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# Clinical Manifestations in the Patients with Primary Immunodeficiencies: Data from One Regional Center

## Primer İmmün Yetersizliği Olan Hastalardaki Klinik Bulgular: Bir Bölge Hastanesinin Verileri

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## Abstract

**Introduction:** Defining clinical signs is very important for timely diagnosis of diseases, as well as primary immunodeficiencies (PID). The aim of our study was to identify manifestations and their specific features in the patients of Ternopil region, Ukraine, in order to improve early detection of primary immunodeficiencies.

**Materials and Methods:** This retrospective and prospective study involved 36 patients with primary immunodeficiencies, whose clinical symptoms were followed up from the disease onset. A prospective analysis was performed for 26 patients, while retrospective analysis based on the review of medical records was conducted for 10 patients.

**Results:** Combined immunodeficiencies with associated or syndromic features such as Nijmegen breakage syndrome, 22q11.2 deletion syndrome, ataxia-teleangiectasia, were diagnosed the most frequently and followed by antibody deficiencies. The mean delay from initial symptoms to diagnosis was 31.5 months, and ranging from one to 156 months. Recurrent bacterial respiratory tract infections were evidenced in 61.1% of patients, recurrent viral respiratory infections-in 44.4% of patients. Skin infections were reported in 25.0% of all cases. Allergies were present in 11.1% and autoimmune diseases in 16.7% of all patients; malignancy was revealed in one case.

**Conclusions:** Infections were the most prominent clinical manisfestation PIDs, although more than 30% of the children have had PID manifestations accompanied by autoimmune disorders, allergies, or malignancies. Taking into account regional features of the PID incidence, more attention should be given to the clinical signs of microcephaly, ataxia, teleangiectasia and congenital heart defects in PID diagnosis. Lymphopenia and characteristic dysmorphic features are also warning signs for PID in the neonatal period and early infancy.

**Keywords:** Primary immunodeficiency, clinical signs, diagnosis

## Öz

**Giriş:** Tüm hastalıkların tanısında olduğu gibi primer immün yetersizliklerde klinik bulguların tanımlanması çok önemlidir. Bu çalışmadaki amaç, Ukrayna'da Ternopil çevresindeki primer immün yetersizlikli hastaların klinik bulgularını ve bu bulguların özelliklerini tanımlayarak hastalıklara erkenden tanı koyulmasını kolaylaştırmak idi.

**Gereç ve Yöntemler:** Bu prospektif ve geriye dönük çalışmada primer immün yetersizliği olan ve hastalıklarının başından beri takip edilen 36 hasta irdelendi. Prospektif irdeleme 26 hastada, 10 hastanın verileri ise tıbbi kayıtlar incelenerek geriye dönük olarak değerlendirildi.

**Bulgular:** Birden fazla bağışıklık yetersizliği görülen Nijmegen kırılma sendromu, 22q11.2 silinme sendromu, ataksia telenjiektezya en sık kaydedilen hastalıklar olup, bunları sıklık olarak antikor eksiklikleri izledi. İlk belirtilerden tanıya kadar geçen süre 1-156 ay arasında idi ve bu değerlerin ortalaması 31.5 ay olarak hesaplandı. Hastaların %61.1'inde tekrarlayan bakteriyel solunum yolu enfeksiyonları saptanır iken %44.4 olguda ise tekrarlayan viral enfeksiyonlar bulunuyordu. Hastaların %25.0'inde cilt enfeksiyonları bildirildi. Allerji %11.1'inde, otoimmün hastalıklar %16.7 hastada saptanır iken bir hastada malignite görüldü.

**Sonuçlar:** Primer bağışıklık yetersizliği hastalığı olan kişilerde enfeksiyonlar en sık görülen klinik durum idi. Bununla birlikte, hastalarda ayrıca otoimmün hastalıklar, allerjiler ve malignite de saptandı. Bu primer bağışıklık yetersizliği olan kişilerde bölgesel özellikler dikkate alınarak, hastalarda mikrosefali, ataksi, telenjiektazi ve doğumsal kalp hastalığı olup olmadığına dikkat edilmelidir. Lenfopeni ve özelliği olan dismorfik özellikler de yeni doğanlar ve bebeklerdeki muhtemel primer bağışıklık yetersizliğin erken tanısı için erken belirleyici olarak dikkat ile kaydedilmelidir.

**Anahtar Kelimeler:** Primer bağışıklık yetersizliği, klinik bulgular, teşhis

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## Introduction

Defining clinical signs is very important for timely diagnosis of diseases. Primary immunodeficiencies (PID) include more than 430 different genetic disorders characterized by immune system abnormalities.[1] A large number of diseases causes variability of clinical symptoms.[2–3]

PIDs are manifested not only by recurrent infections, which are often a leading clinical sign of these diseases, but also by other signs: autoimmune conditions, autoinflammation, allergies and malignancies.[4–6]

The most recent classification of PIDs comprises nine groups. All groups have some common features; however, clinical picture of each group of the diseases has its own characteristics. Regional and ethnic variation in PID incidence also defines specificity of some features of these diseases. Our previous research revealed poor awareness of specific signs of PIDs, even the most common ones, among physicians, postgraduate students and medical students in Ternopil region, Ukraine.[7–9]

The aim of our study was to define the features of PID clinical manifestations in the patients of Ternopil region, Ukraine, in order to improve early detection of these diseases.

## Materials and Methods

Since 2003, 41 patients with PIDs have been registered by Ternopil Regional Registry. Genetic testing confirmed diagnosis in 20 (48.8%) patients. Within the same period, 10 children (24.4%) diagnosed with PIDs died. Five patients were transferred to adult immunologists.

This retrospective and prospective study involved 36 patients with PIDs, whose clinical symptoms were followed up from the disease onset. A prospective analysis was performed for 26 patients still being under medical supervision by an immunology specialist. Retrospective analysis was based on a review of medical (clinical) records. There were 10 patients, three of whom died, two moved to another region due to a change of residence, two were transferred to an adult immunologist after age of 18 years old, and three were diagnosed with transient hypogammaglobulinemia in infancy and currently no signs of immunodeficiency were evidenced.

Five cases, which were not included in the study, had insufficient data for evaluation of clinical symptoms. Four patients died (two diagnosed with SCID during the first 3 months of life, one with agammaglobuliemia at 2.5 years old, and one with ataxia-teleangiectasia at 9 years old from lymphogranelematosis). In one case, a patient with hyper IgE syndrome, who is now 24 years old, the data on clinical course of the disease is lacking.

We paid special attention to the major characteristics of the patients with PID and clinical manifestations of PID.

Informed consents were taken from all participants of the study. The experiments records were conducted following the guidelines of the Helsinki Declaration of 1975, as revised in 2000.

### Statistical analysis

The statistical analysis of the results was carried out using statistical package STATISTICA 10.0 and table editor Microsoft Excel 2003. The comparison of frequency parameters between the groups was performed using a $\chi^2$ test. The differences between the parameters were statistically significant at $p<0.05$.

## Results

The list of diagnoses of the patients involved in the study is presented in Table 1. 22q11.2 deletion syndrome and Nijmegen breakage syndrome (NBS) followed by ataxia-teleangiectasia, transient hypogammaglobulinemia of infancy and selective IgA deficiency were diagnosed the most frequently. Others PIDs were rare (1–2 cases).

The classification of PIDs diagnosed is presented in Table 2. In this study, the majority of diagnoses were within the category of combined immunodeficiencies (CID) with associated or syndromic features (55.6%) followed by antibody deficiencies (30.6%). Congenital defects

**Table 1.** PIDs diagnoses and their frequency

| Diagnosis | n | % |
|---|---|---|
| Nijmegen breakage syndrome (NBS) | 6 | 16.7 |
| 22q11.2 deletion syndrome (Di George syndrome) | 7 | 19.4 |
| Ataxia-teleangiectasia | 4 | 11.1 |
| Hyper IgE-syndrome | 1 | 2.8 |
| Cartilage-hair hypoplasia | 1 | 2.8 |
| Chronic mucocutaneous candidiasis | 1 | 2.8 |
| X-linked agammaglobuliemia (XLA) | 1 | 2.8 |
| Common variable immunodeficiency (CVID) | 2 | 5.6 |
| Selective IgA deficiency | 3 | 8.3 |
| Transient hypogammaglobulinemia of infancy | 4 | 11.1 |
| IgG subclasses deficiency | 1 | 2.8 |
| Leukocyte adhesion deficiency type 1 | 1 | 2.8 |
| Congenital neutropenia, unspecified | 2 | 5.6 |
| X-linked lymphoproliferative syndrome (XLP) | 2 | 5.6 |
| Total | 36 | |

**Table 2.** Diagnosed Primary Immune Deficiency groups (CID: Combined immune deficiency)

| Group | n | % |
|---|---|---|
| Antibody deficiencies | 11 | 30.6 |
| CID with associated or syndromic features | 20 | 55.6 |
| Congenital defects in phagocyte number, function, or both | 3 | 8.3 |
| Defects of immune regulation | 2 | 5.5 |

in phagocyte number or function as well as defects of immune regulation were rare (Table 2).

Baseline characteristics of PID patients depending on PID category are presented in Table 3. In all groups, except the phagocyte defects group, males predominate. The mean age of PID patients at the time of clinical evaluation was 8.9 years old ranging from 7 months to 33 years.

Two patients with the diseases of immune dysregulation died prior to two years of age, thus the mean age of children at the time of clinical evaluation is the lowest in this group. There are no significant differences between the mean ages among patients of others PID groups. The oldest patient is currently 33 years old.

The mean age of the symptoms onset was 14.2 months, ranging from one to 108 months. The latest onset was in a patient with CVID (in the age of 9 years) and in the group of patients with antibody deficiency.

The mean delay from initial symptoms to diagnosis was 31.5 months, ranging from one to 156 months. There were no significant differences between the groups. Two patients with the diseases of immune dysregulation died within three weeks after first clinical signs.

There were also deaths of patients with CID: one patient with ataxia-teleangiectasia died from leukemia at the age of 6 years, and two patients with 22q11.2 deletion syndrome died from complications of congenital heart defects.

Clinical signs of PID in the patients depending on the PID group are presented in Table 4. Recurrent infections occurred in 29 (80.6%) PID patients. Seven patients did not suffer from frequent infections: two patients with 22q11.2 deletion syndrome, two patients with selective IgA deficiency, a one-year-old patient with NBS and two patients with ataxia-teleangiectasia.

Recurrent bacterial respiratory tract infections (otitis, sinusitis, tonsillitis, pneumonia) were evidenced in 22 (61.1%) patients, recurrent viral respiratory infections-in 16 (44.4%) patients. Recurrent pneumonia was present more often in the patients with antibody deficiencies (63.6% vs 35.0% and 33.3%, respectively). Among other infections, skin infections were reported in 25.0% of the cases, and were most frequent in the patients with phagocyte defects (66.7%). Mycoses and unusual infections (such as *Molluscum contagiosum*) took place in the patients with CID.

Allergies occurred in 11.1% of the cases and only as atopic dermatitis. Autoimmune diseases were diagnosed in 16.7% of all patients, in particularly in the patients with antibody deficiencies. Malignancy was diagnosed in one patient with CID.

**Table 3.** Baseline characteristics of Primary Immune Deficiency patients

| Parameter | Antibody deficiencies, n=11 | | Combined Immune Deficiency, n=20 | | Phagocyte defects n=3 | | Diseases of immune dysregulation n=2 | | Total, n=36 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % |
| Gender: | | | | | | | | | | |
| male | 8 | 72.7 | 12 | 60 | 0 | 0 | 2 | 100 | 22 | 61.1 |
| female | 3 | 27.3 | 8 | 40 | 3 | 100 | 0 | 0 | 14 | 38.9 |
| Age, mean range, yrs | 7.3 (1–16) | | 10.5 (7 mos-33) | | 9.3 (3–18) | | 1.5 (11 mos-1.9) | | 8.9 (7 mos-33) | |
| Age of onset of symptoms, mean range, mos | 23.4 (2–108) | | 10.5 (1–60) | | 9.7 (4–15) | | 17 (11–23) | | 14.2 (1–108) | |
| Delay from initial symptoms to diagnosis, mean range, mos | 30.3 (4–96) | | 33.0 (1–156) | | 25.7 (1–60) | | - | | 31.5 (1–156) | |
| Deaths | - | - | 3 | 15 | - | - | 2 | 100 | 5 | 13.9 |

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**Table 4.** Clinical signs in the patients with Primary immune deficincies

| Clinical sign | Antibody deficiencies, n=11 | | Combined Immune Deficiency, n=20 | | Phagocyte defects, n=3 | | Diseases of immune dysregulation, n=2 | | Total, n=36 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % |
| **Infections:** | | | | | | | | | | |
| Recurrent otitis | 1 | 9.1 | 2 | 10.0 | - | - | - | - | 3 | 8.3 |
| Recurrent sinusitis | 1 | 9.1 | 2 | 10.0 | - | - | - | - | 3 | 8.3 |
| Recurrent tonsillitis | 1 | 9.1 | - | - | | | | | 1 | 2.8 |
| Recurrent viral respiratory infections | 4 | 36.4 | 10 | 50.0 | 2 | 66.7 | - | - | 16 | 44.4 |
| Recurrent pneumonia | 7 | 63.6 | 7 | 35.0 | 1 | 33.3 | - | - | 15 | 41.7 |
| Recurrent urinary tract infections | - | - | 3 | 15.0 | - | - | - | - | 3 | 8.3 |
| Chronic diarrhea (over 1 month) with malabsorption | 2 | 18.2 | 2 | 10.0 | - | - | - | - | 4 | 11.1 |
| Recurrent skin infections | 2 | 18.2 | 5 | 25.0 | 2 | 66.7 | - | - | 9 | 25.0 |
| Recurrent oral mucosal infections (stomatitis, gingivitis) | - | - | 1 | 5.0 | 2 | 66.7 | - | - | 3 | 8.3 |
| Recurrent lymphadenitis | 1 | 9.1 | - | - | 1 | 33.3 | - | - | 2 | 5.6 |
| Encephalitis | 1 | 9.1 | - | - | - | - | - | - | 1 | 2.8 |
| Sepsis | - | - | 1 | 5.0 | 1 | 33.3 | - | - | 2 | 5.6 |
| EBV-infection | 1 | 9.1 | - | - | - | - | 1 | 50 | 2 | 5.6 |
| Recurrent Herpes virus infection | 1 | 9.1 | 2 | 10.0 | - | - | - | - | 3 | 8.3 |
| *Molluscum contagiosum* infection | - | - | 1 | 5.0 | - | - | - | - | 1 | 2.8 |
| Mycoses | - | - | 5 | 25.0 | - | - | - | - | 5 | 13.9 |
| Allergies: | | | | | | | | | | |
| Atopic dermatitis | - | - | 3 | 15.0 | 1 | 33.3 | - | - | 4 | 11.1 |
| Autoimmune diseases: | | | | | | | | | | |
| Juvenile idiopathic arthritis | 1 | 9.1 | 1 | 5.0 | - | - | - | - | 2 | 5.6 |
| Vasculitis | 1 | 9.1 | - | - | - | - | - | - | 1 | 2.8 |
| Diabetes mellitus, type 1 | 2 | 18.2 | 1 | 5.0 | - | - | - | - | 3 | 8.3 |
| Malignancies: | | | | | | | | | | |
| Leukemia | - | - | 1 | 5.0 | - | - | - | - | 1 | 2.8 |
| **Other warning signs:** | | | | | | | | | | |
| Bronchiectasis | 1 | 9.1 | - | - | - | - | - | - | 1 | 2.8 |
| Thrombocytopenia and/or their small size | - | - | 1 | 5.0 | - | - | - | - | 1 | 2.8 |
| Neutropenia | - | - | - | - | 2 | 66.7 | - | - | 2 | 5.6 |
| Lymphopenia | 1 | 9.1 | 10 | 50.0 | - | - | - | - | 11 | 30.6 |
| Ataxia | - | - | 4 | 20.0 | - | - | - | - | 4 | 11.1 |
| Teleangiectasia | - | | 4 | 20.0 | - | - | - | - | 4 | 11.1 |
| Microcephaly | - | - | 6 | 30.0 | - | - | - | - | 6 | 16.7 |
| Other dysmorphic features | | | 13 | 65.0 | - | - | - | - | 13 | 36.1 |
| Congenital heart disease (with/without seizures) and hypocalcemia | - | - | 3 | 15.0 | - | - | - | - | 3 | 8.3 |
| Late teeth eruption | - | - | 1 | 5.0 | 1 | 33.3 | - | - | 2 | 5.6 |
| Died sibling due to infectious or oncological diseases | 1 | 9.1 | 2 | 10.0 | 1 | 33.3 | 1 | 50 | 5 | 13.9 |
| Hemophagocytic syndrome | - | - | - | - | - | - | 2 | 100 | 2 | 5.6 |
| **Other signs:** | | | | | | | | | | |
| Cholelithiasis | 1 | 9.1 | - | - | - | - | - | - | 1 | 2.8 |
| Renal aplasia | - | - | 2 | 10.0 | - | - | - | - | 2 | 5.6 |
| Skeletal abnormalities | - | - | 3 | 15.0 | - | - | - | - | 3 | 8.3 |
| Failure to thrive | 3 | 27.3 | 12 | 60.0 | - | - | - | - | 15 | 41.7 |
| Autism | 2 | 18.2 | - | - | - | - | - | - | 2 | 5.6 |

Thus, recurrent infections were the most common clinical manifestation (80.6% vs 11.1% of allergies, p=0.0002; vs 16.7% of autoimmune diseases, p=0.0011; vs 2.8% of malignancies, p<0.0001).

Other warning signs of PIDs occurred predominantly in patients suffering from the diseases in the group of CID with associated or syndromic features: ataxia and teleangiectasia in the patients with ataxia-teleangiectasia syndrome; microcephaly in the patients with NBS; dysmorphic features in the patients with NBS, 22q11.2 deletion syndrome and hyper IgE-syndrome, cartilage-hair hypoplasia. Congenital heart disease was detected in six patients with 22q11.2 deletion syndrome, but only in three cases it was accompanied by hypocalcemia. Lymphopenia was diagnosed in 50.0% of patients with CID, while thrombocytopenia in one patient with 22q11.2 deletion syndrome. Two patients with XLP had clinical manifestations of hemophagocytic syndrome.

Among other signs, developmental delay occurred in 41.7% of patients, more often in the patients suffering from the diseases in the group of CID with associated or syndromic features, especially in the patients with NBS (3), 22q11.2 deletion syndrome (4), ataxia-teleangiectasia syndrome (4), and cartilage-hair hypoplasia (1).

## Discussion

Clinical manifestations are crucial in the presentation and course for many diseases, including PIDs.[2,10] In this study, the diseases comprising PID group of CID with associated or syndromic features (55.6%) were the most common and followed by the group of antibody deficiencies (30.6%). Other studies, including data of ESID registry, prove predominance of antibody deficiencies.[11,12] However, the studies in some PID centers also established the prevalence of CID among the cases.[2,13,14]

Not all PID groups are represented in our regional PID registry. Defects in intrinsic and innate immunity, autoinflammatory disorders, and complement deficiencies were not reported. Severe combined immunodeficiency was diagnosed in two children, who died within the first three months of their life, and thus were not involved into this study. Diseases within these PID groups are also rarer in other populations. However, the lack of them in our registry indicates the probable underdeveloped PID diagnosis infrastructure in Ternopil region, causing underdiagnosing of these diseases, and points out the need of diagnosis improvement.

The mean age of disease onset was 14.2 months, and ranged from 1 month to 9 years. The earliest symptoms were revealed in the patients with CID and phagocyte defects. The mean age of CID onset was 10.5 months, which is slightly later than reported in the literature.[2] This was due to the absence of severe combined immunodeficiency (SCID) in these patients, which are usually manifested during the first months of life. Some diseases in the category of CID with associated or syndromic features, for example ataxia teleangiectasia, are manifested later than during the first year of life. Similarly, not all patients with 22q11.2 deletion syndrome had early warning signs: congenital heart defect was absent in one patient; in another patient the heart defect did not point to Di George syndrome because other typical manifestations were lacking.

The mean delay from the initial symptoms to diagnosis was 31.5 months (2.6 years). Subbarayan et al. (2012) reported the median delay from initial symptoms to a referral for medical advice ranging from 6 to 56 months depending on a PID category, with interquartile range from 1 to 134 months.[2] The European internet-based database for primary immunodeficiencies reports that the mean diagnostic delay between the symptoms onset and the date of diagnosis is 4.08 years (average delay: 2 years).[11] In our study, the longest delay of a diagnosis was in a patient with ataxia-teleangiectasia. The boy's mother first noticed ataxia when he was three years old, but PID was diagnosed only at the age of 16 years old. In a child with cartilage-hair hypoplasia clinical symptoms of the disease were masked by a severe course of diabetes mellitus, which was manifested at the age of 1.5, thus cartilage-hair hypoplasia was diagnosed at the age of 15. According to the ESID registry data, the mean delay in diagnosis of ataxia-teleangiectasia is one of the longest (4.38 years).[11] Because the presence of microcephaly and characteristic dysmorphic features, the majority of children with NBS received a timely diagnosis within the first three months after birth. Only in one case NBS was diagnosed at the age of 9, despite the boy being followed up since one year of age. Thus, the lack of convincing clinical data and a false genetic test led to the delay in diagnosis.

Recurrent infections dominated among the clinical signs (80.6%). Infections were present primarily as recurrent pneumonia (41.7%), especially in the children with

antibody deficiencies (63.6%). Autoimmune disorders were diagnosed in 16.7% of the cases: type 1 diabetes mellitus and juvenile idiopathic arthritis was present the most often (three and two cases respectively). Selective IgA deficiency was diagnosed in two patients with type 1 diabetes mellitus without any other symptoms of immunodeficiency. Autoimmune disorders, including diabetes mellitus in patients with selective IgA deficiency, were also reported in the literature.[15,16] Juvenile idiopathic arthritis was evidenced in the patients with XLA and ataxia-teleangiectasia. Juvenile idiopathic arthritis in the patients with ataxia-teleangiectasia was reported in only one study.[17]

Among other clinical signs, particular attention was paid to frequent cases of lymphopenia (30.6%) and dysmorphic features (36.1%). These signs occurred in more than 50% of the patients with CID. According to the literature, these signs are very important for PID diagnostics in the neonatal period and early infancy.[14] Since there is currently no neonatal screening for PIDs in Ukraine, defining of these symptoms is very important for a timely diagnosis of these diseases.[18]

This study was limited to pool of patients followed up in one regional center.

## Conclusions

Infections was a dominant sign of PID, although more than 30% of children suffered from PID manifestations followed by autoimmune disorders, allergies, or malignancies. Taking into account the regional features of the PID incidence, more attention should be given to the clinical signs of microcephaly, ataxia, teleangiectasia and congenital heart defects in PID diagnosis. Lymphopenia and characteristic dysmorphic features should be considered as also warning signs for PID in the neonatal period and early infancy.

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**Ethics Committee Approval:** This study has been approved by TNMU Committee on Bioethics, and the patients have signed informed consents.

**Informed Consent:** Written informed consents were obtained from the parents of all patients.

**Peer-review:** Externally peer-reviewed.

**Conflict of interest:** The authors have declared no conflict of interest.

**Author Contributions:** Oksana Boyarchuk: *Study conception and design, analysis and interpretation of data, clinical investigator;* Lyubov Dmytrash: *collecting data, proofreading. All authors mentioned above have approved this final manuscript.*

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