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The European internet-based patient and research database for primary immunodeficiencies: update 2011

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Summary

In order to build a common data pool and estimate the disease burden of primary immunodeficiencies (PID) in Europe, the European Society for Immunodeficiencies (ESID) has developed an internet-based database for clinical and research data on patients with PID. This database is a platform for epidemiological analyses as well as the development of new diagnostic and therapeutic strategies and the identification of novel disease-associated genes. Since its start in 2004, 13 708 patients from 41 countries have been documented in the ESID database. Common variable immunodeficiency (CVID) represents the most common entity with 2880 patients or 21% of all entries, followed by selective immunoglobulin A (sIgA) deficiency (1424 patients, 10·4%). The total documented prevalence of PID is highest in France, with five patients per 100 000 inhabitants. The highest documented prevalence for a single disease is 1·3 per 100 000 inhabitants for sIgA deficiency in Hungary. The highest reported incidence of PID per 100 000 live births was 16·2 for the period 1999–2002 in France. The highest reported incidence rate for a single disease was 6·7 for sIgA deficiency in Spain for the period 1999–2002. The genetic cause was known in 36·2% of all registered patients. Consanguinity was reported in 8·8%, and 18·5% of patients were reported to be familial cases; 27·9% of patients were diagnosed after the age of 16. We did not observe a significant decrease in the diagnostic delay for most diseases between 1987 and 2010. The most frequently reported long-term medication is immunoglobulin replacement.

Keywords: epidemiology, ESID, online database, primary immunodeficiency, registry

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Introduction

Primary immunodeficiencies (PID) represent rare inborn errors of the immune system predisposing to recurrent infections, autoimmunity, allergy, cancer and other manifestations of immune dysregulation. So far, more than 130 phenotypically diverse primary immunodeficiency diseases have been identified and more than 190 disease-related genes have been discovered [1].

It is difficult to establish reliable numbers on the disease burden of PID, as there are very different approaches to accessing the incidence and prevalence of PID, including telephone surveys [2] and geographically limited cohort studies [3]. However, patient registries represent the most common approach, and literature provides a large range of results from these registries that have been organized mainly at the national level [4–6].

Patient registries can work as a powerful tool that fulfils a range of purposes, such as describing the natural history of a disease, determining clinical and/or cost-effectiveness of treatment, assessing safety or harm and measuring or improving quality of care [7,8].

Since 2004, the European Society for Immunodeficiencies (ESID; http://www.esid.org) is running a pan-European registry for primary immunodeficiencies (the ESID database). The aim of this database is long-term compilation of PID patient data to answer challenging epidemiological questions as outlined above. In addition, the ESID database serves as a basis for outcome-related research questions and to generate research hypotheses that can be tested further in dedicated (clinical) studies. Using the database, researchers have the possibility of identifying patient cohorts for genetic screening and multi-centre trials. Data sets can be extended flexibly for studies on subgroups of patients using the database as a platform for their reporting forms [9,10]. Current studies include a study on hypogammaglobulinaemia in children (PedPAD; by Esther de Vries, 's-Hertogenbosch), a survey on dedicator of cytokinesis 8 (DOCK8)-deficient patients (Michael Albert, Munich) and a survey on chest computed tomography (CT) findings in antibody-deficient patients (Ulrich Baumann, Hanover; http://www.chest-ct-group.eu).

Some of the diseases present in the ESID database are also the subject of other rare disease registries. These include registries for autoinflammatory syndromes [11,12]), severe neutropenia [13] and a registry for stem cell transplants in PID [14]. The ESID database co-operates with these registries to ensure a high level of completeness and data quality.

ESID provide updates regularly on the development of the database project; this is the third update in this series. First analyses on the data collected from 2006 and 2008 have been published previously in this journal [15,16].

Materials and methods

The ESID online database is a secure, internet-based patient registry which combines both clinical and laboratory data of PID patients. Patients are grouped into nine main categories. These are predominantly T cell deficiencies, antibody disorders, phagocytic disorders, complement deficiencies, other well-defined PIDs, autoimmune and immunedysregulation syndromes, autoinflammatory syndromes, defects in innate immunity and unclassified immunodeficiencies. These are divided further into subcategories that include a total of 138 phenotypically different PID entities. The classification is updated regularly, according to the classification of the International Union of Immunological Societies (IUIS) [1] and progress in research.

The technical structure of the ESID online database has been described in detail previously [17]. The database is used as a data collection platform by several national registries, including France, the Netherlands, Germany, Switzerland, Austria and the Czech Republic. In addition, data are imported on a regular basis from other national and local databases that operate separately. These include the national registries of Spain (REDIP; http://web.hsd.es/redip) and Italy (ipinet; http://www.aieop.org), and local hospital databases at University College London, Newcastle General Hospital and University Medical Center Freiburg. Most of the participating centres are located in Europe, but there are also centres in Egypt. The complete list of documenting centres is available at http://www.esid.org/documenting-centers.

Data are generally collected via electronic case report forms. The database has an inbuilt automatic quality assurance system, including field type, range and plausibility checks. In addition, data sets are checked regularly for plausibility, completeness and double entries.

Study population

As of 13 July 2011, a total of 13 708 patients had been registered in the ESID database. These had been entered by 102

documenting centres and national registries from 30 countries between 2004 and 2011. Some centres also diagnose or treat patients from abroad, so patients were from a total of 41 countries (including North Africa and the Middle East).

The number of documented patients in relation to the total population varied considerably between countries. In addition, the documentation in some countries is biased towards certain diseases because of centres specialized in a particular disease. This is, for example, the case in Hungary: of 367 reported cases, 130 (35·4%) were patients with hereditary angioedema, while the proportion of this disease in the total study population is a mere 3·5%.

In our analyses, we focused on eight countries (core countries) with a high documentation rate, a large number of reporting centres and a disease distribution that does not diverge strongly from the total distribution. These were France (3240), Spain (1662), Turkey (1486), United Kingdom (1148), Germany (1126), Italy (1083), Poland (508) and the Netherlands (433) (number of reported living patients given in brackets).

Furthermore, we restricted some of our analyses to the most frequent diseases (core diseases). These were, ordered according to their frequency, severe combined immunodeficiency (CVID), selective immunoglobulin A (sIgA) deficiency, immunoglobulin (Ig)G subclass deficiency, agammaglobulinaemias, DiGeorge syndrome (DGS), ataxia telangiectasia (AT), chronic granulomatous disease (CGD), Wiskott-Aldrich syndrome (WAS) and severe combined immunodeficiency (SCID).

Data items

We considered a subset of items taken from the core data set that is common to all diseases in the ESID database: disease, year of birth, year of death, sex, status, current place of living, consanguinity, familial case, date of clinical diagnosis, date of genetic diagnosis, date of onset and genetic cause. The onset of disease was defined as the date of first severe infection or characteristic manifestation of the respective PID. The date of clinical diagnosis was defined as the date when the patient was diagnosed based on clinical features and laboratory values. The date of genetic diagnosis was defined as the date when the genetic diagnosis was confirmed. We also describe some basic items on therapy, which are current status of therapy, drug group, route of administration and transplant information.

Prevalence and incidence

For each of the core countries, we calculated the minimum prevalence of PID in the current total population for all PID taken together and for single PID separately. Furthermore, we calculated incidence rates for these countries. As we are dealing with inborn diseases, we defined incidence not based on the time when the disease presented itself, but on the date of birth. Using this definition, the incidence rate tells us how many people born in a given year presented with a PID later on in their life. We report the incidence rate per 100 000 live births for 4-year time-spans from 1963 to 2010 to increase readability. Population and live birth numbers were taken from Eurostat (http://epp.eurostat.ec.europa.eu).

Age and sex

We analysed the age structure within the main disease categories by forming four age groups that are based on the quartiles of the total age distribution. We furthermore calculated the age distribution (frequencies) among male and female living patients.

Diagnostic delay

We analysed the time between the onset of the disease and the correct diagnosis, also known as the 'diagnostic delay'. We examined the development of the diagnostic delay between 1987 and 2010 for the core diseases for the total population and separately for the core countries. Date of diagnosis was taken to be either 'date of clinical diagnosis' or 'date of genetic diagnosis', depending upon which came first. Missing values in 'year of diagnosis' (7%) and 'year of onset' (15%) were seen to be missing completely at random, and in order to not lose any power the respective values were reconstructed by using the median of diagnostic delay from the complete case data set. As month and day values for onset and diagnosis were distributed uniformly among the complete cases, respective missing values were substituted by randomly drawn values from corresponding uniform distributions. Patients were furthermore grouped according to the year of diagnosis and then aggregated into 4-year groups to improve the readability of the results. A potential change in diagnostic delay is quantified by *P*-values resulting from the Jonckheere–Terpstra test, a non-parametric test for trends in population medians, which ranks each observation in a current group according to the number of larger observations in the subsequent group, and so accounts for the complete distribution of data [18]. We tested to an alpha level of 5% for the alternative hypothesis: median 1 > median 2 > . . . > median 6. A *P*-value of smaller than 0·05 indicates that there is a significant improvement in diagnostic delay as time progresses.

Results

Of the 13 708 patients, 12 340 (90%) were reported to be alive at the time of documentation, while 1084 (7·9%) had died and 284 (2·1%) were lost to follow-up. A total of 6017 patients (43·9%) had only been registered at one time-point, 3001 patients (21·9%) had one follow-up and 4690 patients

(34·2%) had two or more follow-up documentations; 5609 patients (40·9%) had been first reported or updated within the last 2 years.

Predominantly antibody disorders represent the largest main disease category with 7567 patients or 55·2% of all patients. This category also contains the most frequently reported single diseases: CVID (21%), sIgA deficiency (10·4%), IgG subclass deficiency (6·5%) and agammaglobulinaemias (5·9%). The complete distribution of patients is shown in Table 1.

Although PID are, by definition, genetic diseases, the genetic cause is still unknown in many patients. In our database, a genetic defect was known in 36·2% of all patients. Information on the affected gene was lacking particularly in antibody disorders, where it was indicated for only 918 of 7567 patients (12·1%) (Table 1).

In total, 1210 patients (8·8%) were reported to have a consanguineous background. Consanguinity was particularly high in T cell deficiencies (306 patients, 28·7%) and autoimmune and immunedysregulation syndromes (110 patients, 21·4%) (Table 1).

A total of 2532 patients (18·5%) were reported to be familiar cases (i.e. other members in family also presented with a PID). The rate of familiar cases was particularly high among complement deficiencies (393 patients, 61·8%), defects in innate immunity (42 patients, 39·3%) and autoimmune and immunedysregulation syndromes (170 patients, 33·1%) (Table 1).

Age and sex

The median of the total distribution was 17 years. Almost 25% of all patients were younger than 10 years (see Table 2). The age distribution varied considerably by disease category. Antibody and complement deficiencies had a particularly high share of older patients, with 35·1% and 50·2% in the group between 34 and 98 years, respectively. Conversely, the proportion of patients in the group between 0 and 9 years was particularly high in T cell deficiencies (47·9%) and autoinflammatory syndromes (56·3%).

A total of 8032 (58·6%) of patients were male and 5676 (41·4%) female. If all patients with diseases showing X-chromosomal inheritance are excluded (1714), there are still more male (6355; 53%) than female (5639; 47%) patients.

Considering the age distribution (frequencies) among male and female living patients in particular (Fig. 1a), the surplus of males is most prominent among patients up to age 30 years. This means that males can be found much more often in patients below 30 years. Interestingly, this is also true if we exclude all 1457 patients with X-chromosomal inheritance (Fig. 1b). In contrast, from 30 years onwards, females were reported more frequently, resulting in an almost doubled probability for observing PID in women compared to men aged 50–80 years.

Prevalence

The documented prevalence for single diseases varies considerably between countries (Table 3). The minimal reported prevalence is highest in France, with 5:100 000 inhabitants. In France, CVID reaches a prevalence of close to 1:100 000 inhabitants, but there were relatively few patients with sIgA deficiency compared to Spain, where the prevalence is above 1:100 000.

Incidence

The calculated incidence rates show variations between countries and over time (between the 4-year groups) (see Fig. 2). France and Spain have the highest overall documented incidence rates, with France showing a somewhat balanced course over the years which peaks at 16·2 in 1999–2002 (Fig. 2a). For many diseases, France reported the highest incidence rates, e.g. for SCID: 1·6 (1999–2001, Fig. 2b), AT: 1·2 (1995–1998) and CGD: 0·8 (1991–1994). Italy shows the highest incidence for DGS (2·8, 1999–2002), WAS (1, 1995–1998) and agammaglobulinaemias (1·1, 1995–1998). SIgA deficiency has an exceptionally high incidence of 6·7 in Spain (1999–2002).

The rates for CVID (Fig. 2c) vary strongly over time for each country, with a maximum of 2·3 in the Netherlands. Interestingly, the incidence of IgG subclass deficiency (Fig. 2d) is mainly below 0·5, but we see a marked increase particularly in France from 1987 onwards, peaking at 3 in 1999–2002. The drop of the curve in Fig. 2c and d for the time-periods after 2003 can be ascribed to the fact that these diseases both have a high share of late-onset patients.

Diagnostic delay

A total of 27·9% of all registered patients were diagnosed at 16 years of age or later. This proportion was particularly high in antibody deficiencies, where 40·2% of patients were diagnosed after the age of 16, and complement deficiencies (55·5%). In CVID, which forms the largest single PID entity, the proportion was above 70%.

Statistically significant overall trends towards a shorter diagnostic delay could be identified for some of the diseases. These are partly restricted to single countries. We observed such positive trends for IgG subclass deficiency and agammaglobulinaemias both in the total cohort and in Spain. Figure 3a and b depicts this result for agammaglobulinaemic patients: they were more often prone to a very long delay (>5 years and >10 years, respectively), in particular for the period before 1990 compared to the following periods. We furthermore observed positive trends for AT in Turkey and WAS in the United Kingdom.

In contrast, no significant trend could be identified for CVID (Fig. 3c), where the subsequent median values for the

Table 1. Distribution of patients on main categories, subcategories and diseases, number of living patients and share of patients with known genetic cause, consanguineous background and familial background of primary immunodeficiencies (PID). Missing values (not answered): genetic cause: 55 patients (0·4%); consanguinity: 2878 patients (20·9%); familial case: 2636 patients (19·2%).

	Total patients	% of total	Living patients	Affected gene known	Consanguinity	Familial case
Total	13 708	100·00%	12340	36·2%	8·8%	18·5%
Predominantly T cell deficiencies	1 066	7·78%	759	53·7%	28·7%	23·3%
CD4 deficiency	60	0·44%	53	100·0%	11·7%	6·7%
CD8 deficiency	7	0·05%	7	85·7%	28·6%	14·3%
Combined immunodeficiency (CID)	68	0·50%	51	72·1%	19·1%	23·5%
Atypical severe combined immunodeficiency (atypical SCID)	17	0·12%	12	5·9%	11·8%	5·9%
Calcium channel dysfunction	3	0·02%	3	100·0%	0·0%	33·3%
CD3 gamma deficiency	8	0·06%	8	62·5%	50·0%	37·5%
Cernunnos/XLF deficiency	3	0·02%	3	100·0%	66·7%	66·7%
DNA-ligase 4 ATP-dependent deficiency (LIG4)	6	0·04%	4	100·0%	16·7%	33·3%
DOCK8 deficiency	5	0·04%	5	100·0%	20·0%	40·0%
Interleukin 2 receptor alpha deficiency (CD25) (T cell deficiency)	13	0·09%	7	100·0%	15·4%	30·8%
ITK deficiency	2	0·01%	1	100·0%	0·0%	0·0%
Nucleoside phosphorylase deficiency (NP)	11	0·08%	8	100·0%	9·1%	9·1%
HLA class I deficiency	1	0·01%	1	100·0%	0·0%	0·0%
HLA class II deficiency	78	0·57%	41	85·9%	53·8%	34·6%
Winged-helix nude deficiency (FoxN1)	3	0·02%	2	100·0%	0·0%	66·7%
Omenn syndrome	32	0·23%	19	28·1%	31·3%	25·0%
Other unclassified T cell disorders	189	1·38%	156	0·5%	18·0%	16·9%
$T-B^+$ severe combined immunodeficiency (SCID)	308	2·25%	215	53·2%	22·7%	25·6%
$T-B^-$ severe combined immunodeficiency (SCID)	317	2·31%	211	65·9%	39·7%	24·6%
ZAP deficiency	3	0·02%	3	100·0%	66·7%	33·3%
Predominantly antibody disorders	7 567	55·20%	7224	12·1%	3·7%	12·2%
Agammaglobulinaemias	813	5·93%	747	85·0%	7·5%	28·0%
Class switch recombination defects (CSR)/HIGM syndromes	297	2·17%	265	57·6%	7·7%	21·5%
Activation-induced cytidine deaminase deficiency (AID)	30	0·22%	29	100·0%	23·3%	33·3%
CD40 deficiency (TNFRSF5)	15	0·11%	7	100·0%	20·0%	46·7%
CD40 ligand deficiency (CD154)	125	0·91%	109	98·4%	4·0%	26·4%
CSR defects and HIGM syndromes with unknown genetic cause	124	0·90%	118	0·0%	5·6%	11·3%
Uracil-DNA glycosylase deficiency (UNG)	3	0·02%	2	100·0%	33·3%	0·0%
Hypogammaglobulinaemias	6 457	47·10%	6212	0·9%	3·0%	9·7%
Common variable immunodeficiency (CVID)	2 880	21·01%	2715	1·5%	3·1%	9·0%
Deficiency of specific IgG	91	0·66%	91	0·0%	2·2%	9·9%
Dystrophia myotonica type2 (PROMM/ZNF9)	4	0·03%	2	100·0%	0·0%	0·0%

Table 1. *Continued*

	Total patients	% of total	Living patients	Affected gene known	Consanguinity	Familial case
IgA with IgG subclass deficiency	11	0·08%	11	0·0%	0·0%	27·3%
Immunoglobulin chain deficiencies	4	0·03%	4	100·0%	0·0%	25·0%
Isolated IgG subclass deficiency	887	6·47%	874	0·0%	2·5%	13·8%
Other hypogammaglobulinaemias	522	3·81%	472	0·2%	3·6%	9·6%
Other immunoglobulin gene deletions	1	0·01%	1	0·0%	0·0%	0·0%
Selective IgA deficiency	1 424	10·39%	1415	0·2%	1·7%	10·7%
Selective IgM deficiency	71	0·52%	68	0·0%	7·0%	18·3%
Thymoma with immunodeficiency	47	0·34%	45	0·0%	8·5%	0·0%
Transcobalamin II deficiency	1	0·01%	1	100·0%	0·0%	0·0%
Transient hypogammaglobulinaemia of infancy	514	3·75%	513	0·0%	5·8%	3·7%
Phagocytic disorders	1 163	8·48%	1026	51·1%	11·0%	22·0%
Chronic granulomatous disease (CGD)	565	4·12%	494	75·4%	10·3%	25·1%
Clericuzio-type poikiloderma with neutropenia syndrome	2	0·01%	1	0·0%	100·0%	100·0%
Cyclic neutropenia	105	0·77%	102	9·5%	0·0%	21·0%
Defects with susceptibility to mycobacterial infection	47	0·34%	40	85·1%	48·9%	27·7%
Leucocyte adhesion deficiency (LAD)	41	0·30%	32	100·0%	34·1%	9·8%
Myeloperoxidase deficiency (MPO)	1	0·01%	1	100·0%	0·0%	0·0%
Neutrophil glucose-6-phosphate dehydrogenase	15	0·11%	15	100·0%	20·0%	13·3%
Other phagocytic disorders	20	0·15%	17	0·0%	5·0%	15·0%
Papillon–Lefevre syndrome	3	0·02%	3	33·3%	33·3%	0·0%
PID with partial albinism	2	0·01%	2	0·0%	100·0%	100·0%
Severe congenital neutropenia	242	1·77%	211	11·6%	9·9%	19·8%
Shwachman–Diamond syndrome	120	0·88%	108	26·7%	0·0%	15·0%
Complement deficiencies	636	4·64%	631	99·8%	14·6%	61·8%
Complement component 1 deficiency	4	0·03%	4	100·0%	25·0%	25·0%
Complement component 2 deficiency	44	0·32%	43	100·0%	9·1%	27·3%
Complement component 3 deficiency (C3)	4	0·03%	4	100·0%	0·0%	25·0%
Complement component 4 deficiency	10	0·07%	10	100·0%	0·0%	0·0%
Complement component 5 deficiency	7	0·05%	6	100·0%	0·0%	71·4%
Complement component 6 deficiency	7	0·05%	7	100·0%	14·3%	0·0%
Complement component 7 deficiency	14	0·10%	14	100·0%	0·0%	21·4%
Complement component 8 deficiency	4	0·03%	4	100·0%	0·0%	25·0%
Complement factor H deficiency	1	0·01%	1	100·0%	0·0%	0·0%
Hereditary angioedema (C1inh)	484	3·53%	482	99·8%	16·1%	73·3%
I Factor deficiency (IF)	16	0·12%	15	100·0%	37·5%	68·8%

Table 1. *Continued*

	Total patients	% of total	Living patients	Affected gene known	Consanguinity	Familial case
Properdin P factor complement deficiency (PFC)	1	0·01%	1	100·0%	0·0%	0·0%
Mannose-binding lectin (MBL)	40	0·29%	40	100·0%	7·5%	10·0%
Other well-defined PIDs	2 139	15·60%	1716	85·3%	11·5%	19·8%
Asplenia syndrome	24	0·18%	15	54·2%	4·2%	58·3%
Asplenia syndrome (Ivemark syndrome)	11	0·08%	10	0·0%	9·1%	18·2%
Isolated congenital asplenia	13	0·09%	5	100·0%	0·0%	92·3%
Cartilage hair hypoplasia	32	0·23%	26	59·4%	0·0%	18·8%
Charge syndrome	2	0·01%	2	100·0%	0·0%	0·0%
DiGeorge syndrome	610	4·45%	547	98·4%	1·3%	3·9%
DNA breakage disorders	795	5·80%	561	93·8%	18·6%	27·2%
AT-like disorder	7	0·05%	6	100·0%	14·3%	28·6%
Ataxia telangiectasia (ATM)	585	4·27%	410	97·6%	21·9%	28·0%
Bloom syndrome (RECQ2)	14	0·10%	13	100·0%	14·3%	21·4%
Fanconi anaemia	16	0·12%	12	0·0%	25·0%	25·0%
Immunodeficiency centromeric instability facial anomalies syndrome (ICF)	20	0·15%	16	35·0%	40·0%	25·0%
Nijmegen breakage syndrome (NBS1)	148	1·08%	99	99·3%	2·7%	24·3%
Other DNA breakage disorder	4	0·03%	4	0·0%	25·0%	50·0%
Seckel syndrome	1	0·01%	1	0·0%	0·0%	0·0%
Dyskeratosis congenita	13	0·09%	9	100·0%	15·4%	23·1%
Dyskeratosis congenita	2	0·01%	0	100·0%	0·0%	0·0%
Hoyeraal–Hreidarsson syndrome	11	0·08%	9	100·0%	18·2%	27·3%
Fc receptor deficiencies	1	0·01%	1	100·0%	0·0%	0·0%
Hyper-IgE syndromes (HIES)	237	1·73%	219	43·5%	12·7%	20·3%
Netherton syndrome	3	0·02%	3	66·7%	33·3%	0·0%
Osteopetrosis	18	0·13%	16	33·3%	27·8%	16·7%
Schimke disease	5	0·04%	3	60·0%	40·0%	0·0%
Hepatic veno-occlusive disease with immunodeficiency (VODI)	1	0·01%	0	100·0%	100·0%	0·0%
Wiskott–Aldrich syndrome (WAS)	398	2·90%	314	79·4%	12·1%	27·6%
Wiskott–Aldrich syndrome (WAS)	365	2·66%	281	77·8%	9·3%	23·8%
X-linked thrombocytopenia with mutations in WASP	33	0·24%	33	97·0%	42·4%	69·7%
Autoimmune and immune dysregulation syndromes	513	3·74%	395	59·5%	21·4%	33·1%
Autoimmune lymphoproliferative syndrome (ALPS)	147	1·07%	137	61·9%	4·8%	27·9%

Table 1. *Continued*

	Total patients	% of total	Living patients	Affected gene known	Consanguinity	Familial case
Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)	29	0·21%	27	79·3%	20·7%	41·4%
Early-onset inflammatory bowel disease	1	0·01%	1	100·0%	0·0%	0·0%
Haemophagocytic lymphohistiocytosis (HLH)	313	2·28%	211	55·9%	30·0%	35·8%
Chediak–Higashi syndrome	40	0·29%	36	12·5%	50·0%	12·5%
Familial haemophagocytic lymphohistiocytosis syndromes (FHLH)	159	1·16%	84	59·1%	32·1%	35·8%
Griscelli syndrome	31	0·23%	24	80·6%	51·6%	45·2%
Hermansky–Pudlak syndrome	2	0·01%	2	0·0%	100·0%	100·0%
X-linked lymphoproliferative syndrome (XLP)	81	0·59%	65	63·0%	6·2%	42·0%
IPEX	19	0·14%	15	57·9%	15·8%	26·3%
FoxP3 deficiency (IPEX)	18	0·13%	14	61·1%	16·7%	27·8%
IPEX-like disease	1	0·01%	1	0·0%	0·0%	0·0%
Other autoimmune and immune dysregulation syndromes	4	0·03%	4	100·0%	0·0%	0·0%
Defects in innate immunity	107	0·78%	98	32·7%	3·7%	39·3%
Chronic mucocutaneous candidiasis (CMC)	61	0·44%	60	6·6%	3·3%	39·3%
Defects of TLR/NF-kappa-B signalling	28	0·20%	23	100·0%	7·1%	32·1%
Epidermodysplasia verruciformis	1	0·01%	1	0·0%	0·0%	0·0%
Warts, hypogammaglobulinaemia infections and myelokathexis (WHIM)	17	0·12%	14	17·6%	0·0%	52·9%
Autoinflammatory syndromes	267	1·95%	263	30·7%	9·4%	15·7%
Blau syndrome–caspase recruitment domain-containing protein 15 deficiency (CARD15)	12	0·09%	12	100·0%	0·0%	41·7%
CINCA syndrome	6	0·04%	6	100·0%	16·7%	33·3%
Familial cold autoinflammatory syndrome	3	0·02%	3	100·0%	0·0%	100·0%
Familial Mediterranean fever	83	0·61%	83	20·5%	10·8%	22·9%
Familial periodic fever	42	0·31%	38	100·0%	7·1%	16·7%
Hyper IgD syndrome (MVK)	27	0·20%	26	100·0%	7·4%	3·7%
TNF receptor-associated periodic fever syndrome (TRAPS)	15	0·11%	12	100·0%	6·7%	40·0%
Muckle–Wells syndrome	2	0·01%	2	100·0%	0·0%	0·0%
Periodic fever aphtous stomatitis, pharyngitis and adenopathy (PFAPA)	119	0·87%	119	0·0%	10·1%	5·0%
Unclassified immunodeficiencies	250	1·82%	228	0·0%	7·6%	14·4%

ATP, adenosine triphosphate; TLR, Toll-like receptor, NF-kB, nuclear factor kappa B; HLA, human leucocyte antigen; CINCA, chronic infantile neurological cutaneous and articular syndrome; MVK, mevalonate kinase; Ig, immunoglobulin; HIGM, hyper-immunoglobulin M syndrome; DOCK8, dedicator of cytokinesis 8; ITK, interleukin-2-inducible T cell kinase; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked; FoxP3, forkhead box protein 3; WASP, Wiskott-Aldrich syndrome protein.

Table 2. Age distribution of living patients by main categories and in total. The numbers in the top row represent the age groups in years. A parenthesis indicates that the end-point is not included in the interval (open interval), while a square bracket indicates that the end-point is included (closed interval).

	Total	[0, 10)	[10, 17)	[17, 34)	[34, 98]
Predominantly T cell deficiencies	760	31·6%	29·6%	17·4%	21·4%
Predominantly antibody disorders	7227	23·3%	26·3%	25·0%	25·4%
Phagocytic disorders	1026	56·3%	21·7%	18·6%	3·4%
Other well-defined PIDs	1721	30·4%	27·6%	36·0%	6·1%
Defects in innate immunity	98	7·9%	13·3%	28·5%	50·2%
Complement deficiencies	631	47·9%	24·6%	22·9%	4·6%
Autoinflammatory syndromes	263	25·5%	27·1%	37·6%	9·8%
Autoimmune and immune dysregulation syndromes	395	32·7%	32·5%	28·8%	6·0%
Unclassified immunodeficiencies	228	20·4%	20·6%	24·0%	35·1%
Total	12349	24·8%	23·1%	26·2%	25·9%

PID, primary immunodeficiencies.

delay are 4·0, 2·5, 3·3, 3·8, 3·2 and 2·6 years. In the total cohort, the median delay for agammaglobulinaemias from 1991 to 2010 lay between 0·8 and 1·4, and between 1·9 and 2·2 for IgG subclass deficiency. In sIgA deficiency, the median delay lay between 1 and 1·8 years. WAS had a median delay between 0·4 and 0·6 years, AT between 1·8 and 3 years, DGS between 0·2 and 0·3 years and CGD between 0·6 and 1·4 years. SCID had a very short median delay of 0·1 to 0·2 years.

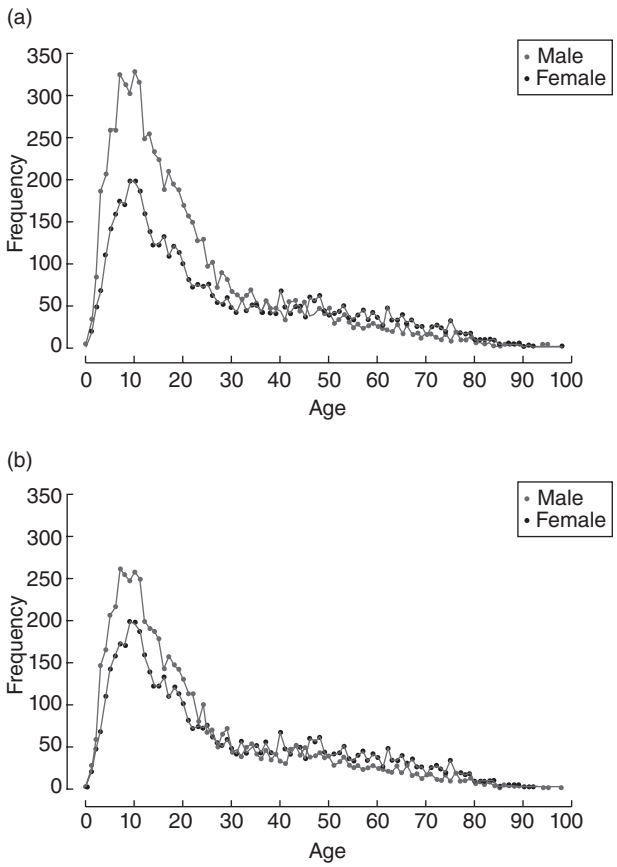

Fig. 1. (a–b) Frequency and plots showing distribution of male and female patients by age. (a) All patients; (b) All patients except those with X-linked inheritance.

Therapy

Details on therapy were reported for 10 091 (81·8%) of the living patients. Of these, 4555 patients (45·1%) received immunoglobulin replacement, which makes it the most frequently reported long-term medication. A total of 3332 patients (73·2%) received immunoglobulins intravenously, while it was administered subcutaneously in 1217 patients (26·7%). Twelve patients (0·3%) received intramuscular immunoglobulins. Six patients received both intravenous and subcutaneous treatment, which explains why the numbers total more than 100%. The next most frequently reported medication concerns antibiotics (both prophylactic and therapeutic), which were given in 2703 patients (26·8%). Other frequently reported medications are steroids (548 patients, 5·4%), anti-fungals (509 patients, 5%), bronchodilators (275 patients, 2·7%) and immunosuppressants (271 patients, 2·7%); 809 patients (8%) had received a stem cell transplant; and 2375 patients (23·5%) had neither received a stem cell transplant nor were they receiving any long-term medication.

Discussion

Since we last published data extracted from the ESID database in September 2008, the number of registered patients has almost doubled from 7430 to 13 708 patients. The distribution of patients with respect to the single PID entities has remained relatively stable since 2008. CVID continues to represent more than 20% of all registered patients. SIgA deficiency has replaced IgG subclass deficiency as the second most frequent entity. This is due mainly to the fact that this disease is reported very frequently in Spain and Hungary, countries that joined the ESID database after 2008. Most individuals with sIgA deficiency are free of

Table 3. Minimum primary immunodeficiencies (PID) prevalence based on reported cases in the ESID database: living patients per 100 000 inhabitants by countries. Total populations source: Eurostat (http://epp.eurostat.ec.europa.eu).

Country	Population	Total patients	Total prevalence	CVID	sIgA deficiency	IgG subclass deficiency	Agamma-globulinaemias
France	65 075 310	3240	4·979	0·977	0·218	0·078	0·287
Spain	46 152 926	1662	3·601	0·657	1·309	0·141	0·134
Netherlands	16 654 979	433	2·6	0·865	0·054	0·126	0·192
Turkey	73 722 988	1486	2·016	0·103	0·357	0·292	0·045
United Kingdom	62 435 709	1148	1·839	0·604	0·066	0·037	0·094
Italy	60 626 442	1083	1·786	0·719	0	0	0·205
Germany	81 751 602	1126	1·377	0·524	0·035	0·035	0·077
Poland	38 200 037	508	1·33	0·073	0·34	0·084	0·071

CVID, common variable immunodeficiency; ESID, European Society for Immunodeficiencies.

infections [19], but are still included in the current ESID diagnostic criteria for PID. However, many centres obviously only report patients presenting with clinical manifestations, which means that reporting of this disease is extremely skewed.

The prevalence numbers we calculated also differ strongly between countries. However, with 3240 living patients documented in the heterogeneous population of France, the overall prevalence of PID will not be less than 5:100 000.

In general, the prevalence and incidence numbers produced from our data collection have to be interpreted with great caution. They can be seen as an indicator towards the actual numbers that would be calculated if the documentation was 100% complete. We believe that the differences we observed between countries and periods can most probably be attributed to under-reporting.

The proportion of patients diagnosed after the age of 16 has increased since the last publication from 21·5% to 27·9%. This illustrates further that PID are not diseases affecting children only and that the awareness for adult presentations of these diseases is increasing. In some of our contributing centres, adults are treated in paediatrics departments because there is no expertise in internal medicine departments. This is an issue that certainly still needs to be given more attention from policy makers, and our observations should help to bring this issue on the agenda.

The genetic basis of their disease remains undefined for a large number of patients, especially for those with antibody deficiencies. The gender distribution shows that males were affected much more frequently by PID than females. Interestingly, in patients younger than 30 years, boys are affected more frequently even if X-linked diseases are excluded. A specific example for this was recently given in autoimmune lymphoproliferative syndrome (ALPS) [20]. The reason for this is unknown, but may reflect additional genetic susceptibility factors encoded on the Y-chromosome. We further observed that among patients older than 30 years, more women than men are affected by a PID. We have no explanation for this.

Another important issue is the diagnostic delay which is a marker for the improvement of awareness of PID. This is especially true in PID that present less severely and may go undiagnosed for many years, such as CVID. We were able to identify positive overall trends towards a shorter diagnosis for agammaglobulinaemias and IgG subclass deficiency. Conversely, CVID in particular continues to present with a very high median diagnostic delay of 3 years in many patients who receive their diagnosis more than 10 or even 20 years after disease onset.

The documentation progress of the ESID database has made it the largest single collection of PID patient data to date. The more countries manage to organize a complete coverage of PID documentation on the national level, the better we can judge the meaning of numbers produced by the ESID database.

In a survey among the database users conducted from July to September 2010, we tried to determine how the system could be made more user-friendly in order to increase reporting. Major issues we identified were slow loading of the web pages and the complicated structure of the system, with more than 210 disease entities. We addressed these issues by upgrading to new hardware and restructuring the data entry system, which led to a reduction to 138 entities.

Conversely, we also realized that our current core data set is obviously too complex and unfocused, because for many patients large parts remain undocumented. Therefore, we decided to define a new, more focused core data set which will be discussed by representatives of all national registries in Freiburg in December 2011. We believe that this effort will lead to a more complete registration and thus will improve future analyses.

Recently, data have also been used frequently to determine treatment outcomes, such as the correlation of dosing of immunoglobulin replacement and immunoglobulin trough levels with CVID patients' quality of life. Results from these analyses were presented at scientific conferences. As they are generated from a patient registry they certainly do not meet the standards of a clinical trial, but they represent a very good example of hypotheses derived from a

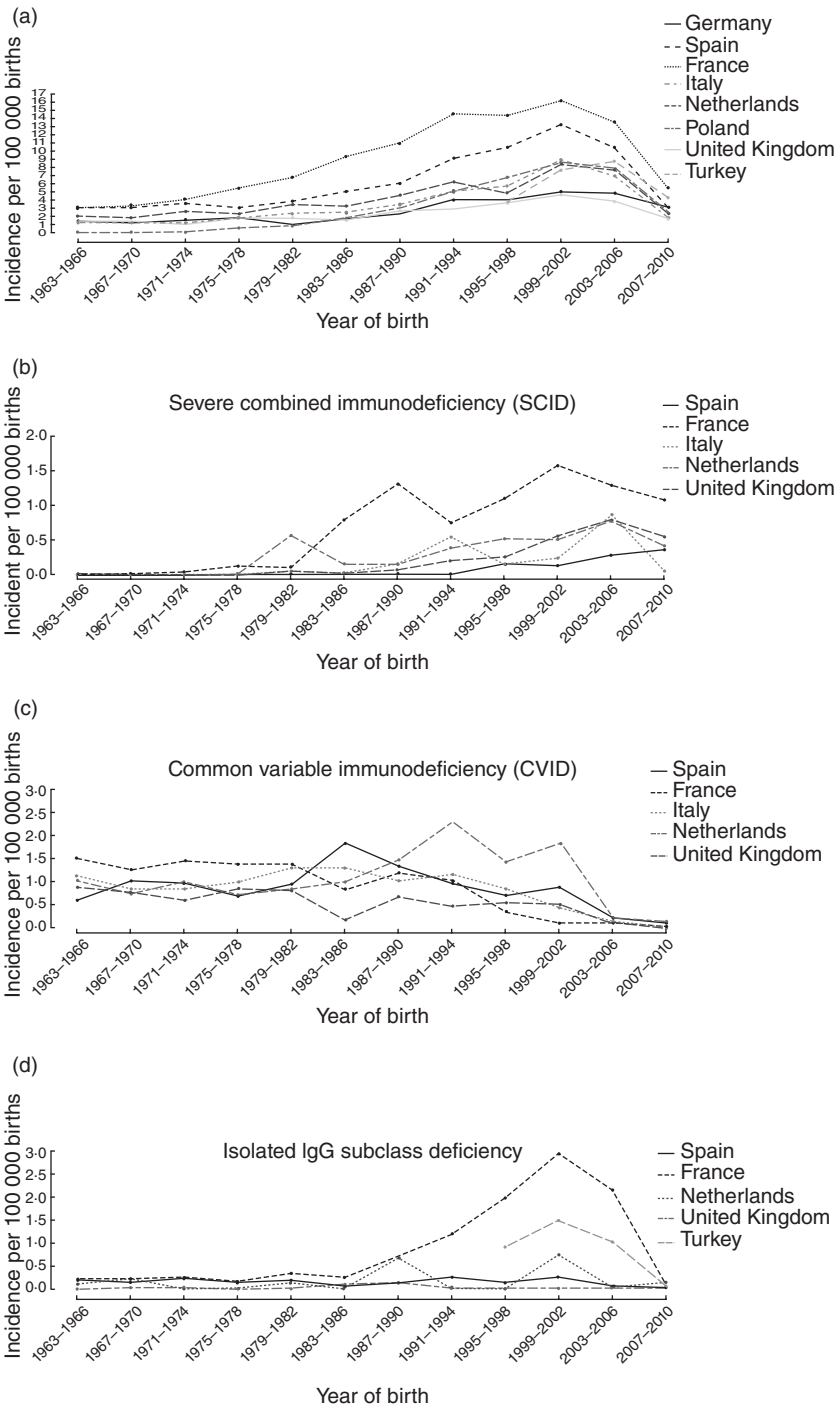

Fig. 2. (a–d) Incidence of primary immunodeficiencies (PID) per 100 000 live births for selected countries and diseases. For better readability, Germany and Poland have been excluded. (b–d) Turkey has been excluded from (b and c) and Italy has been excluded from (d) because these countries have relatively low curves without specific peaks for these diseases. Source for number of live births: Eurostat (http://epp.eurostat.ec.europa.eu). For Turkey, birth numbers were only available for the time from 1995 onwards.

large patient group that could be tested further in dedicated clinical trials.

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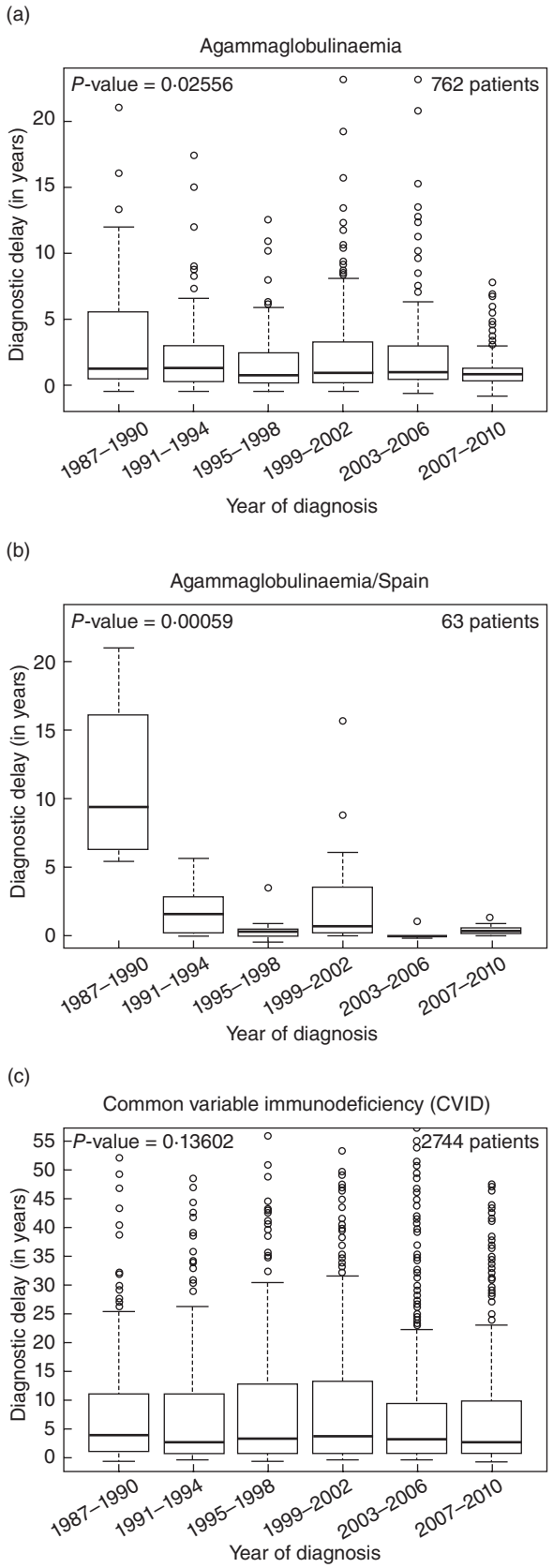

Fig. 3. (a–c) Diagnostic delay according to date of diagnosis in (a) agammaglobulinaemias (total cohort), (b) agammaglobulinaemias (Spain) and (c) common variable immunodeficiency (CVID) (total cohort). Extreme outliers in c are not displayed to improve readability. The farthest outlier was 73.

Disclosure

The authors declare no competing financial interests.

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