *NOP10* gene defects in the context of NS with cataracts, hearing impairment, and enteritis, further evaluation of this variant's pathogenicity is needed as new literature emerges.

As part of practical recommendations regarding our patient and other multidisciplinary patients, we advise primary care physicians to remain actively involved in the diagnostic and therapeutic process by providing follow-up care after referral visits and preparing patients for often challenging age-based transitions.

DISCLOSURES

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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