

Initial presenting manifestations in 16486 patients with primary immunodeficiencies include infections, immune dysregulation, syndromic features, and cancer.

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Abstract

Background: Primary immunodeficiencies (PID) are rare diseases, which makes diagnosis a challenge. Better awareness of the initial presenting manifestations should improve awareness and avoid diagnostic delay. Whilst increased infection susceptibility is a well-known initial PID manifestation, less is known about the frequency of other presenting manifestations.

Objective: To analyze age-related initial presenting manifestations of PID including different PID disease cohorts.

Methods: We analyzed data on 16486 patients of the European Society for Immunodeficiencies (ESID) registry. Patients with autoinflammatory diseases were excluded due to the limited number registered .

Results: Overall, 68% of patients initially presented with infections only, 9% with immune dysregulation only and 9% with a combination of both. Syndromic features were the presenting feature in 12%, 4% had laboratory abnormalities only, 1.5% were diagnosed due to family history only and 0.8% presented with malignancy. Two thirds of PID patients presented before the age of 6 years, but a quarter of patients only developed initial symptoms as adults. Immune dysregulation was most frequently recognized as an initial PID manifestation between 6 and 25 years of age with male predominance until age 10, shifting to female predominance after age 40. Infections were most prevalent as a first manifestation in patients presenting after age 30.

Conclusion: An exclusive focus on infection-centered warning signs would have missed around 25% of PID patients that initially present with other manifestations.

Clinical implications: We provide a data-based rationale to add immune dysregulation and syndromic features to the PID warning signs, which may significantly improve early PID diagnosis.

Capsule summary (30 words).

This analysis of 16574 ESID Registry patients provides a data-based rationale to add immune dysregulation and syndromic features to the warning signs for primary immunodeficiencies favoring earlier diagnosis and treatment.

Key words.

Primary Immunodeficiency; inborn error of immunity; presenting symptom; immune dysregulation; autoimmune; inflammatory; syndromic; warning signs; registry

Abbreviations.

ALPS	Autoimmune lymphoproliferative disease
APDS	Activated PI3K delta syndrome
AID	Autoinflammatory diseases
AT	Ataxia telangiectasia
CVID	Common variable immunodeficiency
CGD	Chronic granulomatous disease
DGS	Di-George-Syndrome
EBV	Epstein Barr Virus
ESID	European Society for Immunodeficiencies
FHL	Familial hemophagocytic lymphohistiocytosis syndromes
HIES	Hyper IgE syndrome
IEI	Inborn Errors of Immunity
IUIS	International Union of Immunological Societies
PID	Primary immunodeficiency
SCID	Severe combined immunodeficiency
WAS	Wiskott-Aldrich syndrome

XLA

X-linked agammaglobulinemia

XLP

X-linked lymphoproliferative syndrome

Introduction

Primary Immunodeficiencies (PID) are rare diseases. The estimated minimum prevalence of PID based on registry documentation ranges from 2.7 to 5.9 to 11:100.000 in Germany, UK and France, respectively¹⁻³. Currently there are more than 450 different PIDs known, most of them with a specific monogenetic cause⁴. The delay from initial manifestation to diagnosis of PID for index cases is often several years². This diagnostic delay can be critical for patients, as they may not receive appropriate therapy in a timely fashion^{5,6}. An important reason for diagnostic delay is the poor specificity of initial presenting symptoms, which are not recognized as indicators of an underlying PID. Indeed, it would not be rational to diagnose a PID in all patients presenting with pneumonia or autoimmune thrombocytopenia, but the combination of these two manifestations or their occurrence in a child with syndromic features should prompt further investigations.

Paediatricians and primary care physicians are in the best position to initiate diagnostic tests to confirm or exclude PID. Their awareness of these rare conditions is critical to reduce diagnostic delay⁷. In 1993, the Jeffrey Modell Foundation published ten warning signs of PID in order to increase awareness for PID⁸. The ten warning signs resulted from an expert consensus. They focus on the nature, number, intensity and localization of infections, their response to therapy, their impact on growth and the family history.

In the last 30 years the understanding of what comprises a PID has significantly expanded. One important step forward was the appreciation that PID patients frequently suffer from immune dysregulation, i.e., autoimmune and autoinflammatory manifestations^{9,10}. In a retrospective study of the national French PID registry¹¹, 26% of 2183 PID patients had experienced at least one manifestation of immune dysregulation during their lifetime. Autoimmune cytopenias and inflammatory bowel disease emerged as the most frequent manifestations¹². In some conditions, immune dysregulation can be the only manifestation in the absence of infection¹³. In order to acknowledge this widening spectrum of PID manifestations, the more comprehensive term inborn error of immunity (IEI) has been introduced to describe these conditions⁴. Based on these insights, several studies have suggested additions to the ten warning signs, but these suggestions were not based on large datasets focusing on initial manifestations^{7,14-16}.

While many large cohort studies have reported on the prevalence of various clinical manifestations in PID, the question of the initial presenting manifestation has received less attention^{3,11,12}. Improved knowledge about presenting features is however critical to early recognition of PID, particularly for non-specialists who play a key role in recognizing early warning signs of PID and IEI. To address this, the redesign of the European Society for Immunodeficiencies (ESID) registry in 2013¹⁷ introduced data fields to record the initial disease-related clinical features of PID patients. Here, we present an analysis of 16486 patient datasets with information on the initial clinical presentation. Our results provide a data-based rationale to add immune dysregulation and syndromic features to the PID warning signs, which we hope will improve the early diagnosis of PID.

Methods

Patients

As of March 2019, 21,485 patients of 68 nationalities were documented by 29 countries participating in the ESID Registry based on informed consent (No. 493/14 of the ethical committee Freiburg). From these were excluded: 161 patients without a PID diagnosis and 304 patients with “unclassified immunodeficiency”, as there was concern if these patients indeed represent patients with IEI, or rather secondary immunodeficiencies or other diseases. Another 3362 patients were excluded because data on presenting symptoms were unavailable. We excluded 127 patients with mannose binding lectin (MBL) deficiency, since its classification as a PID is debated^{4,18}. Moreover, 611 patients with hereditary or acquired angioedema were not considered as this large group of patients presents in a distinct way that might distort global analysis. The 87 patients with “unclassified complement deficiencies” also mostly presented with angioedema and were thus also excluded. Finally, we excluded 346 patients with autoinflammatory diseases, since these patients are mostly documented in other registries resulting in an incomplete picture of these disease entities. Overall, 16486 patients were included (Fig. 1). Diseases were grouped based on the 2019 IUIS classification³ with minor modifications as detailed in Table I.

Initial presenting manifestations

Registry participants were asked to record the presenting symptom(s) associated with their PID diagnosis as judged by the treating physician at the time, irrespective of the date of final clinical or genetic diagnosis. Six main categories for presenting symptoms were offered and for each patient it was possible to select more than one category: (1) infection, (2) immune dysregulation, defined as at least one of: lymphoproliferation (splenomegaly, hepatomegaly, lymphadenopathy), granuloma, autoimmunity (e.g. cytopenia, thyroid disease, joint disease, hepatitis, vitiligo, alopecia, diabetes), inflammatory bowel disease, celiac disease, vasculitis, eczema or autoinflammatory manifestation (e.g. fevers, rashes), (3) malignancy, (4) syndromic manifestation, defined as dysmorphic features such as short stature, facial abnormalities, microcephaly, skeletal abnormalities, other organ manifestations such as albinism, hair or tooth abnormalities, heart or kidney defects, hearing abnormalities, primary neurodevelopmental delay, seizures, (5) other symptoms and (6) no symptoms. This last category allowed documentation of patients, in whom a diagnosis was established before the onset of clinical manifestations, e.g., due to family history or based on laboratory abnormalities.

Data analysis

Initial presenting manifestations were analyzed by descriptive statistics for all PID, for PID disease subgroups as defined above and for individual PID conditions. As almost a quarter of patients presented with various combinations of initial manifestations, we grouped them according to the most frequently observed combinations as follows: i) infection without dysregulation (including infection only), ii) dysregulation without infection (including dysregulation only), iii) infection and dysregulation, manifestations other than infection or dysregulation only (including syndromic features and malignancy). The patients without clinical manifestations were grouped in a) diagnosis based on family history and b) laboratory abnormalities only.

Age at onset was analyzed according to the pattern of manifestation across all diseases. The ESID Registry allows documentation of the time of initial manifestation as a range of years (within the 1st year of life, years 1-5, followed by 5-year intervals) or as a precise date with month and year. Age at onset was documented for 14596 of the 16486 patients (89%).

Distribution of disease groups, age at onset, and initial manifestation were analyzed by country of residence of the patients. Each analysis considered only countries contributing at least 1% of total patients to avoid skewing. To assess the impact of immigration we compared the country of residence and the country of birth of patients.

Statistical analysis was performed with IBM SPSS Statistics version 24 and figures were created with GraphPad Prism version 5 and 8 and Adobe Illustrator version 11.

Results

Infection is the most frequent initial presenting manifestation of PID

Of 16486 PID patients documented in the ESID Registry and eligible for this study, 12741 (77%) initially presented with infection, 2955 (18%) with immune dysregulation, 1983 (12%) with syndromic features and 137 (0.8%) with malignancy (Fig. 2). 1292 (8%) presented with “other” symptoms (including e.g., aphthae, asthma, alopecia, fatigue, ataxia), 254 of them (1.5% of all patients) as the only initial manifestation. Abnormal laboratory tests (e.g. hypogammaglobulinaemia, thrombocytopenia) alone were documented in 539 patients (3.3%). A positive family history prior to onset of symptoms was documented in 256 patients (1.5%) (Fig. 2). This percentage may be underestimated as some patients with affected family members may have been assigned to “presenting symptoms unknown” instead of “no symptoms at presentation” leading to exclusion from this analysis.

Symptoms of immune dysregulation are important initial manifestations of PID and are relevant in PID subgroups primarily presenting with infections.

Overall, 3063 patients (19%) initially presented with more than one manifestation, most frequently a combination of immune dysregulation and infection (48%). We analyzed this combination of presenting symptoms in more detail in disease subgroups. Patients presenting with various combinations of manifestations excluding infections or immune dysregulation were categorized as “other manifestations only”. Overall, 68% of patients initially presented with infections without immune dysregulation, 9% presented with immune dysregulation without infections, 9% had infection and immune dysregulation, 9% other manifestations only, 1.6% were diagnosed with positive family history only and 3.3% had laboratory abnormalities only (Fig. 3a).

We then looked at the initial presenting manifestations in disease subgroups and specific disease entities (Fig. 3b, Table I). 61% of patients with diseases of immune dysregulation initially presented with immune dysregulation. Importantly, however, infection was not the initial or not the only initial presenting feature in 20-25% of patients in groups 1 “Immunodeficiencies affecting cellular and humoral immunity”, 3a “CVID”, 3b “Antibody deficiencies other than CVID”, 5 “Congenital defects of phagocyte number or function”, and 6 “Defects in intrinsic and innate immunity. In fact, 10%, 11%, 9%, 6% and 7% initially presented with immune dysregulation and infections and 8%, 6%, 5%, 7% and 3% with immune dysregulation in the absence of concomitant infections in these respective disease groups (Fig. 3b).

The significance of immune dysregulation as initial manifestation was also evident in a subgroup analysis of 921 CGD and 920 SCID (including Omenn and “leaky SCID”) patients (Table II). In both groups, 13% initially presented with immune dysregulation, around 5% in the absence of infection. Notably, in this era before newborn screening for severe T cell deficiency in Europe, 9% of SCID patients were diagnosed without clinical symptoms, 5% due to family history and 4% due to laboratory

abnormalities only. This asymptomatic initial presentation was also in the range of 5-10% in the other patients of groups 1, 3a, 3b, 5 and 6 (Fig. 3b).

Syndromic features are frequent initial signs of PID before or at presentation with other clinical manifestations

In group 2 “Combined immunodeficiencies with associated or syndromic features”, 44% patients initially presented with “non-infectious and non-immune dysregulation symptoms only” (syndromic features in 89%), followed by “infection without dysregulation” (37%) (Figure 3b). Ataxia telangiectasia (AT), DiGeorge syndrome (DGS), STAT3 associated Hyper IgE Syndrome (HIES) and Wiskott-Aldrich syndrome (WAS) were analyzed in more detail (Table II). Initial manifestation of a syndrome in the absence of infection or immune dysregulation was documented in 53% of AT, 65% of DGS, 3% of HIES and 13% of WAS patients respectively. Correspondingly “infection without dysregulation” was much less prominent and represented the single initial presenting manifestation in 32% of AT, 27% DGS, 67% HIES and 25% of WAS patients. While “immune dysregulation without infection” as initial presenting manifestation was below 5% in AT and DGS patients it was present in 21 % of HIES and 29% of WAS patients. Moreover, 10% of WAS patients initially presented with “laboratory abnormalities only”, i.e., thrombocytopenia.

Infection is an important initial presenting symptom in diseases of immune dysregulation

As expected, the most frequent initial manifestation in group 4 “Diseases of immune dysregulation” (n = 1018) was “immune dysregulation without infection” (47%). However, “infection without dysregulation” was also prominent (25%), followed by “immune dysregulation and infection” in another 14%. Initial presentation with “immune dysregulation without infection” reached 65% in the subgroup of 236 patients with autoimmune lymphoproliferative syndrome (ALPS). Unexpectedly, however, 17% of ALPS patients presented with infection, about half of them in combination with dysregulation. However, 50 of the 236 ALPS patients were registered without a genetic diagnosis and ALPS-like diseases with infection susceptibility may have skewed the initial presentation. Positive family history led to diagnosis in 9% of ALPS patients, which is more than for most other PID. Among 182 patients with familial hemophagocytic lymphohistiocytosis syndromes, 61% initially presented with dysregulation without infection. Interestingly, infection without dysregulation was documented more commonly than infection with dysregulation (19% vs. 11%) suggesting that not every infection, considered the presenting manifestation, was immediately associated with hemophagocytic lymphohistiocytosis.

In group 7 'Complement deficiencies', infection without immune dysregulation was the most common presentation (78%), whereas 12% presented based on a positive family history only. Immune dysregulation alone was rare as a presenting manifestation (1%), which may in part be explained by limited registration of patients with lupus-like diseases treated in rheumatology centers.

Malignancies can be the initial presenting symptom of various PIDs

In 137 PID patients, malignancy was documented as the initial manifestation. One third of presentations with malignancies (45/137) occurred in patients with CVID. Thymoma with immunodeficiency (Good's syndrome) was the second most frequent initial presentation with PID-associated cancer (18/118), followed by Nijmegen-breakage-syndrome 1 (n = 17; 13% of NBS1 patients). Remarkably 3 out of 4 patients with CD27 deficiency and 9/45 (20%) patients with X-linked lymphoproliferative disease type 1 (XLP1) had a malignancy at initial presentation. PID-associated malignancies occurred within the first year of life in 14 or 0.3% of all patients. Notably, in adults, 1 out of 50 PID patients had a malignancy as an initial manifestation (Table III).

Age at initial presenting manifestation

Altogether 89% of our cohort (14.677 patients) were analyzed for their age at symptom onset (Fig. 4a). According to the treating physician, one third of patients (33%) showed a first manifestation retrospectively related to the PID within the first year of life; another third (30%) between the ages of 1 to 5 (Table IV). More than 75% of patients had had symptoms before the age of 16, while 9% presented after the age of 40. When looking at the pattern of manifestations, initial presentation in the absence of infection or immune dysregulation was particularly frequent in the first 6 years of life, when 15% presented with other manifestations, mostly syndromic features (Fig. 4c). Between 6 and 25 years of age, almost a quarter of patients initially manifested with immune dysregulation in the presence or absence of infection (Table III). Beyond the age of 30, infection without immune dysregulation was the presenting manifestation in around 80% of PID patients (Fig. 4c).

Age-related sex differences in presenting manifestations

The ESID Registry contains more registrations of male than female patients (56% vs. 44%), explained by the X-linked inheritance of many PIDs such as X-linked agammaglobulinemia (XLA), X-linked SCID, X-CGD, XLP and WAS. Their usual presentation before age 6 leads to a particular male predominance within the first years of life (Fig. 4d). This shifts to a female predominance with increasing age, most evident after the age of 50 (Fig. 4d). Notably, we observed a significant change in the sex ratio of patients presenting with immune dysregulation with increasing age. Up to age 10, more than 60% of patients with immune dysregulation as only or concomitant presenting manifestation were boys. Male/female ratios were roughly similar between age 10 and 30 and only thereafter (Figure E1), females predominated, reaching up to 70% after age 40.

Differences between countries

We observed a different distribution of the contribution of the various disease groups and of the age at onset between countries (Figure E2, E3). This led to differences in the pattern of initial manifestation between participating countries (Figure E4). The impact of immigration could not be estimated since the country of birth and the country of living was different only in 4.6% of patients. Since the nationality of the parents was not documented, a migration effect is likely to be underestimated by this number.

Discussion

Here we report the age-related presenting manifestations of PID in general and in different PID disease groups across a cohort of 16,574 patients documented in the ESID registry. Our results emphasize the importance of both immune dysregulation and syndromic features (18% and 12% of all patients, respectively) in addition to infections as the initial manifestation of PID. A third of patients (33%) showed initial manifestation of their PID within the first year of life, another third (30%) between age 1 and 5. Different initial manifestations were prominent in specific age groups: (i) syndromic features (in the absence of infection or immune dysregulation) in the first 6 years of life (10%), (ii) immune dysregulation (with or without infection) between age 6 and 25 years (25%) with a male predominance, and (iii) infection without immune dysregulation in PID patients above age 30 (80%). These findings provide a data-based rationale to update widely used warning signs for primary immunodeficiencies.

An important goal of this study was to provide information across all types of PID in order to better advise primary care physicians how to identify PID patients, enhance referral to immunologists and reduce diagnostic delay. The ESID Registry with its contributions from 29 countries is a unique resource for such analysis. Nevertheless, registry data have obvious limitations. Not all patients are registered and rates of registration per country vary¹⁹. In particular, incomplete registration of certain patient groups can significantly skew the overall distribution of initial presenting manifestations. We therefore decided not to include the 346 patients documented in IUIS category VII (autoinflammatory diseases, AID). While for most other IEI, the ESID Registry is the main European documentation platform, it captures only a small fraction of patients with autoinflammatory diseases as many more (> 4000) of these patients are documented in the EUROFEVER registry²⁰. A similar limitation probably applies to patients presenting with malignancy or isolated immune dysregulation as they may only be seen and diagnosed by specialists not affiliated to the ESID registry.

It is also important to note that there are potentially subjective and retrospective elements to classifying a clinical problem as the initial presenting symptom of a PID. This includes for example the judgement as to which infection marked the beginning of an abnormal infection susceptibility or interpreting e.g. whether chronic diarrhoea was caused by prolonged infection or an inflammatory aetiology. Moreover, infection or immune dysregulation may be more obvious as presenting features than syndromic features which may be mild or evolve over time, as may developmental delay. A more precise analysis of the different aspects of immune dysregulation would have been interesting, but unfortunately this data was not available. In particular, initial presentations with allergy were included as immune dysregulation. Finally, the results of this study represent a snapshot of the diagnostic approaches and possibilities of the last 25 years. The widespread implementation of newborn screening for severe T cell lymphopenia will increase the number of patients diagnosed before onset of symptoms, to the benefit of these patients²¹.

With these limitations in mind, several important observations emerged from this study. While previous studies have emphasized the importance of autoimmune and inflammatory manifestations in the course of PID, this is the first study focusing on the initial presenting manifestations in a large patient cohort. More than 20% of patients across all immunodeficiencies did not initially manifest with an infection. Eighteen percent of patients were documented with initial autoimmune or inflammatory manifestation and this may be an underestimate because of limited awareness of the association of such manifestations with PID. Moreover, AID, which frequently manifests with fever and other features of immune dysregulation, were excluded from this analysis, but represent an important group of all IEI. Immune dysregulation was most prominently recognized as the initial manifestation in the age group from 6-25 years. Notably, among patients presenting with immune dysregulation, boys dominated until age 10 and only after age 40, the female predominance expected from non-PID cohorts was observed. The fact that

immune dysregulation as the initial manifestation was less prominent in patients presenting at a later age may indicate that IEI are still underdiagnosed particularly in adults presenting with autoimmunity or inflammation. Interestingly, the percentage of PID patients recorded as not demonstrating immune dysregulation decreased from 89% in 1991 to 71% in 2019 (Fig. E5). This may reflect an increasing awareness of immune dysregulation as well as the recent description of several more frequent autosomal-dominant disorders of immune dysregulation such as activated PI3K delta syndrome (APDS), STAT3 gain-of-function disease, NFkB1 or CTLA4 deficiency.

Notably, 12% of patients had syndromic features as part of their initial presentation. This was particularly relevant within the first 6 years of life, when around 10% of children initially presented with syndromic features in the absence of infection or immune dysregulation. This observation reflects that many genes relevant for a functional immune system are also involved in pathways relevant for development of other organs. While our data cannot answer the question how frequently relevant immune manifestations occur in children with syndromic diseases in general, they support the view to consider the immune system as another organ in the context of “organ screening” in syndromic patients, in particular if presenting with infections, autoimmunity, or inflammatory disease²².

Less than 1% of patients presented with malignancy and only 45 patients (0.3%) presented with malignancy in the absence of other clinical manifestations. These figures have to be taken with caution, since the initial presentation of these patients to oncologists may favor underreporting. On the other hand, some malignancies, in particular lymphomas, can be associated with hypogammaglobulinaemia, leading to documentation as CVID of some patients with secondary immunodeficiency in the context of lymphoma.

From a global perspective our mostly European findings deserve some additional comments. A world-wide review of primary immunodeficiency registries, pointed out the significant heterogeneity in the distribution of IEI in different regions of the world²³. Thus, the contribution of CID ranged from 5-27%, phagocytic disorders from 3-18% and complement disorders from 0.5 -13% of all documented IEI. Founder mutations and the frequency of consanguinity in a society will influence the distribution of IEI with a relevant impact on the overall distribution of presenting symptoms²⁴. Paucity of diagnostic facilities, limited financial resources and limited expertise will further skew the documented prevalence of different IEI due to a lack of awareness and underdiagnoses²⁵. In addition to these overall effects, the presenting manifestations of individual IEI are also influenced by the epidemiological, climate-related and living conditions in different regions of the world²⁶. This includes effects of the prevalence of infectious diseases and of vaccination schedules²⁷. Based on these considerations, adaptation of warning signs to different areas of the world may be required²⁶.

What are the implications of this study? Making a precise diagnosis is the prerequisite for disease-specific therapies, which are increasingly available for PID²⁸. Diagnostic delay is associated with poorer health outcomes^{29,30}. Successful efforts have been made to raise awareness for PID among the public and the medical community by publication of the 10 warning signs by the Jeffrey Modell Foundation. However, in recent years several smaller studies have demonstrated insufficient sensitivity and specificity of these warning signs especially in the infant and pediatric population and discussed the need for adjustment^{7,14-16,31,32}.

Our study provides a rationale based on an exceptionally large dataset to add immune dysregulation and syndromic features as an additional element to these warning signs. To stimulate discussion for such a revision, we refer to the German national guideline on the diagnosis of PID, which was the result of an interdisciplinary expert consensus process in 2010³³. This guideline proposes two acronyms as pillars summarizing the PID warning signs³⁴. ELVIS focuses on pathological susceptibility of infection and is

short for **exciting pathogen, localization, variation from the usual course of infection, intensity, and total sum of infections** ³⁵. GARFIELD focuses on immune dysregulation and is short for **granuloma, autoimmunity, recurrent fever, eczema, lymphoproliferation, diarrhea** ¹². In addition, this guideline mentions syndromic features, family history, growth failure, and laboratory abnormalities - specifically hypogammaglobulinaemia, neutropenia, and lymphopenia. The 10 warning signs promoted by the Jeffrey Modell Foundation have greatly contributed to raise awareness of PID. The ever-increasing number of novel IEI and phenotypes of known IEIs over the last 25 years has changed our view on these diseases and how to diagnose them. This analysis of initial presenting manifestations in the ESID Registry contributes important data allowing improvement of the warning signs with the goal of a further reduction in the diagnostic delay for our patients.

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Author contributions

JT, GK and SE designed the study and verified, analyzed, and interpreted the data. GK, AN and SR technically implemented the registry in its present form. MS, AF, BG, DE, MB, NM and SE implemented and coordinated the ESID registry and/or its key contributing national registries. All other authors contributed to data collection. J.T. and S.E. drafted the manuscript, which was critically revised by all other authors. All authors approved the final version of the manuscript.

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Data sharing

Deidentified patient data collected for this study are available to others with publication of this manuscript according to the ESID registry data access and publication rules (<https://esid.org/Education/Call-for-studies/Data-access-and-Publication-rules-Research-Proposal-Form>).

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Figure legends

Figure 1: Criteria for selection of patients for study inclusion

Figure 2: Initial presenting manifestations

For documentation of initial presenting manifestations, multiple categories could be selected for an individual patient (e.g., infection and immune dysregulation). Most patients (77%) presented with 1 category of presenting symptoms, 2757 (17%) had 2 categories, and 282 (1.7%) had 3 categories.

Figure 3: Pattern of initial presenting manifestations

(A) Patterns of initial presenting manifestations in the complete cohort. “Other” summarizes initial presentation with syndromic features, malignancy, or other symptoms. (B) Patterns of initial presenting manifestations by PID disease groups.

Figure 4: Age and sex dependence of initial presenting manifestations

(A) Age at initial presenting manifestation in 14596 patients with known age at onset of symptoms (B) The percentage of symptomatic patients is depicted by age at onset of symptoms for the different disease groups. (C) Percentage of patients presenting with the indicated patterns of initial manifestation by age groups. “Other” summarizes initial presentation with syndromic features, malignancy, or other symptoms. (D) Sex distribution by age groups of manifestation as percentage of total patients.

Table I: Analyzed disease groups

This paper	IUIS	Disease Group*	n	Most relevant diseases (n)
Group 1 incl. APDS	1	Immunodeficiencies affecting cellular and humoral immunity	1832	SCID (807), CID w/o genetic diagnosis (454), CD40 and CD40 Ligand def (159), APDS (131), Omenn syndrome (59), HLA class II def (52), selective CD4 def (50), DOCK8 def (47), atypical SCID (46)
Group 2 incl. Bone marrow failure	2	CID with associated or syndromic features	2463	AT (677), DGS (613), HIES (354), WAS (291), XLT (42), NBS (143), unclassified syndromic PID (75), CHH (48), NEMO and NFKBIA def (36), DC (25), ICF (22), Netherton syndrome (16), Bloom syndrome (14)
Group 3a	3	Predominantly antibody deficiencies	4228	Common variable immunodeficiency (CVID; 4228): no genetic diagnosis (4069); genetic diagnosis: TACI (98), NFKB1 (25), NFKB2 (21)
Group 3b without APDS, incl. thymoma with immunodef.	3	Predominantly antibody deficiencies	4853	unclassified antibody def (1325), sel. IgA def (946), agammaglobulinemia (943), isolated IgG subclass def (745), THI (222), SPAD (220), IgA with IgG subclass def (121), thymoma with immunodef (120), CSR and Hyper IgM syndromes (AID and no genetic cause) (99), sel. IgM def (86),
Group 4	4	Diseases of immune dysregulation	1018	ALPS (236), FHL (182), XLP (132), unclassified disorders of immune dysregulation (99), APECED (74), CHS (59), IPEX (39), CTLA4-def (38), GS2 (31), STAT3 GOF (29), LRBA-def (42)
Group 5	5	Congenital defects of phagocyte number or function	1459	CGD (921), congenital neutropenia (169), unclassified phagocytic disorders (121), SDS (83), cyclic neutropenia (75), GATA2 (43), LAD (25)
Group 6	6	Defects in intrinsic and innate immunity	452	CMC (134), MSMD (111), unclassified defects in innate immunity (63), isolated congenital asplenia (35), IRAK4 and Myd88 def (29), WHIM (24), Herpetic encephalitis (15), asplenia syndrome (15)
excluded	7	Autoinflammatory disorders	-	-
Group 7	8	Complement deficiencies	181	Complement component 2 def. (80)
Group 2	9	Bone marrow failure	-	Classified in group 2 like in IUIS 2017
excluded	10	Phenocopies of IEI	-	-

* IUIS 2019 classification of IEI.

ALPS = Autoimmune lymphoproliferative disease, APDS = Activated PI3K delta syndrome, APECED = Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, AT = Ataxia teleangiectasia, CID = Combined immunodeficiency, CHH = cartilage hair hypoplasia, CHS = Chediak Higashi Syndrome, CMC = Chronic mucocutaneous candidiasis, CVID = Common variable immunodeficiency, CGD = Chronic granulomatous disease, CSR = class switch recombination defects, DC = Dyskeratosis congenita, DGS = Di-George-Syndrome, Def = deficiency, FHL = Familial hemophagocytic lymphohistiocytosis syndromes, GS2 = Griscelli syndrome type 2, HIES = Hyper IgE syndrome, ICF = immunodeficiency centromeric instability facial anomalies syndrome, IPEX = Immunodysregulation polyendocrinopathy enteropathy X-linked, LAD = leucocyte adhesion deficiency, IUIS = International Union of Immunological Societies, MonoMAC = Monocytopenia and mycobacterial infection, MSMD = Defects with susceptibility to mycobacterial infection, NBS = Nijmegen breakage syndrome, PID = Primary immunodeficiency, SCID = Severe combined immunodeficiency, SDS = Shwachman-Diamond-syndrome, sel = selective, SPAD = Specific antibody deficiency, THI = transient hypogammaglobulinemia of infancy, WAS = Wiskott-Aldrich syndrome, WASP = Wiskott-Aldrich syndrome protein, WHIM = Warts hypogammaglobulinemia infections and myelokathexis, XLP = X-linked lymphoproliferative syndrome, XLT = X-linked thrombocytopenia

Table II: Initial presenting symptoms in specific immunodeficiencies

PID	Total patients	Infections	Immune dysregulation	Syndromic	Malignancy	Laboratory abnormalities only	Family history only	Other
SCID	920	82	13	7	0.1	4	5	9
APDS	131	88	31	4	2	-	2	4
WAS	291	41	44	24	0.3	10	2	19
AT	677	34	3	74	4	1	0.3	20
DGS	613	31	8	83	-	1	2	8
HIES	354	75	28	15	0.2	0.3	1	28
CVID	4244	89	18	2	1	3	0.1	4
ALPS	236	17	74	7	0.4	5	9	10
FHL	182	30	73	2	-	0.5	6	3
CGD	921	87	13	2	0.2	1	3	4

Percentage of patients presenting with the indicated symptoms in the given subgroups of PIDs. Multiple presenting symptoms could be documented for a single patient. For example, a patient presenting with infections and malignancy will be counted in each of these two categories. This accounts for the fact, that the total sum of percentages can exceed 100 in one column. SCID includes SCID, atypical/leaky SCID and Omenn syndrome. HIES contains STAT3-associated HIES only. See table 1 for disease abbreviations.

Table III: Initial presenting symptoms by age groups

	<1	1-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40	41-45	46-50	>50	Total
Infections	74	81	82	79	86	84	87	92	89	92	88	93	11746
Immune dysregulation	18	18	24	28	25	24	21	15	21	22	16	12	2791
Malignancy	0.3	0.5	1	1.1	1.7	1.3	1.9	1.2	1.9	2.4	4.3	2.2	127
Syndromic	21	15	8	7	2	3	3	1	1	0.3	0	1	1899

Percentage of patients presenting with the indicated symptoms by age groups for 14596 patients in the ESID Registry. Multiple categories could be documented (see also comment to Table II)

Table IV: Age at initial presentation for selected immunodeficiencies

	Total patients	< 1 year	Age 1-5	Age range (y) at which >70% had symptoms	Age range (y) at which >90% had symptoms
All PID	14677	33	30	6-10	36-40
SCID	833	87	12	<1	1-5
APDS	122	36	53	1-5	6-10
WAS	254	82	15	<1	1-5
AT	631	12	78	1-5	1-5
DGS	579	81	15	<1	1-5
HIES	333	50	32	1-5	11-15
CVID	3663	6	18	31-35	> 50
ALPS	195	25	43	6-10	11-15
FHL	169	68	17	1-5	6-10
CGD	844	45	39	1-5	6-10

Table of age at onset of presenting manifestations for specific PIDs. Presentations within the first year of life and at age 1-5 are shown in percent. The age range at which 70% and 90% of patients had their initial presenting manifestations is shown in the right columns. SCID includes SCID, atypical/leaky SCID, and Omenn syndrome. HIES contains STAT3-associated HIES only. See table 1 for disease abbreviations.

