Original Article

Distribution of primary immunodeficiency disorders diagnosed in the Children's Medical Center in Iran

A. Farhoudi, A. Aghamohammadi, M. Moin, N. Rezaei, Z. Pourpak, M. Movahedi, M. Gharagozlou, S. Amir Tahaei, B. MirSaeid Ghazi, M. Mahmoudi, A. Kouhi, L. Atarod, A. Ahmadi Afshar, N. Bazargan, A. Isaeian

Department of Allergy and Clinical Immunology, Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran

Summary. Primary immunodeficiency disorders include a variety of diseases that render patients more susceptible to infections. To determine the percentage of different primary immunodeficiency disorders diagnosed in the Children's Medical Center Hospital affiliated to Tehran University of Medical Sciences in Iran, we retrospectively reviewed the charts of the patients being referred to our hospital for immunologic evaluation of recurrent infections during a 20 year period. Among these patients, antibody deficiencies were the most frequent ones and were found in 52.6% of patients (n=130). T-cell disorders, phagocytic disorders and complement deficiencies were found to be present in 24.69% (n=61), 22.2% (n=55) and 0.4% (n=1) respectively.

On the whole, common variable immunodeficiency was the most frequent disorder (n=65), followed by ataxia telangiectasia (n=39), X-linked agammaglobulinemia (n=33), chronic granulomatous disease (n=29) and selective IgA deficiency (n=20). This study reveals that antibody deficiencies are the most common type of disorders as shown in other studies. A comparative study shows some differences between our results and other registries. This article also indicates that immunodeficiency disorders should be considered in patients with recurrent infections.

Key words: Primary immunodeficiency disorders; Infection; Frequency; Iran.

Introduction

Primary immunodeficiency disorders (PID) are characterized by susceptibility to infection with a predisposition to the development of autoimmune disease and malignancy [1]. There are more than 100 different primary (inherited) immunodeficiency disorders [2]. Although there is an increased trend towards the recognition of new type of primary immunodeficiency disorders due to improvement in molecular and cellular techniques, physicians rarely know enough about the clinical presentation, diagnostic approach, importance, and health effect of PID. The reports on prevalence of different types of immunodeficiency disorders vary among different regions of the world [3-7]. In order to study the frequency of various phenotypes of PID in a pediatric referral hospital, we retrospectively analyzed the charts of all our patients who were diagnosed and treated as PID in a period of 20 years based on WHO criteria [8].

Materials and Methods

We retrospectively reviewed the charts of all the patients who were evaluated in our allergy/immunology

clinic from 1981 to 2001 and identified to have Primary Immunodeficiency based on WHO criteria [8]. Only patients with well-established immunodeficiency and the clinical manifestations compatible with their diagnosis were included in our registry. Laboratory analysis for our immunodeficient patients included blood smear, immunoglobulin levels, IgG subclasses titer, isohemagglutinins, Schick test, delayed cutaneous hypersensitivity reaction (Mantoux test, *Candida* skin test), lymphocyte subpopulation (T and B) enumeration from 1981-1992 with rosette formation and between 1992-2001 by flow cytometry method, chemotaxis evaluation, Nitro Blue Tetrazolium (NBT) dye test, chemiluminescence, complement component and hemolytic titration of complement (CH50) as needed.

We then designed a four-page questionnaire which contained the patients' demographic information including name, date and place of birth, the diagnosis of PID; past medical history including first clinical presentation, age of onset, age at time of PID diagnosis; family history of immunodeficiency, recurrent infections, autoimmune diseases and malignancies; basic immunological laboratory tests and follow-up information including various infections during the

Table 1. Frequency of PID by phenotype with demographic index

	Frequency	Percent	Age of study (range)	Male	Female
Antibody deficiency	130	52.6%	20m-44y	87	43
Common variable immunodeficiency	65	26.3%	23m-44y	37	28
X-Linked Agammaglobulinemia	33	13.3%	20m-30y	33	0
Selective IgA deficiency	20	8%	6m-18y	10	10
Hyper IgM Syndromes	4	1.6%	5y-12y	2	2
Subclass IgG deficiency	8	3.2%	7y-23y	5	3
T-cell deficiency	61	24.6%	2m-25y	33	28
Combined immunodeficiency	6	2.4%	4m-18y	3	3
Severe combined immunodeficiency	6	2.4%	2m-3y	6	0
Ataxia telangiectasia	39	15.7%	4y-18y	19	20
Wiscott-Aldrich syndrome	4	1.6%	2y-15y	4	0
Chronic mucocutaneous candidiasis	6	2.4%	4y-25y	1	5
Phagocytic defects	55	22.2%	1y-24y	34	21
Chronic granulomatouse disease	29	11.7%	4y-24y	19	10
Leukocyte adhesion defect	10	4%	1y-10y	6	4
Hyper IgE syndrome	8	3.2	9y-18y	4	4
Schwachmann's syndrome	4	1.6%	9y-20y	3	1
Chediac-Higashi syndrome	4	1.6%	8y-22y	2	2
Complement deficiency	1	0.4%	16y	0	1
Total	247	100%	2m-44y	154	93

course of the illness. All the data were then collected and analyzed with the statistical software SPSS 10.

Results

This study identified 247 patients (154 males and 93 females) with PID. The overwhelming majority had predominantly antibody deficiencies 52.6% (n=130),T-cell disorders 24.69% (n=61), phagocytic disorders 22.2% (n=55) and complement deficiencies 0.4% (n=1) followed respectively.

Approximately half of the patients belonged to the pediatric age group (53.3%). The patients' age at study ranged from 2 months to 44 years. The gap between the onset of clinical symptoms and PID diagnosis for some types like common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA) and chronic granulomatous disease (CGD) were respectively: 74 months, 79 months and 42 months. From 247 patients, 33 (13.36%) died and 51 (20.64%) were inaccessible for further evaluation and follow- up. The frequency and demographic variations of different types of PID is presented (Table 1).

The number of PID diagnosed in 5-year intervals (until 1981, 1982-1986, 1987-1991, 1992-1996, 1997-2001) was calculated (Figure 1).

Antibody deficiencies were by far the most frequently diagnosed immunodeficiency disorders, reported in 130 cases (52.6%) (Table 1), including common variable immunodeficiency (CVID) in 65 cases, X-linked agammaglobulinemia (XLA) in 33 cases, selective IgA deficiency in 20 cases, selective IgG subclass deficiency in 8 cases (all had a defect in IgG2) and finally hyper-IgM syndrome in 4 patients. Approximately two third of the patients with antibody deficiency presented with pneumonia and gastrointestinal infections. The most frequently associated infections in CVID were pneumonia followed by diarrhea, otitis media and sinusitis in this order. In XLA patients the symptoms were more severe and almost all of them presented with upper and lower respiratory tract infections, recurrent diarrhea, meningitis and septic arthritis. The main symptom of IgG subclass deficiency syndrome was sinopulmonary infections due to a defect in IgG2.

The frequency of T-cell deficiency was 61 (24.69%), including ataxia telangiectasia (AT) in 39 patients with the predominant symptom of recurrent respiratory infections. The rest of T-cell disorders were as follows: severe combined immunodeficiency (SCID) was found in 6 patients from 2 month to 3 years old; chronic mucocutaneous candidiasis (CMCC) and combined immunodeficiency (CID) were both found in 6 patients, and finally Wiscott-Aldrich syndrome in 4 patients.

55 patients with phagocytic disorders (22.2%) had associated variable infections like upper and lower respiratory infections and diarrhea. Chronic granulomatous disease (CGD) was the most common phenotype in this category and consanguinity was found

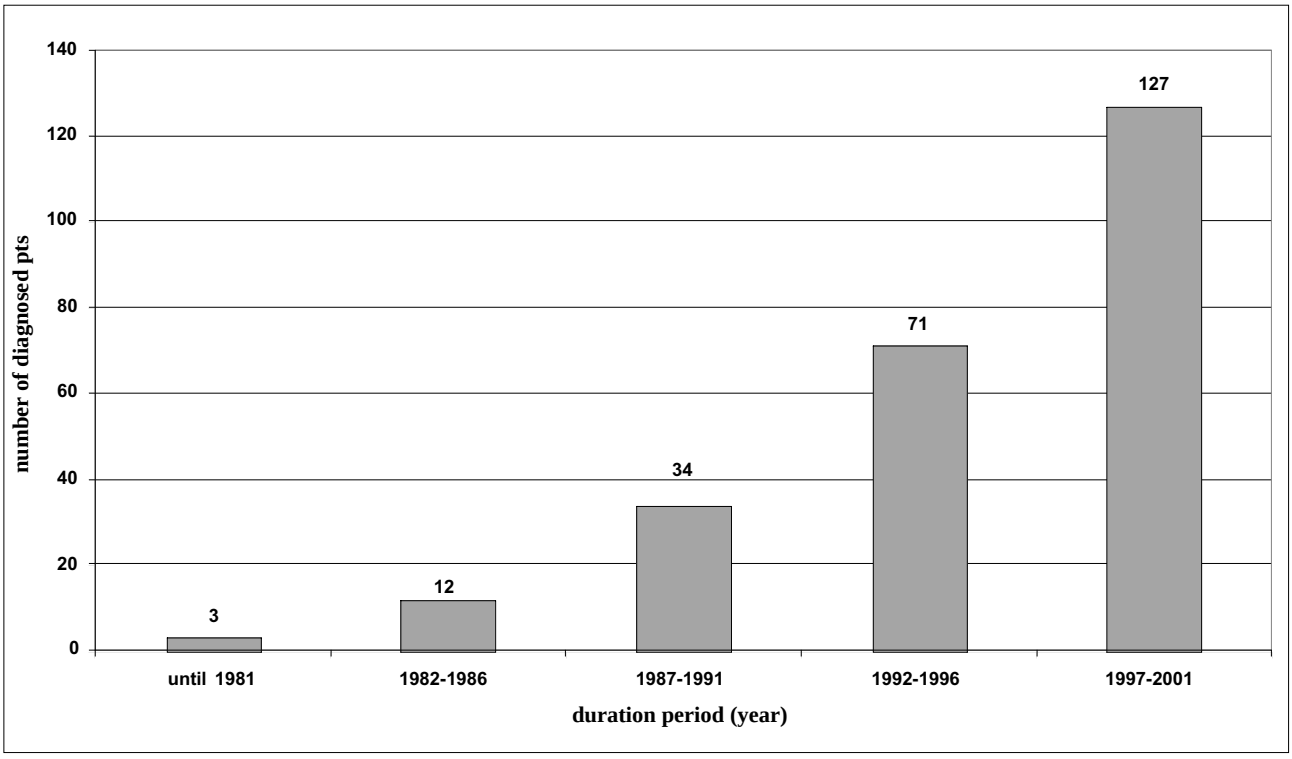

Figure 1. The number of patients diagnosed in 5-year intervals.

Table 2. Frequency of common infection in different phenotypes of primary immunodeficiency disorders.

	Pneumonia	**Otitis media**	**Sinusitis**	**Diarrhea**	**Osteo-myelitis**	**Septic arthritis**	**Meningitis/ Encephalitis**	**Superficial abscess**	**Deep abscess**	**Candidiasis**	**BCG-osis**
Humoral def (n=130)	88 (67.6%)	67 (51.5%)	62 (47.6%)	80 (61.5%)	4 (3%)	10 (7.6%)	19 (14.6%)	10 (7.6%)	13 (10%)	10 (7.6%)	0 (0%)
CVID (n=65)	48	34	36	43	2	2	8	7	3	7	0
XLA (n=33)	25	20	15	22	1	5	9	2	7	3	0
Selective IgA def (n=20)	8	7	5	12	1	3	1	0	1	0	0
Hyper-IgM syn (n=4)	2	3	2	2	0	0	0	1	1	0	0
Selective subclass IgG def (n=8)	5	3	4	1	0	0	1	0	1	0	0
T-cell def (n=61)	26 (42.6%)	19 (31.1%)	11 (18%)	17 (27.8%)	2 (3.2%)	0 (0%)	4 (6.5%)	5 (8.1%)	0 (0%)	17 (27.8%)	3 (4.9%)
CID (n=5)	3	1	0	3	1	0	1	1	0	2	2
SCID (n=7)	5	2	1	3	1	0	1	1	0	6	1
AT (n=39)	13	13	9	7	0	0	0	1	0	3	0
Wiscott Aldrich syn (n=4)	3	3	0	3	0	0	2	2	0	0	0
CMCC (n=6)	2	0	1	1	0	0	0	0	0	6	0
Phagocytic def (n=55)	32 (58.1%)	20 (36.3%)	9 (16.3%)	21 (38.1%)	7 (12.7%)	7 (12.7%)	1 (1.8%)	25 (45.4%)	20 (36.3%	16 (29%)	6 (10.9%)
CGD (n=29)	15	6	4	10	7	6	0	11	9	6	6
LAD (n=10)	5	3	0	3	0	0	0	6	5	4	0
Hyper-IgE syn (n=8)	7	5	3	5	0	1	1	4	6	3	0
Schwachmann's syn (n=4)	2	4	1	2	0	0	0	4	0	3	0
Chediac-Higashi syn (n=4)	3	2	1	1	0	0	0	0	0	0	0
Complement def (n=1)	0	0	0	0	1	0	0	0	0	0	0

in almost all of the patients' families. Pneumonia, tuberculosis, aspergilosis and pulmonary abscesses were their main clinical presentations. 10 cases of leukocyte adhesion defect (LAD), 8 cases of hyper-IgE syndrome, 4 cases of Chediac-Higashi syndrome and finally 4 cases of Schwachmann's syndrome were found in the other patients.

There was only 1 female patient with complement deficiency who presented with septic arthritis.

As septic diseases were the majority of our complications, we categorized the frequency of various common infections in different phenotypes of PID (Table 2).

Discussion

In this study we gathered 247 patients who were identified as PID based on WHO criteria [8] at our referral immunology/allergy clinic during a period of 20 years. In fact, the goal of this study is of greater interest than merely the epidemiological data that it may provide. It can also show the health impact of PID and highlights the importance of detection of immunodeficiency disorders in patients with other diseases like recurrent infections without any underlying disease.

Although an increasing trend in recognition of more PID may be due to improvement in the pediatrician's awareness and increase in the number of sub specialist; due to lack of knowledge by most physicians and to poor available diagnostic capabilities, the frequency of patients in this study does not reflect the actual prevalence of primary immunodeficiency disorders.

Comparison of frequencies of different specific types of PID reveals striking differences; for example antibody deficiencies were the most common disorders as expected from other studies [5-7, 9-12]. As regards IgA deficiency, it was the most common phenotype of PID identified in other registries [6-7], but in our study we could only identify 20 patients. This low incidence of IgA deficiency in our patients' population is consistent with other studies from Japan and Australia which found other immunoglobulin abnormalities like CVID more frequent than IgA deficiency [4, 9, 13]. It may be due to asymptomatic presentation of IgA deficiency in most of the cases.

Our XLA patients experienced their initial symptoms after their first birthday which is compatible with other reports (14-16); however there has been earlier diagnosis in recent years in Iran compared to previous studies [14-15].

In contrast to other reports, we found less cases of SCID. It may be due to delay in diagnosis which leads to death in most patients in their early life. (5-7, 9-12)

Ataxia telangiectasia (AT) and chronic granulomatous disease (CGD) were much more frequent in this study compared to other registries, the reason depending not only on available not-sophisticated tests but also on the genetic background in Iranian population which concerning AT could be supported by the results of the registries in nearby countries like Turkey [17].

An increase in knowledge and available facilities for detecting primary immunodeficiency disorders is important, not only for earlier diagnosis but also to treat the patients more appropriately and diminish their possible complications more effectively.

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Asghar Aghamohammadi

Immunology, Asthma and Allergy Research Institute,
Children's Medical Center, Nº 62, Dr. Gharib St, Keshavarz Blvd.,
Tehran 14194, Iran, P.P. Box: 14185-863
Tel.: + 98 21 693 58 55
Fax: + 98 21 642 89 95
Email: info@iranianpia.org

