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RISK FACTORS AND EARLY MARKERS OF PRIMARY IMMUNODEFICIENCIES IN PEDIATRIC PRACTICE

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ABSTRACT

The article presents an analytical review of contemporary national and international data on the risk factors and early diagnostic markers of primary immunodeficiencies (PID) in children. It discusses genetic, epigenetic, and environmental factors influencing the development of congenital defects of the immune system, as well as the clinical and immunological characteristics that make it possible to suspect immune deficiency at early stages. The importance of timely identification of patients with PID in pediatric practice is emphasized, as it plays a crucial role in preventing severe infectious and autoimmune complications.

KEYWORDS: Primary Immunodeficiencies, children, risk factors, early markers, immune status, diagnostics.

Relevance. The problem of primary immunodeficiencies (PIDs) has gained increasing significance over the past decades due to the growing number of diagnosed cases, advances in molecular genetic technologies, and improved awareness among physicians of various specialties.[1,3] According to the International Union of Immunological Societies (IUIS, 2022), more than 480 genetically determined forms of PIDs have been described to date, encompassing all components of the immune system.[4] Their prevalence is estimated to range from 1 in 10,000 to 1 in 2,000 live births; however, the actual incidence is likely higher because of insufficient clinical awareness among pediatricians and limited access to laboratory diagnostics, especially in developing countries.[5,6]

For the pediatric population, PIDs represent a particular medical and social challenge, as disease onset most often occurs at an early age, when the immune system is still functionally immature and highly sensitive to infectious, metabolic, and environmental stressors.[7] The absence of early diagnosis and delayed initiation of replacement therapy lead to recurrent infections, chronic inflammatory conditions, growth retardation, disability, and increased mortality.[8,10]

In this regard, studies aimed at identifying the risk factors contributing to immune deficiency, detecting early clinical and laboratory markers, and developing effective screening algorithms for the timely diagnosis of PIDs in pediatric practice are of particular relevance.[11,13]

The aim of the review is to summarize current knowledge on the risk factors and early clinical–immunological markers of primary immunodeficiencies in children, emphasizing their significance in pediatric practice.

Main Risk Factors

The development of primary immunodeficiencies (PIDs) in children results from a combination of hereditary, genetic, and environmental influences. The most significant contributors are congenital mutations in genes responsible for the development and regulation of the immune system, including lymphocyte differentiation and activation, phagocytosis, and immunoglobulin synthesis.[4,9] Genetic predisposition may manifest under the influence of additional factors formed during the antenatal and early postnatal periods.

Among perinatal risk factors, special importance is attributed to pregnancy complications, maternal chronic infections, fetal hypoxia, and exposure to toxic and environmentally unfavorable conditions. Exogenous determinants include air pollution, contact with heavy metals and pesticides, and residence in regions with high levels of chemical air pollutants.[7,23]

Nutritional and metabolic factors also play a crucial role. Deficiencies in protein, iron, zinc, selenium, and vitamins B and D weaken both cellular and humoral immunity, reduce phagocytic activity and cytokine production, thereby increasing susceptibility to infections.[4,15]

Family history often reveals certain maternal pathologies that can be considered potential etiological or marker signs of hereditary predisposition. Etiologically significant factors include the presence of malignant neoplasms in the mother or her close relatives, which likely reflect the role of impaired immune surveillance and dysregulated differentiation of immunocompetent cells prone to malignancy at early developmental stages. Genealogical observations confirm that hereditary predisposition to oncological processes may correlate with congenital insufficiency of the immune response.[6]

Marker factors include chronic inflammatory and infectious diseases in mothers — recurrent sinusitis, tonsillitis, bronchopulmonary infections, as well as candidiasis and herpetic lesions of the skin and mucous membranes. These conditions may not always have a direct causal link to congenital immune deficiency but may reflect subclinical immunosuppression and serve as indicators of an unfavorable immune status within the family lineage.[3,12]

Of particular importance is the effect of chronic upper respiratory and bronchopulmonary diseases in parents. The functional state of mucosal immunity in the respiratory tract is closely related to the level of secretory immunoglobulins, especially IgA. A deficiency of secretory IgA and impaired mucociliary clearance create favorable conditions for microbial persistence and chronic inflammation. Under such circumstances, the child's risk of developing immune dysfunction of varying severity increases.

Moreover, prolonged inflammatory lung diseases are often accompanied by reduced phagocytic activity, complement system dysfunction, and secondary ciliary dyskinesia. These processes intensify infectious load and may contribute to the manifestation of congenital immune insufficiency.[13,16]

Thus, the combination of hereditary mutations with adverse perinatal, infectious, and environmental factors forms the foundation for the manifestation of primary immunodeficiencies in childhood. The presence of oncological or chronic infectious diseases in parents should be regarded as an important risk component that warrants careful attention during screening and early diagnosis of congenital immune disorders.[7,11]

Fungal Infections and Maternal Factors in the Development of Primary Immunodeficiencies

Fungal infections — mycoses of the skin and mucous membranes of various localizations, primarily candidiasis — as well as chronic herpes infections, from a pathogenetic standpoint, reflect an underlying state of immunosuppression. Therefore, these conditions should be regarded as marker manifestations of immunodeficiency states.

An analysis of family medical histories of children with primary immunodeficiency disorders (PIDs) revealed that mycoses and herpes infections occurred predominantly in mothers, with frequencies of 13.6 ± 3.4 and 36.3 ± 7.2 per 100 pedigrees, respectively.[19,21] These findings suggest that fungal infections serve as nonspecific but indicative markers of immune insufficiency of various origins.[11,20]

The significance of risk factors for the development of PIDs was further assessed by comparing the course of pregnancy in mothers who gave birth to children with and without immunodeficiency. It was established that polyhydramnios, acute infections during the first and third trimesters, and persistent urogenital infections (including Chlamydia trachomatis) are key predictors of congenital immunodeficiency. All of these conditions have an infectious nature and can alter the immune homeostasis of the pregnant woman. In most cases, acute infections were represented by influenza and other respiratory viral diseases.[11,17]

Polyhydramnios is often regarded as a consequence of intrauterine fetal infection. According to Landor M.[10,16] the presence of latent infections in pregnant women — such as herpesvirus, cytomegalovirus, or urogenital infections — is associated with the development of mild, subclinical disturbances of the immune response. These changes may not significantly affect the mother's health but can adversely influence the immune system of the fetus and newborn.[7,18]

The pathological sequence of events can be represented as follows
Chronic viral infection → Maternal immune alterations (regulatory antibody imbalance) → Fetal immune dysfunction → Neonatal adaptation disorders.

Thus, the identification of acute infections in the first or third trimester of pregnancy, polyhydramnios, and chlamydial infection should be considered key criteria for identifying risk groups for congenital immunodeficiencies.

Examination of placental tissue revealed a correlation between the presence of PID in a child and hematogenously disseminated placental infection, confirming the influence of maternal infections on fetal immune development.[14,22]

Therefore, congenital immunodeficiencies, as hereditary disorders, can be recognized by several familial markers of immune dysfunction — chronic ENT and bronchopulmonary diseases, recurrent fungal and herpetic infections, delayed wound healing, and a history of oncological diseases in the family. The combination of these signs can be used for risk stratification among newborns.[5,12]

Even manifestations of acquired immunodeficiency in a child may have a genetic predisposition, evidenced by similar clinical features in the family history.[4,14]

Further analysis showed that endocrine disorders (diabetes mellitus, thyroid dysfunction) in mothers and their close relatives, as well as maternal anemia, were statistically significant indicators of immune deficiency. These conditions may be considered potential etiological factors in the formation of primary immunodeficiencies.[1,16]

An increased frequency of collagenopathies was also observed in fathers or along the paternal line. This phenomenon occurred only in the pedigrees of children with morphologically confirmed PIDs (17.6 ± 7.2 per 100 pedigrees) and was absent in children without immune deficiency.[2,13]

The development of collagenopathies is closely related to disturbances in immunogenesis, characterized by leukocytic and plasmacytic tissue infiltration, alterations in bone marrow and lymph nodes, elevated autoantibody production, and increased expression of IL-2 and T-lymphocyte proto-oncogenes. These findings indicate the involvement of immune mechanisms in the disease pathogenesis.

Fungal infections — mycoses of the skin and mucous membranes — as in PIDs, should be regarded not as a cause of immunodeficiency, but as one of its clinical manifestations, a kind of “mask” of immune dysfunction.[11,18]

Immunodeficiency states are almost always accompanied by infectious pathology. In children with immune insufficiency, the infectious process may present as localized forms — bronchitis, pneumonia, enteritis, dermatitis — or as generalized infections, such as sepsis, bacteremia, or meningococcemia.[9]

Infectious Pathology in Children with Immunodeficiency Disorders

An analysis of infectious morbidity in children with immunodeficiency disorders (IDDs) demonstrated that generalized forms of infections predominated among complications and occurred significantly more frequently than in patients without immune pathology.[3,12,22] The course of such infections in this category of children is notably more severe, which is determined not only by the baseline immune insufficiency but also by the subsequent suppression of protective mechanisms due to the infection itself. This creates a vicious cycle: infection → immune suppression → disease progression → new infectious complications.

The highest frequency of generalized infections was observed among newborns with IDDs, particularly in combination with severe congenital malformations, Down syndrome, and other chromosomal abnormalities.[9] Among children with primary immunodeficiency disorders (PIDs), infection generalization occurred most frequently in the presence of congenital anomalies and intrauterine infection. In cases where comorbid conditions were absent, generalized infections were typically caused by Gram-negative bacteria or Candida species. These pathogens possess significant virulence, leading to severe disease even in localized forms and often resulting in fatal outcomes.[2,12,18,21]

In infancy, generalized infections more commonly developed in children with PIDs in the presence of multiple predisposing factors — congenital malformations, intrauterine infections, and metabolic disturbances. Such a clinical picture indicates functional insufficiency of the immune system and its inability to control infectious processes effectively.[16,20,22]

Results from prospective monitoring of children in neonatal intensive care units revealed that infection rates in patients with morphologically confirmed immunodeficiency and those showing clinical-immunological signs of IDDs were comparable — 1440 ± 225.1 and 1385 ± 81.4 cases per 1000 autopsies, respectively ($p > 0.05$). These rates were significantly higher than those in children without immunodeficiency — 1035.7 ± 23.9 per 1000 autopsies ($p > 0.05$).[5,10]

At the present stage of medical practice, primary prevention — a system of measures aimed at eliminating or reducing the impact of risk factors that may trigger immune dysfunction — plays a key role. This approach is particularly relevant for preventing adverse consequences of immunodeficiency states in early childhood.[2,18]

An analysis of official health statistics on morbidity among children during the first year of life revealed that disorders associated with immune dysregulation occupy a leading position in overall disease structure. Blood and hematopoietic disorders, as well as endocrine and metabolic diseases with an immune component, rank third and fifth, respectively, following upper respiratory tract infections and neurological diseases. This

emphasizes the high prevalence of immune dysfunction-related conditions even at an early age.

The study of epidemiological patterns of immunodeficiency development has made it possible to define key criteria for identifying high-risk groups among young children. One of the most significant indicators is the presence of signs of immune dysfunction in the family history, suggesting a possible genetic predisposition. Even at birth, certain families can thus be identified as having a higher risk of IDDs than the general population.[3,14]

The establishment of an epidemiological monitoring system and the formation of family-based risk groups using genetic, immunological, and clinical data are essential for effective preventive work. The application of population genetics methods and neonatal immunological screening enables the early detection of predisposition to immune disorders before clinical manifestations appear.

Creating regional registries of children with suspected or confirmed immunodeficiencies, regularly assessing the territorial prevalence of these conditions, and implementing targeted preventive measures allow for timely detection and management of IDDs. This reduces the risk of severe infectious complications and improves patients' quality of life.

Thus, even though complete prevention of immunodeficiency development may not always be possible, targeted prevention of complications and infections represents a realistic and effective goal of modern pediatrics.[15]

Early Clinical and Immunological Markers

Early signs of primary immunodeficiencies (PIDs) include frequent and prolonged respiratory tract infections, chronic sinusitis, otitis media, pneumonia, recurrent skin inflammations, and abscesses. Often, infections have an atypical course, respond poorly to antibacterial therapy, show a tendency toward fungal infections, and are followed by a slow recovery period. Immunological markers may include decreased levels of immunoglobulins (IgG, IgA, IgM), altered lymphocyte subset ratios, reduced phagocytic activity, and abnormal cytokine profiles.[3,14]

Diagnostic Significance of Early Indicators

Early diagnosis of PIDs is based on the comprehensive evaluation of both clinical and laboratory findings. Screening tests such as quantitative immunoglobulin measurement, lymphocyte subpopulation analysis, and assessment of phagocyte function make it possible to identify patients requiring advanced immunological investigation. In recent years, molecular genetic diagnostic methods, including next-generation sequencing (NGS), have become increasingly widespread, allowing for the early detection of monogenic forms of PID.[3,14]

Management Features in Pediatric Patients

Children suspected of having primary immunodeficiency require comprehensive monitoring, including regular immune status assessments, infection prevention, nutritional correction, and immunotherapy. Multidisciplinary collaboration among pediatricians, immunologists, and infectious disease specialists is essential. The use of immunoglobulin replacement therapy, vaccination tailored to the defect type, and complication prevention significantly improve long-term outcomes.[3,14]

CONCLUSION

Risk factors and early markers of primary immunodeficiencies are key components in the early diagnosis and prevention of severe infections in children. Timely detection of PID requires pediatric vigilance, implementation of basic immunological tests, and, when indicated, molecular genetic analysis. The modern pediatric approach focuses on early recognition of immune insufficiency and the development of individualized monitoring and treatment programs, which contribute to improved quality of life and reduced mortality in the pediatric population.

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