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Idiopathic nephrotic syndrome – contemporary views on immune-mediated pathogenetic mechanisms

Idiopatyczny zespół nerczycowy – współczesne poglądy na immunologiczne mechanizmy patogenetyczne

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Abstract

Idiopathic nephrotic syndrome is a rare kidney disease characterised by nephrotic proteinuria, hypoalbuminemia, hyperlipidaemia and oedema. The incidence of idiopathic nephrotic syndrome ranges from 2 to 7 cases per 100,000 children per year. Children between 1 and 10 years of age are mainly affected. The pathogenesis is associated with damage to the microstructure of glomerular filtration barrier, which may be caused by a variety of immune-mediated factors. Circulating factors such as hemopexin, cathepsin, soluble form of urokinase plasminogen activator receptor may be responsible for proteinuria in idiopathic nephrotic syndrome. Another possible cause of nephrotic proteinuria is dysregulation of T cells, including regulatory T cells and B cells. Nephrotic proteinuria occurs in other diseases that are associated with pathological action of lymphocytes, such as immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX syndrome), and Hodgkin's lymphoma. Numerous relapses of proteinuria in idiopathic nephrotic syndrome may be associated with latent Epstein–Barr virus infection via antigenic mimicry. Relapses of proteinuria may also occur in response to gluten or allergens in patients with coeliac disease or food allergy. Idiopathic nephrotic syndrome is managed with immunosuppressants. They inhibit immune system activity, which consequently allows for reaching and maintaining remission of the disease.

Keywords: allergy, idiopathic nephrotic syndrome, T cells, lymphocyte B cells

Streszczenie

Idiopatyczny zespół nerczycowy to choroba nerek zaliczana do chorób rzadkich, która objawia się białkomoczem nerczycowym, hipoalbuminemią, hiperlipidemią i obrzękami. Zapadalność wynosi 2–7 przypadków na 100 000 osób rocznie i dotyczy przede wszystkim dzieci od 1. do 10. roku życia. Patogeneza jest związana z uszkodzeniem mikrostruktury błony filtracyjnej kłębuszków nerkowych, do którego może prowadzić wiele różnorodnych czynników o podłożu immunologicznym. Za wystąpienie białkomoczu mogą odpowiadać czynniki krążące, takie jak hemopeksyna, katepsyna i rozpuszczalna postać urokinazowego receptora aktywatora plazminogenu. Kolejną możliwą przyczyną białkomoczu nerczycowego jest dysregulacja aktywności limfocytów T, w tym grupy limfocytów T regulatorowych oraz limfocytów B. Białkomocz nerczycowy występuje także w innych, związanych z patologicznym działaniem limfocytów jednostkach chorobowych, takich jak zespół dysregulacji immunologicznej, poliendokrynopatii i enteropatii sprzężony z chromosomem X oraz chłoniak Hodgkina. Liczne nawroty białkomoczu w idiopatycznym zespole nerczycowym mogą być związane z latentnym zakażeniem wirusem Epsteina–Barr poprzez mechanizm mimikry antygenowej. Nawroty białkomoczu mogą również być reakcją na kontakt z glutenem lub alergenem u osób z celiakią lub alergią pokarmową. W terapii idiopatycznego zespołu nerczycowego stosuje się leki immunosupresyjne. Mechanizmy ich działania prowadzą do hamowania aktywności układu immunologicznego, co w konsekwencji umożliwia osiągnięcie i utrzymanie remisji choroby.

Słowa kluczowe: alergia, idiopatyczny zespół nerczycowy, limfocyty T, limfocyty B

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INTRODUCTION

Idiopathic nephrotic syndrome (INS) is an immune-mediated disorder accounting for 90% of nephrotic syndrome (NS) cases in patients aged 1 to 10 years and 50% in older children. NS is a set of symptoms (hypoalbuminemia, hyperlipidaemia, and oedema) that occur due to excessive protein loss in the urine, i.e. nephrotic proteinuria (NP). Nephrotic proteinuria is defined as:

- urinary protein loss of 50 mg/kg body weight/day in children and >3.5 g/day in adults;
- >2 mg protein/1 mg creatinine in a urine sample or >300 mg/dL;
- dipstick 3+ in urine collection[1,2].

NP leads to hypoalbuminemia, which in turn results in oedema and hyperlipidaemia. General urinalysis does not reveal microscopic haematuria, haematuria or active urine sediment. Blood pressure, renal function parameters and serum complement C3 and C4 levels remain normal. INS has an incidence of 2–7 cases per 100,000, and a prevalence of 16/100,000[1], and therefore meets the definition of a rare disease. The onset of INS most often occurs between 1 and 10 years of life[1]. The disease is recurrent, with relapses and remissions.

Renal biopsy pathology in INS may reveal minimal change disease (MCD), diffuse mesangial sclerosis (DMS), or focal segmental glomerulosclerosis (FSGS). FSGS may develop alongside MCD in patients with INS[3]. Immunofluorescence of the biopsy shows no deposits in the glomerular basement membrane (GBM), while electron microscopy shows only diffuse changes in podocyte foot processes (FPs)[1]. Renal biopsy is not routinely performed in INS.

FILTRATION MEMBRANE STRUCTURE

The pathophysiology of the disease primarily involves the glomerular filtration membrane, which is responsible for the formation of primary urine from plasma, and its damage and dysfunction lead to proteinuria. Under physiological conditions, the glomerular filtration membrane consists of endothelium, GBM, and podocytes with processes (Fig. 1).

Due to the presence of podocalyxin, the endothelium has a negative charge, which prevents filtering proteins with a similar charge (albumin). Endothelial cells form a fenestrated membrane, in which the number of cytoplasmic windows depends on the vascular-epithelial growth factor produced by podocytes. The basement membrane consists of three layers: the lamina lucida (electron-lucent), lamina densa (electron-dense), and lamina fibro-reticularis (electron-lucent). It is

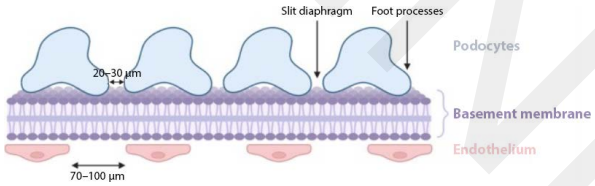

Fig. 1. Schematic structure of podocyte filtration membrane

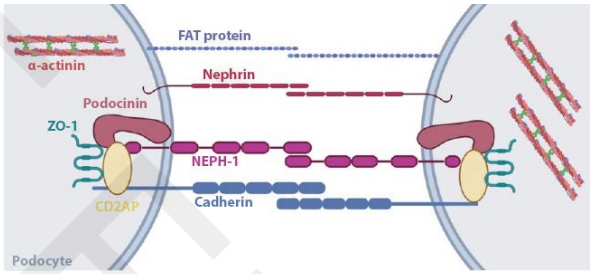

Fig. 2. Schematic structure of podocyte slit diaphragm

composed of type IV collagen, laminin, fibronectin and proteoglycans. The basement membrane is lined by podocytes, which are among the most diverse cells in the body. Each podocyte adheres to several capillaries by means of processes. Podocytes lack regenerative capacity, and their destruction by pathogenic factors is irreversible[4,5]. Under pathological conditions, podocytes may lose their foot processes. In such cases, the adherence surface area between a podocyte and the basement membrane is large, causing thickening of the filtration membrane and thus reducing its ability to filter plasma[5].The slits between podocyte foot processes are covered by the slit diaphragm (Fig. 2). It is the most crucial part of filtration membrane, composed of many proteins, including CD2-associated protein (CD2AP), nephrin-like protein (Neph1), actinin 4, zonula occludens-1 (ZO-1), cadherin, FAT and podocin[5]. Nephrin and podocin, which are transmembrane proteins, transmit the signal from the outside of the podocyte to its interior. Nephrin influences the maturation of the slit diaphragm in the process of prenatal glomerulogenesis[5]. Nephrin, NEPH-1 and FAT form slit diaphragm cytoskeleton and connect to the cytoskeleton of the foot processes via CD2AP, podocin and ZO-1. Nephrin induces generation of a signal that allows the flow of water, proteins and electrolytes through the filtration membrane[5], while cadherins are responsible for the adhesion of cells to each other. Due to its three-layer structure, the glomerular filtration membrane forms a molecular filter that allows molecules of a specific size and a specific electrical charge to pass through. This is where the excretion of protein molecules, erythrocytes and water into the primary urine is regulated. Each of its components may be damaged[5].

ETIOPATHOGENESIS OF IDIOPATHIC NEPHROTIC SYNDROME

Despite many years of research, the cause of proteinuria in INS has not yet been determined. Recurrent nephrotic proteinuria is probably multifactorial, and the efficacy of steroid therapy confirms the predominance of immune-mediated mechanisms.

Circulating factors

In 1993, Sewell and Short demonstrated that patients with NS had serum polycation, which alters the charge of the

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filtration membrane and allows the passage of protein molecules, causing proteinuria[6]. This thesis is supported by FSGS recurrence after kidney transplantation. NP resolves or decreases after plasmapheresis and modified immunosuppression in most transplant recipients with recurrent FSGS[7]. Since the causative agent passes through the placenta, proteinuria was observed in newborns and infants of mothers with INS, which subsided in the subsequent months of the children's life[8]. Le Berre et al. found changes similar to those in INS humans in their studies in Buffalo/Mna rats with NS associated with FSGS in histopathological evaluation of kidney biopsy. It was shown that rats with NS after kidney transplantation from a healthy donor develop FSGS in the transplanted kidney and that administration of serum collected from an NS patient induced proteinuria in the animals[3,9]. Kidney transplantation from an NP rat to a healthy animal caused proteinuria regression[9,10]. Addition of serum from NS patients to podocyte cell cultures led to altered cytoskeletal structure, resulting in proteinuria[11].

Circulating factors that may be responsible for the onset or recurrence of NS symptoms include hemopexin, urokinase plasminogen activator surface receptor (uPAR), cathepsin, and angiopoietin-like factor 4 (ANGPTL4)[2,3,11].

Hemopexin is an acute phase protein which, among others, delivers heme to the liver. It can modulate intracellular signalling. In their experiment on rats, Cheung et al. showed that hemopexin induced proteinuria. Histopathological examination of NP rat kidneys showed podocytopathy typical of MCD[11,12]. Increased hemopexin levels have been detected in children with INS and MCD. Elevated hemopexin correlates with altered podocyte actin cytoskeleton[11].

UPAR exists both in cell-bound and soluble forms (soluble urokinase plasminogen activator surface receptor, suPAR) in body fluids, including serum and urine. It is found on immune cells, i.e. monocytes, macrophages and neutrophils[13], and is involved in fibrinolysis and regulation of immune processes by inducing migration of immune cells, as well as influencing chemotaxis and cell adhesion[11,13]. Increased suPAR levels are observed in individuals with inflammatory and autoimmune disorders, cancers, and infections, especially in the case of their generalisation[13,14]. High serum levels translate into increased suPAR deposition in the basement membrane of podocytes. Acting through integrin, a protein that connects podocyte processes to the basement membrane, it causes fusion of glomerulus podocyte foot processes in INS patients. Increased suPAR levels are found in patients with NS and FSGS, and increasing urinary suPAR levels may precede FSGS in the transplanted kidney[13,14].

Cathepsins are enzymatic proteins that affect cell migration and adhesion, as well as antigen presentation. They participate in the activation of Toll-like receptors (TLRs) due to the recognition of viral proteins. The immune response to infections depends on their activity[15]. Cathepsin L is found in the basement membrane of the kidneys, and its increased level correlates with damage to podocyte basement membrane and increased proteinuria in INS patients[16].

ANGPTL4 is an acute phase protein expressed in adipose and muscle tissue, as well as in podocytes. Its elevated level negatively affects the basement membrane, leading to increased filtration membrane permeability to proteins. Elevated ANGPTL4 levels are observed in patients with INS[3,11].

T cells

Aberrant T-cell activity is considered to be the causative factor of INS. This thesis is supported the regression of INS symptoms following immunosuppressants that target T-cells, recurrences of proteinuria after infections, vaccinations or allergen exposure, and remission after eliminating the causative factor. Some patients experience temporary INS remission after measles, which impairs, among other things, T-cell-mediated cellular immunity[11].

The damage to the filtration membrane that induces proteinuria occurs during infection via the activation of lymphocytes and complement proteins. T-cell stimulation and subsequent activation of B-cells lead to antibody production, activation of CD80 cells on the glomerular basement membrane, and podocyte damage[2,3]. The CD80 molecule is found on antigen-presenting cells, it binds to T-cell receptors, and stimulates their activity. CD80 expression on podocytes and its urinary levels increase during INS relapses, especially in MCD patients[11]. Shimada et al. reported that properly functioning regulatory T cells (Tregs) can reduce CD80 expression on podocytes, thereby preventing their damage and damage to the glomerular filtration membrane[17,18].

IPEX syndrome (immunodysregulation polyendocrinopathy enteropathy X-linked syndrome) is also an example of the role of T cells in the initiation of nephrotic proteinuria. It is an inborn error of immunity associated with type 1 diabetes, autoimmune thyroiditis, enteropathy and atopic dermatitis, and often co-occurring NP. Symptoms develop already in the neonatal period or infancy. The syndrome is caused by mutation of the *FOXP3* gene (Xp11.23) located on the X chromosome, which is responsible for Treg dysregulation. Under normal conditions, precursor cells evolve into Tregs following a trigger (infection) in healthy individuals. However, patients with IPEX syndrome present with low levels of these cells despite the trigger. Overactivation of effector T cells occurs. Supplementation with IL-2, which is the main growth factor of Tregs, reduces proteinuria and causes regression of histopathological changes in the kidneys[10,19,20].

The relationship between proteinuria in INS and T cell activity is also confirmed by the involvement of Th17 cells and IL-17 they produce in the development of an inflammatory reaction. Th17 cells, which derive from T helper precursors, influence the maturation of B cells, cytotoxic T cells and macrophages. They are responsible for the development

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of an inflammatory reaction. Their levels increase in allergies, autoimmune and inflammatory disorders[20,21]. Wang et al. confirmed higher IL-17 in INS patients compared to controls. Additionally, increased Th17 counts are inversely proportional to the counts of Tregs, which are responsible for suppressing inflammatory processes[21,22]. May et al. described a correlation between steroid resistance in INS and high serum levels of Th17[22].

B cells

B cells are also involved in the pathogenesis of INS. This is evidenced, among other things, by remission with rituximab (RTX). According to Colucci et al., B-cell counts increase during the first and subsequent flares of INS[23,24]. RTX reduces serum CD20 cells, including memory T cells, thus diminishing humoral response to a trigger and the likelihood of another flare[24]. Additionally, RTX affects the basement membrane cytoskeleton, thereby reducing apoptosis[24].

The association between nephrotic proteinuria and Hodgkin's lymphoma (HL) is another evidence for the role of B cells in the pathogenesis of INS. Audard et al. described a population of adult MCD patients who developed NP as the first manifestation of HL preceding haematological symptoms by several or a dozen months, with NS symptom resolution after anti-cancer treatment[25].

Allergens and gluten

Pérez-Sáez et al. conducted a prospective study in 17 children and young adults with INS to investigate the effect of a gluten-free and cow's milk protein-free diet on the severity of proteinuria. Two out of 17 patients achieved remission of proteinuria with the elimination diet alone. Proteinuria recurred after discontinuing food restrictions. High serum levels of ZO-1, an adhesion protein of epithelial cells and slit diaphragm, and IL-17 were observed in these patients during proteinuria. Elimination of gluten and cow's milk protein from the patients' diet resulted in a fourfold decrease in ZO-1, a decrease in IL-17, lower IL-8 and TNFα levels and an increase in the Treg/IL-17 ratio[26]. Previous studies have already reported a positive correlation between Th17 and IL-17 and inflammatory and allergic disorders[24]. Th2-mediated IL-13 also plays a role in inducing proteinuria. Acting through membrane receptors on podocytes, IL-13 increases CD80 expression, cytoskeletal reorganisation through a negative effect on nephrin and podocin, thereby increasing permeability of the filtration membrane in INS patients (Fig. 3). INS patients have higher levels of IL-13[3]. Upon allergen exposure triggering an IgE-dependent reaction, T cells differentiate into Th2, which in turn stimulate B cells to secrete IgEs. IgE is responsible for the degranulation of mast cells, which release inflammatory mediators. As in IgE-mediated allergy, higher levels of total IgEs are sometimes observed in INS patients. IgE secretion by

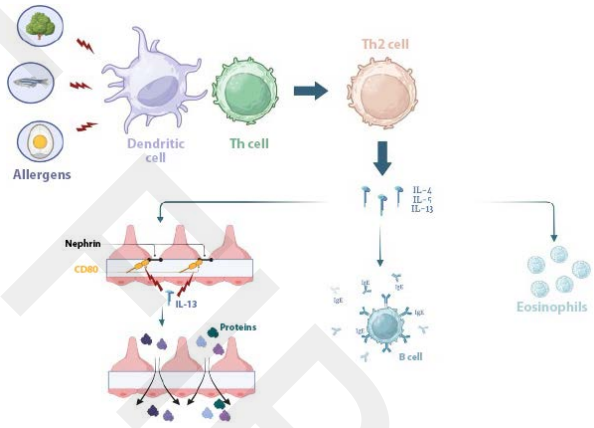

Fig. 3. Pathomechanism of proteinuria following allergen exposure

B cells is stimulated by interleukins 4, 5, 13 and 17 (Th2-mediated response)[26,27]. Tregs are responsible for regulating Th2-mediated responses. Elevated IL-4, which stimulates IgE secretion by B cells, is observed both in atopic diseases and INS[26,27].

Antigenic mimicry

The antigenic similarity of viral proteins to those that build individual organs, including the kidneys, may lead to an inflammatory reaction initiated by pathogen cells in the body, but also targeting the body's own proteins.

Serum EBV DNA is found in about half of patients with the first INS attack. EBV inhabits epithelial and B cells, where it can survive, causing latent infection[3,28]. Infected B cells, which are memory cells, migrate to lymph nodes and, owing to proteins produced by the virus (BCRF1-viral IL-10), they do not undergo apoptosis[28]. Antibodies against the EBNA-1 antigen of EBV, also specific for the podocyte, attack filtration membrane proteins, causing its damage and increasing proteinuria (Fig. 4). Immunosuppressants, such as cyclophosphamide, glucocorticoids or RTX, directly or indirectly reduce B cells and antibodies, including those against the EBNA-1 antigen, leading to proteinuria resolution. Dossier et al. suggested that the natural course of autoimmune diseases, including INS, in the form of relapses

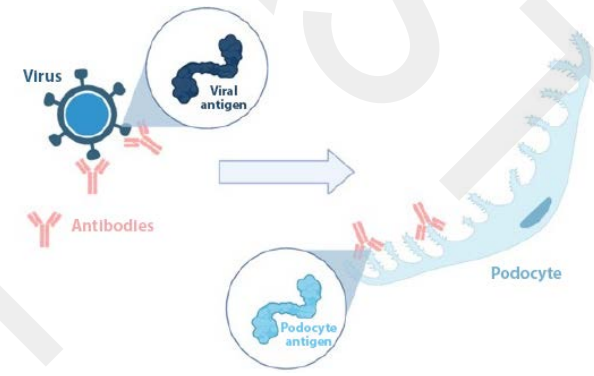

Fig. 4. Antigenic mimicry

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and remissions may be related to the course of EBV infection and a periodic increase in viral proliferation in B cells. Nephrotic proteinuria also occurs in some patients with mononucleosis[28].

TREATMENT OUTCOMES OF IMMUNOSUPPRESSANTS AS EVIDENCE OF THE AUTOIMMUNE AETIOLOGY OF INS

Glucocorticoids (GCs)

About 80% of patients with INS are steroid-sensitive, which means that they respond to GCs within 4–6 weeks[1]. GCs exert their immunosuppressive effects to limit inflammatory processes by inhibiting the transcription and translation of genes encoding inflammatory mediators, i.e. cytokines produced by T cells, and their receptors. GCs impair the function of antigen-presenting dendritic cells, as well as bind to a specific nuclear or cytoplasmic receptor (genomic effect) and membrane receptors (non-genomic effect) [29]. Genomic effects involve changes in the structure of histones, limiting access of transcription factors to DNA and affecting mRNA structure, which prevents the production of inflammatory factors such as IL-2, IL-3, IL-6, TNFα and interferon γ. Genomic effects are observed at least several dozen minutes after GC administration[29]. Non-genomic action involves GC membrane receptors or, at high doses, does not involve receptors. Non-receptor effects of GCs involve transmembrane channels, causing, for example, inhibition of neutrophil degranulation. Additionally, GCs stabilise the podocyte cytoskeleton by actin polymerisation.

Calcineurin inhibitors (cyclosporine A, tacrolimus) are used in the case of steroid resistance or steroid dependence. Calcineurin is an enzymatic protein with serine-threonine phosphatase activity, activating T cells. Complexes of cyclosporine A or tacrolimus with their receptors bind to calcineurin, which prevents dephosphorylation of nuclear proteins. Phosphorylated proteins do not have the ability to penetrate the cell nucleus membrane and there is no expression of genes for cytokines activating T cells (IL-2, IL-4, TNFα, interferon γ). Cyclosporine A also stabilises the podocyte membrane by inhibiting the dephosphorylation of synaptopodin, thereby reducing the permeability of the filtration membrane to proteins and reducing proteinuria[30].

Immunosuppressants used in the treatment of INS also include mycophenolate mofetil. By inhibiting the formation of guanosine nucleotides from inosine, it reduces T and B cell production, monocytes and antibodies, as well as the number of adhesion molecules on lymphocytes. The drug does not affect the production of cytokines[30].

Cyclophosphamide is an alkylating agent. The addition of an alkyl group to the molecule leads to its inactivation and apoptosis. The drug has an affinity for DNA and RNA nucleic acids, leading to their fragmentation, which reduces protein production and causes cell disintegration. It affects B and T cells in immunosuppressive doses[30].

Monoclonal antibodies (RTX, ofatumumab, obinutuzumab) against B cells are also used in the treatment of INS. These are chimeric or humanized antibodies composed of human IgG1 sequences and mouse variable sequences, which, by binding to the transmembrane antigen CD20 on B cells, lead to their apoptosis. The CD20 antigen is not expressed on stem cells or precursor B-cells, therefore, after about 6–18 months of treatment, the pool of B cells is rebuilt, which may result in NP recurrence[27].

CONCLUSIONS

INS is a disorder with complex etiopathogenesis. Given the clinical course and response to treatment, it seems that the symptoms are influenced by immune disorders, both T and B cells, as well as various circulating factors. Inflammatory disorders and allergens may be the triggering factors in children predisposed to INS. This issue requires further research.

Conflict of interests

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: AO, MMW. Collection, recording and/or compilation of data; analysis and interpretation of data; writing of manuscript: AO, WW, MMW. Critical review of manuscript; Final approval of manuscript: MMW.

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