

Frequency and clinical spectrum of immune dysregulation in primary immunodeficiencies: experience of a single Central European Adult Care Centre

VIKTÓRIA OROSZ, KATALIN T. KOVÁCS, GÁBOR KUMÁNOVICS

Department of Rheumatology and Immunology, Medical School, University of Pécs, Hungary

Abstract

Introduction: Primary immunodeficiencies (PIDs) encompass not only recurrent infections but also a wide range of manifestations of immune dysregulation, including autoimmunity, lymphoproliferation, granulomatous disease, and malignancies.

The aim of the study was to analyse the prevalence and clinical features of immune dysregulation among adult patients with PID, and to evaluate the relationship between age at diagnosis, diagnostic delay, and the development of non-infectious complications.

Material and methods: We retrospectively reviewed the records of 28 adult patients with PID receiving immunoglobulin replacement therapy. Features of immune dysregulation were analysed in relation to age at diagnosis and diagnostic delay.

Results: We were able to diagnose PID in 28 patients (estimated prevalence of adult-onset PID in the area of our centre is 3.01/100.000), among these, the most common group was primary antibody deficiency (PAD: 25/28, 89%). Immune dysregulation was observed in 22 patients (79%), three of whom presented without any infectious manifestations. The prevalence of autoimmune disease was significantly higher among patients diagnosed after the age of 50 than among those diagnosed in childhood (58% vs. 0%, $p = 0.0377$). ROC analysis identified age ≥ 41 years at diagnosis as a significant discriminator of immune dysregulation-related complications (AUC = 0.724, $p = 0.025$). Malignancy accounted for half of all deaths (3/6, 50%), while no patient died of infection.

Conclusions: Immune dysregulation represents a hallmark of adult-onset PID, often preceding or occurring independently of recurrent infections. Malignancy, rather than infection, emerged as the leading cause of death. The observed gap between expected and diagnosed prevalence highlights an unmet need for improved recognition of PID in adults and better transition pathways from paediatric to adult care in Central and Eastern Europe.

Key words: inborn errors of immunity, adult-onset primary immunodeficiencies, immune dysregulation, CVID, autoimmunity.

(Cent Eur J Immunol 2026; 51 (4): 1-8)

Introduction

Primary immunodeficiency diseases (PIDs), also known as inborn errors of immunity (IEI), are congenital, hereditary conditions characterised by recurrent infections and immune dysregulation, such as granulomatosis, autoimmune diseases, lymphoproliferation, and malignancy [1, 2]. The number of people affected by PID worldwide is estimated to be around 6,000,000. However, the number of confirmed PID diagnoses is believed to be between 27,000 and 60,000 [3]. Initially, in the first few years, PID commonly appears in the form of subclinical symptoms among

patients with adulthood-onset PID, which may lead to a delayed diagnosis of several years [4, 5].

Primary immunodeficiency diseases are classified based on the combination of their mechanism and clinical presentation [2, 6]. Primary antibody deficiencies (PADs) are the most frequent type of PID [7, 8]. Among PADs, common variable immunodeficiency (CVID) is the most prevalent symptomatic disorder. CVID is a heterogeneous group of PIDs with infectious and non-infectious manifestations [9]. The risk of developing both autoimmune or inflammatory processes is higher than in the general population [10].

Correspondence: Gabor Kumanovics, MD, PhD, Department of Rheumatology and Immunology, Medical School, University of Pécs, Akác u. 1, 7362 Pécs, Hungary, e-mail: kumanovics.gabor@pte.hu
Submitted: 02.07.2025, Accepted: 06.02.2026

Copyright © Polish Society of Experimental and Clinical Immunology. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0). License (<http://creativecommons.org/licenses/by-nc-sa/4.0/>)

The human lung is one of the most affected organs, in which bronchiectasis and lung fibrosis may draw attention to PID [5]. Malignant tumours often originate from tissues that carry the molecular defects that cause immunodeficiency [11]. The gastrointestinal system may also be affected. Malabsorption, abdominal pain and inflammatory bowel diseases may occur simultaneously [12]. The presence of atopy in combination with other infectious and non-infectious clinical features could suggest the presence of PID. [3]. The study of PID and its associated immune dysregulation is difficult due to the low number of cases. There are few single-centre studies in the published literature, particularly those focusing on adulthood [13], and it is widely known that Central and Eastern Europe are at a disadvantage when it comes to the diagnosis and treatment of PID compared to other European regions [14].

We aimed to analyse the prevalence of immune dysregulation among adult patients with PID, and to evaluate the relationship between age at diagnosis, diagnostic delay, and the development of non-infectious complications. Our goal was to review the clinical spectrum of PID in adulthood by processing data from a single centre.

Material and methods

Study design and patient selection

We conducted a retrospective, single-centre study at the Department of Rheumatology and Immunology, University of Pécs, Hungary, which serves as a tertiary referral centre for systemic autoimmune diseases and primary immunodeficiencies (PIDs). The study period extended from August 1, 2002 to June 30, 2023. Patients were eligible for inclusion if they: 1) were ≥ 18 years of age at the time of the last follow-up in our department, 2) fulfilled the European Society for Immunodeficiencies (ESID) diagnostic criteria for PID (used the “clinical criteria for a probable diagnosis = working definitions for clinical diagnosis classification”) [15], and 3) were receiving regular immunoglobulin replacement therapy (intravenous immunoglobulin [IVIG] or subcutaneous immunoglobulin [SCIG]) in our centre. Patients were excluded if they had secondary immunodeficiency (e.g., malignancy, human immunodeficiency virus [HIV], immunosuppressive therapy without underlying PID) or insufficient documentation.

Our department serves ~730,000 adults in our region. We provide long-term care for more than 5,000 patients with inflammatory rheumatic diseases, including 1,500 patients receiving targeted therapy, and 2,000 new patients are referred annually.

Data collection

Clinical data included demographics, age at onset/diagnosis, diagnostic delay, PID subtype, infections, immune dysregulation (autoimmunity, lymphoproliferation,

granulomatous disease, malignancy, lung abnormalities based on HRCT), basic laboratory investigations (blood cell count; chemistry; liver, pancreas and renal function tests; C-reactive protein [CRP]; erythrocyte sedimentation rate [ESR]; thyroid-stimulating hormone [TSH]; glycosylated hemoglobin A_{1c} (HbA_{1c}); urine analysis); immunological parameters (serum complement levels (C3, C4), $\beta 2$ microglobulin [B2MG], serum electrophoresis test, titre of immunoglobulins (IgG, IgM, IgA), lymphocytes subgroups by flow cytometry (CD3⁺, CD4⁺, CD8⁺, CD19⁺, CD19⁺CD27⁺IgD⁺ cells), vaccination status (antibody response after COVID-19 vaccines: depending on the type of vaccine, after 2-3 vaccinations (according to official recommendations), on average 6-12 weeks after the last vaccination), and therapies (IVIG/SCIG, steroids, disease-modifying antirheumatic drugs [DMARDs], biologics).

Definitions

Diagnostic delay was dichotomized as ≤ 6 vs. > 6 years, based on prior studies showing worse outcomes with longer delay [16]. Immune dysregulation was defined as autoimmunity, lymphoproliferation, granulomatous disease, or malignancy. Morphological lung abnormalities included bronchiectasis, fibrosis, or chronic inflammatory changes confirmed by CT imaging.

Statistical analysis

Statistical analysis was performed using StatPlus version 7. Fisher's exact test was used for comparisons of categorical variables, and Spearman's correlation was used to assess associations between continuous variables. Receiver operating characteristic (ROC) curve analysis was performed to determine optimal age cut-offs. Significance: A p -value < 0.05 was considered statistically significant.

Ethics

All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the University of Pécs (KK/1188-1/2022).

Results

Cohort overview

A total of 28 patients with PID (14 females, 14 males) were included in the study. Median age at diagnosis was 46.5 years (range 2-76). Based on ESID criteria, 25 patients (89%) were diagnosed with PADs, including CVID ($n = 11$), unclassified antibody deficiency (unPAD, $n = 12$), hyper-IgM syndrome ($n = 1$), and X-linked agammaglobulinaemia ($n = 1$). Three patients (11%) were diagnosed with combined immunodeficiency (CID).

Age at diagnosis and prevalence

At diagnosis, 22 patients (79%) were older than 20 years, while 6 (21%) were childhood-onset cases who remained under follow-up in adulthood (Table 1). The estimated prevalence of adult-onset PID in the catchment area of our centre was 3.01/100,000 individuals.

Clinical manifestations

Overall, 22 patients (79%) exhibited signs of immune dysregulation in addition to infections (Table 2). This included autoimmunity ($n = 10$, 36%), lymphoproliferation ($n = 11$, 39%), granulomatous disease ($n = 5$, 18%), and malignancy ($n = 8$, 29%). In three patients (11%), immune dysregulation was the first or only manifestation, occurring in the absence of recurrent infections.

Diagnostic delay

The mean diagnostic delay was 15.4 years (range 1-52). When comparing patients diagnosed within 6 years

vs. > 6 years of symptom onset, no significant difference was observed in the frequency of immune dysregulation-related complications ($p > 0.05$) (Supplementary Table 1). Even with ROC analysis, we did not find a diagnostic delay time that would significantly increase the rate of non-infectious manifestations (Supplementary Fig. 1).

Therapy and outcome

All patients received immunoglobulin replacement therapy (IVIG or SCIG). In addition, 12 patients (43%) required immunosuppressive or immunomodulatory treatment, including corticosteroids, conventional disease-modifying antirheumatic drugs, and biologics (rituximab in selected cases). Six patients (21%) died during follow-up: malignancy (adenocarcinoma of the caecum in a patient with CID, diffuse large B cell lymphoma in a patient with unPAD, hepatocellular carcinoma in a patient with unPAD) was the cause in three cases (50% of deaths), cirrhosis in one case, heart failure in one case, and unknown

Table 1. Clinical characteristics of 28 patients based on age at diagnosis

Variable	Age at diagnosis			p value		
	0-20 ($n = 6$)	21-50 ($n = 10$)	50+ ($n = 12$)	0-20 vs. 21-50	0-20 vs. 50+	21-50 vs. 50+
Childhood onset, n (%)	6 (100.0)	2 (20.0)	2 (16.67)	0.0069	0.0015	1
Female patients, n (%)	4 (66.67)	6 (60.0)	4 (33.33)	1	0.3213	0.3913
Recurrent infections, n (%)	6 (100.0)	8 (80.0)	11 (91.67)	0.5	1	0.5714
Morphological lung abnormalities, n (%)	3 (50.0)	5 (50.0)	11 (91.67)	1	0.0833	0.0557
Lymphoproliferation, n (%)	2 (33.33)	5 (50.0)	4 (33.33)	0.6329	1	0.6656
Autoimmunity, n (%)	0 (0)	3 (30.0)	7 (58.33)	0.25	0.0377	0.2305
Granulomatosis, n (%)	0 (0)	2 (20.0)	2 (16.67)	0.5	0.5294	1
Malignancy, n (%)	1 (16.67)	1 (10.0)	6 (50.0)	1	0.3156	0.0743

$p > 0.05$ – no significant difference was found between the two groups. Morphological lung abnormalities: air trapping, bronchial wall thickening, bronchiectasis, emphysema, ground glass opacities, parenchymal consolidation, pulmonary nodules, scarring/fibrosis, different forms of interstitial lung disease

Table 2. Categorization of 28 patients based on infectious and immune dysregulation manifestations

Variable	Patients with infectious symptoms only ($n = 6$, 21%)	Patients with immune dysregulation abnormalities		
		Patients with both infectious and immune dysregulation abnormalities ($n = 19$, 68%)	Patients with immune dysregulation abnormalities without infectious events ($n = 3$, 11%)	All patients with immune dysregulation abnormalities ($n = 22$, 79%)
Childhood onset, n (%)	6 (100.0)	0 (0)	0 (0)	0 (0.0)
Adult onset, n (%)	0 (0.0)	19 (68)	3 (11)	22 (79)
Female patients, n (%)	4 (66.67)	10 (52.63)	0 (0)	10 (45.45)
Disease duration at diagnosis (years)	12.5	12	2	8.0
IgG levels at diagnosis (g/l)	1.38	2.76	2.04	2.66
Death, n (%)	0 (0)	6 (31.58)	0 (0)	6 (27.27)

Table 3. Comparison of clinical characteristics according to outcome

Parameter	Deceased patients (n = 6)	Patients currently in care (n = 20)	p value
Childhood onset, n (%)	1 (16.67)	8 (40.0)	0.3798
Female patients, n (%)	3 (50.0)	10 (50.0)	1
Disease duration at diagnosis (years)	7.0	10.0	0.3764
IgG levels at diagnosis (g/l)	2.6	1.795	0.76
Recurrent infections, n (%)	6 (100)	18 (90.0)	1
Morphological lung abnormalities, n (%)	5 (83.33)	13 (65.0)	0.6279
Lymphoproliferation, n (%)	4 (66.67)	7 (35.0)	0.3478
Autoimmunity, n (%)	3 (50.0)	6 (30.0)	0.6279
Granulomatosis, n (%)	1 (16.67)	3 (15.0)	1
Malignancy, n (%)	4 (66.67)	4 (20.0)	0.0510
Patient with immune dysregulation manifestations, n (%)	6 (100.0)	15 (75.0)	0.2981

p > 0.05 indicates no significant difference between groups. All deceased patients exhibited features of immune dysregulation (100%), whereas among survivors, 75% showed such manifestations. Statistical analysis was performed using Fisher's exact test

in one case. Notably, no patient died from infectious complications (Tables 2 and 3).

Correlation between age and immune dysregulation

Age at diagnosis showed a positive correlation with the occurrence of immune dysregulation (Spearman's rho = 0.318, $p = 0.048$). ROC analysis demonstrated that age ≥ 41 years at diagnosis discriminated patients with immune dysregulation-related manifestations with 68% sensitivity and 83% specificity (AUC = 0.723, $p = 0.025$) (Supplementary Fig. 2). Autoimmune complications were particularly associated with diagnosis after age 34 (AUC = 0.800, $p = 0.003$).

Detailed clinical characteristics

We found no significant differences in the occurrence of individual clinical manifestations among the three sub-

groups comprising relatively higher numbers of patients (Table 4, Supplementary Table 2).

CID subgroup

Three patients were classified as having combined immunodeficiency (CID), diagnosed clinically. All three developed both autoimmune and malignant complications during their disease course. Two patients presented with systemic autoimmune disorders (temporal arteritis and inclusion body myositis with antiphospholipid syndrome), while one patient developed organ-specific autoimmunity (autoimmune gastritis). Malignancies included basal cell carcinoma, mucinous adenocarcinoma of the caecum, and a neuroendocrine tumour. Infections were not uniformly present: one patient was diagnosed with PID during evaluation of autoimmune disease, while another experienced recurrent upper respiratory tract infections only after the age of 50. All three patients exhibited morphological lung

Table 4. Comparison of clinical manifestations based on PID subtype

Parameter	CID (n = 3)	CVID (n = 11)	unPAD (n = 12)
Childhood onset, n (%)	0 (0)	4 (36.36)	4 (33.33)
Rate of female patients, n (%)	1 (33.33)	5 (45.45)	8 (66.67)
Recurrent infections, n (%)	2 (66.67)	10 (90.91)	11 (91.67)
Morphological lung abnormalities, n (%)	3 (100.0)	7 (63.64)	7 (58.33)
Lymphoproliferation, n (%)	1 (33.33)	2 (18.18)	6 (50.0)
Autoimmunity, n (%)	3 (100.0)	3 (27.27)	4 (33.33)
Granulomatosis, n (%)	0 (0)	1 (9.09)	3 (25.0)
Malignancy, n (%)	3 (100.0)	2 (18.18)	3 (35.0)

CID – combined immunodeficiency, CVID – common variable immunodeficiency, unPAD – unclassified antibody deficiency

abnormalities on imaging, and additional features included lymphadenopathy and gastrointestinal or cutaneous manifestations.

CVID subgroup

Among 11 patients with CVID, ten (91%) experienced recurrent infections, predominantly of the respiratory and gastrointestinal tract. In five patients (45%), infections represented the main manifestation of PID, whereas in others autoimmunity or lymphoproliferation also contributed. Autoimmune disorders included chronic inflammatory demyelinating polyneuropathy (CIDP), autoimmune cytopenia (immune thrombocytopenia [ITP] and autoimmune hemolytic anemia [AIHA]), and autoimmune encephalitis. Lymphoproliferation and solid tumours were each observed in two patients, while one patient developed sarcoidosis. Morphological lung abnormalities were present in seven patients (64%), including bronchiectasis and residual changes of prior inflammation. Gastrointestinal symptoms were noted in three patients, ranging from diarrhoea and weight loss to gluten-sensitive enteropathy. Cutaneous involvement was recorded in four cases (eczematous dermatitis in 2 patients, cheilitis with dermatitis of the surrounding skin in one patient, leukoderma in another patient). Vaccination response was variable: among patients tested after COVID-19 immunization, only half mounted an adequate antibody response despite IVIG therapy. Four patients required immunosuppressive therapy in addition to immunoglobulin replacement (because of autoimmune cytopenia, autoimmune encephalitis, CIDP and sarcoidosis).

unPAD subgroup

Twelve patients were classified as having unclassified antibody deficiency (unPAD). Recurrent infections were the predominant feature (11/12, 92%), mainly affecting the respiratory and gastrointestinal tracts. In six patients, increased susceptibility to infections began in adulthood, with a mean diagnostic delay of seven years. One patient, however, had no history of recurrent infections and was diagnosed with PID during the evaluation of Raynaud's phenomenon, when hypogammaglobulinaemia was detected. Morphological lung abnormalities were common (7/12, 58%), including bronchiectasis, fibrosis, and residual inflammatory changes. Autoimmunity was observed in four patients (autoimmune gastritis, cutaneous vasculitis, chronic motor axonal neuropathy, myasthenia gravis), and granulomatous disease in three (erythema nodosum, granulomatous colitis, cutaneous sarcoidosis). Gastrointestinal symptoms, particularly chronic diarrhoea, were present in five cases, sometimes associated with weight loss. Malignancies occurred in three patients, including lymphoma and carcinoma. Immunosuppressive therapy was required in five patients (42%) (due to autoimmunity and sarcoidosis in one patient), reflecting the complexity of disease management in this subgroup.

Discussion

Our study highlights the complex interplay between infection, immune dysregulation, and malignancy in patients with PIDs under adult care in Central Europe. Although our cohort is relatively small, several clinically relevant observations emerge that contribute to the understanding of PID in adulthood.

Immune dysregulation as a hallmark of adult-onset PID

In our cohort, nearly 80% of patients displayed manifestations of immune dysregulation, which frequently coexisted with or even preceded infectious symptoms. The high prevalence of immune dysregulations in PIDs demonstrates the complex relationships between the mechanisms of these two conditions [17]. Autoimmune disease was particularly associated with later age at diagnosis, in line with data from Gathmann *et al.* and Fischer *et al.*, who reported that non-infectious complications such as autoimmunity, splenomegaly, and malignancy increase with advancing age in CVID and other PIDs [18, 19]. Our ROC analysis identified 41 years as a cut-off age predicting the occurrence of immune dysregulation, supporting the notion that late diagnosis not only delays treatment but also increases the risk of irreversible complications. For this reason, based on the results of our ROC analysis, we consider it reasonable that basic PID tests should also be performed on patients over 40 years of age presenting with inflammatory phenomena of unknown origin or abnormalities suggestive of malignancy. Importantly, three patients in our cohort presented with immune dysregulation in the absence of recurrent infections, underscoring that PID should be considered in adults with unexplained autoimmune or lymphoproliferative disease [4, 5]. Positive familial history, association of multiple autoimmune disorders, features of lymphoproliferation, or hyperinflammation represent important elements in the identification of high-risk patients [20]. The most common ($n = 19$, 68%) non-infectious manifestation was morphological abnormalities in the lungs (air trapping, bronchial wall thickening, bronchiectasis, emphysema, ground glass opacities, parenchymal consolidation, pulmonary nodules, scarring/fibrosis, different forms of interstitial lung disease), consistent with previous literature data [21-23].

Malignancy as a leading cause of death

Half of all deaths in our cohort were due to malignancies, whereas no patient died from infection. This aligns with international observations that malignancy, rather than infection, has become the leading cause of mortality

in adult PID [11, 18]. The spectrum of malignancies in our patients – lymphoma, carcinoma, neuroendocrine tumour – reflects both intrinsic genetic susceptibility and chronic immune dysregulation, as previously described [11]. Our findings emphasize the need for regular malignancy surveillance in PID patients, even when infectious complications are well controlled by immunoglobulin replacement therapy.

Diagnostic delay and underdiagnosis

The mean diagnostic delay of over 15 years is concerning but not unexpected in Central and Eastern Europe. Previous reports from the J Project and other regional registries have demonstrated that delayed recognition, lack of awareness among non-specialist physicians, and limited access to specialized immunology centres all contribute to late diagnoses [14, 16]. Although our data did not reveal a direct statistical association between diagnostic delay and immune dysregulation, the small sample size may have limited statistical power. Other cohorts, such as those reported by Ziętkiewicz *et al.*, did demonstrate worse outcomes with delayed diagnosis [16]. Importantly, six of our patients were diagnosed in childhood but remained in follow-up in adulthood, highlighting the urgent need for structured transition programmes from paediatric to adult care [24].

Therapeutic considerations

To reduce the incidence and severity of long-term complications, international recommendations include administering non-live vaccines to some patients with primary immunodeficiency (PID). However, as our own vaccination results show (we obtained an effective antibody response to SARS-CoV-2 vaccines in 10 out of 15 patients in whom we were able to measure the response), their effectiveness varies significantly from person to person, beyond the underlying PID condition. We therefore consider it necessary to prepare an individualised vaccination plan for each patient with PID, monitor the results and, if necessary, consider the possibility of revaccination, the use of higher vaccine doses or passive immunisation [25].

All patients received immunoglobulin replacement, but nearly half also required immunomodulatory or immunosuppressive therapy for autoimmune or lymphoproliferative complications. Corticosteroids, conventional DMARDs, and rituximab were the most frequently used agents. Similar therapeutic challenges have been described internationally, where infection control by IVIG does not prevent the emergence of non-infectious manifestations [9]. PIDs associated with autoimmunity and pathogenic variants in immune-regulatory genes (e.g. CTLA4, LRBA, PI3K δ , NFKB1 and RAG) have a broad clinical spectrum and variable treatment outcomes, and may benefit from early recognition [26]. Our findings support the notion that

the management of adult PID requires not only infection prevention but also careful long-term surveillance and treatment of autoimmune and malignant complications.

Strengths and limitations

The main strength of our study is the detailed clinical characterization of a real-world adult PID cohort from a Central European tertiary centre with a focus on systemic autoimmune diseases. To our knowledge, this is among the few single-centre studies from the region that systematically documents immune dysregulation in adult PID. Limitations include the relatively small number of patients, the lack of genetic testing, and incomplete flow cytometry data in earlier years. It has been reported that some patients diagnosed with CVID may in fact harbour monogenic defects (e.g., CTLA4 deficiency, APDS), which highlights the importance of integrating genetic diagnostics into routine care [8, 26]. This is also true for adult PID, although sometimes the genetic and environmental background may be different from that of childhood forms [27]. The importance of genetic testing is also demonstrated by the fact that patients with genetically confirmed PID had a significantly higher incidence of malignancies than those who were only clinically suspected of having PID but without genetic evidence [28]. In Hungary, state health insurance does not cover gene sequencing for PID patients, so data in this area are not widely available. Our colleagues usually have to work without these data when treating “average” patients (genetic testing was available for one patient, which also confirmed the diagnosis of X-linked agammaglobulinaemia). Similarly, the precise identification of lymphocyte subgroups (such as class-switched memory B cells) has only become routine for our patients in recent years, making it difficult to differentiate accurately between PID subgroups. The ESID registry allows patients with a ‘clinical’ diagnosis to be entered, even if a gene defect is not known, and it also enables us to make a possible diagnosis rather than a definite one. Based on these considerations, we chose the ESID criteria as the starting point for our work instead of the genetically based IUIS (International Union of Immunological Societies) classification [1, 8]. Our data may also be biased in admitting the fact that our clinic predominantly cares for systemic autoimmune adult patients [29, 30], where a thorough investigation may have led to the discovery of PID cases with a short disease duration without a history of infection and, at the same time, increase the proportion of non-infectious manifestations. In addition, referring colleagues are more likely to think of us in connection with autoimmune diseases than recurrent infections. This may lead to fewer patients with such a medical history being referred to us, so we need to increase training for referring colleagues in this area. Based on the results of this publication, we have begun working with our paediatric colleagues to ensure a high rate of transition of patients diagnosed in childhood into adult care.

Implications and future directions

Our findings underscore the need for greater awareness of PID among physicians caring for adult patients with autoimmunity, lymphoproliferation, or malignancy. In addition, earlier diagnosis and structured transition from paediatric to adult care are essential to prevent diagnostic delays and improve outcomes. Emerging collaborations within the J Project and international PID networks will hopefully reduce the diagnostic gap and allow access to genetic testing and targeted therapies.

Conclusions

Immune dysregulation is a hallmark of adult PID, often preceding or independent of infections. Malignancy, not infection, is the leading cause of death. The diagnostic gap in Central and Eastern Europe calls for improved recognition in adults and structured transition programmes from paediatric to adult care.

Funding

This work was supported by a grant (TKP-2021-EGA-10) provided from the National Research, Development and Innovation Fund of Hungary, financed under the TKP-2021-EGA funding scheme.

Disclosures

All patients provided informed written consent to the study, which was conducted according to the Declaration of Helsinki and was approved by the Institutional Review Board (Data Protection and Research Ethics Committee, University of Pécs, Hungary, code: KK/1188-1/2022).

The authors declare no conflict of interest.

Supplementary material is available on the journal's website.

References

- Seidel MG, Kindle G, Gathmann B, et al. (2019): The European Society for Immunodeficiencies (ESID) registry working definitions for the clinical diagnosis of inborn errors of immunity. *J Allergy Clin Immunol Pract* 7: 1763-1770.
- Bonilla FA, Khan DA, Ballas ZK, et al. (2015): Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol* 136: 1186-1205.e78.
- De Wit, J, Brada RJK, Van Veldhuizen J, et al. (2019): Skin disorders are prominent features in primary immunodeficiency diseases: A systematic overview of current data. *Allergy* 74: 464-482.
- Azizi G, Ziaee V, Tavakol M, et al. (2017): Approach to the management of autoimmunity in primary immunodeficiency. *Scand J Immunol* 85: 13-29.
- Abolhassani H, Rezaei N, Mohammadinejad P, et al. (2015): Important differences in the diagnostic spectrum of primary immunodeficiency in adults versus children. *Expert Rev Clin Immunol* 11: 289-302.
- McCusker C, Upton J, Warrington R (2018): Primary immunodeficiency. *Allergy Asthma Clin Immunol* 14: 61.
- Janssen LMA, Reijnen ICGM, Milito C, et al. (2022): Protocol for the unclassified primary antibody deficiency (unPAD) study: Characterization and classification of patients using the ESID online Registry. *PLoS One* 17: e0266083.
- Poli MC, Aksentijevich I, Bousfiha AA, et al. (2025): Human inborn errors of immunity: 2024 update on the classification from the International Union of Immunological Societies Expert Committee. *J Hum Immunol* 1: e20250003.
- Ho H, Cunningham-Rundles C (2020): Non-infectious complications of common variable immunodeficiency: updated clinical spectrum, sequelae, and insights to pathogenesis. *Front Immunol* 11: 149.
- Lehman HK (2015): Autoimmunity and immune dysregulation in primary immune deficiency disorders. *Curr Allergy Asthma Rep* 15: 53.
- Hauck F, Voss R, Urban C, et al. (2018): Intrinsic and extrinsic causes of malignancies in patients with primary immunodeficiency disorders. *J Allergy Clin Immunol* 141: 59-68.e4.
- Agarwal S, Mayer L (2013): Diagnosis and treatment of gastrointestinal disorders in patients with primary immunodeficiency. *Clin Gastroenterol Hepatol* 11: 1050-1063.
- Baloh C, Reddy A, Henson M, et al. (2019): 30-year review of pediatric- and adult-onset CVID: Clinical correlates and prognostic indicators. *J Clin Immunol* 39: 678-687.
- Abolhassani H, Avcin T, Bahceciler N, et al. (2022): Care of patients with inborn errors of immunity in thirty J Project countries between 2004 and 2021. *Front Immunol* 13: 1032358.
- Abunin M, Albert M, Cohen SB, et al. (2019): ESID Registry – Working definitions for clinical diagnosis of PID. <https://esid.org/working-parties/registry-working-party/diagnosis-criteria/>
- Ziętkiewicz M, Wiśnik-Szewczyk E, Matyja-Bednarczyk A, et al. (2020): Shorter diagnostic delay in Polish adult patients with common variable immunodeficiency and symptom onset after 1999. *Front Immunol* 11: 982.
- Amaya-Urbe L, Rojas M, Azizi G, et al. (2019): Primary immunodeficiency and autoimmunity: A comprehensive review. *J Autoimmun* 99: 52-72.
- Gathmann B, Mahlaoui N, Gérard L, et al. (2014): Clinical picture and treatment of 2212 patients with common variable immunodeficiency. *J Allergy Clin Immunol* 134: 116-126.e11.
- Fischer A, Provot J, Jais JP, et al. (2017): Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. *J Allergy Clin Immunol* 140: 1388-1393.e8.
- Costagliola G, Peroni DG, Consolini R (2022): Beyond infections: new warning signs for inborn errors of immunity in children. *Front Pediatr* 10: 855445.
- Jolles S (2013): The variable in common variable immunodeficiency: a disease of complex phenotypes. *J Allergy Clin Immunol Pract* 1: 545-556.
- Milota T (2022): Lung manifestation of Common variable immunodeficiency – the results from the nationwide multicenter study. In 01.01 – Clinical problems – no related to asthma or COPD European Respiratory Society. 3513.
- Maglione PJ, Overbey JR, Radigan L, et al. (2014): Pulmonary radiologic findings in common variable immunodeficiency.

- ciency: clinical and immunological correlations. *Ann Allergy Asthma Immunol* 113: 452-459.
24. Israni M, Alderson E, Mahlaoui N, et al. (2025): Recommendations for transitioning young people with primary immunodeficiency disorders and autoinflammatory diseases to adult care. *J Clin Immunol* 45: 57.
25. Bonilla FA (2020): Vaccines in patients with primary immune deficiency. *Immunol Allergy Clin North Am* 40: 421-435.
26. Walter JE, Ayala IA, Milojevic D (2019): Autoimmunity as a continuum in primary immunodeficiency. *Curr Opin Pediatr* 31: 851-862.
27. Staels F, Collignon T, Betrains A, et al. (2021): Monogenic adult-onset inborn errors of immunity. *Front Immunol* 12: 753978.
28. Segura-Tudela A, Nieto-López C, Bermejo-Olivera FJ, et al. (2025): Malignancy and autoimmune susceptibility in adult patients with human inborn errors of immunity. *J Clin Immunol* 45: 136.
29. Csóka DL, Kovács KT, Kumánovics G (2024): A clinical picture of unselected patients with systemic lupus erythematosus in a tertiary Hungarian center – a spectrum ranging from pure lupus to overlap syndromes. *J Clin Med* 13: 3251.
30. Nagy G, Dobrota R, Becker MO, et al. (2023): Characteristics of ScleroID highlighting musculoskeletal and internal organ implications in patients afflicted with systemic sclerosis. *Arthritis Res Ther* 25: 84.