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ORIGINAL RESEARCH

Primary Immunodeficiency Diseases in Saudi Arabia: a Tertiary Care Hospital Experience over a Period of Three Years (2010–2013)

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Abstract
Purpose Primary immunodeficiencies (PID) are a group of heterogeneous diseases. Epidemiological studies from databases worldwide show geographical variation. In this study the objective is to determine the spectrum of PID in Saudi Arabia by analyzing the database in a referral tertiary hospital.
Methods This is a prospective data collection by interviews and medical chart review for all PID patients followed at the King Faisal Specialist Hospital & Research Center (KFSH&RC) from May 2010 to April 2013.
Results A total of 502 patients presented (53 % male and 47 % female). Combined immunodeficiencies were the most common (59.7 %), followed by predominantly antibody deficiencies (12.3 %), congenital defects of phagocyte (9.4 %), combined immunodeficiencies with associated or syndromic features (6.2 %), disease of immune dysregulation (6 %), complement deficiencies (5.8), and defects in innate immunity (0.6 %). The most common combined immunodeficiencies phenotype was T-B-SCID (17 %). The patients' ages ranged from less than 1 year old to 78 years, and 394 patients (78.2 %) are in the paediatrics age group (<14 years). The overall mean age of symptoms onset was 17 months and the overall mean delay in diagnosis was 21.6 months. Recurrent infections were the most common occurring clinical presentation (66 %), followed by family history (26 %). Consanguinity was found in 75 % of the patients. A total of 308 (61 %) patients had undergone stem cell transplantation (SCT).
Conclusion The study revealed that combined immunodeficiencies are not uncommon and are the most frequent occurring diagnosis in our patient population. This study is a prerequisite to establish a national registry of primary immunodeficiency in Saudi Arabia.

Keywords Primary immunodeficiencies disorders · severe combined immunodeficiency (SCID) · infections · epidemiology · stem cell transplantation

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Introduction

Primary immunodeficiency diseases (PID) are considered to be rare disorders worldwide. Therefore, establishing a database is important to determine the magnitude, types and spectrum of PID disease encountered in a certain population. Similar databases worldwide have shown geographical and racial variation in the spectrum of PIDs [1–14]. Registry data from Saudi Arabia are limited to two studies. Both are from a homogeneous population and from only one region of the country, and hence likely does not represent the whole nation [15,

16]. Nevertheless, they are important preliminary results, and highlight the need for ongoing, systematic data collection to learn more about PIDs in Saudi Arabia. Furthermore; consanguineous marriages (first cousin marriages) in Saudi Arabia are high, present up to 60 % [17]. This has provided a background for genetic diseases to be abundant in the Saudi population. The elevated rate of consanguineous marriages was shown in the studies of a relatively large number of patients diagnosed with an autosomal recessive inherited form of PIDs as in severe combined immunodeficiency (SCID) [18], hyper-IgE syndrome [19], and hyper-IgM syndrome [20]. Therefore a registry data from Saudi Arabia is important in particular to autosomal recessive inherited PIDs. Moreover the overall incidence of combined immunodeficiencies (CID) is estimated to be 1 in 75,000 to 100,000 live births [21] and since most forms of CID are inherited as autosomal recessive traits, therefore anecdotal experience suggests that the incidence of CID is higher in our region than in western countries, probably exceeding 1 in 10,000 live births [22]. However accurate epidemiologic data remain scarce.

In order to determine the spectrum of PIDs in a Saudi tertiary hospital, we established a database and registered all presenting patients diagnosed with PIDs. Thus we report here the results for the past 3 years. Our goal is for this database to be the foundation for a national registry.

Methods

The King Faisal Specialist Hospital and Research Center (KFSHRC) is a tertiary level hospital for both pediatric and adult patients in the Kingdom of Saudi Arabia. The hospital has received referrals from all around the country since its opening in 1975. A pediatric clinical immunology service was established in 1984 and since then the hospital began to be a major referral for PIDs patients. In May of 2010 a PID database was established as a prospective ongoing hospital-based registry of all patients diagnosed with any of the PID diseases that meet the criteria for diagnosis by the World Health Organization. Data capture forms were developed. Permission was sought and granted by the local Institutional Review Board. Consent was obtained by the patients or their parents. The variables identified in the data capture forms are basic demographic, diagnosis details and treatment procedures. The medical diagnoses are coded with the International Classification of Diseases 10 (ICD-10 AM). Microsoft SQL Server was used to develop and administer the database, which itself is accessed using a standard web browser. All data are confidential and access is restricted to persons with a valid username and password.

Statistical analysis was done using the SAS® software package, version 9.4 (Statistical Analysis System, SAS Institute Inc., Cary, NC, USA). Descriptive statistics were reported for all variables in the study. All categorical variables were reported as counts and percentages. Continuous variables were reported as means, medians, standard deviations, minima, maxima and ranges.

Results

Patient's Distribution

A total of 502 patient encounters were registered in the database from May 2010 to April 2013. The patients were diagnosed with 34 different primary immunodeficiency diseases which belong to 7 main PID categories. None of the patients were identified in the autoinflammatory disorders category or the phenocopies of PID. Combined immunodeficiencies it's the predominant category, forming 59.7 % of the patients (300 patients), followed by predominantly antibodies deficiency in 12.3 % (62 patients), congenital defect of phagocyte in number and/or function in 9.4 % (47 patients), combined immunodeficiencies with associated or syndromic features in 6.2 % (31 patients), diseases of immune dysregulation in 6 % (30 patients), complement deficiencies in 5.8 % (29 patients), and innate immunity in 0.6 % (4 patients) (Fig. 1 and Table 1). Among the combined immunodeficiencies, SCID T^-B^- was the most common type in 17 % (85 patients). SCID T^-B^+ was found in 5 % (25 patients), followed by Omenn syndrome in 3.6 % (18 patients). SCID patients who did not match any phenotype of the combined immunodeficiencies by the IUIS classification was diagnosed as SCID- not otherwise specified (SCID- NOS) and this was in 3.2 % (16 patients). ADA deficiency and combined immunodeficiency (CID) (CID are defined as patients with partial T&B cell abnormalities who survived after the age of 2 years without immunologic reconstitution) were in 2.8 % (14 patients) each. The least common diagnoses were PNP and CD8 deficiency in 0.8 % (4 patients each) and reticular dysgenesis in 0.6 % (3 patients). Major Histocompatibility Class II deficiency (MHCII deficiency) was the second most common diagnosis in 12.4 % of the patients (62 patients) (Table 1). Common variable immunodeficiency (CVID), chronic granulomatous disease (CGD), Wiskott-Aldrich syndrome, and Griscelli syndrome were the most commonly diagnosed PID diseases in their respective categories, and they were diagnosed in 7.6, 6.2, 3.8, and 3.8 % respectively among the total number of patients (Table 1). In the Complement Deficiencies category, Hereditary Angioedema due to C1-estrease deficiency was diagnosed in 5 % (25 patients). The Innate Immunity category had the least number of patients. The regional distribution of patients was determined on the basis of the patient's home address (Fig. 2).

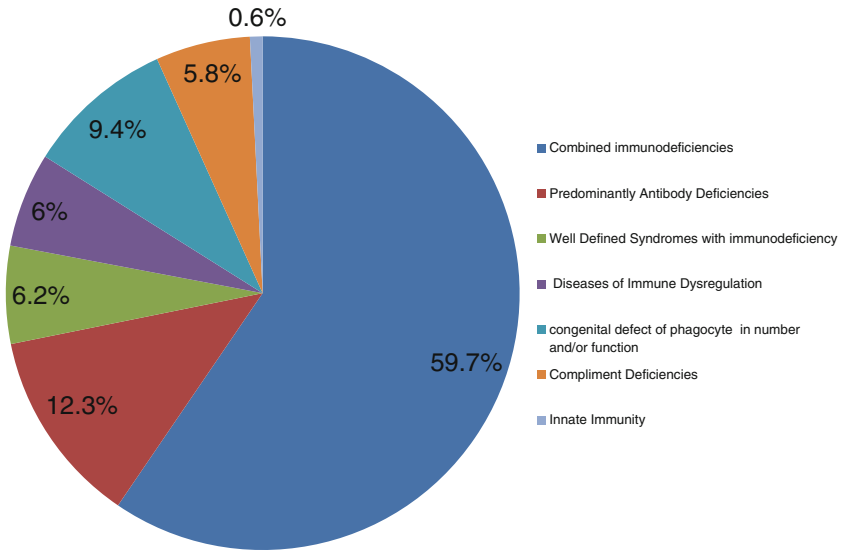

Fig. 1 Patients distribution by main primary immunodeficiencies classification

Age, Gender and Race

The patients' ages ranged from 0 to 78 years, and 394 patients (78.2 %) were in the pediatrics age group (<14 years) (Table 2 and Fig. 3). The male to female (M: F) ratio was 1.1:1.0 overall. This (M: F) ratio remains the same in the combined immunodeficiencies and in the diseases of immune dysregulation category. In contrast the ratio (M:F) was 2.1:1.0 for well-defined syndrome with immunodeficiency, predominantly antibodies deficiency (0.7:1), congenital defect of phagocyte in number and/or function category (1.6:1), Complement Deficiencies (0.7:1) and in The Innate Immunity category (3:1) (Table 2). 97 % of the patients were from a Saudi Arabian ethnic background and 3 % were from other Arabian or Asian ethnic background.

Symptoms Onset, Diagnosis and Delay of Diagnosis

The overall mean age of symptoms onset was 17 months, where combined immunodeficiencies had the earliest onset of symptoms (7.3 months) while the complement deficiencies had the latest onset of symptoms (103 months) (Table 2). The mean age of diagnosis was 39 months for all PID categories. Majority of the patients (470 patients 93 %) were diagnosed during their childhood (<14 years); from among these (280 patients 56 %) were diagnosed before 1 year of age. Combined immunodeficiencies were diagnosed at a mean age of 21 months, in contrast to predominantly antibodies deficiencies which were diagnosed at a mean age of 76.4 months (Table 2). The overall mean for delay in diagnosis was 21.6 months (ranging from less than 1 month to 38 years). The delay in diagnosis in combined immunodeficiencies was 13.5 months and that for those with predominantly antibodies deficiencies were 46 months (Table 2). There were no antenatal diagnoses among patients registered in the database.

Clinical Presentation

Recurrent infections were the most common occurring clinical presentation (66 %), followed by family history (26 %), atypical infection (22 %), failure to thrive (11 %), recognized clinical syndrome (8 %). Atypical infections among the registered patients were disseminated Mycobacterium bovis secondary to Bacillus Calmette- Guerin (BCG) vaccination, Cytomegalovirus (CMV), Pneumocystis jiroveci pneumonia (PJP), Epstein–Barr virus (EBV), and aspergillus in 54, 18, 6, 4 and 2 patients respectively. Disseminated Mycobacterium bovis was found in 49 SCID patients out of 114 SCID receiving the BCG vaccine at birth (43 %). Overall the most common type of recurrent infection at presentation was lower respiratory tract infection (50 %), skin Infections (cellulitis, abscesses) (25 %), chronic diarrhea (24 %), upper respiratory tract infection (21 %), oral thrush (13 %), and deep abscesses (6 %).

Consanguinity and Family History

Consanguinity is defined in this study as patients for whom their parents are first degree cousins. The overall rate for consanguinity was 75 % of all patients. The rate of consanguinity varied among the groups of PID (Table 1). Immune dysregulation had the highest rate of consanguinity at 83 %, followed by combined immunodeficiencies at 78 %, while in the other groups the rates were - predominantly antibodies deficiencies (74 %), phagocytic defects (72 %), well-defined immunodeficiency syndrome (61 %), and complement deficiencies (45 %).

Table 1 Frequency and characteristic of PID patients

Diagnosis	Total	% of total	Male	Female	Family history # (%)	Consanguinity # (%)	Target NBS # (%)
Combined immunodeficiencies	300	59.76 %	159	141	183 (61)	238 (79)	92 (31)
T^- B^{--} Severe combined immunodeficiency	85	17 %	40	45	57 (67)	70 (82)	36 (42)
T^- B^+ Severe combined immunodeficiency	25	5.0 %	13	12	16 (64)	18 (72)	9 (36)
Omenn Syndrome	18	3.6 %	12	6	10 (55)	16 (88)	7 (39)
Adenosine deaminase deficiency	14	2.8 %	7	7	13 (93)	12 (86)	8 (57)
Combined immunodeficiencies	14	2.8 %	5	9	7 (50)	11 (78)	1 (7)
CD 8 Deficiency	4	0.8 %	3	1	3 (75)	2 (50)	1 (25)
Purine nucleoside phosphorylase deficiency	4	0.80 %	4	0	2 (50)	4 (100)	2 (50)
Reticular dysgenesis severe combined immunodeficiency	3	0.60 %	3	0	2 (67)	2 (67)	2 (67)
Severe combined immunodeficiency - NOS	16	3.2 %	7	9	9 (56)	12 (75)	3 (19)
Major histocompatibility complex class II deficiency	62	12.4 %	31	31	37 (60)	50 (81)	15 (24)
Hyperimmunoglobulin E syndrome	30	6.0 %	15	15	12 (40)	23 (77)	2 (7)
Hyperimmunoglobulin M syndrome	25	5.0 %	19	6	15 (60)	18 (72)	6 (24)
Predominantly Antibody Deficiencies	62	12.35 %	27	35	33 (53)	46 (74)	7 (11)
Common variable immunodeficiency	38	7.6 %	12	26	18 (47)	30 (79)	3 (8)
Agamaglobulinaemia	13	2.6 %	8	5	9 (69)	8 (61)	4 (31)
Dysgammaglobinaemia	8	1.6 %	5	3	5 (62)	5 (62)	0 (0)
Selective deficiency of immunoglobulin A	2	0.4 %	1	1	1 (50)	2 (100)	0 (0)
Transient hypogammaglobulinemia of infancy	1	0.2 %	1	0	0 (0)	1 (100)	0 (0)
Combined immunodeficiencies with associated or syndromic features	31	6.2 %	21	10	15 (48)	19 (61)	5 (16)
Wiskott-Aldrich syndrome	19	3.8 %	16	3	15 (79)	9 (47)	5 (26)
Ataxia Telangiectasia	5	1.0 %	2	3	0 (0)	4 (80)	0 (0)
Di George's syndrome	3	0.6 %	2	1	0 (0)	2 (67)	0 (0)
Immunodeficiency with Centromeric Instability and Facial Abnormalities	3	0.6 %	0	3	0 (0)	3 (100)	0 (0)
Dyskeratosis Congenita	1	0.2 %	1	0	0 (0)	1 (100)	0 (0)
Diseases of Immune Dysregulation	30	6.0 %	16	14	17 (57)	25 (83)	11 (37)
Griscelli syndrome	19	3.8 %	9	10	9 (47)	15 (79)	7 (37)
Chediak Higashi Syndrome	9	1.8 %	6	3	8 (89)	9 (100)	5 (45)
X-linked lymphoproliferative disease	1	0.2 %	1		1 (100)	0 (0)	0 (0)
Immunodeficiency following hereditary defective response to Epstein-Barr virus	1	0.2 %		1	0 (0)	1 (100)	0 (0)
Congenital defect of phagocyte in number and/or function	47	9.4 %	29	18	31 (69)	34 (72)	14 (30)
Chronic granulomatous disease	31	6.2 %	19	12	22 (71)	23 (74)	11 (35)
LAD deficiency	13	2.6 %	7	6	8 (61)	11 (85)	3 (23)
MSMD - NOS	2	0.4 %	2	0	1 (50)	0 (0)	0 (0)
Neutropenia - NOS	1	0.2 %	1	0	0 (0)	0 (0)	0 (0)
Compliment Deficiencies	29	5.8 %	13	16	25 (86)	14 (48)	3 (10)
Hereditary Angioedema	25	5.0 %	9	16	22 (88)	9 (36)	3 (12)
Complement Deficiency	4	0.8 %	4	1	1 (20)	5 (100)	0 (0)
Innate Immunity	3	0.6 %	3	1	2 (50)	1 (25)	0 (0)
Chronic Mucocutaneous Candidiasis	3	0.6 %	2	1	2 (67)	1 (33)	0 (0)
Total	502	100.00 %	268	235			

NBS newborn screening, *NOS* not otherwise specified

The lowest rate of consanguinity was recorded for Innate Immunity at 25 %. Family history of PID in other members of the patient's family was found in 306 patients (61 %) (Table 1). 132 patients (26 %) were diagnosed at birth through targeted newborn screening because of family history of previous siblings affected (Table 1).

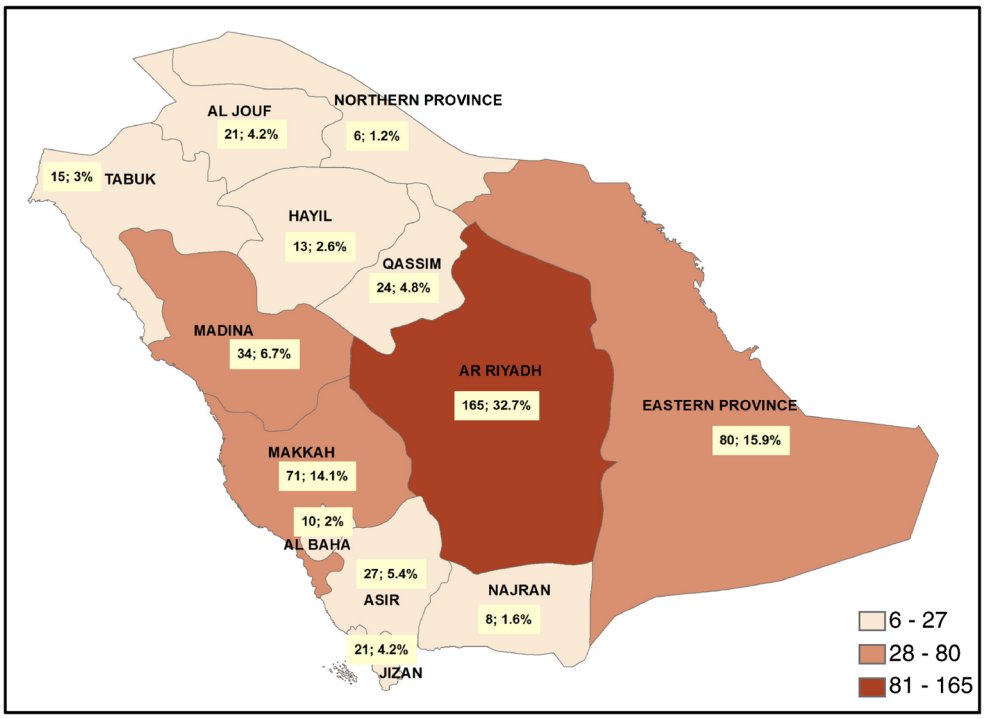

Fig. 2 Regional distribution of PID patients

Treatment

Treatment modalities were captured in the database. Intravenous immunoglobulin (IVIG) replacement was documented for 386 (76 %) of the patients. The mean duration for IVIG replacement was 19.2 months (ranging from 0 to 199 months). In 9 patients IVIG was discontinued because of side effects. Prophylaxis antibiotics were used in 330 patients (65 %). A total of 308 (61 %) patients had undergone stem cell transplantation (SCT). SCT sources were bone marrow in 255 patients (82.8 %) and cord blood in 53 patients (17.2 %). The bone marrow transplant donors were match related donor (MRD) in 218 patients (sibling in 162, parents in 37, and other family related donor in 19 patients), mismatch related donor (MMRD) in 18 patients, haploidentical donor in 17 patients, and matched unrelated donor (MUD) in 2 patients The mean age of transplant was 21.2 months (ranging from 0.5 to 197 months).

Mortality

Out of the 502 patients in the database, 52 patients (31 males and 21 females) died (10.3 %) at some point following registration. The age range of death was 4 to 403 months with a mean age of death of 52 months. 45 patients (88 %) died during childhood, which includes 20 patients before 1 year of age, 32 patients before 2 years, and 41 patient before 5 years of age (38, 63 and 79 %, respectively). The diagnosis of these patients was SCID (27 patients), MHCII deficiency (8 patients), CGD (4 patients), Griscelli Syndrome (3 patients), Hyper-IgE syndrome (2 patients), EBV related lymphoproliferative disorder (2 patients), and dyskeratosis congenital, CVID, ataxia telangiectasia, Wisckott Aldrich syndrome, hyper-IgM syndrome, and leukocyte adhesion deficiency 1 (1 patient each). 34 of these patients (67 %) underwent stem cell transplantation. The donor sources were HLA-matched related in 15 patients, unrelated cord blood in 13 patients, and mismatched related in 6 patients. The most common immediate cause of death was severe pneumonia presenting or progressing to acute respiratory distress syndrome / air leak syndrome with or without pulmonary hemorrhage. The other causes were septic shock, multiorgan failure and refractory cytopenia.

Discussion

Studies of PID databases worldwide are important contributors to our knowledge of the epidemiology, characteristics and features of PIDs in different regions of the world. This study analysed the PID database from the KFSH&RC - a tertiary care hospital in Saudi Arabia with 800 beds, and a major referral centre for stem cell and organ transplants, cancer therapy and inherited diseases. KFSH&RC is the only centre in the country which provides HSCT for PID patients.

The Kingdom of Saudi Arabia's population census (up to 2013) has reported a population 19,838,448 million and 27.6 % are children [23]. The PID prevalence has been calculated for the Saudi pediatrics age groups (0–14 years) since the majority at the time of the study are in this age group (394

Table 2 Current age and age of symptoms, diagnosis and delay in diagnosis for PID patients

Diagnosis	Current age mean (range) in years	Age at symptoms onset mean (range) in months	Age at diagnosis mean (range) in months	diagnostic delay mean (range) in months
Combined immunodeficiencies	7.4 (0.0–33.0)	7.3 (0.0–225.0)	21.0 (0.0–257.0)	13.5 (0–176.0)
T^-B^- Severe combined immunodeficiency	5.6 (0.0–18.0)	1.8 (0.0–20.0)	4.0 (0.0–29.0)	2.1 (0.0–14.0)
T^-B^+ Severe combined immunodeficiency	6.9 (0.0–19.0)	3.3 (0.0–47.0)	12.0 (0.0–121.0)	8.6 (0.0–121.0)
Omenn Syndrome	4.5 (0.0–16.0)	4.4 (0.0–60.0)	8.3 (0.0–74.0)	3.7 (0.0–35.0)
Adenosine deaminase deficiency	9.3 (2.0–29.0)	7.1 (0.0–36.0)	23.3 (0.0–190.0)	16.1 (0.0–176.0)
Combined immunodeficiencies	9.6 (3.0–19.0)	17.4 (0.0–50.0)	72.9 (10.0–158.0)	55.1 (3.0–133.0)
CD 8 Deficiency	9.0 (1.0–20.0)	2.5 (1.0–4.0)	15.0 (4.0–32.0)	12.3 (2.0–28.0)
Purine nucleoside phosphorylase deficiency	5.0 (2.0–8.0)	18.3 (0.0–48.0)	27.5 (0.0–53.0)	8.5 (0.0–27.0)
Reticular dysgenesis severe combined immunodeficiency	6.3 (2.0–15.0)	5.7 (0.0–16.0)	6.7 (0.0–16.0)	1.0 (0.0–3.0)
Severe combined immunodeficiency - NOS	9.1 (1.0–23.0)	2.1 (0.0–7.0)	7.3 (0.0–27.0)	5.0 (0.0–25.0)
Major histocompatibility complex class II deficiency	6.3 (1.0–17.0)	4.3 (0.0–38.0)	13.9 (0.0–134.0)	9.2 (0.0–108.0)
Hyperimmunoglobulin E syndrome	10.3 (1.0–25.0)	22.3 (0.0–225.0)	66.9 (2.0–225.0)	44.5 (12.0–154.0)
Hyperimmunoglobulin M syndrome	12.0 (2.0–33.0)	18.8 (0.0–214.0)	39.8 (0.0–257.0)	20.9 (0.0–155.0)
Predominantly Antibody Deficiencies	15.4 (1.0–45.0)	31.3 (0.0–263.0)	76.4 (0.0–460.0)	44.8 (0.0–460.0)
Common variable immunodeficiency	19.3 (6.0–45.0)	42.6 (0.0–263.0)	103.8 (0.0–460.0)	60.9 (0.0–460.0)
Agamaglobulinaemia	11.8 (1.0–33.0)	15.2 (0.0–89.0)	34.7 (0.0–119.0)	19.2 (0.0–94.0)
Dysgammaglobinaemia	6.3 (1.0–17.0)	3.5 (0.0–7.0)	24.4 (3.0–117.0)	20.4 (0.0–111.0)
Selective deficiency of immunoglobulin A	8.5 (1.0–16.0)	46.5 (0.0–93.0)	62.5 (8.0–117.0)	16.0 (8.0–24.0)
Transient hypogammaglobulinemia of infancy	3.0 (3.0–3.0)	2.0 (2.0–2.0)	19.0 (19.0–19.0)	16.0 (16.0–16.0)
Combined immunodeficiencies with associated or syndromic features	9.3 (0.0–23.0)	10.9 (0.0–0.97)	33.3 (0.0–146.0)	22.2 (0.0–73.0)
Wiskott-Aldrich syndrome	8.3 (0.0–23.0)	9.5 (0.0–97.0)	23.5 (0.0–146.0)	13.9 (0.0–73.0)
Ataxia Telangiectasia	10.6 (7.0–16.0)	15.6 (0.0–35.0)	54.4 (26.0–82.0)	38.6 (2.0–67.0)
Di George's syndrome	8.3 (5.0–10.5)	12.3 (0.0–37.0)	47.7 (28.0–63.0)	35.0 (15.0–63.0)
Immunodeficiency with Centromeric Instability and Facial Abnormalities	19.3 (12.0–23.0)	16.3 (1.0–36.0)	61.0 (23.0–87.0)	44.7 (11.0–72.0)
Dyskeratosis Congenita	4.0 (4.0–4.0)	4.0 (4.0–4.0)	15.0 (15.0–15.0)	11.0 (11.0–11.0)
Diseases of Immune Dysregulation	10.6 (1.0–37.0)	23.9 (0.0–193.0)	46.3 (0.0–411.0)	22.1 (0.0–239.0)
Griscelli syndrome	10.0 (1.0–22.0)	13.6 (0.0–92.0)	29.3 (0.0–158.0)	15.4 (0.0–106.0)
Chediak Higashi Syndrome	9.8 (3.0–16.0)	31.6 (0.0–193.0)	45.9 (0.0–193.0)	14.3 (0.0–58.0)
X-linked lymphoproliferative disease	37.0 (37.0–37.0)	171.0 (171.0–171.0)	411.0 (411.0–411.0)	239.0 (293.0–293.0)
Immunodeficiency following hereditary defective response to Epstein-Barr virus	6.0 (6.0–6.0)	24.0 (24.0–24.0)	48.0 (48.0–48.0)	24.0 (24.0–24.0)
congenital defect of phagocyte in number and/or function	9.0 (1.0–34.0)	8.7 (0.0–140.0)	27.6 (0.0–269.0)	18.7 (0.0–129.0)
chronic granulomatous disease (CGD)	10.4 (1.0–34.0)	12.5 (0.0–140.0)	35.5 (0.0–269.0)	22.8 (0.0–129.0)

Table 2 (continued)

Diagnosis	Current age mean (range) in years	Age at symptoms onset mean (range) in months	Age at diagnosis mean (range) in months	diagnostic delay mean (range) in months
leukocyte adhesion deficiency 1	6.6 (1.0–17.0)	0.2 (0.0–2.0)	4.2 (0.0–24.0)	3.8 (0.0–24.0)
MSMD (NOS)	6.5 (2.0–11.0)	4.5 (2.0–7.0)	51.0 (3.0–99.0)	46.5 (1.0–92.0)
Neutropenia NOS	3.0 (3.0–3.0)	9.0 (9.0–9.0)	40.0 (40.0–40.0)	30.0 (30.0–30.0)
Compliment Deficiencies	21.8 (3.0–78.0)	103.9 (0.0–556.0)	157.9 (0.0–608.0)	53.8 (0.0–459.0)
Hereditary Angioedema	23.7 (3–78)	114.4 (0.0–556.0)	174.4 (0.0–608.0)	59.7 (0–459.0)
Compliment Deficiency	10.0 (4.0–19.0)	38.3 (2.0–109.0)	55.0 (21.0–111.0)	16.5 (1.0–26.0)
Innate Immunity	8.0 (6.0–10.0)	9.3 (1.0–24.0)	75.3 (31.0–98.0)	66.0 (28.0–97.0)
Chronic Mucocutaneous Candidiasis	8.0 (6.0–10.0)	9.3 (1.0–24.0)	75.3 (31.0–98.0)	66.0 (28.0–97.0)

NOS not otherwise specified

patients). Furthermore, the total number of registered predominant antibodies deficiency (the most frequent in adult group), does not reflect the actual number of patients in the population, and therefore the prevalence in the whole population will be underestimated. Accordingly, a minimal estimate for the prevalence of all PIDs is 7.2 in 100,000 Saudi children population. The prevalence and incidence for CID, SCID and MHCII is reported in Table 3. Since the hospital is the major referral centre for the Kingdom, this may present an almost complete number of cases in the country. CID estimated prevalence from our data is 4.82 / 100 000 Saudi children population (Table 3) this high prevalence was also shown in previous publications from regional studies to be at 7 and 2.6 / 100 000 from the eastern province of Saudi Arabia [16] and Kuwait [6] respectively. This in compared to CID prevalence reported from other registries in the UK [1], France [2] and Germany [11] at 0.35, 0.52 and 0.05 respectively. As well as SCID prevalence and incidence (Table 3) from our data showed to be high and up to 10 times that published in studies from other countries as UK [1], France [4], Australia and New Zealand [3], Latin America [4], and Japan [5]. Moreover MHC class II deficiency registered in our database in 62 patients, this is another rare autosomal recessive disease where only about 150 patients reported in the literature, the majority are from a similar highly inbred tribes in north Africa [24] and the Arabian peninsula [25]. This could be attributed to the high rate of consanguineous marriages and autosomal recessive diseases in our population. The overall consanguinity (first degree cousin marriages) rate in our registry was 75 %; this high rate has also been reported in other regional PID registries as in Kuwait [6], Oman [7], Egypt [8], Tunisia [9] and Iran [10] at a rate of 77, 81, 63, 46 and 63.1 % respectively. This in contrast to the rate of consanguinity in registries from other countries as, UK [1], France [2], Germany [11] South Africa [12], at 3, 15, 8.6, and 1.2 %, respectively.

The distribution pattern of PID in our center shows a higher frequency of combined immunodeficiencies (59.7 %) (Table 1 and Fig. 1), This estimate from our center could be biased because of the fact that our center is the referral center for stem cell transplantation (SCT) in the country as well as diagnostic and therapeutic modalities for other form of PIDs, especially for antibodies deficiency patients are available in other regional hospital cross the country. However, registries from other Arab populations have showed that the rate of combined immunodeficiency is higher than that in the rest of the world; the eastern province of Saudi Arabia (47 %) [16], Egypt (29 %) [8], Tunisia (24 %) [9], and Kuwait (21 %) [6], as compared to data from other worldwide registries; the European Society for Immunodeficiencies registry (7.78 %) [13], Australian / New Zealand (6.2 %) [3], USA (8.8 %) [12], Japan (7 %) [5] and Latin America (10.1 %) [4].

Autosomal Recessive (AR) SCID is the most common type of SCID in our population (90 % of SCID patients). This is

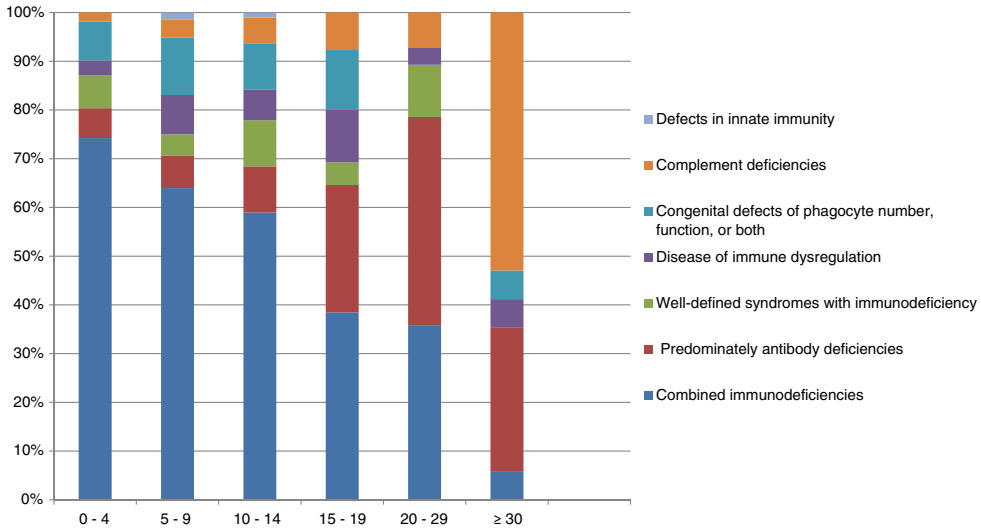

Fig. 3 Patients distribution in each age group

consistent with previous regional studies. For example, AR-SCID for the eastern province of Saudi Arabia [16], Kuwait [6], and Oman [5], were 83, 87, and 96 % respectively. Moreover AR-SCID was also found to be the most common type in other registries, as in the Australian/New Zealand [3] and the ESID [13] (88 and 82 % respectively). X-linked SCID has been widely recognized as the most common type of SCID. This is probably true in only certain parts of the world as in North America [26] and Japan [5]. This emphasizes the racial and geographical variation of PID in different countries. This can also be explained by the higher rate of consanguineous marriages (75 %) in our PID population which in turn leads to a higher prevalence of Autosomal Recessive inherited diseases.

Since they are genetically inherited disorders, the majority of cases manifest in the first year of life. 93 % of our patients were diagnosed during childhood (<14 years). As a result, paediatricians should maintain a high index of suspicion, because early diagnosis and treatment improve the quality of life of patients [27]. Moreover, in severe combined immunodeficiency (SCID), R. Buckley has shown the fact that 36 (97 %) of 37 infants transplanted in her centre in the first 3.5 months of life had survived up to 22 years [28]. This emphasizes the importance of early diagnosis and therapeutic intervention. No new-born screening program for PID is available in our country; however, 26 % (132 patients) were diagnosed at birth by targeted new-born screening for affected families (Table 1). A screening program in our country would be of great benefit in the early case identification of patient with PID, and would lead to an effective enrolment of patients in treatment programs before a life-threatening infection develops. A pilot study is ongoing at our centre using the TREC/KREC assay. The results of this study will help in the developing and adding the TREC/KREC to the national new born screening program.

The mean age at symptoms onset, diagnoses and delay in diagnosis are shown to be variable (Table 2). This reflects the diversity of PIDs. The overall mean for delay in diagnosis for all PIDs was 21.6 months; this is considerably less than what is reported by the EISD registry at 49 months [13]. This finding could be attributed to the low frequency of predominantly antibodies deficiency at 12 % in our registry compare to 55 % in the EISD registry. Patients diagnosed with predominantly antibodies deficiency do have a relatively high delay in their diagnosis [29, 30]; this was also shown in our patients to be at a mean of 44.8 months (Table 2). In addition the mean delay in

Table 3 Estimated incidence and prevalence for CID, SCID and MHC II deficiency in Saudi children population of 5,475,411 million (based upon the 2013 census for the Kingdom of Saudi Arabia)

Disease	Number of cases	Prevalence/ 100 000	Number of new cases in 2011	Incidence/ 100 000 live birth (Live Births 321,070 in 2011)	Number of new cases in 2012	Incidence/ 100 000 live birth (Live Births 333,774 in 2012)
CID	264	4.82	29	9.03	35	10.48
SCID	165	3.01	15	4.67	18	5.39
MHC II deficiency	57	1.04	7	2.18	9	2.69

CID combined immunodeficiency, *SCID* severe combined immunodeficiency, *MHC II deficiency* Major histocompatibility complex class II deficiency

diagnosis from other regional registries was also less than the EISD registry at 15.4, 18.1 and 28 months in Oman [7], Qatar [31] and Kuwait [6] respectively.

Stem cell transplantation was the mode of treatment in 61 % of patients in the database. The donor commonly was a HLA-genoidentical siblings or phenotypic HLA match, this as a result of the high rate of consanguinity and the number of sibling in the families. For example in 50 % of SCID patients a HLA-genoidentical siblings was the best donor option. The mortality rate in our registry was 10.3 % this in compare to a mortality rate of 7.9 % from the ESID registry [13]; however the mortality rate was variable from other registries around the world and may be related to the severity of the type of PID encountered, the early awareness of PID and/ or the availability of diagnostic and therapeutic modalities as stem cell transplantation. for example the mortality rate were 20, 21.4, 23.4 and 28.8 % in Kuwait [6], Qatar [31], Egypt [8], and Morocco [32] respectively this in contrast to 3.5, 13, and 3.1 % in the UK [1], France [2] and Germany [11] respectively.

BCG vaccine derived from multiple passages of wild-type Mycobacterium bovis is administered routinely at birth to all newborns in Saudi Arabia. BCG vaccine is part of national vaccine program in the developing countries to prevent tuberculosis; however, it is only documented to be protective against meningitis and miliary tuberculosis [33]. Adverse reaction to BCG vaccine is uncommon in immunocompetent individuals and mainly results in local subcutaneous abscess and regional lymphadenopathy, occurring in up to 1 % depending on the vaccine strain [34]. Serious complications in the form of disseminated Mycobacterium bovis disease is common in children with immunodeficiency such as SCID, CGD and IL 12-INF gamma defects and is reported in 30–50 % of SCID patients which compares to our rate of 43 % of SCID patients [35]. BCG-itis in its disseminated form requires an intensive treatment and may result in high morbidity and mortality [36, 37]. Delaying BCG vaccine to at less 6 month of age, where most SCID patients by then are diagnosed, is recommended [38].

Conclusion

This study showed a high incidence and prevalence of PIDs in the country. It is only a single center study and multicenter data collection is needed in order to have a comprehensive analysis of PIDs in the country. Nevertheless, this database is a cornerstone for a PIDs Saudi national registry in the future. Combined immunodeficiencies and SCID, in particular, are not uncommon in the country. Therefore, strategic planning in the prevention and the early diagnosis is needed in order to improve patient outcomes by early intervention and avoiding disease complications. This can be achieved by increasing the public's and the health care provider's awareness in PIDs, their clinical features and presentations. Moreover, newborn screening for SCID is an emerging and cost-effective tool in the early Identification of cases [39, 40]. Other key areas of concern include BCG vaccine schedule, consanguinity and the high risk for autosomal recessive inherited disease, and outreach clinical and educational programs to suburban areas for PID patients' care and management.

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