# IMMUNODEFICIENCY STATE: A MODERN PERSPECTIVE ON THE ISSUE OF "CHILDREN WITH RECURRENT INFECTIONS"

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***Abstract.*** *This article focuses on the current issues of primary immunodeficiencies (PID) and children with recurrent infections (frequently ill children) and their immune status (immune imbalance). As primary immunodeficiencies are rare diseases, few people, including the medical community and patients, are aware of this pathology. This leads to delays in diagnosis and untimely treatment, which can result in disability, high mortality rates, as well as high costs for treating complications and paying for disability. However, with timely and adequate therapy, patients with PID can live active lives without signs of disability and have healthy offspring.*

***Keywords****: Children, recurrent infection, primary immunodeficiencies (PID), prevalence.*

***Аннотация****. Данная статья посвящена текущим проблемам первичных иммунодефицитов (ПИД) и детям с рекуррентными инфекциями (часто болеющим детям) и их иммунному статусу (иммунному дисбалансу). Поскольку первичные иммунодефициты являются редкими заболеваниями, мало кто, включая медицинское сообщество и пациентов, осведомлены о данной патологии. Это приводит к задержке в диагностике и несвоевременному лечению, что в свою очередь может привести к инвалидности, высокой смертности, а также высоким затратам на лечение осложнений и оплату нетрудоспособности. Однако, благодаря своевременной и адекватной терапии, пациенты с ПИД могут жить активной жизнью без признаков инвалидизации и иметь здоровое потомство.*

***Ключевые слова****: Дети, рекуррентная инфекция, первичные иммунодефициты (ПИД), распространенность.*

Relevance. In modern pediatrics, children with recurrent infections are commonly referred to as frequently ill [4]. This group under outpatient observation corresponds to the concept of "patients with recurrent acute respiratory infections (ARI)" in foreign literature. Thus, a condition where the occurrence of repeated infections is established begins to be perceived as a diagnosis [5]. Factors contributing to the development of frequently ill children, as described in various literature sources, include delayed development of the immune system, anatomical and physiological features of the respiratory tract in children (bronchial structure peculiarities), nutrition, and living conditions [12]. It is believed that frequently recurring or persistent infectious conditions are the main manifestation of primary immunodeficiency.

Primary immunodeficiencies (PID) are inherited disorders caused by gene defects that regulate the immune system. The nature and severity of immune defects, clinical manifestations, and molecular abnormalities can vary. In PID, recurrent and severe infectious processes are often observed, primarily affecting the respiratory system, ENT organs, skin, and mucous membranes. The disease can manifest as purulent lymphadenitis, abscesses, osteomyelitis, meningitis, and sepsis. Some forms of PID may also exhibit allergic reactions, autoimmune diseases, and an increased risk of certain types of tumors. Currently, more than 200 types of PID have been

described, and the genes responsible for the development of the majority of these conditions have been identified [2,11].

PID is characterized by the impairment of various components of the immune system, such as lymphoid cells, antibodies, complement, phagocytes, etc. The abnormalities can be caused by mutations in the genes encoding these components, resulting in partial or complete deficiency. Some forms of PID have a hereditary nature and can be inherited from parents, while others can occur due to new mutations [8].

There are over 400 different types of primary immunodeficiencies (PID) described worldwide, which can be categorized into more than 10 groups depending on the specific immune functions affected. They can be classified based on various criteria, such as the type of immune system impairment, age of onset, presence or absence of autoimmune manifestations, and so on. However, the most common classification of PID is based on the type of immune system impairment and includes the following groups:

Disorders of cellular immunity
Disorders of humoral immunity
Combined defects of cellular and humoral immunity
Phagocytic system disorders
Complement system disorders
Innate immunity disorders
Disorders of immune response regulation

Primary immunodeficiencies (PID) are classified as rare disorders; however, their exact prevalence is unknown due to several factors. Many forms of PID can be asymptomatic or present with nonspecific symptoms. PID symptoms can overlap with those of other diseases, making diagnosis challenging. According to the International Patient Organisation for Primary Immunodeficiencies (IPOPI), the prevalence of PID is estimated to be 1 case per 2,000-10,000 newborns. Some forms of PID, such as phagocytic function disorders, may be more prevalent than others. For example, phagocytic function disorders occur in approximately 1 in 2,000-5,000 newborns, while common variable immunodeficiency, a form of PID associated with B-cell dysfunction, occurs in approximately 1 in 50,000-100,000 newborns [7].

The prevalence of PID significantly varies between different countries. For example, in the United States, the frequency of the disease is reported to be 1 case per 1,200 individuals, while in Turkey, it is 30 cases per 100,000 individuals, and in European countries, it is 60 cases per 100,000 population. However, by 2013, the scientific group of the World Health Organization had identified over 150 forms of immunodeficiencies, more than 120 gene defects, and over 4,500 mutations [4].

Previously, individuals with primary immunodeficiency (PID) had a poor prognosis and posed a significant social burden. They often experienced recurrent severe infections that required prolonged hospitalization and costly antibacterial and antifungal therapies, leading to early disability and mortality. Patients with severe forms of PID had a 100% fatality rate, with death occurring primarily in childhood. Chronic and severe infections in patients with PID and defects in humoral defense quickly led to irreversible organ damage, limiting their ability to fulfill essential social functions. Patients faced employment challenges and restrictions in daily activities due to the fear of recurrent exacerbations, while chronic inflammatory processes significantly affected their ability to have healthy children [3].

However, the situation has changed nowadays due to the emergence of immunoglobulins, which are actively used as replacement therapy for PID with antibody deficiencies (approximately 80% of all PID forms). Timely initiation of regular replacement therapy at an appropriate dosage significantly reduces the risk of developing severe infections, allows patients to lead active social lives, and even have healthy offspring. Thus, if previously a diagnosis of PID could be considered a death sentence, now, thanks to new treatment methods, the prognosis for patients has significantly improved [5,10].

The possibility of bone marrow transplantation in PID patients, who previously had a 100% mortality rate due to severe combined immunodeficiency and other factors, has provided them with a chance to survive and not experience disease symptoms during treatment. Although this therapy method is relatively recent, and there is currently limited data on the long-term outlook for such patients, the achieved results are inspiring [1,5].

Diagnosing PID can be challenging as its symptoms can be nonspecific and resemble manifestations of other diseases. Various methods are used to identify PID, including blood tests, evaluation of immune system functions, and genetic testing. Consultation with specialists in immunology and genetics may be necessary for accurately determining the type of PID and refining the diagnosis [6,7].

One of the main issues with PID, like all rare diseases, is insufficient diagnosis, which can lead to inadequate and delayed treatment. The symptoms of PID are usually nonspecific, making them difficult to identify. Instead, symptoms of common respiratory, skin, ear, and other organ infections often take the forefront, which can have a severe course and may not respond to standard treatment regimens. Some patients may also experience gastrointestinal symptoms, autoimmune manifestations, and malignancies, which are often associated with PID. Therefore, knowledge about this condition is essential for all healthcare professionals, regardless of their specialty [3,9].

The symptoms of primary immunodeficiency (PID) in children can vary depending on the type and severity of the condition. The most common symptoms of PID in children include:

Frequent and/or difficult-to-treat infections such as bronchitis, pneumonia, sinusitis, otitis, and other respiratory infections.

Increased susceptibility to infections caused by common bacteria and viruses.

Increased susceptibility to infections that are usually rare in healthy individuals, such as candidiasis, herpes, cytomegalovirus, and others.

Frequent recurrence of infections after completing treatment.

Unusual and/or difficult-to-treat infections, such as deep fungal infections or infections caused by uncommon bacteria.

Prolonged diarrhea and/or recurrent gastrointestinal infections.

Development of autoimmune diseases, such as rheumatoid arthritis or systemic lupus erythematosus.

Low height and/or low weight.

Frequent and/or difficult-to-treat inflammatory skin and mucosal disorders.

If a child exhibits one or more of these symptoms, it is advisable to consult an immunologist for further evaluation and diagnosis of PID.

To account for patients with primary immunodeficiencies (PID), national registries are established. The objectives of creating registries are to track patients with immune deficiencies,

study the characteristics of disease progression, establish genetic databases, develop diagnostic criteria, and treatment protocols for primary PIDs.

To collect information on children with PID, a form for recording patients with immune defects is created. The form serves as a diagnostic protocol and includes information on the age of disease onset, primary clinical manifestations, immunological and molecular-genetic defects, detailed data on laboratory investigations, therapy, and its effectiveness. Establishing a registry for primary immunodeficiencies and utilizing modern mathematical analysis of the collected data will help determine the frequency of occurrence, timely diagnosis, as well as the specific clinical manifestations and treatment approaches for patients with immunodeficiencies [3].

The treatment of immunodeficiency disorders (PID) depends on the severity and type of the condition, as well as the patient's age, and aims to support the immune system and prevent infections. Treatment may involve regular infusion of immunoglobulins, antibiotic therapy, immunomodulators, bone marrow transplantation, and more. However, the high cost of treatment and the rarity of the disease often leave patients with PID without proper support from society and the government. This can lead to a lack of adequate funding for educational programs and treatment [7]. Although preliminary studies on the pharmacoeconomic effectiveness of appropriate PID therapy show that properly selected therapy can save money for the state in the long term, currently, such research is in a pilot phase.

Conclusion: Children with a history of frequent recurrent, severe, or unusual infectious diseases (CID) require a high degree of suspicion regarding the diagnosis of immunodeficiency. Recurrent or persistent infection is the main manifestation of PID. Although most children with recurrent infections have normal immunity, it is important to remain vigilant in cases of unusually frequent or severe infections. Early referral to a clinical immunologist in cases of suspected immunodeficiency plays a crucial role, as early detection and treatment of PID can prevent significant organ damage and improve survival and long-term prognosis.

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