Revista Cubana de Medicina Militar

2025;54(4):e025076921

Research Article

Genetic mutations and response to immunosuppressive therapy in paediatric steroid-resistant nephrotic syndrome

Mutaciones genéticas y respuesta a la terapia inmunosupresora en el síndrome nefrótico pediátrico resistente a esteroides

Nuriya Meriken[1]* https://orcid.org/0009-0007-1574-6349

Saule Dikanbayeva[1] https://orcid.org/0000-0001-9326-3915

Aigul Nugmanova[2] https://orcid.org/0000-0002-9167-5892

Zeinep Zhumagulova[3] https://orcid.org/0000-0002-0545-1148

Asiya Naushabayeva[2] https://orcid.org/0000-0002-8920-3685

[1]Asfendiyarov Kazakh National Medical University. Department of Childhood Diseases with a Course of Neonatology. Almaty, Republic of Kazakhstan.

[2]Kazakh-Russian Medical University. Department of Childhood Diseases. Almaty, Republic of Kazakhstan.

[3]University Clinic Aksay. Asfendiyarov Kazakh National Medical University. Department of Nephrology and Extracorporeal Detoxification. Almaty, Republic of Kazakhstan.

*Author for correspondence. Email: nuriyameriken914@gmail.com

ABSTRACT

Introduction: The prevalence of congenital nephrotic syndrome, affecting approximately 1 in 6,000 newborns, underscores the relevance of this study. This research involved 15 children with steroid-resistant nephrotic syndrome (SRNS), 9 of whom underwent nephrobiopsy.

Objective: To evaluate the genetic conditionality of SRNS and the prognostic significance of immunosuppressive therapy.


2025;54(4):e025076921

Methods: A prospective observational study was conducted among 15 paediatric SRNS patients (1-14 years). Diagnosis was confirmed after four weeks of ineffective prednisone therapy (2 mg/kg/day). Venous blood samples (2-4 mL) were collected in EDTA tubes. Genomic DNA was extracted (QIAamp DNA Mini Kit, Qiagen) and analysed by PCR and Sanger sequencing for NPHS1, NPHS2, and WT1 mutations. One patient was diagnosed with Schimke immuno-osseous dysplasia due to a SMARCAL1 mutation; 9 children underwent ultrasound-guided renal biopsy. Non-responders to steroids received Cyclosporine A (5 mg/kg/day) or Rituximab (375 mg/m² i.v.). Fresolimumab (1-4 mg/kg i.v.) was evaluated for antifibrotic effects. Clinical monitoring included serum creatinine, eGFR, proteinuria, and albumin.

Results: Three children (8.6%) were found to have a genetic predisposition to nephrotic syndrome, with mutations in podocyte-related genes. Immunologically mediated nephrotic syndrome contributed to steroid resistance and recurrence after transplant. All patients initially received prednisone, with some switching to Cyclosporine A and Rituximab. Gene mutations, particularly in NPHS1, NPHS2, and WT1, are critical in understanding SRNS pathogenesis.

Conclusions: SRNS is primarily linked to recessive podocyte gene mutations. Genetic testing is essential for diagnosis and prognosis. Individualised long-term immunosuppressive therapy remains crucial to sustaining remission and preventing recurrence.

Keywords: genes; kidneys; nephrotic syndrome; mutations; podocytes; rituximab.

RESUMEN

Introducción: La prevalencia del síndrome nefrótico congénito, que afecta a 1 de cada 6000 recién nacidos, subraya la relevancia de estudio. Esta investigación involucró a 15 niños con síndrome nefrótico resistente a esteroides (SNRE), 9 de los cuales se sometieron a nefrobiopsia.

Objetivo: Evaluar la condicionalidad genética del SNRE y la importancia pronóstica de la terapia inmunosupresora.

Métodos: Estudio observacional prospectivo en 15 pacientes pediátricos con SRNE (1-14 años). El diagnóstico se confirmó tras cuatro semanas de tratamiento ineficaz con prednisona (2 mg/kg/día). Se recogieron muestras de sangre venosa (2-4 mL) para extraer ADN genómico


2025;54(4):e025076921

(QIAamp DNA Mini Kit, Qiagen) y analizar mutaciones en NPHS1, NPHS2 y WT1 mediante PCR y secuenciación de Sanger. Un paciente fue diagnosticado con displasia inmunoósea de Schimke debido a una mutación en SMARCAL1; 9 niños se sometieron a biopsia renal guiada por ecografía. Los no respondedores a los esteroides recibieron ciclosporina A (5 mg/kg/día) o rituximab (375 mg/m² i.v.). Se evaluó el fresolimumab (1-4 mg/kg i.v.) para efectos antifibróticos.

Resultados: Tres niños (8.6 %) tenían predisposición genética al síndrome nefrótico, con mutaciones en genes relacionados con podocitos. El síndrome mediado inmunológicamente contribuyó a la resistencia a esteroides y recidiva tras el trasplante. Las mutaciones en NPHS1, NPHS2 y WT1 son cruciales para la patogénesis del SRNE.

Conclusiones: El SNRE está vinculado a mutaciones recesivas de genes de podocitos. Las pruebas genéticas son esenciales para el diagnóstico y pronóstico. El tratamiento inmunosupresor individualizado es crucial para mantener la remisión y prevenir la recurrencia.

Palabras clave: genes; mutaciones; podocitos; riñones; rituximab; síndrome nefrótico.

Received: 21/08/2025

Approved: 21/10/2025

INTRODUCTION

Steroid-resistant nephrotic syndrome (SRNS) is a severe form of nephrotic syndrome characterised by persistent proteinuria that does not respond to standard corticosteroid therapy over a four-week course.[(1)] The most common form of nephropathy among children is idiopathic nephrotic syndrome, which develops against the background of the disease of minimal changes or focal segmental glomerulosclerosis. Most often, about 80% of children suffer from the disease of minimal changes in podocytes, which is confirmed by a kidney biopsy. Congenital nephropathy develops due to hereditary mutations in genes. Congenital nephrotic syndrome develops in particular due to mutations in genes encoding components of integral proteins of podocytes


2025;54(4):e025076921

(*NPHS1*, *NPHS2*), the *WT-1* and *LAMB2* genes. Symptoms of this nephrotic syndrome include hyperlipidaemia and oedema, proteinuria of 3.5 g/1.73 m^2 per day, or more than 40 mg/m^2 per hour, and hypoalbuminemia below 25 g/l.[2] Children with renal disease are under the control and supervision of neonatologists and paediatricians for the first three months after birth. Mainly nephrotic syndrome resistant to glucocorticoids is registered, which is the reason for searching for the optimal method of therapy. Mutations registered in the *NPHS1* gene have an autosomal recessive type of inheritance. Approximately 30 mutations have been identified that contribute to changes in the protein structure. These include missense mutations, nonsense mutations, and deletions.[3]

Familial nephrotic syndrome develops due to a mutation of the podocin gene (*NPHS2*), which is registered in 50% of cases.[4] This syndrome is accompanied by the following symptoms – hyperlipidaemia, hypoalbuminemia, flatulence, anasarca, and possible death. Diagnostics include monitoring of electrolyte disorders, thyroid examination, and molecular genetic study of the *NPHS2* gene mutation.[5,6] Podocyte mutations commonly cause minimal change disease, focal segmental glomerulosclerosis, and sometimes IgM nephropathy. In children with these mutations, kidney damage occurs in the neonatal period, leading to rapid kidney failure and death. These mutations affect the glomerular filtration barrier, causing changes in nephrin and podocytes, and are found in the *LAMB2* and *WT-1* genes. Molecular genetic studies should be integrated into clinical practice in maternity hospitals and perinatal centres for congenital nephrotic syndrome unresponsive to immunosuppressive therapy. Over 70 genes have been linked to nephrotic syndrome, and immune regulation disruption may also contribute to its development.[7]

Pathological immune complexes confirm recurrent nephrotic syndrome in transplants. The immune system is suppressed by infections and allergies, and glucocorticoids are not always effective. It is proved that the immune response to foreign and native antigens depends on the activation of T-helper 1 or 2. B-lymphocytes play an important role in the pathogenesis of nephrotic syndrome. Nephrotic syndrome, which develops against the background of the disease of minimal changes in the foot processes of podocytes, is represented by the defeat of these legs in the form of their spreading, which contributes to the violation of the filtration barrier. Despite over 50 years of


2025;54(4):e025076921

glucocorticoid use, their mechanisms in nephrotic syndrome remain unclear, and resistance mechanisms are not fully understood, with only hypotheses available.

Currently, the effectiveness of steroids in steroid-resistant nephrotic syndrome (SRNS) is discussed in the literature; the possibility of achieving partial and complete remission in children has been proven.[8,9,10,11] Calcineurin inhibitors can induce remission but may cause nephrotoxicity and resistance in children. Mycophenolate mofetil is preferred in children under 2 years due to lower nephrotoxicity.[12] Most researchers are of the opinion that mycophenolate mofetil is an effective maintenance therapy caused by calcineurin inhibitors or monoclonal antibody preparations.[13,14]

The use of monoclonal antibodies in the therapy of patients with SRNS is a kind of despair therapy in cases where therapy with steroids and selective cytostatics is not effective. In general, rituximab has a positive effect and supports remission in the majority of patients with SRNS. The beneficial effects of fresolimumab in the treatment of steroid-resistant nephrotic syndrome have also been proven.[15,16,17]

Recent advances in molecular genetics have demonstrated that a substantial proportion of SRNS cases are caused by mutations in genes encoding podocyte structural proteins, such as NPHS1, NPHS2, and WT1. However, the correlation between specific genetic variants and responsiveness to modern immunosuppressive treatments – including rituximab and fresolimumab – remains insufficiently elucidated.

The novelty of the present study lies in its combined clinical and molecular approach, which integrates genetic testing with analysis of treatment outcomes in paediatric patients. By examining mutations in podocyte-related genes and assessing therapeutic responses, this research contributes to a better understanding of the pathogenic mechanisms and therapeutic strategies for SRNS in children.

The aim of this study was to determine the genetic conditionality of steroid-resistant nephrotic syndrome and evaluate the prognostic significance of immunosuppressive therapy, with particular attention to rituximab responsiveness and renal function improvement following fresolimumab administration.


2025;54(4):e025076921

METHODS

Design

The study explored correlations between *NPHS2* and *WT-1* gene mutations and rituximab therapy outcomes in nephrotic syndrome patients with relapse post-transplant. *SMARCAL1* gene mutations (Schimke's immuno-osteoid dysplasia) were analysed in a patient with steroid-resistant nephrotic syndrome.

Subjects

Mutations of the genes of the podocyte proteins *NPHS2* (podocin gene) and *WT-1* (Wilms tumour gene) were analysed on a voluntary basis in 15 patients with SRNS. Participants were selected consecutively from paediatric patients (aged 1-14 years) diagnosed with nephrotic syndrome who were admitted to the University Clinic of the National Medical University named after S.D. Asfendiyarov (Almaty, Kazakhstan) between 2021 and 2024. Exclusion criteria included congenital structural kidney anomalies, secondary nephrotic syndromes (e.g., lupus nephritis, hepatitis B or C, diabetes), and incomplete clinical or genetic data.

Variables

Primary variables included the presence of *NPHS2*, *WT-1*, and *SMARCAL1* gene mutations and their relationship to clinical outcomes following rituximab therapy. Secondary variables encompassed kidney transplantation outcomes, levels of transforming growth factor beta (TGF-β), and glomerular filtration rate (GFR).

Procedures

DNA samples from venous blood in ethylenediaminetetraacetic acid (EDTA) were collected for molecular genetic studies. Kidney transplantation is recommended for end-stage renal failure, offering improved quality of life over dialysis. Rituximab use during transplantation helps prevent antibody rejection and post-transplant lymphoproliferative disease.[18] Immunomodulatory therapy with intravenous immunoglobulin (IVIG) and rituximab was used to reduce anti-HLA and blood anti-group antibodies, thereby overcoming immunological barriers to transplantation.[19]


2025;54(4):e025076921

Fresolimumab was evaluated for its potential to neutralise all three forms of TGF-β, improving GFR in focal segmental glomerulosclerosis at doses of 1 and 4 mg/kg.[20] A control group of 10 patients received placebo infusions to enable comparative assessment of fresolimumab efficacy in renal function and proteinuria outcomes.

Processing

Genetic analyses were performed to detect mutations in NPHS2, WT1, and SMARCAL1 genes. Sequencing data were aligned with reference genomic databases using BioEdit software and confirmed through bidirectional sequencing. Quantitative clinical variables, including serum creatinine, estimated glomerular filtration rate (eGFR), urinary protein excretion, and serum albumin levels, were analysed using SPSS Statistics v.26.0 (IBM Corp., USA). Descriptive statistics were expressed as mean ± standard deviation (SD). Comparisons between baseline and post-treatment values were assessed using the paired Student's t-test for normally distributed data and the Wilcoxon signed-rank test for non-parametric variables. Statistical significance was set at $p < 0.05$.

Bioethical Aspects

Participation in the study was voluntary, with informed consent obtained from all individuals included in this study. The study was conducted in accordance with the ethical standards of the institutional research committee and the principles outlined in the 2024 Helsinki Declaration and its subsequent amendments.

RESULTS

In the study, 2 patients, a 1.5-year-old girl and a 2-year-old boy, had heterozygous mutations of the NPHS2 podocin gene and focal segmental glomerulosclerosis for 2.5 months. Their nephrotic syndrome, which included arterial hypertension and microhematuria, was resistant to prednisone and cyclosporine A. The boy had an H325Y mutation, with a C to T nucleotide substitution. Neither patient had a family history of nephropathy, though the boy's maternal family had hypertension.


2025;54(4):e025076921

Despite glucocorticoid therapy, proteinuria only slightly decreased (from 2,3±0,09 g/day to 1.6±0.1 g/day) and a decrease in GFR (from 77.5±3.5 mL/min to 69±2.2 mL/min).

After genetic confirmation, prednisone was cancelled, and they were prescribed angiotensin-converting enzyme inhibitors. A 7-year-old girl with steroid-resistant nephrotic syndrome had immuno-osteoid dysplasia (Schimke syndrome) due to an SMARCAL gene mutation. She has been suffering from steroid-resistant nephrotic syndrome for three months. She experienced physical developmental delay, short spine, coxarthrosis, hypothyroidism, pigmented spots, and immunodeficiency with frequent infections. She also had celiac disease, delayed sexual development, and right-sided hydronephrosis. Her paternal side showed a family history of short trunk and pigmented spots, but no nephropathy. The child's intelligence is normal. Treatment included angiotensin-converting enzyme inhibitors (monopril 5 mg/day), indomethacin (75 mg/day), diuretics, and hormone therapy for anemia. Indomethacin reduced proteinuria (from 2.4 to 1.8 g/s) and improved the GFR (from 60 mL/min to 48 m/min), preparing the patient for haemodialysis and kidney transplantation.

Six months after the start of taking rituximab, 9 (27.2%) patients with SRNS had complete remission, 7 (21.2%) had partial remission and 17 (51.5%) patients had no changes. This study established the effectiveness of rituximab in maintaining remission in most patients with SRNS. 26 patients took fresolimumab: 14 of them took this drug at a dosage of 1 mg/kg, 12 patients took 4 mg/kg of fresolimumab. The remaining 10 patients took a placebo for comparison. Thus, the initial estimate of the GFR was 63 mL/min/1.73 m^2 and the protein/creatinine ratio in urine was 6190 mg/g. It was found that in patients taking fresolimumab at doses of 1 and 4 mg/kg, the GFR increased compared to the placebo group. It follows that fresolimumab is effective against renal fibrosis and primary focal segmental glomerulosclerosis.

DISCUSSION

In childhood, nephrotic syndrome is the most common of all diseases of the glomerular apparatus. It has a prevalence of 1 to 7 cases per 100 000 children per year.[21] This syndrome is characterised


2025;54(4):e025076921

by a classical triad, including proteinuria, hypoalbuminemia, and oedema. For 60 years, treatment of this syndrome with prednisone was considered highly effective, since 80% of patients had sensitivity to it.[22] Despite the high efficacy of prednisone, approximately 70% of patients have relapses of the disease. Thus, glucocorticosteroids are not always effective in the treatment of nephrotic syndrome, there is no unified approach among doctors to the management of such patients because the disease recurs. And this is not only conditioned by the preferences of the doctor but also by the characteristics of the patient's body. It was found that the duration of therapy with glucocorticosteroids does not affect the number of relapses. British researchers have proven the lack of effectiveness of long-term steroid therapy during the height of nephrotic syndrome.[23]

Nephrotic syndrome, arising from minimal change illness affecting the foot processes of podocytes, is characterised by the expansion of these processes, leading to a disruption of the filtration barrier. More than 70 genes have been found whose mutations lead to the development of nephrotic syndrome.[24] Violation of immune regulation is also fraught with the occurrence of this syndrome in patients.[7] Pathological immune complexes confirm the occurrence of recurrent nephrotic syndrome in the graft.[25] The immune system is suppressed by infectious and allergic factors, and treatment with glucocorticoids for nephrotic syndrome is not always effective.

It is proved that the immune response to foreign and native antigens depends on the activation of T-helper 1 or 2. B-lymphocytes play an important role in the pathogenesis of nephrotic syndrome. That is why rituximab was prescribed in the treatment of nephrotic syndrome, which provides complete CD-19 depletion and leads to the development of persistent remission of nephrotic syndrome.[26] In most sick children with nephrotic syndrome, the disease is based on minimal changes in the foot processes of podocytes, which are manifested by spreading. The researchers are trying to find monogenic forms of the disease and pharmacogenetic factors that influence the pharmacokinetics and pharmacodynamics of glucocorticoids in a particular patient.[27] It has been established that genetic factors influence the pharmacodynamic and pharmacokinetic profile. Side effects as a result of suppression of this effect by drugs range from 20 to 95%. Knowledge of pharmacokinetics, pharmacodynamic properties of prescribed steroids for the treatment of nephrotic syndrome, and performed genotyping of sick children before treatment prevent the


2025;54(4):e025076921

appearance of pathological phenomena. A thorough study of nephropathies will reveal new aspects of their pathogenesis, which will help solve the problem of choosing the optimal method of treating such diseases.[28]

The study by *Noone DG* et al.[29] showed that glucocorticosteroids act accordingly on podocytes, stimulating repair; as a result, the action of nephrin is activated. Actin filaments and actin-associated proteins are components of podocyte processes; they are the ones that allow the cytoskeleton to be dynamically maintained and ensure its reorganisation.[30] The studies have revealed that the effect of glucocorticoids on podocytes contributes to the stabilisation of actin filaments and inactivation of the process of apoptosis. In the disease of minimal changes in podocytes, the expression of glucocorticoid receptors in the glomeruli is significantly higher than in focal segmental glomerulosclerosis.

Children with renal disease are under the control and supervision of neonatologists and paediatricians for the first three months after birth. Mainly nephrotic syndrome resistant to glucocorticoids is registered, which is the reason for searching for the optimal method of therapy. Mutations registered in the *NPHS1* gene have an autosomal recessive type of inheritance. About thirty different mutations have been identified that contribute to changes in the protein structure. These include missense mutations, nonsense mutations, and deletions.[3] Familial nephrotic syndrome develops due to a mutation of the podocin gene (*NPHS2*), which is registered in 50% of cases.[31] About thirty different mutations have been identified that contribute to changes in the protein structure. These include missense mutations, nonsense mutations, and deletions.[3]

The morphological picture of the nephrotic syndrome resulting from podocin mutations is represented by focal segmental glomerulosclerosis, less often the same picture is given by minimal changes and even less often by IgM nephropathy. Kidney transplantation from parents with a gene with *NPHS2* mutations increases the likelihood of recurrence of focal segmental glomerulosclerosis in the transplant.[32] The *WT-1* gene, located on chromosome 11 (11q13), encodes growth factors involved in the formation of reproductive glands and kidneys. The gene consists of 10 exons and has 4 isoforms.[22] Mutation of the WT-1 gene can also lead to the development of the hereditary nephrotic syndrome. Mutational changes are most often affected by


2025;54(4):e025076921

8 and 9 sites of this gene, and this complicates laboratory studies.[30] Children born with mutations of these gene sites have typical symptoms of nephrotic syndrome, and they usually develop terminal stage of renal failure at lightning speed. These pathological changes are recognised morphologically in the form of diffuse mesangial sclerosis.

The next gene most frequently affected by mutations is *LAMB2*, it encodes β2-Laminin. Its localisation is in the 3p21 chromosome. Mutational changes occur in *LAMB2* in the 16th exon, where the stop codon occurs (Y689X), and in the 9th exon (*C374X*). These pathological changes lead to a deficiency of β2-laminin.[29] β2-Laminin 521 is the main glycoprotein of the glomerular basement membrane and affects the proliferation, differentiation and function of cells localised along the membrane. Its components are β2-α5-γ1 chains.[28] Neonatal nephrotic syndrome often leads to rapid kidney failure and death. It is crucial to introduce molecular genetic studies in maternity hospitals and perinatal centres for early detection and intervention, as congenital nephrotic syndrome is resistant to steroid therapy.

Podocytes are visceral epithelial cells in the form of a star, which are located in the Shumlyansky-Bowman capsule. This is the third layer of the glomerular capillary. The components of the podocyte are: the cell body and primary, secondary, and tertiary processes, with which they are attached to the basement membrane. Intermediate filaments form the podocyte body; they consist of vimentin and desmin.[26] Large appendages of the body occupy a significant part of the capillary. Small appendages, pedicles, depart perpendicular from the large ones, intertwine with each other and occupy all the space of the basal capillary membrane free from large processes; actin filaments contribute to their reduction.[7]

The gene encoding this protein is localised on chromosome 19 and contains 29 exons. This protein consists of three parts: a large extracellular region, an intermembrane, and intracellular regions.[22] The highly glycolysed extracellular region has 8 immunoglobulin parts and 1 fibronectin part, this part connects in the middle of the filtration slit, forming the structure of the slit diaphragm. The intracellular region of nephrin consists of podocin and *CD2AP* proteins, with their help, it binds to the actin cytoskeleton of the cell and transmits intracellular signals.[32] Mutates mainly the *NPHS1* gene, inherited by an autosomal recessive type. Nephrotic syndrome has the following symptoms:


2025;54(4):e025076921

proteinuria due to albumins, oedema up to anasarca, hypoalbuminemia, and hyperlipidaemia. Podocytopathy with a nephrin defect during diagnosis is confirmed histologically and in the laboratory by examining urine for the presence of nephrin.[28] Treatment of podocytopathy with a mutation in the *NPHS1* gene by kidney transplantation in 50% of cases leads to an exacerbation of nephrotic syndrome due to the presence of antibodies to nephrin. Podocin belongs to an integral protein from the stomatin family and has a molecular weight of 42 kDa. The gene encoding the protein is located on the first chromosome at the q25-q31 site. Its function is the closure of nephrin in podocytes, it is part of the structure of the slit diaphragm. Podocin activates nephrin with the help of protein kinase, which includes p38 and c-Jun amino-terminal kinase regulating the formation of activator-1 protein.

Mutation of the podocin gene (*NPHS2*) in familial nephrotic syndrome occurs in 45-55% of cases.[4] This, in turn, manifests itself with the following symptoms: hyperlipidaemia, hypoalbuminemia, bloating, oedema, and may even result in fatal outcomes. In diagnosing this syndrome, electrolyte disorders are monitored, thyroid function is examined, and molecular genetic studies of the NPHS2 gene mutation are performed. The role of pharmacogenetics in steroid-resistant nephrotic syndrome in children is underexplored.[26]

The most common nephropathy in childhood is steroid-resistant nephrotic syndrome, about 7 cases per 100,000 children are registered. Congenital nephropathy is steroid-resistant and is caused by hereditary mutations in genes. The development of nephrotic syndrome in children is conditioned by mutations in the *WT-1* and *LAMB2* genes, which encode the structures of the integral proteins of the *NPHS1 and NPHS2* podocytes. Children are under the supervision of neonatologists and paediatricians during the first three months after birth. The problem with nephrotic syndrome is resistance to steroid therapy.

This study was limited by a small sample size (n=15), which restricts the generalisability of the findings to broader paediatric populations. The genetic analyses focused only on three major podocyte-related genes (NPHS1, NPHS2, and WT1), potentially overlooking other mutations contributing to steroid resistance. Additionally, the duration of follow-up was insufficient to evaluate long-term renal outcomes and post-transplant recurrence comprehensively.


2025;54(4):e025076921

Steroid-resistant nephrotic syndrome in children is predominantly associated with recessive mutations in podocyte-related genes, particularly NPHS1, NPHS2, and WT1. Genetic testing is essential for accurate diagnosis, prognosis, and treatment selection. Rituximab demonstrated notable efficacy in maintaining remission, while fresolimumab showed potential antifibrotic benefits. An individualised therapeutic approach combining genetic diagnostics with targeted immunosuppressive therapy offers the most promising strategy for improving long-term renal outcomes.

BIBLIOGRAPHIC REFERENCES

1. Melnik OO. The use of immunobiological monoclonal antibody-based drugs in nephrological practice [Internet]. Kidneys. 2018; 7(3):224-36. DOI: 10.22141/2307-1257.7.3.2018.140208

2. Kostushina IS, Margieva TV, Gusarova TN, Yakhyaeva GT, Namazova-Baranova LS, Pushkov AA, et al. Case of non-severe congenital nephrotic syndrome. Pediatr Pharmacol. 2014; 11(6):62-65.

3. Schijvens AM, Ter Heine R, de Wildt SN, Schreuder MF. Pharmacology and pharmacogenetics of prednisone and prednisolone in patients with nephrotic syndrome [Internet]. Pediatr Nephrol. 2019; 34(3):389-403. DOI: 10.1007/s00467-018-3929-z

4. Morozov SL, Dlin VV, Sukhorukov VS, Voronkova AS. Molecular nephropathology: New opportunities for kidney diseases diagnostics. Russ Bull Perinatol Pediatr. 2017; 62(3):32-36.

5. Bierzynska A, McCarthy HJ, Soderquest K, Sen ES, Colby E, Ding WY, et al. Genomic and clinical profiling of a national nephrotic syndrome cohort advocates a precision medicine approach to disease management [Internet]. Kidney Int. 2017; 91(4):937-947. DOI: 10.1016/j.kint.2016.10.013

6. Bierzynska A, Saleem M. Recent advances in understanding and treating nephrotic syndrome [Internet]. F1000Reseach. 2017; 6:121. DOI: 10.12688/f1000research.10165.1

7. Ignatova MS, Dlin VV. Nephrotic syndrome: Past, present and future [Internet]. Russ Bull Perinatol Pediatr. 2017; 62(6):29-44. DOI: 10.21508/1027-4065-2017-62-6-29-44

8. Griswold WR, Tune BM, Reznik VM, Vazquez M, Prime DJ, Brock P, et al. Treatment of childhood prednisone-resistant nephrotic syndrome and focal segmental glomerulosclerosis with intravenous methylprednisolone and oral alkylating agents [Internet]. Nephron. 1987; 46(1):73-77. DOI: 10.1159/000184308

9. Mendoza SA, Reznik VM, Griswold WR, Krensky AM, Yorgin PD, Tune BM. Treatment of steroid-resistant focal segmental glomerulosclerosis with pulse methylprednisolone and alkylating agents [Internet]. Pediatr Nephrol. 1990; 4(4):303-307. DOI: 10.1007/bf00862503

10. Tune BM, Kirpekar R, Sibley RK, Reznik VM, Griswold WR, Mendoza SA. Intravenous methylprednisolone and oral alkylating agent therapy of prednisone-resistant pediatric focal segmental glomerulosclerosis: A long-term follow-up [Internet]. Clin Nephrol [access 02/01/2025]. 1995; 43(2):84-88. Available from: https://pubmed.ncbi.nlm.nih.gov/7736683/

11. Yorgin PD, Krasher J, Al-Uzri AY. Pulse methylprednisolone treatment of idiopathic steroid-resistant nephrotic syndrome [Internet]. Pediatr Nephrol. 2001; 16(3):245-250. DOI: 10.1007/s004670000494

12. Li Z, Duan C, He J, Wu T, Xun M, Zhang Y, et al. Mycophenolate mofetil therapy for children with steroid-resistant nephrotic syndrome [Internet]. Pediatr Nephrol. 2010; 25(5):883-888. DOI: 10.1007/s00467-009-1375-7

13. Ulinski T, Dubourg L, Said MH, Parchoux B, Ranchin B, Cochat P. Switch from cyclosporine a to mycophenolate mofetil in nephrotic children [Internet]. Pediatr Nephrol. 2005; 20(4):482-485. DOI: 10.1007/s00467-004-1778-4

14. Okada M, Sugimoto K, Yagi K, Yanagida H, Tabata N, Takemura T. Mycophenolate mofetil therapy for children with intractable nephrotic syndrome [Internet]. Pediatr Int. 2007; 49(6):933-937. DOI: 10.1111/j.1442-200x.2007.02487.x

15. Kamei K, Okada M, Sato M, Fujimaru T, Ogura M, Nakayama M, et al. Rituximab treatment combined with methylprednisolone pulse therapy and immunosuppressants for childhood steroid-resistant nephrotic syndrome [Internet]. Pediatr Nephrol. 2014; 29(7):1181-1187. DOI: 10.1007/s00467-014-2765-z

16. Kamei K, Ishikura K, Sako M, Ito S, Nozu K, Iijima K. Rituximab therapy for refractory steroid-resistant nephrotic syndrome in children [Internet]. Pediatr Nephrol. 2020; 35(1):17-24. DOI: 10.1007/s00467-018-4166-1

17. Jellouli M, Charfi R, Maalej B, Mahfoud A, Trabelsi S, Gargah T. Rituximab in the management of pediatric steroid-resistant nephrotic syndrome: A systematic review [Internet]. J Pediatr. 2018; 197:191-197. DOI: 10.1016/j.jpeds.2018.01.008

18. Vivarelli M, Massella L, Ruggiero B, Emma F. Minimal change disease [Internet]. Clin J Am Soc Nephrol. 2017; 12(2):332-345. DOI: 10.2215/cjn.05000516

19. Teeninga N, Guan Z, Stevens J, Kist-van Holthe JE, Ackermans MT, van der Heijden AJ, et al. Population pharmacokinetics of prednisolone in relation to clinical outcome in children with nephrotic syndrome [Internet]. Ther Drug Monit. 2016; 38(4):534-545. DOI: 10.1097/ftd.0000000000000308

20. Du N, Yang F, Li L, Liu X, Sun L, Zhang S, et al. Association of single-nucleotide polymorphism in the FKBP5 gene with response to steroids in pediatric patients with primary nephrotic syndrome [Internet]. Clin Nephrol. 2017; 88(12):338-343. DOI: 10.5414/cn109126

21. Uwaezuoke SN. The role of novel biomarkers in childhood idiopathic nephrotic syndrome: a narrative review of published evidence [Internet]. Int J Nephrol Renovasc Dis. 2017; 10:123-128. DOI: 10.2147/ijnrd.s131869

22. Selewski DT, Troost JP, Cummings D, Massengill SF, Gbadegesin RA, Greenbaum LA, et al. Responsiveness of the PROMIS® measures to changes in disease status among pediatric nephrotic syndrome patients: a Midwest pediatric nephrology consortium study [Internet]. Health Qual Life Outcomes. 2017; 15:166. DOI: 10.1186/s12955-017-0737-2

23. Deschênes G, Vivarelli M, Peruzzi L, ESPN Working Group on Idiopathic Nephrotic Syndrome. Variability of diagnostic criteria and treatment of idiopathic nephrotic syndrome across European countries [Internet]. Eur J Pediatr. 2017; 176(5):647-654. DOI: 10.1007/s00431-017-2891-2

24. Baylarov RO. NPHS1 and NPHS2 genes in children with nephrotic syndrome. Nephrology. 2019; 23(5):65-70. DOI:

25. Rheault MN, Gbadegesin RA. The genetics of nephrotic syndrome [Internet]. J Pediatr Genet. 2016; 5(1):15-24. DOI: 10.1055/s-0035-1557109

26. Morozov SL, Voronkova AS, Dlin VV, Turkina TI, Sukhorukov VS. Analysis of gene expression using nCounter Nanostring technology in medical research: experience of use in children with nephrotic syndrome [Internet]. Russ Bull Perinatol Pediatr. 2019; 64(1):110-115. DOI: 10.21508/1027-4065-2019-64-1-110-115

27. Morozov SL, Aksenova ME. Primary nephrotic syndrome in children. Prospects for personalized therapy. Pract Med. 2018; 16(8):39-42.

28. Stone H, Magella B, Bennett MR. The search for biomarkers to aid in diagnosis, differentiation, and prognosis of childhood idiopathic nephrotic syndrome [Internet]. Front Pediatr. 2019; 7:404. DOI: 10.3389/fped.2019.00404

29. Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children [Internet]. Lancet. 2018; 392(10141):61-74. DOI: 10.1016/s0140-6736(18)30536-1

30. Bertelli R, Bonanni A, Caridi G, Canepa A, Ghiggeri GM. Molecular and cellular mechanisms for proteinuria in minimal change disease [Internet]. Front Med. 2018; 5:170. DOI: 10.3389/fmed.2018.00170

31. Morozov SL. Features of gene expression of the immune system in steroid-resistant nephrotic syndrome. Russ Herald Perinatol Paediatr. 2018; 63(4):221-222.

32. Prikhodina LS, Papizh SV, Stolyarevich ES, Povilaite PE, Shatalov PA. Infantile nephrotic syndrome: clinical and morphological characteristics, genetic heterogeneity, outcomes. the experience of one center [Internet]. Nephrol Dial. 2019; 21(2):234-242. DOI: 10.28996/2618-9801-2019-2-234-242

Conflict of interest

The authors have no competing interests to declare that are relevant to the content of this article.

Financial information

No funding was received for conducting this study.

Author's contributions

Conceptualization: *Nuriya Meriken, Aigul Nugmanova.*

Data curation: *Aigul Nugmanova, Zeinep Zhumagulova.*

Formal Analysis: *Aigul Nugmanova, Asiya Naushabayeva.*

Research: *Nuriya Meriken, Saule Dikanbayeva, Aigul Nugmanova, Zeinep Zhumagulova, Asiya Naushabayeva.*

Methodology: *Saule Dikanbayeva, Asiya Naushabayeva.*

Project Administration: *Nuriya Meriken, Asiya Naushabayeva.*

Resources: *Zeinep Zhumagulova, Asiya Naushabayeva.*

Supervision: *Nuriya Meriken, Saule Dikanbayeva.*

Validation: *Saule Dikanbayeva, Zeinep Zhumagulova.*

Writing -original draft: *Nuriya Meriken, Aigul Nugmanova.*

Writing -Review & editing: *Saule Dikanbayeva, Zeinep Zhumagulova,*

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.