

Childhood Nephrotic Syndrome and Immunologic Disorders: Current Concepts and Clinical Perspectives

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Abstract

Childhood nephrotic syndrome (NS) is one of the most common glomerular disorders encountered in pediatric nephrology. It is characterized clinically by heavy proteinuria, hypoalbuminemia, edema, and variable hyperlipidemia. Although the majority of children have steroid-sensitive nephrotic syndrome (SSNS), a significant subgroup develops steroid resistance or frequent relapses, increasing the risk of complications and chronic kidney disease. Increasing evidence suggests that immune dysregulation plays a central role in the pathogenesis of childhood NS, particularly in steroid-sensitive disease. Abnormal T-cell and B-cell function, circulating permeability factors, cytokine imbalance, and abnormalities in immune-cell signaling have all been implicated. This review summarizes the current understanding of the relationship between childhood NS and immunologic disorders, with emphasis on pathogenesis, clinical phenotypes, immunologic mechanisms, and therapeutic implications.

Keywords: Childhood nephrotic syndrome, Immunologic disorders, Recurrent infections, Steroid-resistant nephrotic syndrome

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Introduction

Nephrotic syndrome in childhood is defined by nephrotic range proteinuria associated with hypoalbuminemia and edema, with hyperlipidemia being a frequent accompanying feature. The most common histopathological pattern in children is minimal change disease, which generally responds well to corticosteroid therapy. However, steroid-resistant nephrotic syndrome (SRNS) represents a major therapeutic challenge and may progress to chronic kidney disease or kidney failure. The association between NS and the immune system has been recognized for decades. The excellent response of many children with NS to corticosteroids and other immunosuppressive therapies supports an important immunologic component.

Nevertheless, the mechanisms are complex and appear to differ between patients. In some children, particularly those with genetic forms of SRNS, intrinsic abnormalities of the podocyte rather than primary immune dysfunction are likely to be responsible.

Immunologic basis of childhood nephrotic syndrome

The glomerular filtration barrier consists principally of fenestrated endothelial cells, the glomerular basement membrane, and

podocytes. Podocyte integrity is essential for preventing excessive urinary protein loss. Immune-mediated alterations in this barrier may increase glomerular permeability and result in proteinuria.

Historically, T lymphocytes were considered the major immune cells involved in NS. Several studies suggested abnormalities in T-cell activation and cytokine production, including altered secretion of interleukins and other inflammatory mediators. More recently, attention has expanded toward B cells, regulatory T cells, monocytes, and interactions between different components of the immune system.

The concept of a circulating permeability factor has also been proposed. According to this hypothesis, abnormal immune cells may produce circulating mediators capable of altering podocyte structure and function. The precise identity of such factors remains uncertain, and no single molecule has been universally accepted as the pathogenic factor responsible for all cases of NS.

Podocytes themselves are increasingly recognized as active participants in immune signaling. They express receptors and signaling molecules that can respond to inflammatory and immunologic stimuli. Disturbances in these pathways may contribute to cytoskeletal rearrangement, foot-process effacement, and increased protein permeability.

Nephrotic syndrome associated with primary immunologic disorders

Although most childhood NS is not caused by a recognizable systemic immunodeficiency, nephrotic syndrome can occur in association with immune dysregulation and primary immunologic disorders.

Children with primary immunodeficiencies or immune-dysregulation syndromes may develop glomerular disease as part of a broader phenotype. These disorders may involve abnormal T-cell or B-cell function, impaired immune tolerance, excessive inflammation, or autoimmunity. In such patients, NS may coexist with recurrent infections, autoimmune manifestations, lymphoproliferation, cytopenias, enteropathy, or other systemic findings.

Recognition of these clinical clues is particularly important in children with atypical NS. A history of severe or recurrent infections, persistent lymphadenopathy, hepatosplenomegaly, unexplained cytopenias, autoimmune manifestations, or a strong family history should prompt consideration of an underlying immunologic or genetic disorder.

Genetic and immunologic interactions

The distinction between immune-mediated and genetic NS is increasingly important. Mutations affecting podocyte proteins—including NPHS1, NPHS2, WT1, and other genes—can cause SRNS. These patients generally respond poorly to immunosuppressive therapy because the primary defect is structural or functional rather than immune-mediated.

However, genetic susceptibility and immune dysregulation may coexist. Some genetic disorders affecting immune pathways can produce both immunologic abnormalities and renal disease. Therefore, children with early-onset, familial, syndromic, or steroid-resistant NS may benefit from genetic testing alongside appropriate immunologic evaluation.

The availability of next-generation sequencing has significantly improved the diagnostic approach to SRNS. Identification of a pathogenic genetic variant can prevent unnecessary exposure to prolonged immunosuppression and may provide important information regarding prognosis and eligibility for kidney transplantation.

Clinical and therapeutic implications

Corticosteroids remain the cornerstone of initial treatment for childhood idiopathic NS. Most children with SSNS achieve remission with corticosteroid therapy. However, frequent relapses and steroid dependence may require steroid-sparing agents, including calcineurin inhibitors, mycophenolate mofetil, cyclophosphamide, levamisole, or rituximab, depending on the clinical phenotype.

The effectiveness of rituximab in selected patients has further emphasized the potential contribution of B-cell pathways to disease activity. Nevertheless, the response is variable, and treatment decisions should be individualized according to relapse pattern, previous therapy, infection risk, and underlying diagnosis.

In suspected immune-dysregulation syndromes, management should extend beyond treatment of proteinuria. Comprehensive evaluation may include immunoglobulin levels, lymphocyte subsets, assessment of vaccine responses, complement studies, autoimmune testing, and targeted genetic investigations when clinically indicated.

Importantly, immunosuppression in children with underlying immune deficiency requires careful consideration because it may increase susceptibility to infections. Collaboration between pediatric nephrologists, clinical immunologists, geneticists, and infectious disease specialists may therefore be necessary in complex cases.

Future directions

The relationship between the immune system and podocyte biology represents an important area of ongoing research. Better characterization of immune-cell subsets, circulating permeability mediators, cytokine pathways, and podocyte signaling may lead to more precise biomarkers and targeted therapies.

A major future objective is to move from a broad classification based mainly on steroid response toward a biologically driven classification incorporating clinical phenotype, genetics, immunologic characteristics, and molecular biomarkers. Such an approach may allow clinicians to identify which children are most likely to benefit from immunosuppressive therapy while avoiding unnecessary treatment in patients with genetic or nonimmune forms of SRNS.

Conclusion

Childhood nephrotic syndrome represents a heterogeneous group of disorders in which immune mechanisms, podocyte dysfunction, genetic susceptibility, and environmental factors may interact. Immunologic dysregulation appears particularly important in many cases of steroid-sensitive disease, whereas genetic podocytopathies account for an important proportion of steroid-resistant cases. Recognition of clinical features suggesting an underlying immune or genetic disorder is essential for appropriate investigation and treatment.

Future research integrating nephrology, immunology, and molecular genetics may facilitate personalized management and improve outcomes for children with nephrotic syndrome.