CLINICO-EPIDEMIOLOGICAL ANALYSIS OF CHILDREN WITH DIFFICULT-TO-DIAGNOSE DISEASES SUSPECTED OF PRIMARY IMMUNODEFICIENCIES

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Abstract. *The aim of this study was to investigate the clinical and epidemiological features of children with hard-to-diagnose diseases suspected of primary immunodeficiencies (PID) in the Aral Sea region. A total of 312 children (159 boys and 153 girls) aged 0 to 18 years, who sought medical care at the Republican Multidisciplinary Children's Center of the Republic of Karakalpakstan and district medical associations, were examined. Inclusion criteria comprised frequent and severe infections, poor response to standard therapy, growth retardation, congenital anomalies, and recurrent or chronic diseases. The study revealed immune abnormalities in 30.1% of patients, and confirmed forms of PID (according to ESID and IUIS criteria) in 13.1%. Humoral and syndromic PIDs were the most common types, with a considerable diagnostic delay of more than three years observed in one-third of cases. The findings emphasize the urgent need for the implementation of diagnostic protocols, the establishment of a regional PID registry, and the training of healthcare professionals to improve early diagnosis and management of affected children.*

Keywords: *primary immunodeficiencies, children, clinical and epidemiological analysis, Aral Sea region, humoral immunodeficiencies, syndromic PID, diagnosis, infections, immunological assessment.*

Relevance. Primary immunodeficiencies (PIDs) represent a heterogeneous group of hereditary diseases characterized by impairments in one or more components of the immune system [1,7]. In recent years, there has been a considerable increase in interest in PIDs, which is associated both with the advancement of molecular genetic diagnostic methods and with the growing number of identified cases [8]. However, in clinical practice, these conditions often remain difficult to recognize, especially in the early stages, when their manifestations mimic frequent recurrent respiratory infections, congenital anomalies, and chronic diseases [3,5].

In the Aral Sea region, children are often treated for recurrent infections, pneumonias, anemias, bronchial asthma, and other diseases, while the possible immunological basis of the pathology is frequently overlooked [1].

A particularly challenging group of PID patients includes children with so-called difficult or diagnostically complex cases, where establishing a diagnosis is hindered by atypical clinical presentation, masking symptoms, a combination of several pathologies, or the absence of timely immunological assessment [4,6]. Such situations often lead to prolonged treatment for incorrect diagnoses, increased hospitalization rates, the development of complications, disability, and even fatal outcomes [2,9].

In the Republic of Karakalpakstan, no systematic studies to date have been devoted to the analysis of diagnostically complex forms of PID in children. Meanwhile, such research is crucial, as it not only helps identify common diagnostic errors but also contributes to developing criteria for early recognition of these conditions, raising physician awareness, and reducing the time between the onset of symptoms and the establishment of an accurate diagnosis.

Objective of the study — to conduct a clinical and epidemiological analysis of diagnostically challenging cases in children living in the Aral Sea region, in order to identify characteristic features contributing to delayed diagnosis and to determine strategies for improving early detection and management of patients with primary immunodeficiencies (PIDs).

Materials and Methods. The study included 312 children (159 boys and 153 girls) aged from birth to 18 years who sought medical care at the Republican Multidisciplinary Children's Center of the Republic of Karakalpakstan and pediatric departments of district medical associations.

Referral criteria for examination included frequent, severe, or atypical infectious diseases; insufficient response to antibacterial therapy; delayed physical development; the presence of congenital anomalies or diagnostically complex conditions; as well as chronic, recurrent, or treatment-resistant diseases.

The main inclusion criteria were:

– frequent infectious diseases;

– severe or atypical forms of infections;

– insufficient effectiveness of conventional therapy.

International diagnostic criteria for PIDs were applied, including the list proposed by the European Society for Immunodeficiencies (ESID). Indications for immunological examination in pediatric inpatients were defined, such as:

– recurrent pneumonias (two episodes per year or three or more in a lifetime);

– more than seven episodes of acute otitis in history or more than three within one year;

– persistent or recurrent fungal infections;

– deep-seated infections (meningitis, osteomyelitis, abscesses);

– sepsis (except neonatal);

– prolonged or recurrent diarrhea;

– family history of PID or relatives who died in childhood due to infections;

– complications following administration of live attenuated vaccines.

Screening diagnostics included clinical and biochemical blood tests and measurement of serum immunoglobulin levels. The study evaluated sex distribution, age at onset of first symptoms, and diagnostic delay.

Diagnostic delay was defined as the interval between the onset of first clinical manifestations and confirmation of the diagnosis. Medical records and follow-up data were analyzed for infectious complications, comorbidities, and treatment received.

Immunological examination was performed both during acute and protracted infectious-inflammatory processes. Serum levels of IgA, IgG, and IgM, as well as concentrations of IL-10 and IL-6, were measured using ELISA with reagents from OOO "Cytokin" (Research Institute of Highly Pure Biopreparations, St. Petersburg).

Statistical analysis was carried out on an IBM-AT personal computer using MS Excel (MS Office), STATISTICA 6, R, and Statgraphics Plus 5.0. Differences were considered statistically significant at $p < 0.05$.

Results and Discussion. The conducted clinical and epidemiological analysis revealed a wide spectrum of diseases for which children sought medical care when PID was suspected. The most common were chronic respiratory disorders, congenital anomalies and developmental defects, as well as a number of other chronic conditions. The distribution of the main nosological forms is presented in Figure 1.

Chronic respiratory diseases (n = 192; 61.5%): prolonged pneumonias – 108 (34.6%), chronic bronchitis – 56 (17.9%), bronchiectasis – 18 (5.8%), atelectasis – 7 (2.2%), pleuritis – 3 (0.9%).

Congenital anomalies and developmental defects (n = 83; 26.6%): cardiovascular malformations – 39 (12.5%), gastrointestinal anomalies – 24 (7.7%), endocrinopathies – 20 (6.4%).

Other chronic diseases (n = 37; 11.9%).

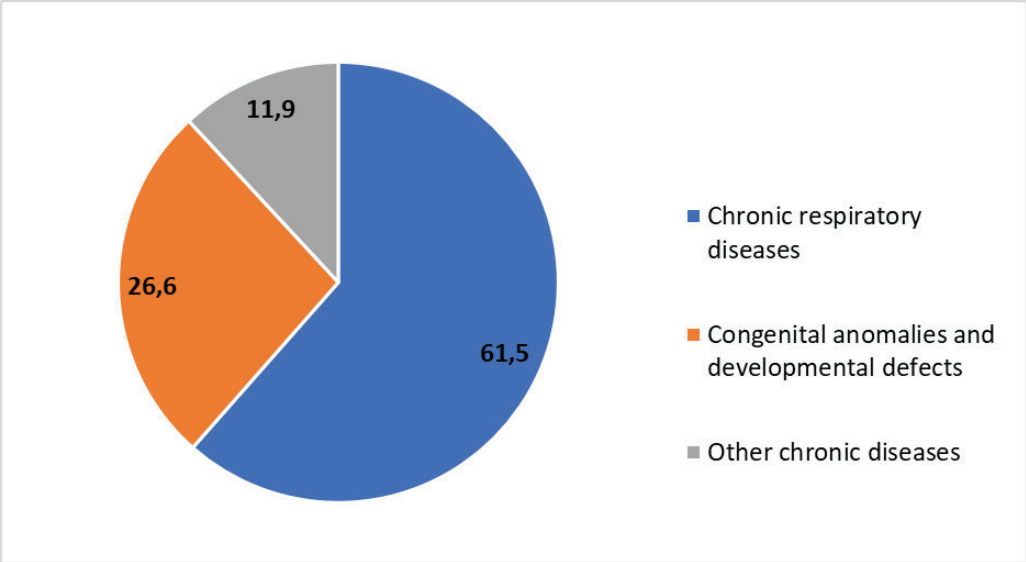


Fig. 1. Main diseases among the examined children

All children included in the study had frequent infectious diseases with recurrent or prolonged courses and low effectiveness of standard therapy, which served as the basis for performing immunological examinations.

All patients underwent a standard set of diagnostic procedures, including clinical and biochemical blood tests, determination of immunoglobulin levels and lymphocyte formula, and, in some cases, consultations with an immunologist and molecular genetic testing.

The study of immune status revealed various immune disorders in 94 children (30.1%). Signs of immunodeficiency conditions requiring further diagnostic clarification were found in 67% of the examined patients. Confirmed forms of primary immunodeficiencies, diagnosed according to international ESID and IUIS criteria, were identified in 41 children (13.1%). In 43 children (13.8%), reduced immune parameters requiring dynamic follow-up were registered. Fig. 2. Forms of PID identified among children (n = 41)

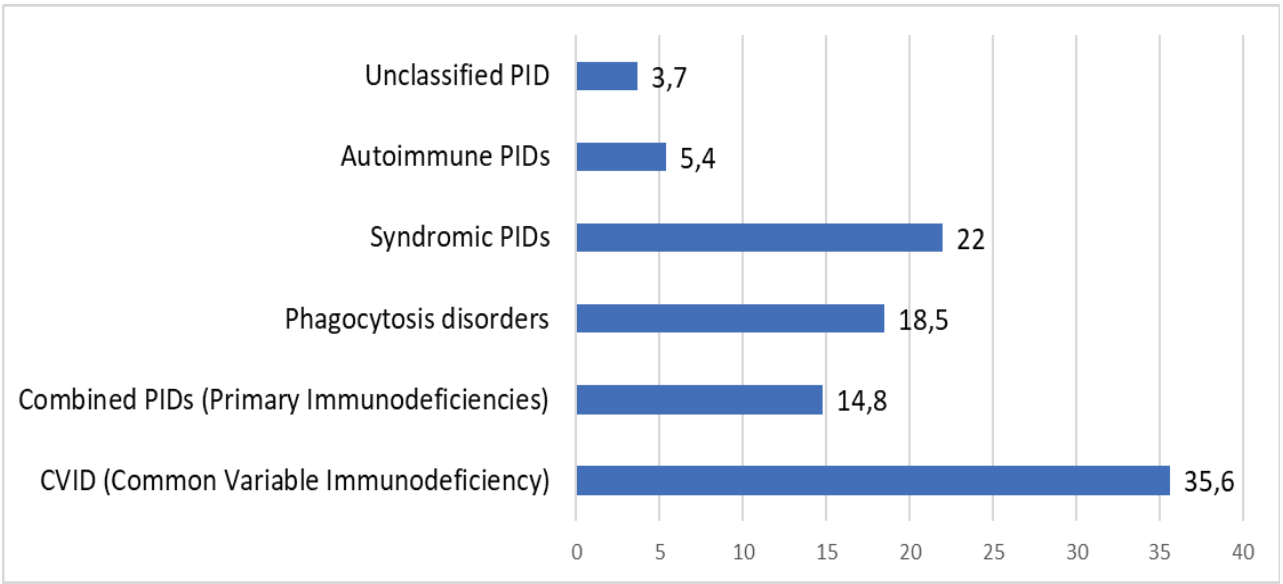


Fig. 2. Various forms of PID among children

The largest number of patients belonged to the groups of humoral (CVID) and syndromic PIDs — 26 (35.6%) and 16 (22.0%) patients, respectively. The second most common were phagocytic defects and complement deficiencies — 14 (14.0%) and 11 (12.0%) patients, respectively. The third most frequent were autoimmune PIDs (8; 5.4%) and combined PIDs (4; 9.0%).

According to the ESID classification, combined PIDs with syndromic phenotypes are divided into several pathogenetically distinct groups. The most common were immunodeficiency conditions associated with impaired DNA repair — in 3 patients (7.2%), as well as Wiskott–Aldrich syndrome — in 2 patients (4.6%). Among DNA repair disorders, ataxia-telangiectasia (Louis–Bar syndrome) was observed in 2 patients, and Nijmegen breakage syndrome in 1 patient.

Among secondary immunodeficiencies (n = 24), the following were identified: post-infectious immunodeficiencies — in 11 patients (45.8%), immunoglobulin deficiencies associated with chronic pathology — in 8 patients (33.3%), and immunosuppression after long-term antibiotic therapy — in 5 patients (20.8%).

A comparative analysis of children with and without PID showed that in patients with immunodeficiencies, the frequency of recurrent infections was 63% higher, the rate of hospitalizations was 47% higher, and the incidence of complications (bronchiectasis, pleuritis) was 55% higher.

Among children with congenital cardiovascular malformations (n = 39), immunodeficiency conditions were detected in 14 (35.9%), including PIDs in 5 (12.8%). Among children with gastrointestinal anomalies (n = 24), immunodeficiencies were diagnosed in 9 (37.5%), of which PIDs were confirmed in 4 (16.7%).

Delayed diagnosis of primary immunodeficiencies (PIDs) often results in unfavorable clinical outcomes. In one-third of the examined children, the diagnosis was confirmed only more than three years after the first manifestations of the disease. Most frequently, recurrent infections served as the main reason for in-depth evaluation, while in approximately 20% of patients, immunodeficiency was established on the basis of a combination of clinical and laboratory findings, though diagnostic delays remained considerable.

Among 12 patients with severe forms of PID diagnosed during their lifetime, only three were identified at the outpatient stage (two by an immunologist and one by a professor of immunology). Another child was diagnosed in a somatic ward during repeated hospitalization. Of these four children, only one received the diagnosis later than three years after the onset of symptoms.

Due to intensified diagnostic efforts in 2023, four children with severe PID were identified, whereas between 2010 and 2022 such cases were detected no more than once a year. Notably, only one boy was referred to an immunologist from a hospital in another district because of persistent fever, hepatosplenomegaly, and pancytopenia (after excluding malignancy). The remaining three children were admitted on an emergency basis to our pediatric department.

When PID is suspected, special attention must be paid to thorough history-taking. Physicians should consider:

family history of malignancies, autoimmune diseases, chronic infections, or previously diagnosed PIDs;

reports of early childhood deaths from infections, stillbirths, or consanguineous marriages;

clinical or laboratory signs characteristic of certain PID forms (e.g., bleeding tendency, neurological symptoms);

adverse reactions to vaccinations;

complicated course of viral infections;

frequency and severity of infections;

the need for prolonged or high-dose antibiotic therapy.

The clinical manifestations of PID are often disguised as chronic infections or treatment-resistant allergic conditions. Children may present with delayed physical and mental development,

gastrointestinal involvement, lymphoid and hematological abnormalities, as well as severe dermatological signs such as pyoderma, chronic dermatitis, and recurrent furunculosis.

The most common syndrome in PID is infectious (95–100%), while allergic (18%), autoimmune (6%), and neoplastic (2%) manifestations are less frequent. Clinical observations demonstrate a broad spectrum of nonspecific syndromes, which should alert clinicians to possible immune pathology, particularly when recurrent infections, developmental delay, congenital malformations, and hematological changes occur together.

The leading role is played by PIDs with profound defects in antibody production or cellular immunity. For example, X-linked agammaglobulinemia is typically associated with recurrent otitis, pneumonia, and sepsis caused mainly by Gram-positive bacteria.

In our cohort, 9 children (20.9%) had severe pneumonia, 17 (39.5%) developed sepsis, 2 (4.7%) suffered from purulent meningoencephalitis, 13 (30.2%) had generalized viral infections, and 2 (4.7%) presented with necrotizing enterocolitis. A total of 28 patients (65.1%) were premature. Congenital anomalies were diagnosed in 19 children (44.2%), including cardiac defects (23.3%), gastrointestinal malformations (7%), respiratory abnormalities (7%), CNS defects (7%), as well as Edwards' and Down syndromes.

Illustrative cases included a newborn with congenital heart disease and late-onset neonatal sepsis (bilateral pneumonia, carditis, hepatitis, meningoencephalitis, and ventriculitis) and another infant with hemolytic disease and severe pneumonia.

A comprehensive approach, combining active PID screening in inpatient settings and multidisciplinary collaboration among pediatricians, immunologists, otolaryngologists, and hematologists, facilitated earlier diagnosis and timely initiation of therapy. This strategy improves prognosis and enhances patients' quality of life.

Our findings confirm that PID underdiagnosis remains a major issue in the Republic of Karakalpakstan, reducing the effectiveness of medical care. For the first time, data were obtained on diagnostic trends in the Aral Sea region, highlighting diagnostic delays and the under-recognition of humoral forms of PID, laying the groundwork for further epidemiological research in the region.

It should be emphasized that in none of the cases was PID diagnosed at an early stage by primary care physicians. Suspicion of immunodeficiency arose only after multiple hospitalizations and lack of response to therapy. This indicates the need to increase awareness and vigilance among healthcare professionals.

Conclusion. The conducted analysis demonstrated that a significant proportion of children in the Aral Sea region present with clinical and epidemiological features suggestive of primary immunodeficiency (PID). However, in real clinical practice such cases often remain unrecognized. Timely identification of patients is hindered by the limited availability of immunological testing, insufficient training of specialists, and the absence of diagnostic algorithms at the level of primary healthcare.

Implementation of programs aimed at improving the qualifications of healthcare professionals, expanding laboratory capacities, introducing standardized clinical diagnostic protocols for PID, and establishing a regional registry of children with suspected immunodeficiency conditions is essential. These measures would significantly enhance the efficiency of early diagnosis, ensure timely initiation of appropriate therapy, and reduce the risk of severe infectious complications in children.

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