Comprehensive Report of Primary Immunodeficiency Disorders from a Tertiary Care Center in Marrakesh.

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Abstract

Introduction Recent advances in immunologic techniques have lead to increase recognition of primary immunodeficiency diseases (PID). Objective We sought to analyze and describe the spectrum of PID at a tertiary care center in Morocco. Methods A retrospective study from 2011 to 2017 was conducted on 27 children diagnosed with PID. Result Over the study period, combined immunodeficiencies with associated or syndromic features were the most common category (48.15%) followed by immunodeficiencies affecting cellular and humoral immunity (25.9%), congenital defects of phagocyte number or function (14.81%), predominantly anti-body deficiencies (7.4%), and diseases of immune dysregulation (3.7%). The most frequent disorder was Ataxia-telangiectasia (44.4%). The mean age at diagnosis was 4.62 years. The consanguinity rate was 74.1%. The principal clinical signs were lower respiratory tract infections (59.2%), neurological manifes-tations (44.4%), failure to thrive (51.8%) and skin infections (33.3%). Two patients who have immunodeficiencies affecting cellular and humoral immunity died. Conclusion This study indicates that PIDs are not rare in Morocco and that combined immunodeficiencies with associated or syndromic features are the most common category. Future research should focus on identifying gene defect for PID patients.

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Keywords

Primary immunodeficiency diseases, epidemiology, Inborn errors of immunity, clinical feature, Marrakesh.

Abbreviations

AT Ataxia-telangiectasia

CID Less profound combined immunodeficiencies

CGD Chronic granulomatous disease

CVID Common variable immunodeficiency disorder

ENT Ear, nose and throat

ESID European Society for Immunodeficiency

HIES Hyper IgE syndrome

HIGM Hyper-IgM syndrome

HIV Human Immunodeficiency Virus

HSCT Hematopoietic stem cell transplantation

Ig Immunoglobulin

IUIS International Union of Immunological Societies

IVIG Intravenous immunoglobulin

LAGID Latin American Group for Primary Immunodeficiencies

PID Primary immunodeficiency disease

SCID Severe combined immunodeficiency

Summary

Introduction Recent advances in immunologic techniques have lead to increase recognition of primary immunodeficiency diseases (PID).

Objective We sought to analyze and describe the spectrum of PID at a tertiary care center in Morocco.

Methods A retrospective study from 2011 to 2017 was conducted on 27 children diagnosed with PID.

Result Over the study period, combined immunodeficiencies with associated or syndromic features were the most common category (48.15%) followed by immunodeficiencies affecting cellular and humoral immunity (25.9%), congenital defects of phagocyte number or function (14.81%), predominantly antibody deficiencies (7.4%), and diseases of immune dysregulation (3.7%). The most frequent disorder was Ataxia-telangiectasia (44.4%). The mean age at diagnosis was 4.62 years. The consanguinity rate was 74.1%. The principal clinical signs were lower respiratory tract infections (59.2%), neurological manifestations (44.4%), failure to thrive (51.8%) and skin infections (33.3%). Two patients who have immunodeficiencies affecting cellular and humoral immunity died.

Conclusion This study indicates that PIDs are not rare in Morocco and that combined immunodeficiencies with associated or syndromic features are the most common category. Future research should focus on identifying gene defect for PID patients.

Introduction

Inborn errors of immunity, also referred to as primary immunodeficiencies (PID) are a heterogeneous group of inherited conditions, caused by defects in the immune system, and characterized by an unusual increased susceptibility to infections and a predisposition to allergy, autoimmunity, and malignancy [1]. The classification of PID is reviewed periodically and based on the responsible immune disorder or deficit. The most

current classification includes over 416 different diseases and 64 gene defects, classified into 8 main categories [2]. Primary Immunodeficiency disorders are more common than generally thought, a random digit dialing telephone survey in 2007 estimate that one in 1200 people within the United States are diagnosed with an immunodeficiency [3], patients may suffer from long-term morbidity without proper treatment due to wrong diagnosis, and some may die [4]. Efficient methods are expected to be developed for timely diagnosis and treatment. Collections of clinical data may help people recognize the features of these diseases. Databases or national registries for PID cases have been established in many countries and regions, which helped to improve the diagnosis level in those areas [5].

Objective

The objective of this study is to describe the epidemiological, clinical, and laboratory characteristics of patients with PID diagnosed at Department of Pediatrics, Mohammed VI University Hospital, Marrakesh, Morocco over a 6 years period.

Patients and Methods

Patient Enrollment

Twenty seven patients with primary immunodeficiency hospitalized in our department and who were diagnosed during the period from January 1st, 2011 to March 31st, 2017 were included in the study. The diagnosis was established according to IUIS Primary Immunodeficiency Classification Committee [2]. We have followed the steps proposed by Admou et al for the diagnosis of PID patients [6]. Secondary immunodeficiencies (such as related to drug, HIV infection, or other conditions) were eliminated by doing relative tests.

Evaluation Sheet

An evaluation sheet was developed to contain all patients demographic information including: name, date of birth, parental consanguinity, sex, number of sibs, order between sibs, previous sib death whether unexplained or due to infection, history of previous medications and vaccination, and family history of PID and/or recurrent infection. Any abnormal clinical finding during clinical examination was notified. Laboratory analyses included HIV test, complete blood count with differential, platelet count, measurement of serum immunoglobulins (IgG, IgA, IgM, and IgE), IgG subclasses, peripheral blood lymphocyte subsets including the basic panel of T-cell subset (CD3, CD4, CD8), B-cell (CD19) and natural killer cell (CD56/16) by flow cytometry. If required, antibody response following immunization, delayed cutaneous hypersensitivity (purified protein derivative), nitroblue tetrazolium dye testing, measurement of serum alpha fetoprotein, and assessment of the expression of CD18/CD11 on neutrophils by flow cytometry were performed. Genetic testing was not available.

Result

Distribution of diseases

In this study, 27 patients were distributed in five main categories of PIDs (Fig1). None of the patients were identified in any category of diseases of immune dysregulation, autoinflammatory disorders, or complement deficiencies. Combined immunodeficiencies with associated or syndromic features were the most common category (13 patients, 48.15%), followed by immunodeficiencies affecting cellular and humoral immunity (7 patients, 25.9%), congenital defects of phagocyte number or function (4 patients, 14.81%), predominantly antibody deficiencies (2 patients, 7.4%), and defects in intrinsic and innate immunity (one patients, 3.7%) (Table I). Among combined immunodeficiencies with associated or syndromic features category, ataxia–telangiectasia was the most frequent phenotype, which existed in 44% of all patients (12 patients). T-B+ severe combined immunodeficiency (SCID) had the most patients in immunodeficiencies affecting cellular and humoral immunity category, and chronic granulomatous disease (CGD) was more common than any other phenotype in congenital defects of phagocyte category (Table I).

Population characteristics and age distribution

The patient population included 15 boys and 12 girls, with a male-to-female ratio of 1.25:1. The median age at diagnosis was 4.16 years and the mean age was 4.62 years (range, 23 days–15 years), no antenatal diagnosis was made.

Consanguinity and family history

Twenty patients (74.1%) were from consanguinity families, in which 15 patients (75%) were 1st degree consanguineous, 3 patients (15%) were 2nd degree consanguineous and 2 patients (10%) were 3rd degree consanguineous.

Eleven patients (40.7%) had family histories of previous sib deaths at an early age, additionally, 15 patients (55.5%) had family histories of PIDs.

Clinical Manifestations of PIDs

The clinical signs observed are listed in Table II. Pneumonia topped the list of symptoms shown in PID patients, manifested by more than half of the patients (16 patients, 59.2%), followed by failure to thrive (14 patients, 51.8%), neurological manifestations -mainly ataxia- (12 patients, 44.4%), skin infections (9 patients, 33.3%), psychomotor retardation (6 patients, 22.2%) and chronic diarrhea (5 patients, 18.5%). The less common manifestations were onychomycosis (2 cases), allergic disease (1 case), and necrosis of the penis (1 case). However, the frequency of these signs depended on the group of PIDs considered. For example, ear, nose, and throat (ENT) infections, lower respiratory infections, and failure to thrive (all 80%) were particularly frequent in immunodeficiencies affecting cellular and humoral immunity. Similarly, bronchiectasis was found to be a common complication of antibody deficiencies (58.3%). As for combined immunodeficiencies with syndromic features neurological manifestations (69.2%), failure to thrive (53.8%), and lower respiratory infections (53.8%) were more common. In patients with congenital defects of phagocyte, oral thrush (75%), deep abscess (50%), and chronic diarrhea (50%) were the most frequent symptoms.

Therapy

Antibiotics were the most widely used treatments for PID patients. Seventeen patients (65.8%) used antibiotics. The most used antibiotic was sulfamethoxazole-trimethoprim (83.3%, 22 patients), followed by amoxicillin-clavulanate (8.3%, 2 patients), and itraconazole (4.2%, 1 patients).

Four patients (14.6%) received intravenous immunoglobulin (IVIG) replacement therapy. IVIG was used in two conditions: immunodeficiencies affecting cellular and humoral immunity (3 patients) and combined immunodeficiencies with syndromic features (1 patient). We have not recorded any side effects in our patients. Two patients who have SCID received Hematopoietic stem cell transplantation (HSCT) therapy.

Mortality

Two patients (7.4 %) died. Causes of death were fulminant infection and respiratory failure. Both patients died had SCID and did not receive HSCT, because it was impossible.

Discussion

This study presents the first report of PID from the department of pediatrics in Mohammed VI University Hospital, Marrakesh, and covers approximately all the south of Morocco. Moreover, it provides a description of the epidemiological characteristics of the PID patients. This study covers patients of one single-center, and the prevalence of these disorders in our country is certainly higher. Certainly, our data underestimates the disease burden in Morocco; asymptomatic PID patients (such as asymptomatic selective IgA deficiencies) were not included in the study because no screening test is routinely done, moreover the study does not include patients with mild forms of PID managed as outpatients. Finally severe forms of PID such as SCID usually die from severe infections during infancy without having diagnosis [7].

The percentages of PID in our cohort show similarities with some studies worldwide and differences with others. We have expected that the combined immunodeficiencies with associated or syndromic features were the most common in our study including 48.15% of patients. Also, the predominant category of PIDs in the

ESID, LAGID registries is antibody deficiencies [8–15], however, this category represents only 7.4% in our study.

In contrast with the ESID registry, patients in North African population tend to be equally distributed between immunodeficiencies affecting cellular and humoral immunity, predominantly antibody deficiencies and combined immunodeficiencies with associated or syndromic features [17–19]. This difference is due to the limits of PID exploration encountered in less developed regions, leading to the over representation of severe phenotypes of patients who presented with symptoms needing referral to a tertiary center. We also had no patient diagnosed with common variable immunodeficiency that represents a large proportion of predominantly antibody deficiencies, because our patients were exclusively children. Moreover, only symptomatic PIDs were diagnosed in our series, whereas other registries generally include cases of asymptomatic PIDs like asymptomatic IgA deficiency.

In our series, severe PID phenotypes are more common than mild forms. As a consequence, immunodeficiencies affecting cellular and humoral immunity were the second common PID category comprising 25.9% of our patients which is much higher than the ESID registry (8.35%) and occident registries [5,14]. However, the high frequency of CID in our cohort is similar to results reported in Iran [20], Kuwait [21], Egypt [22], Saudi Arabia [23], and Tunisia [18]. Those similarities can be explained by the high prevalence of consanguineous marriages in arabe world, and genetic predisposition of certain PID diseases. In fact, the rate of consanguinity seen in our cohort was 74.1% compared to 22.7% in the general population [24] and it was nearly similar to the high rates reported from other countries in the region [19–21,25], and could offer an explanation for the relatively high rate of autosomal recessive disorders seen in our study, especially AT, SCID and CGD. Indeed, consanguinity has also been considered as an important contributing factor for the high frequency of predominantly antibody deficiencies and SCID in Saudi Arabia [23], SCID, AT, and CGD reported in Iran [20], and SCID and AT in both Kuwait and Tunisia [18,21].

The high frequency of AT and T-B + SCID could be due to the genetic backgrounds and the high consanguinity rate. The idea of genetic backgrounds in north African populations can be supported by other studies that have noted a high frequency of AT [17,19,26]. The c.5644C>T mutation is the most common in Morocco [27]. The rate of consanguineous marriages in our PID patients was very high (74.1%), and this could be an indicator of an important social and health problem in our country.

Meanwhile, PID registries in other countries with low rates of family marriages have mentioned familial cases indicating the occurrence of PID in more than one family member who were not necessarily consanguineous. Familial cases were seen in 31.2% of all PID patients in Australia and New Zealand [15].

In the combined immunodeficiencies with associated or syndromic features, ataxia telangiectasia was the most frequently reported in our study and in other similar studies from Morocco, Iran, Tunisia, and Turkey [18,19,25,26,28]. We have expected that T-B+ severe combined immunodeficiency (SCID) had the most patients in immunodeficiencies affecting cellular and humoral immunity category, the same proportion is found by Shabestari et al and Wang et al [25,29].

In our study, the incidence of PIDs in males was much higher (males: females 1.25:1). This ratio is in line with worldwide trends, except Iceland [11], and similar to the registries of Australia, Sweden, Kuwait, and Iran, and likely due to X-linked conditions such as X-linked SCID and X-linked CGD [15,20,21,30].

The mean age of our patients was 4.62 years. This indicates that there is an important delay in diagnosis of PID because most physicians have poor knowledge about these disorders. That was similar to other reports [10,14,15]. This delay has definitely led to significant morbidity that were seen in our patients with chronic lung infections and other infections, which definitely could have been prevented if the diagnosis had been established early [31].

Recurrent and severe infections were the commonest manifestation of our PID patients. The patients with recurrent and severe infections should be evaluated for possible PID, as early diagnosis and successful management of these patients improve the prognosis and prevent further complications [20].

The discovery of new therapeutic modalities has significantly improved the morbidity and mortality in PID patients [32]. 65.8% of our patients were maintained on prophylactic oral antimicrobials in order to decrease the frequency of infections, and 14.6% of patients were on IVIG replacement therapy, which is even less than the percentage reported from Middle East countries [21,33] and the ESID registry [34]. Definitive cure of many PIDs is currently achieved by HSCT. In our country we still have poor experience in HSCT in PID conditions: only two patients belonged to SCID receiving HSCT in our study. The disease spectrum treated by transplantation was much lower than that reported in other countries [35–37].

Around 6.7 % of patients (two patients) died during the time of the study which is similar to the ESID registry (7.9%) [8], but lower than other reports (around 18.7_34.5%) [38,39] and due to the lack of developed methods of diagnosis and treatment for these patients. However, this low rate of mortality is explained by a recruitment bias, due to the fact that many patients die before being diagnosed. All our deaths were patients with SCID, this is consistent with other reports [18,19]. This leads to the importance of early diagnosis and HSCT early as a curative therapy for SCID and hence, providing opportunities to improve the life quality of PID patients.

Conclusion

Our cohort represents a sample of south Moroccan children having a variety of primary immunodeficiency disorders with high frequency of combined immunodeficiencies with associated or syndromic features. This study indicates that PIDs are not rare in Moroccan children and that combined immunodeficiencies with associated or syndromic features are the most common category.

We have highlighted the effect of high parental consanguinity rates on the emergence of autosomal recessive diseases, and the over-representation of severe phenotypes. Significant epidemiological differences exist among PID registries.

To sum up, reinforcing awareness and education of the practicing physicians, introducing of further diagnostic tests, and establishing national HSCT program should be done to reduce both morbidity and mortality of PID patients.

Conflict of Interest

There is no actual or potential conflict of interest in relation to the study.

Ethical approval

Local Ethical Committee approval was received for the study.

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Table I: Frequency and Characteristics of Children with Different primary Immunodeficiency Phenotypes

category	Diagnosis
Immunodeficiencies affecting cellular and humoral immunity	

	SCID
	T-B+NK+SCID
	T-B+NK-SCID
	T-B-NK+SCID
	T-B-NK-SCID
	Less profound combined immunodeficiencies (CID)
Combined immunodeficiencies with associated or syndromic features	
	Ataxia –telangiectasia
	Hyper IgE Syndrome
Predominantly antibody deficiencies	
	Hyper-IgM Syndrome
Congenital defects of phagocyte	
	Chronic Granulomatous Disease
	Cyclic neutropenia
Defects in intrinsic and innate immunity	
	Chronic mucocutaneus candidiasis
TOTAL	

Table II Clinical presentation of PID

Type of symptome	All PID, N=27 (%)	Immunodeficiencies affecting cellular and humoral immunity, N=7 (%)	Combined immunodeficiencies with associated or syndromic features, N=13 (%)	Predominantly antibody deficiencies, N=2 (%)	congenital defects of phagocyte, N=4 (%)	defects in intrinsic and innate immunity, N=1 (%)
Pneumonia	16 (59.2)	6 (85.7)	7 (53.8)	1 (50)	2 (50)	0
Sinusitis	9 (33.3)	6 (85.7)	1 (7.7)	1 (50)	1 (25)	0
Bronchiectasis	4 (14.8)	1 (14.28)	2 (15.4)	1 (50)	0	0
failure to thrive	14 (51.8)	6 (85.7)	7 (53.8)	0	1 (25)	0
Neurological manifestations	12 (44.4)	1 (14.28)	9 (69.2)	0	2 (50)	0
oral thrush	7 (25.9)	3 (42.8)	0	0	3 (75)	1 (100)
onychomycosis	2 (7.4)	0	0	0	1 (25)	1 (100)
Chronic diarrhea	5 (18.5)	1 (14.28)	2 (15.4)	0	2 (50)	0
Psychomotor retardation	6 (22.2)	1 (14.28)	4 (30.8)	0	1 (25)	0
Auto-immune inflamma-tory disease	4 (14.8)	0	0	1 (50)	2 (50)	1 (100)
Abscess	5 (18.5)	0	1 (7.7)	1 (50)	2 (50)	1 (100)
Allergic disease	1 (3.7)	1 (14.28)	0	0	0	0
Necrosis of the penis	1 (3.7)	1 (14.28)	0	0	0	0

Table III Comparisons with other PID registries

Items	U.S	ESID	Japan	Australia and New Zealand	Brazil	Middle east	Tunisia	South of Africa	Ethnic Turk	Casablanca
Number of cases	22781	13708	1240	1209	1008	1990	520	168	59	421
Period of the report	2004_-2013	1999_-2011	1974_-2007	1990_-2006	1978_-2011	_2013	1988_-2012	1983_-2009	2001_-2006	1998_-2012
Age group	All	All	All	All	All	Pediatric	Pediatric	Pediatric	Pediatric	Pediatric
Diseases composition (%)										
Immunodeficiencies affecting cellular and humoral immunity	5.5%	7,78%	7%	6.3%	6.74%	13.2%	27%	15.5%	37.2%	20.66%
Combined immunodeficiencies with associated or syndromic features	20.9%	15,60%	16%	7.5%	8.33%	17.6%	22%	23.8%	23.7%	27.55%
Predominantly antibody deficiencies	47.3%	55,20%	40%	77.0%	60.81%	35.4%	21%	50.6%	23.7%	6.88%
Immune dysregulaton	5.4%	3,74%	4%	0%	5.25%	3%	2%	0%	0%	2.13%
congenital defects of phagocyte	5.0%	8,48%	19%	3.3%	8.73%	25%	26%	5.4%	5%	17.57%
Defects in intrinsic and innate immunity	1.2%	0,78%	1%	4.5%	5.95%	0.3%	1%	0.6%	6.8%	2.85%
Autoinflammatory disorders	2.8%	1,95%	9%	0%	1.28%	0%	0%	0%	0%	2.85%

Complement deficiencies	3.5%	4,64%	3%	1.3%	2.87%	5%	1%	4.2	3.4%	3.08%
Gender ratio (M/F)	1.32:1	1.41:1	2.3:1	1.17:1	1.28:1	1.67:1	1.4:1	1.5:1	1.56:1	1.17:1
Mortality (%)	/	7.9%	/	/	/	18.7%	34.5%	25%	25.4%	28.8%
patients receiving Ig replacement (%)	67%	45.1%	/	76.2%	/	46%	13.5%	45%	/	/
References	[3,16]	[8]	[40]	[15]	[14]	[38]	[18]	[39]	[25]	[19]

Fig1 : Distribution of primary immunodeficiency disorders in Marrakesh. A high predominance of combined immunodeficiencies with associated or syndromic features is noticed.