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The German national registry for primary immunodeficiencies (PID)

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Summary

In 2009, a federally funded clinical and research consortium (PID–NET, http://www.pid-net.org) established the first national registry for primary immunodeficiencies (PID) in Germany. The registry contains clinical and genetic information on PID patients and is set up within the framework of the existing European Database for Primary Immunodeficiencies, run by the European Society for Primary Immunodeficiencies. Following the example of other national registries, a central data entry clerk has been employed to support data entry at the participating centres. Regulations for ethics approvals have presented a major challenge for participation of individual centres and have led to a delay in data entry in some cases. Data on 630 patients, entered into the European registry between 2004 and 2009, were incorporated into the national registry. From April 2009 to March 2012, the number of contributing centres increased from seven to 21 and 738 additional patients were reported, leading to a total number of 1368 patients, of whom 1232 were alive. The age distribution of living patients differs significantly by gender, with twice as many males than females among children, but 15% more women than men in the age group 30 years and older. The diagnostic delay between onset of symptoms and diagnosis has decreased for some PID over the past 20 years, but remains particularly high at a median of 4 years in common variable immunodeficiency (CVID), the most prevalent PID.

Keywords: chronic granulomatous disease (CGD), common variable immunodeficiency (CVID), DiGeorge syndrome, immunodeficiency-primary, X-linked agammaglobulinaemia (XLA)

Introduction

Primary immunodeficiency disorders (PID) represent rare inborn errors of the immune system predisposing to recurrent infections, autoimmunity and cancer. Identifying underlying genetic causes and the pathophysiological basis of these rare diseases is important for the development of innovative gene-based therapeutic strategies, but also has a major impact on the understanding of the more common immunological disorders. So far, more than 130 phenotypically distinct primary immunodeficiency diseases have been identified and more than 190 disease-related genes have been discovered [1].

To gain knowledge about the natural history and approximate the prevalence of PID, it is mandatory to collect patient data in central electronic patient registries. During the past 20 years, patient registries have been set up on both the national [2–4] and international levels [5]. These have aimed mainly at questions such as prevalence and incidence, frequency of symptoms and treatment options. Furthermore, such registries provide researchers with sufficient numbers of cases for genetic research and clinical trials.

In Germany, no reliable collection of PID patients had been established before 2009. Therefore, a consortium of researchers within the German working group for paediatric immunology (Arbeitsgemeinschaft Pädiatrische Immunologie – API; http://www.kinderimmunologie.de) decided to apply for a national registry for PID within a national consortium for PID. This consortium (PID–NET; http://www.pid-net.org) is funded by the German Federal Ministry of Education and Research (BMBF, 01GM0896). The national registry was set up to analyse the epidemiology and natural course of primary immunodeficiencies, assess the diagnostic delay for a single PID, identify factors affecting the clinical course, evaluate the impact of therapeutic strategies and to compare and evaluate treatment regimens between medical centres in Germany. Furthermore, the registry is also intended for establishing links between medical centres within Germany and beyond. Since the start of the PID–NET project, participating centres in Germany have contributed their data to several European and international multi-centre studies, such as a study on chest computed tomography (CT) in antibody deficiencies (http://www.chest-ct-group.eu) and the PedPAD study on hypogammaglobulinaemia in children (http://www.esid.org/registry-studies-132-0).

Materials and methods

The PID–NET consortium decided to use the database platform provided by the European Society for Immunodeficiencies (ESID; http://www.esid.org) for setting up its national registry. Since 2004, ESID has been running this pan-European database for PID which is also used, among others, by national registries in France, the United Kingdom, Switzerland, Austria, the Netherlands and the Czech Republic.

The national registry is co-ordinated at the Centre of Chronic Immunodeficiency (CCI) at the University Medical Center Freiburg, which also runs the ESID database. The structure of the ESID online database has been described in detail previously [6]. Data are entered using a standard web browser with SSL-protected internet connection and password-protected access. Data are stored on secure servers at the hospital IT centre. The database system was approved by data protection authorities in Germany before the start of the national registry.

The ESID database for PID currently consists of 139 disease-specific registries, which are grouped within nine main categories and 70 subcategories. The categorization is based on the classification established by the IUIS (International Union of Immunological Societies) [1].

The PID–NET consortium defined a core data set which is used for all PID. It is based on the data set used in the ESID database, which also makes it easier to use the data in international surveys and studies. Furthermore, a set of driving epidemiological research questions was defined.

A large number of paediatric and medical departments see PID patients in Germany. Some of these take care of fewer than 10 or even five patients. The aim of the first funding period was to incorporate all centres (academic and non-academic) that are specialized in the treatment of PID. Forty-three such centres were identified. Before the initiation of the PID–NET Registry, only seven of these centres were reporting patients to ESID, amounting to 630 patients over a period of 6 years (2004–09). By March 2012, the number of centres contributing data actively had increased to 21, and a total of 30 had already received ethics approval. Details on all active centres can be found at http://www.esid.org/documenting-centers. Further information on the documentation progress is available at http://www.pid-net.org/registry. Once the process that focuses on hospitals is complete, the registry will also incorporate data from community-based local physicians (specialists and general practitioners who are not based at hospitals) into the registry.

A central asset of the registry is a medical data entry clerk who sets up contacts with new centres, helps them in applying for ethics approval and provides on-site training courses introducing users to the PID–NET registry. As many centres have no or little study personnel to enter the data, the central data entry clerk visits some centres regularly to enter data into the online system.

The registry contains built-in mechanisms to check data for completeness and plausibility. In addition, data are monitored manually in particular to check for patients who have been reported twice by different centres (e.g. due to referral for bone marrow transplantation).

Due to the complexity of the diseases, verification of the PID diagnosis according to the ESID diagnosis criteria is the responsibility of the medical specialist in charge of each patient.

Data items

For the current analysis, we used a subset of items taken from the core data set that is common to all diseases: disease, year of birth, year of death, gender, status (alive/dead/lost to follow-up), current country of living, consanguinity, familial case, date of clinical diagnosis, date of genetic diagnosis, date of onset and affected gene. The onset of disease was defined as the date of first severe infection or characteristic manifestation of the respective PID. It must be noted that this item represents 'soft data', as it relies upon patients' and parents' information and retrospective evaluation. The date of clinical diagnosis was defined as the date when the patient was diagnosed based on clinical features and laboratory results. The date of genetic diagnosis was defined as the date when the genetic diagnosis was confirmed. We also describe some basic items on therapy: current status of therapy, drug group, route of administration and information on bone marrow or stem cell transplantation, respectively. It must be noted that not all items were completed in all patients. The respective numbers are indicated in the Results section as 'patients with available data'.

Patient distribution by year of birth

In order to analyse the rate of diagnosis, we calculated the patient distribution as a function of the year of birth. We did so for the most frequent diseases, which were common variable immunodeficiency (CVID), chronic granulomatous disease (CGD), isolated immunoglobulin (Ig)G subclass deficiency, agammaglobulinaemias, DiGeorge syndrome and ataxia telangiectasia. To increase readability, we report the rate of PID patients for 4-year time-spans from 1963 to 2010.

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 for patients diagnosed between 1987 and 2010 for the most frequent diseases (see above).

The date of diagnosis was taken to be either 'date of clinical diagnosis' or 'date of genetic diagnosis', depending on which came first. Data on 'year of diagnosis' was missing in 14% of patients, and the 'year of onset' was missing in 29·9%. These patient data sets were excluded from the analysis. Furthermore, patients were 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 [7]. 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 positive trend in diagnostic delay as time progresses.

Results

The total number of registered patients was 1368 (9 March 2012). Of these, 1232 were alive, while 44 were deceased and 92 patients were lost to follow-up. Of all patients, 783 (57·2%) were male and 585 (42·8%) were female.

The affected gene was determined by molecular diagnosis in 414 patients (31·2% of 1329 patients with available data). The proportion of genetic diagnosis varied considerably between diseases that are, by definition, genetic defects (such as CD40 ligand deficiency) and diseases where underlying genetic defects have largely not been determined, such as selective IgA (sIgA) deficiency or common variable immunodeficiency (CVID). Please see Table 1 for detailed information on each disease. Consanguinity was reported in 79 of 917 patients with available data (8·6%). Of 922 patients with available data, 190 were familial cases (20·6%).

Antibody deficiencies formed the largest PID group, with 858 patients (62·7%). Within this group, common variable immunodeficiency (CVID) was by far the most frequent single disease, with 512 patients (37·4% of total patients); of these, 465 were reported to be alive at the last follow-up.

The next most frequent diseases were antibody disorders such as isolated IgG subclass deficiency (76 patients), agammaglobulinaemias (73 patients) and the heterogeneous group of other hypogammaglobulinaemias (88 patients). Frequently reported PID that affect other components of the immune system were chronic granulomatous disease (CGD) (77 patients), DiGeorge syndrome (53 patients) and ataxia telangiectasia (51 patients). There is also a considerable group of patients with an undefined immunodeficiency (54 patients). The complete list of diseases, including information on the number of patients with known genetic mutation, consanguinity and familial background, is given in Table 1.

Five hundred and fifty-three patients (44·8%) were aged less than 18 years. In that age group, there are significantly more male than female patients (Fig. 1a). In particular, in children below 12 years of age, there are more than twice as many boys than girls. This imbalance diminishes with increasing age, but there are still 28% more men than women in patients aged 18–29 years. In contrast, from age 30 onwards, there are 15·7% more women than men (199

Table 1. Distribution of patients on main categories, subcategories and diseases, number of patients who were deceased or lost to follow-up and share of patients with known genetic cause, consanguineous background and familial background of primary immunodeficiencies (PID).

Main category	Subcategory	Disease	Patients	Deceased	Lost to follow-up	Affected gene identified	Consangu-inity	Familial case
Predominantly antibody disorders	Agammaglobulinaemias	Agammaglobulinaemia	73	0	3	77·5%	5·8%	35·2%
	Class switch recombination defects (CSR) /HIGM syndromes	Activation-induced cytidine deaminase deficiency (AID)	5	0	0	100·0%	66·7%	0·0%
		CD40 deficiency (TNFRSF5)	1	0	0	100·0%	0·0%	0·0%
		CD40 ligand deficiency (CD154)	5	0	0	100·0%	0·0%	40·0%
		CSR defects and HIGM syndromes with unknown genetic cause	8	1	0	0·0%	0·0%	25·0%
	Hypogammaglobulinaemias	Common variable immunodeficiency (CVID)	512	15	32	2·6%	2·4%	12·9%
		Deficiency of specific immunoglobulin (Ig)G	20	0	0	0·0%	10·5%	25·0%
		Dystrophia myotonica	3	1	1	100·0%	0·0%	0·0%
		IgA with IgG subclass deficiency	7	0	0	0·0%	14·3%	14·3%
		Isolated IgG subclass deficiency	76	0	0	0·0%	10·9%	15·2%
		Other hypogammaglobulinaemias	88	1	8	1·1%	13·3%	17·4%
		Other Ig gene deletions	1	0	0	0·0%	0·0%	0·0%
		Selective IgA deficiency	34	0	6	0·0%	0·0%	11·8%
		Selective IgM deficiency	8	0	1	0·0%	0·0%	0·0%
		Thymoma with immunodeficiency	2	0	0	0·0%	0·0%	0·0%
		Transient hypogammaglobulinaemia of infancy	15	0	4	0·0%	0·0%	0·0%
Predominantly T cell deficiencies	CD4 deficiency	Selective CD4 cell deficiency	6	0	0	100·0%	0·0%	0·0%
	Combined immunodeficiency (CID)	Atypical severe combined immunodeficiency (atypical SCID)	2	1	1	0·0%	100·0%	0·0%
		Calcium channel dysfunction	3	0	0	100·0%	33·3%	66·7%
		Cernunnos/XLF deficiency	2	0	0	100·0%	100·0%	100·0%
		DNA-ligase 4 ATP-dependent deficiency (LIG4)	5	2	1	100·0%	0·0%	60·0%
		DOCK8 deficiency	2	0	0	100·0%	100·0%	0·0%
		ITK deficiency	1	0	0	100·0%	0·0%	0·0%
		Nucleoside phosphorylase deficiency (NP)	1	0	0	100·0%	0·0%	0·0%
	Omenn syndrome	Omenn syndrome	1	1	0	100·0%	0·0%	0·0%
	Other unclassified T cell disorders	Other unclassified T cell disorders	4	0	0	0·0%	0·0%	0·0%
	T-B+ severe combined immunodeficiency (SCID)	T-B+ severe combined immunodeficiency (SCID)	8	1	0	50·0%	25·0%	0·0%
	T-B– severe combined immunodeficiency (SCID)	T-B– severe combined immunodeficiency (SCID)	25	0	0	78·3%	47·1%	29·4%
Phagocytic disorders	Chronic granulomatous disease (CGD)	Chronic granulomatous disease (CGD)	77	2	0	77·5%	12·1%	26·3%
	Cyclic neutropenia	Cyclic neutropenia	8	0	1	37·5%	0·0%	20·0%
	Defects with susceptibility to mycobacterial infection (MSMD)	Defects with susceptibility to mycobacterial infection (MSMD)	5	0	2	100·0%	0·0%	75·0%
	Leucocyte adhesion deficiency (LAD)	Leucocyte adhesion deficiency (LAD)	1	1	0	100·0%	0·0%	0·0%
	Myeloperoxidase deficiency (MPO)	Myeloperoxidase deficiency (MPO)	1	0	0	100·0%	0·0%	0·0%
	Neutrophil glucose-6-phosphate dehydrogenase	Glucose-6-phosphate dehydrogenase deficiency (G6PD)	1	0	0	100·0%	100·0%	0·0%
	Other phagocytic disorders	Other phagocytic disorders	2	0	0	0·0%	0·0%	50·0%
	Severe congenital neutropenia	Severe congenital neutropenia	11	0	0	40·0%	0·0%	11·1%
	Shwachman–Diamond syndrome	Shwachman–Diamond syndrome	5	0	0	100·0%	20·0%	0·0%
Complement deficiencies	Complement deficiency	Complement component 1 deficiency	1	0	0	100·0%	100·0%	0·0%
		Complement component 2 deficiency	5	0	0	100·0%	0·0%	0·0%
		Complement component 7 deficiency	1	0	0	100·0%	0·0%	0·0%
		Hereditary angioedema (C1inh)	5	0	0	100·0%	0·0%	100·0%
		Properdin P factor complement deficiency (PFC)	1	0	0	0·0%	0·0%	0·0%

Main category	Subcategory	Disease	Patients	Deceased	Lost to follow-up	Affected gene identified	Consanguinity	Familial case
Other well-defined PIDs	Asplenia syndrome	Asplenia syndrome (Ivemark syndrome)	1	0	0	0·0%	0·0%	0·0%
	Cartilage hair hypoplasia	Cartilage hair hypoplasia	2	0	0	100·0%	0·0%	100·0%
	CHARGE syndrome	CHARGE syndrome	1	0	0	100·0%	0·0%	0·0%
	DiGeorge syndrome	DiGeorge syndrome	53	0	2	96·2%	0·0%	0·0%
	DNA-breakage disorder	Ataxia telangiectasia (ATM)	51	12	1	92·0%	18·8%	22·9%
		Bloom syndrome (RECQ2)	1	0	0	0·0%	0·0%	0·0%
		Immunodeficiency centromeric instability facial anomalies syndrome (ICF)	1	1	0	0·0%	0·0%	0·0%
		Nijmegen breakage syndrome (NBS1)	7	0	1	100·0%	0·0%	42·9%
		Other DNA-breakage disorder	3	0	0	0·0%	0·0%	100·0%
	Dyskeratosis congenita	Dyskeratosis congenita	1	0	0	0·0%	100·0%	0·0%
	Fc receptor deficiencies	Fc receptor deficiencies	1	0	0	100·0%	0·0%	0·0%
	Hyper-IgE syndromes	Hyper-IgE syndrome (HIES)	34	1	4	76·5%	25·0%	43·3%
	Netherton syndrome	Netherton syndrome	1	0	0	100·0%	0·0%	0·0%
	Schimke disease	Schimke disease	2	0	0	100·0%	50·0%	0·0%
	VODI	Hepatic veno-occlusive disease with immunodeficiency (VODI)	1	1	0	100·0%	100·0%	0·0%
	Wiskott–Aldrich syndrome (WAS)	Wiskott–Aldrich syndrome (WAS)	9	0	1	77·8%	0·0%	33·3%
		X-linked thrombocytopenia with mutations in WASP	2	0	0	100·0%	0·0%	0·0%
Autoimmune and immunedysregulation syndromes	Autoimmune lymphoproliferative syndrome (ALPS)	Autoimmune lymphoproliferative syndrome (ALPS)	19	0	5	33·3%	0·0%	6·7%
	Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)	Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)	4	0	1	100·0%	0·0%	0·0%
	Haemophagocytic lymphohistiocytosis (HLH)	Chediak Higashi syndrome	1	0	0	100·0%	0·0%	0·0%
		Familial haemophagocytic lymphohistiocytosis syndromes (FHLH)	5	0	0	100·0%	0·0%	25·0%
		X-linked lymphoproliferative syndrome (XLP)	14	0	2	100·0%	0·0%	0·0%
	IPEX	FoxP3 deficiency (IPEX)	2	0	0	100·0%	0·0%	0·0%
		IPEX-like disease	1	0	0	0·0%	0·0%	0·0%
Autoinflammatory syndromes	CINCA syndrome	CINCA syndrome	4	0	0	100·0%	25·0%	50·0%
	Familial Mediterranean fever	Familial Mediterranean fever defect	11	0	0	45·5%	20·0%	50·0%
	Familial periodic fever	Hyper-IgD syndrome (MVK)	2	0	0	100·0%	0·0%	0·0%
		TNF-receptor associated periodic fever syndrome (TRAPS)	8	0	0	100·0%	0·0%	37·5%
	Muckle–Wells syndrome	Muckle–Wells syndrome	2	0	0	100·0%	0·0%	0·0%
	PFAPA	Periodic fever aphtous stomatitis, pharyngitis and adenopathy (PFAPA)	15	0	0	0·0%	7·1%	0·0%
Defects in innate immunity	Chronic mucocutaneous candidiasis (CMC)	Chronic mucocutaneous candidiasis (CMC)	10	0	1	22·2%	25·0%	28·6%
	Defects of TLR/NF-κB signalling	Defects of TLR/NF-κB signalling	3	0	0	100·0%	0·0%	33·3%
Unclassified immunodeficiencies	Immunodeficiencies of unknown cause	Unclassified immunodeficiencies	54	3	14	0·0%	7·9%	35·1%

Missing values (not answered): genetic cause: 39 patients (2·8%); consanguinity: 462 patients (33·3%); familial case: 455 patients (32·8%). ATP: adenosine triphosphate: DOCK8: cytokinesis 8 gene; ITK: IL-2-inducible T cell kinase; FoxP3: forkhead box protein 3 ; CINCA: chronic infantile neurological cutaneous and articular syndrome; HIGM: hyper-immunoglobulin syndrome; TNF: tumour necrosis factor; TLR/NF-kB: Toll-like receptor/nuclear factor kappa B; PFAPA: periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome.

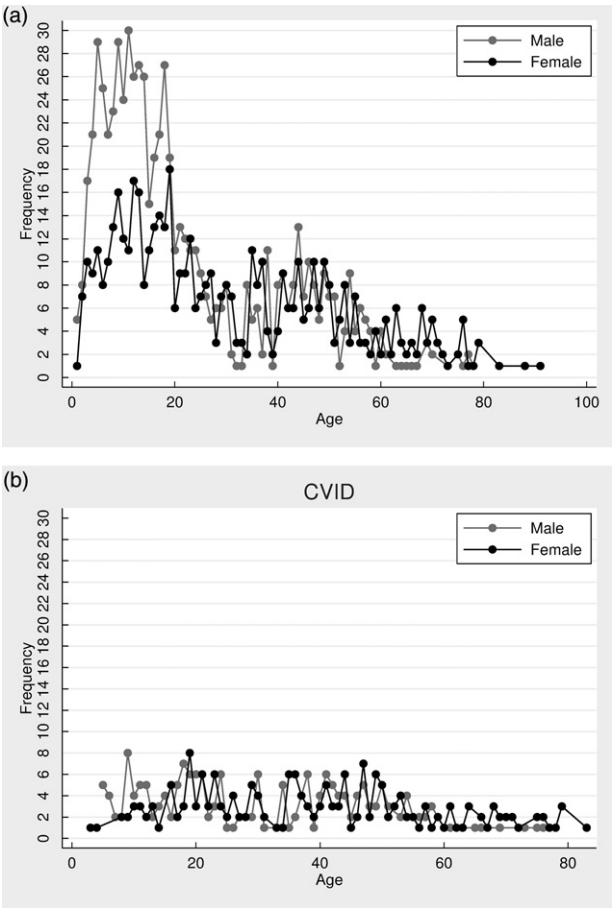

Fig. 1. (a,b) Frequency (number of patients) and plots showing distribution of male and female patients by current age. (a) All patients; (b) all patients with a diagnosis of common variable immunodeficiency (CVID).

men, 236 women). In the 465 CVID patients the proportion of children is much smaller but, among these, there are still slightly more males than females (Fig. 1b).

Geographic distribution

Figure 2 shows the geographical distribution of PID centres in Germany, as well as point markers that are proportional to the number of reported patients. Centres that are in the process of applying for ethics or have only recently started collecting informed patient consent have no point marker. It should be mentioned that patients are often treated in a referral centre far from their place of residence. This is the case for the centre in Freiburg, in particular, which has become a large national referral centre through BMBF funding. In addition, patient registration in Freiburg is particularly high because the registry is run from Freiburg.

Conversely, some centres, such as Berlin Charité and Ulm, have registered only a fraction of their patients. The Charité has only recently started reporting its patients, while Ulm differs from all other centres, as it is a large transplant centre in Germany to which many patients are referred by other centres for transplantation. The registry requires that patients should be reported by the centre where they are usually followed, which explains in part why Ulm has reported few patients.

Patient distribution by year of birth

The patient distribution as a function of year of birth since 1963 is displayed in Fig. 3. The figure shows a steady increase in diagnosed patients for most of the diseases. This is true in particular for agammaglobulinaemias, DiGeorge syndrome and CGD. There is a marked drop at the end of the curve for CVID, which is due to the fact that this presents a mainly adulthood-onset disease.

Diagnostic delay

The diagnostic delay for each of the six diseases we analysed reflects the clinical diversity of PID. Some diseases had a somewhat short median delay over the whole observation period from 1987 until 2010, and no statistically significant change could be observed. This was true for CGD (between

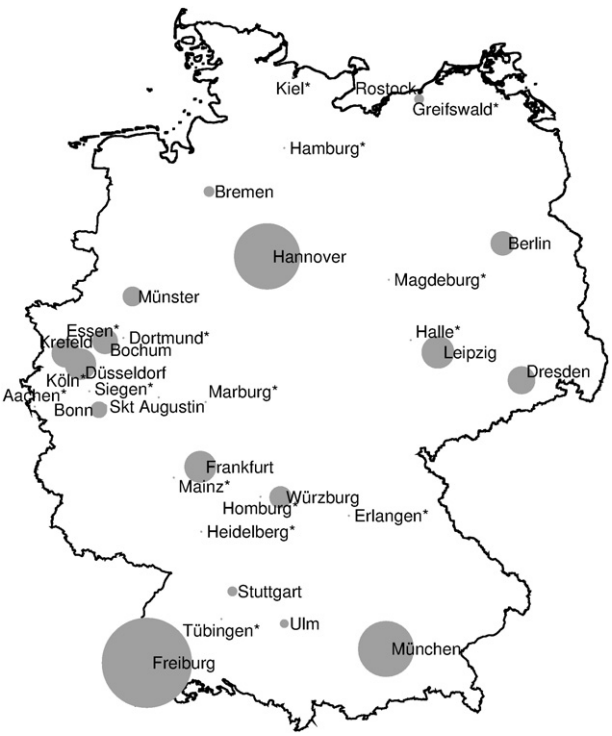

Fig. 2. Geographic distribution of centres in Germany. Centres that are located in the same city are subsumed under the city's name. Point markers are proportional to the number of reported patients. Cities with an asterisk (*) represent centres that have not yet documented any patient but are in the process of joining the registry. Graphical data from http://www.gadm.org were used to produce this figure.

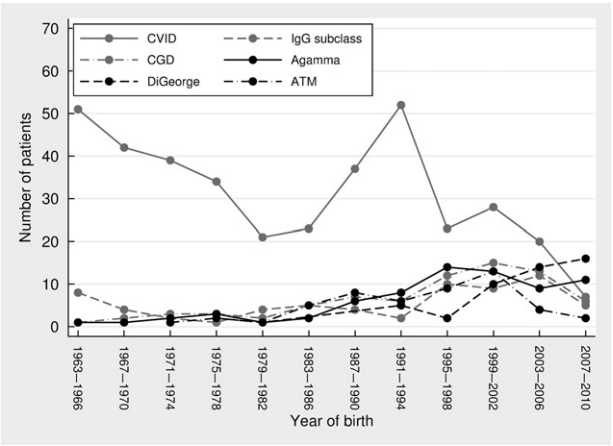

Fig. 3. Patient distribution as a function of year of birth: number of patients in 4-year time-spans.

1 and 2 years), agammaglobulinaemias (1 year) and DiGeorge syndrome (less than 1 year; all values presented are median values).

In contrast, in CVID the diagnostic delay has remained at a relatively high level since 1987; it was at 4 years for patients diagnosed since 2003 but, surprisingly, it was 3 years for patients diagnosed from 1991 to 1998 (Fig. 4a).

We observed a trend towards a shorter diagnostic delay in ataxia telangiectasia which was not quite statistically significant ($P = 0{\cdot}05$); this is due most probably to the small number of patients (Fig. 4b). Three patients diagnosed from 1987 to 1990 had a delay of 10·5 years, and in the following 4 years the delay was 3 years for seven patients. In the most recent period (2007–10) the delay was only 1 year, based on two patients.

The only disease that showed a statistically significant positive trend of diagnostic delay was IgG subclass deficiency ($P = 0{\cdot}02$). The median delay decreased from 8 years in 1995–98 to 2 years in 2007–10 (Fig. 4c).

Treatment

Ig replacement was the most frequently reported permanent medication. Five hundred and eighty-nine of the living patients (47·8%) received Ig replacement. Two hundred and twenty-seven (18·4%) received antibiotic prophylaxis. Eighty-nine patients (7·2%) used bronchodilators and 72 patients (5·8%) received steroids. Other treatments such as immunosuppressants were reported in fewer than 5% of patients.

Seventy-eight (5·77%) of the total of 1368 patients had received one or several haematopoietic stem cell transplants. A total of 88 transplantations were reported. Eighty of these were performed after the year 2000. The centres with the most transplanted patients were Munich Children's Hospital (30 patients), Freiburg CCI (23) and Hannover MHH (12). It must be noted that these transplantations were not necessarily performed at the reporting centre; there are currently no data items that store information on the place of transplantation.

Discussion

The German PID–NET Registry started with 630 patients who had been reported over 6 years from 2004 to 2009 into

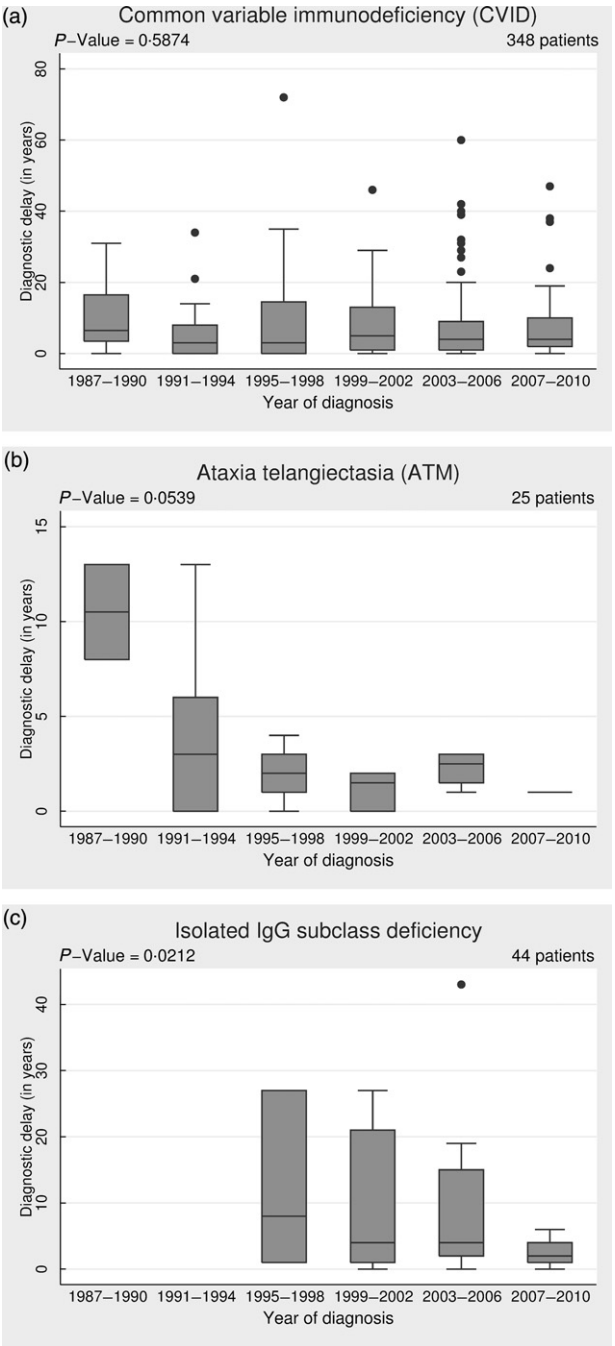

Fig. 4. (a–c) Diagnostic delay by year of diagnosis (grouped in 4-year groups) (a) Common variable immunodeficiency (CVID); (b) ataxia telangiectasia (AT); (c) immunoglobulin (Ig)G subclass deficiency.

the ESID database. In the project's first 3 years, from 2009 to 2012, 738 additional patients have been reported. This marked increase in the speed of patient registration suggests that employing a central data entry clerk who alleviates the participating centres from the burden of documentation is an efficient way to improve registration. The same effect has been shown by the French national PID registry, CEREDIH (http://www.ceredih.fr), which has achieved an even faster reporting rate by employing several data entry clerks to collect patient data [4]. A data entry clerk is especially helpful for centres that have very limited resources. Larger centres employ mainly dedicated study nurses who enter data into the registry.

Data protection is regulated at the level of each federal state ('Bundesland'). As data protection laws differ between states, a huge bureaucratic effort is required to enable the running of such a registry. There are ethics committees at the Bundesland level which are responsible for non-academic hospitals, while university hospitals maintain their own ethics committees. Due to this, almost every centre that intends to join the registry has to apply formally for ethics approval locally. Although our team supported the centres in this task, in some cases it has caused a delay of years before documentation could start. On average, it took centres 10 months from first contact until receiving ethics approval (total range 2–25 months). Only then could they start collecting informed consent from their patients and subsequently enter their patients' data into the database. This long delay is due mainly to prolonged communication with ethics committees and data protection authorities for the respective responsible physicians. In addition, many ethics committees requested modifications to the informed patient consent form which had already been approved at other centres.

The prospect of additional paperwork, associated with ethical approval, makes centres averse to joining the registry, and therefore complicates the task of reaching complete coverage of PID patients. It is certainly desirable to simplify regulations for non-interventional patient registries in Germany.

It must be noted that other registries exist at the local, national and international levels that also collect data on patients fulfilling the inclusion criteria for the PID–NET registry. Two of these are the German AID–NET registry [8], which collects data on autoinflammatory patients, and the European SCETIDE registry [9], which collects data on stem cell transplantations in PID patients. The existence of several possible registries for the same patient cohort poses a challenge to the reporting centres, because they must complete various report forms for the same patient which sometimes cover similar items. The associated workload is difficult to manage. For example, the centre in Ulm continues to report all its transplanted patients to the SCETIDE registry, but only some of these to the PID–NET registry because the workload is too extensive. Therefore, the PID–NET registry has already begun collaborations with these other databases and works on solutions to tackle the issue of double reporting. A direct transfer of data is not a viable solution due to different data formats, as well as data protection laws that make it virtually impossible to match patient data sets. An interesting perspective for tackling the existence of concurring registries is the EU initiative for a European Platform for Rare Disease Registries (http://ec.europa.eu/health/rare_diseases/policy/registries/index_en.htm).

In addition, some diseases are probably being strongly under-reported because they are followed mainly at departments with specialities other than immunology, such as haemophagocytic lymphohistiocytosis (HLH), which is treated mainly by haematologists, or autoinflammatory diseases which are treated by rheumatologists. Therefore, complete coverage of these diseases within the PID–NET registry is not realistic for the time being.

In March 2012, the PID registry reported 1232 patients alive. Based on a current population of 81·751 million in Germany, this comprises 1·51 PID patients per 100 000 living inhabitants. With caution, this number can be interpreted as a first approximation for PID prevalence. The PID registry is still at an early stage because some centres have not yet reported all their patients, and some have not even started reporting. Hence, 1·51 PID patients per 100 000 living inhabitants can be regarded as a lower limit for PID prevalence only in Germany. Determination of epidemiological indicators requires the long-term collection of patient data, in particular to reach a good approximation of the prevalence and incidence of single diseases. Tackling under-reporting and ascertainment biases is therefore first of all a matter of time and perseverance. Once the large majority of specialized centres have attained the necessary documents and the registration process is well established, we aim to include community-based local physicians in the second funding period, which starts in April 2012; it will then be interesting to compare patient numbers with the results presented in this paper.

We attribute the high number of PID in boys to diseases that are linked to the X-chromosome, such as X-linked agammaglobulinaemia (Btk) and Wiskott–Aldrich syndrome (WASP). It remains to be explained, however, why there are more women than men in the age group aged 30 years and older.

As a first informative analysis, in this paper we have presented the diagnostic delay. Because only patients who have already been diagnosed are registered, we analysed the diagnostic delay retrospectively. With a median of 4 years and singleton cases with a delay of more than 20 years, the time to diagnosis or diagnostic delay remains extremely problematic for CVID.

When discussing the diagnostic delay it must be noted that, by choosing the median, we eliminate the effect of extreme values. For example, while the median delay was

only 1–2 years in our CGD group of 60 patients, there was one patient with a delay of 20 and another with even a delay of 26 years. An analysis of the frequency of extreme cases over the years could serve as an additional indicator for the development of the diagnostic delay. We suggest performing such analyses in future studies. Efforts to improve the awareness of CVID, antibody deficiencies and PID in general should certainly be continued and intensified further.

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Disclosure

The authors declare no competing financial interests.

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