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Frequency and Clinical Manifestations of Patients with Primary Immunodeficiency Disorders in Iran: Update from the Iranian Primary Immunodeficiency Registry

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Primary immunodeficiency disorders (PID) are a heterogeneous group of diseases, characterized by an increased susceptibility to infections. A total of 930 patients (573 males and 357 females) are registered in Iranian PID Registry (IPIDR) during three decades. Predominantly antibody deficiencies were the most common (38.4%), followed by congenital defects of phagocyte number and/or function (28.3%), other well-defined immunodeficiency syndromes (17.7%), combined T- and B-cell immunodeficiencies (11.0%), complement deficiencies (2.4%), and diseases of immune dysregulation (2.3%). Common variable immunodeficiency was the most frequent disorder (20.8%), followed by chronic granulomatous disease, ataxia-telangiectasia, btk deficiency, selective IgA deficiency, and T-B-severe combined immunodeficiency. The frequency of other PID disorders was less than 50 in number ($< 5\%$). There is an increasing trend in recognition of more PID in the recent years. Construction of such registry is not only important for its epidemiological aspect but also for its role in increasing the physician's knowledge about such disorders.

KEYWORDS: Epidemiology; immunological deficiency syndromes; infection; Iran.

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INTRODUCTION

Primary immunodeficiency disorders (PID) are a heterogeneous group of rare inherited conditions, caused by defects of different components of the immune system, and characterized by an unusual increased susceptibility to infections and a predisposition to autoimmunity and malignancy (1–5). Since Bruton described agammaglobulinemia in a patient with recurrent sinopulmonary infections in 1952 (6), more than 100 different types of PID have been recognized till now (2, 7, 8). An increased trend in recognition and characterization of new types of PID is due to advances in our knowledge about the immune system and molecular biology and also recent developments in immunological and molecular diagnostic techniques (2). Physicians poorly know about the clinical and laboratory manifestations of PID, leading to an increased diagnosis lag and inappropriate treatment, which are the main causes of morbidity and mortality in these patients (9–12).

Reports on PID registries are currently available from different countries; these reports show wide geographical

variations in the prevalence of PID, in addition to increasing epidemiological information and new important knowledge about PID (13–25). These registries have shown wide geographical and racial variations in the prevalence and the type of PID. The presence of such registries in other countries prompted us to establish a national registry for patients, both children and adults, with PID (1). The main objectives of Iranian Primary Immunodeficiency Registry (IPIDR) was to determine the frequency of different PID in Iran, to enhance the knowledge of physicians about such disorders, to construct a database for further investigations, to emphasize the importance of early diagnosis and treatment, and to provide better clinical assistance to all patients and better health planning. Four hundred and forty patients were reported in the first report of IPIDR from seven medical centers (1) in which predominantly antibody deficiencies were the most common. This paper provides an update on the frequency of PID from 16 medical centers in Iran and describes the geographical distribution, clinical features, and the overall outcomes of 930 registered patients.

METHODS

Iranian Primary Immunodeficiency Registry

Iran, with a population of 68,467,413 (growth rate 1.1%), is a Middle-East country, situated in the south of the Caspian Sea and north of the Persian Gulf. It shares borders with Turkey, Iraq, Afghanistan, Pakistan, Azerbaijan, and Turkmenistan (Fig. 1).

IPIDR was established in August 1999 (1); however, the clinical files of all patients were reviewed in the past 20 years and afterward. Nine hundred and thirty patients with PID were registered during three decades (before 1980 to March 2006). Asymptomatic cases, including asymptomatic IgA deficiency, were not included in this database.

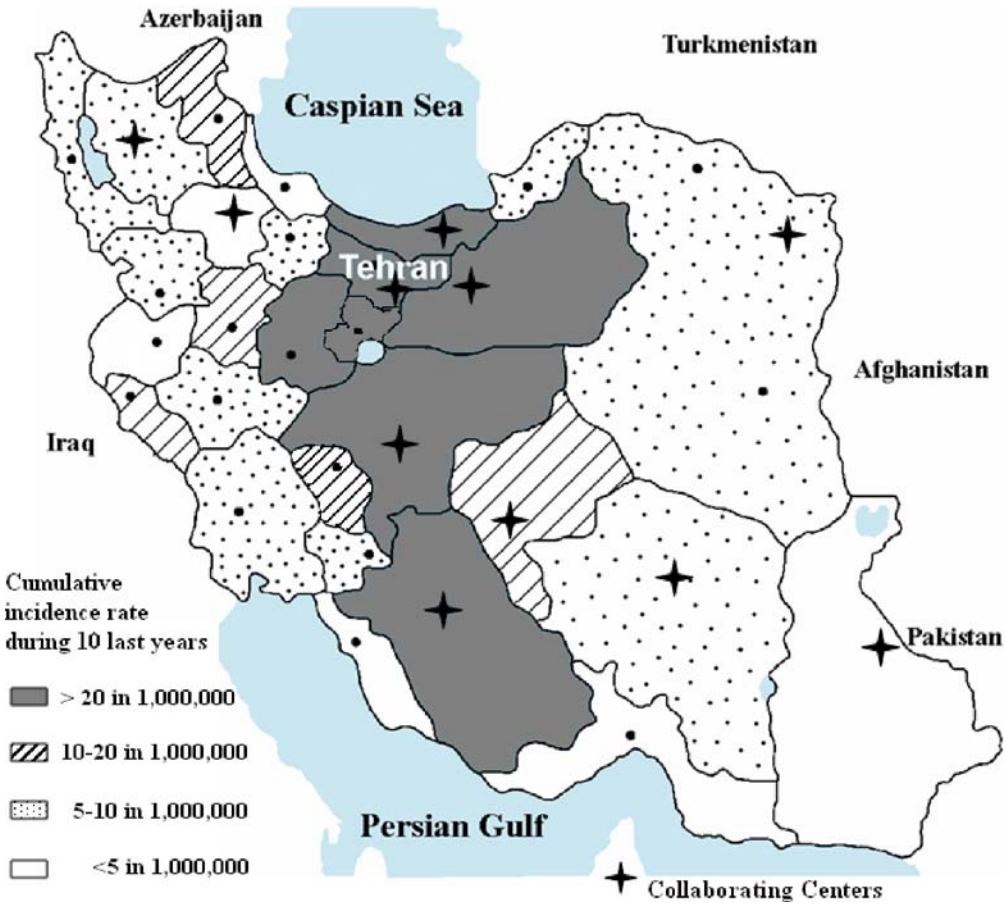

Fig. 1. Geographic distribution of collaborating centers and cumulative incidence of PID patients in Iran during the last 10 years.

Data Collection

The registration of patients consists of following steps: First, the preliminary one-page questionnaires was sent to all participating centers. When necessary, the centers were asked for sending us additional information using four-page questionnaires. All of the questionnaires were completed by the immunologists, involved in the care of the reported patients. After checking the questionnaire by the secretary, patients were registered preliminary in our database. An incomplete form would be returned to the contributing centers for correction. Finally, the diagnosis should be confirmed by one of the scientific committee of registry in order to full entering in the database.

Patient Enrolment

The diagnosis of PID was based on standard criteria, which has been introduced by the Expert Committee of International Union of Immunological Societies (IUIS) on Primary Immunodeficiency (8). Only patients with well-established PID and the clinical manifestations, compatible with their diagnosis, were included in our registry. Secondary immunodeficiencies (like HIV infection) have been ruled out by doing related tests in suspicious cases. Laboratory studies for our immunodeficient patients were performed, including immunoglobulin levels, isohemagglutinins, functional post-vaccination antibody response (e.g., anti-tetanus and anti-diphtheria), lymphocyte subpopulation (T- and B cells) enumeration by flowcytometry method, IgG subclasses titer, chemotaxis evaluation, nitro blue tetrazolium dye test, granulocyte function tests (e.g., chemotaxis and phagocytosis), complement component and hemolytic titration of complement (C3, C4, CH50), as needed. DNA Mutation analysis studies were performed only in some of recent patients for confirmation of diagnosis.

Registry Questionnaire

A preliminary one-page questionnaire was designed for introducing the patients from the contributing centers. It was designed to include only the data for confirming the diagnosis of the patients. A four-page questionnaire was also designed to contain the patient's demographic information, including personal data, age, sex, date of birth, place of birth, the diagnosis of PID, first clinical manifestations, onset age of symptoms, diagnosis age of PID, consanguinity, family history of PID, immunologic laboratory tests, and clinical manifestations, and complications in the course of disease.

Registry Computer Database

A computerized database program was designed based on our questionnaire, written with Visual Basic language programming and using Access Database software. This software allows data entry of all the information, changing the information according to follow-up data, exporting data to Microsoft Office Programs, and also allows direct statistical analysis of data. All the information was centralized and stored in this database. Patient's administrative and personal data were coded when registered in order to meet legal requirements. The coordinator of the protocol has access to patients' data and also has the permission to change the data. The referring physicians could access the data of only their registered patients but could access other data after the permission of the executive committee of the registry.

Contributing Centers

IPIDR was constructed in Children Hospital Medical Center, as the majority of PID patients were referred and diagnosed in this center. However, 16 centers were collaborated with this registry as specialized hospitals affiliated to 14 universities of medical sciences from 12 major states of Iran, including; Tehran, Fars (Shiraz), Khorasan (Mashhad), Isfahan, Mazandaran (Babol), Azarbaijan (Tabriz), Zanjan, Kerman, Semnan, Zanjan, Yazd, Sistan, and Balochistan (Fig. 1). They have been treating patients with PID and have immunologic laboratories for the diagnosis of PID patients. The patients from other states usually are referred to these centers.

Statistical Analysis

Data analysis was done using registry computer database and also SPSS statistical software package (version 11.0). A linear regression analysis was used in order to determine the association between birth date and diagnosis lag. *P*-value of less than 0.05 was considered significant.

RESULTS

Frequency of Different Types of PID

A total of 930 patients representing 40 different diagnoses are registered in IPIDR. Among them, predominantly antibody deficiencies were the most common, constituting 38.4% of our patients (357 cases), followed by congenital defects of phagocyte number and/or function in 28.3% (263 cases), other well-defined immunodeficiency syndromes in 17.7% (165 cases), combined T- and B-cell

immunodeficiencies in 11.0% (102 cases), complement deficiencies in 2.4% (22 cases), and diseases of immune dysregulation in 2.3% (21 cases) (Table I).

In our patient population, a group of disorders which considered common variable immunodeficiency (severe reduction in at least 2 serum Ig isotypes with normal or low numbers of B cells) was the most frequent disorder with one-fourth of all patients (193 patients), followed by chronic granulomatous disease (166 patients, 17.8%), ataxia-telangiectasia (94 patients, 10.1%), a group of disorders which considered btk deficiency (severe reduction in all serum Ig isotypes with absent B cells) (69 patients, 7.4%), selective IgA deficiency (55 patients, 5.9%), and T-B-severe combined immunodeficiency (55 patients, 5.9%). Other PID disorders have a frequency of less than 50 in number (Table I).

Geographical Distribution

There was an increasing trend in recognition of more PID in the recent years. Seven hundred and four patients (75.7% of all patients) were diagnosed in the recent decade, while only 226 cases had been diagnosed before 1995; before 1980, only five patients were diagnosed with PID (Fig. 2). The approximate number of PID diagnosed each year has increased from 7 per year in 1980s to 30 per year during the early 1990s and 58 per year after 2000. According to our data and population estimation, the estimated occurrence of PID is about 6 per 100,000 live births (excluding asymptomatic IgA deficiency). The cumulative incidence of PID is about 11.9 per 1,000,000 population during last 10 years, with a regional variation from 3 to 28 per 1,000,000 population (Fig. 1). According to the geographic distribution of the patients, significantly more patients lived in the Tehran, capital of Iran. The frequency of PID patients was more common in the central and northern parts of Iran compared to that in the eastern and western parts of the country (Fig. 1).

Characteristics of Patients

Five hundred and seventy-three males and 357 females were registered in IPIDR. The male-to-female ratio was 1.7, which differs among different types of PID; all patients with X-linked form of PID, such as CD40 ligand deficiency, btk deficiency, and Wiskott–Aldrich syndrome, were male; meanwhile some types of PID such as complement deficiencies were more common in female patients (Table I).

Age Distribution

The mean age of patients was 13.98 ± 9.3. The youngest patient was a child less than 1 year old, and the oldest patient was a woman 82 years old. More than half of these patients are in pediatric age group (59.3% of patients <14 years old).

The first infectious manifestation had occurred at a median age of 7 months (range <1 month to 49 years). Two hundred and forty-eight cases (26.7%) experienced symptoms by the age of 1 month, 73.3% have been presented their first manifestations by the age 2 years, while only 26 patients (2.8%) did not experience any symptoms until the age of 14 years (Table II).

The median age of the patients at the time of diagnosis was 57 months (range 2 months to 54 years), with a median diagnosis delay of 31 months (range 1 month to 40 years). Although 45% of the patients were diagnosed in 2 years after onset age, one-fourth of patients (233 cases) were not diagnosed until 6 years after onset age. One hundred and four patients (11.2%) were diagnosed after the age 14 years. No antenatal diagnoses were made. The age of patients at the diagnosis and the delay of diagnosis varied considerably in different types of PID (Table II). Statistical analysis of these data was complicated by the fact that the diagnosis has increasingly been made at an earlier age in more recent years ($r = -0.625$, $F = 374.6$, P-value < 0.001). A reverse association was observed between the year of birth and the diagnosis lag (Fig. 3). This diagnosis delay has been decreased from 7 years before the year 1990 to 3 years in the years 1990–1995, and 15 months after the year 1995.

Consanguinity and Family History

Consanguineous marriage is defined as two partners having at least one ancestor in common, with the ancestor being no more distant than a great great grandparent. For descendants who are of the same generation, a consanguineous marriage would be between one person and a third cousin or a closer relative. The overall rate of consanguineous marriages was 68.5% (637 cases). The rate of such marriages varied among different types of PID; it was most common in parents of patients with Kostman syndrome, Chediak–Higashi syndrome, isolated IgG subclass deficiency, Shwachman–Diamond syndrome, ataxia telangiectasia, T-B-severe combined immunodeficiency, Omenn syndrome, and chronic granulomatous disease. The cumulative incidence of PID in consanguineous families was $8.2/10^6$ population during last 10 years, while it was $3.7/10^6$ population in PID patients from nonconsanguineous families. A history of PID and/or recurrent infections or other manifestations compatible with

Table I. Frequency and Characteristics of Iranian Patients with Different Types of PID

Category	Disease	Total	Sex		Dead	Consan-guinity	Family history of PID	Cumulative Incidence in the last 10 years (in 10^6 population)
			Male	Female				
Combined T- and B-cell immunodeficiencies	T^-B^+ Severe combined immunodeficiency	18 (1.9%)	11	7	9 (50.0%)	11 (61.1%)	10 (55.6%)	0.27
	T^-B^- Severe combined immunodeficiency	55 (5.9%)	30	25	31 (56.4%)	45 (81.8%)	28 (50.9%)	0.88
	Omenn syndrome	11 (1.2%)	7	4	8 (72.7%)	9 (81.8%)	2 (18.2%)	0.17
	CD40 ligand deficiency	4 (0.4%)	4	–	–	2 (50.0%)	2 (50.0%)	0.07
	MHC class II deficiency	14 (1.5%)	9	5	3 (21.4)	10 (71.4%)	9 (64.3%)	0.19
	Total	102 (11.0%)	61	41	51 (50.0%)	77 (75.5%)	51 (50.0%)	1.57
Predominantly antibody deficiencies	Severe reduction in all serum Ig isotypes with absent B cells	69 (7.4%)	69	–	13 (18.8%)	29 (42.0%)	50 (72.5%)	0.83
	Severe reduction in at least 2 serum Ig isotypes with normal or low numbers of B cells	193 (20.8%)	117	76	37 (19.1%)	139 (72.0%)	99 (51.3%)	2.50
	Severe reduction in serum IgG and IgA with increased IgM and normal numbers of B cells	11 (1.2%)	4	7	3 (27.3%)	6 (54.5%)	6 (54.5%)	0.14
	Isolated IgG subclass deficiency	14 (1.5%)	9	5	2 (14.3%)	12 (85.7%)	12 (85.7%)	0.24
	IgA with IgG subclass deficiency	4 (0.4%)	4	–	1 (25.0%)	1 (25.0%)	1 (25.0%)	0.03
	Selective IgA deficiency	55 (5.9%)	31	24	2 (3.6)	27 (49.1%)	18 (32.7%)	0.57
	Specific antibody deficiency with normal Ig concentration	5 (0.5%)	1	4	–	1 (20.0%)	1 (20.0%)	0.07
	Transient hypogammaglobulinemia of infancy	6 (0.6%)	5	1	–	4 (66.7%)	2 (33.3%)	0.05
	Total	357 (38.4%)	240	117	58 (16.2%)	219 (61.3%)	189 (52.9%)	4.43
Other well-defined immunodeficiency syndromes	Wiskott–Aldrich syndrome	12 (1.3%)	12	–	3 (25.0%)	5 (41.7%)	7 (58.3%)	0.14
	Ataxia-telangiectasia	94 (10.1%)	45	49	6 (6.4%)	78 (82.9%)	47 (50.0%)	0.86
	Nijmegen breakage syndrome	3 (0.3%)	2	1	–	2 (66.6%)	2 (66.7%)	0.05
	Thymic defects Di George syndrome	5 (0.5%)	4	1	5 (100%)	3 (60.0%)	3 (60.0%)	0.08
	Hyper-IgE syndrome	27 (2.9%)	15	12	5 (18.5%)	17 (62.9%)	11 (40.7%)	0.25
	Chronic mucocutaneous syndrome	24 (2.6%)	11	13	–	15 (62.5%)	4 (16.7%)	0.32
	Total	165 (17.7%)	89	76	19 (9.7%)	120 (72.7%)	74 (44.8%)	1.71
Diseases of immune dysregulation	Chediak–Higashi syndrome	15 (1.6%)	8	7	3 (20.0%)	13 (86.7%)	6 (40.0%)	0.19
	Griscelli syndrome, type 2	3 (0.3%)	2	1	–	–	–	0.05
	X-linked lymphoproliferative syndrome (XLP)	1 (0.1%)	1	–	1 (100%)	1 (100%)	–	0.02
	Autoimmune lymphoproliferative syndrome (ALPS)	2 (0.2%)	1	1	–	–	1 (50.0%)	0.03
	Total	21 (2.3%)	12	9	4 (19.0%)	14 (66.7%)	7 (33.3%)	0.29

Table I. Continued

Category	Disease	Total	Sex		Dead	Consan-guinity	Family history of PID	Cumulative Incidence in the last 10 years (in 10^6 population)
			Male	Female				
Congenital defects of phagocyte number, function, or both	Severe congenital neutropenia	11 (1.2%)	2	9	4 (36.4%)	2 (18.2%)	1 (9.1%)	0.17
	Kostman syndrome	6 (0.6%)	5	1	–	6 (100%)	2 (33.3%)	0.10
	Cyclic neutropenia	30 (3.2%)	20	10	2 (6.7%)	22 (73.3%)	21 (70.0%)	0.42
	Leukocyte adhesion deficiency type 1	37 (4.0%)	24	13	4 (10.8%)	25 (67.6%)	15 (67.6%)	0.49
	Papillon–Lefevre syndrome	2 (0.2%)	1	1	–	–	–	0.03
	Specific granule deficiency	3 (0.3%)	3	–	–	2 (66.7%)	1 (33.3%)	0.02
	Shwachman–Diamond syndrome	6 (0.6%)	4	2	1 (16.7%)	5 (82.3%)	1 (16.7%)	0.03
	Chronic granulomatous disease (CGD)	166 (17.8%)	104	62	15 (9.0%)	133 (80.1%)	78 (46.9%)	2.25
	IL-12p40 deficiency	1 (0.1%)	1	–	1 (100%)	1 (100%)	1 (100%)	0.02
	IFN-gamma receptor 1 deficiency	1 (0.1%)	1	–	–	1 (100%)	–	0.02
	Total	263 (28.3%)	165	98	27 (10.3%)	197 (74.9%)	120 (45.6%)	3.55
Complement deficiencies	C4 deficiency	5 (0.5%)	1	4	–	3 (60.0%)	–	0.07
	C2 deficiency	2 (0.2%)	1	1	–	1 (50.0%)	1 (50.0%)	0.03
	C3 deficiency	1 (0.1%)	1	–	–	–	–	0.02
	C6 deficiency	1 (0.1%)	–	1	–	–	–	0.02
	C1 inhibitor deficiency	8 (0.9%)	2	6	1 (12.5%)	4 (50.0%)	1 (12.5%)	0.14
	C1q deficiency	4 (0.4%)	–	4	–	2 (50.0%)	1 (25.0%)	0.07
	C1r deficiency	1 (0.1%)	1	–	–	–	–	0.02
	Total	22 (2.4%)	6	16	1 (4.5%)	10 (45.5%)	3 (13.6%)	0.35

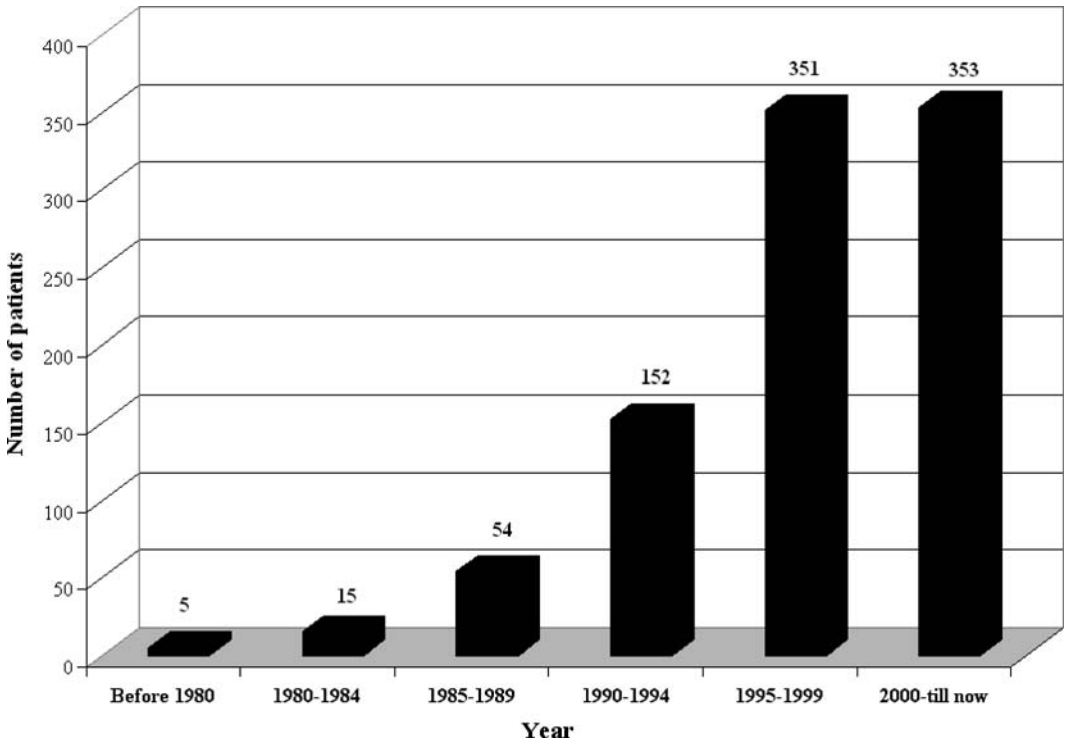

Fig. 2. The number of patients diagnosed in 5-year intervals before 1980 till now.

PID in other members of the patients' family was found in 444 families (47.7%).

Presenting Manifestations

The most common presenting feature of PID patients was pneumonia, which was seen in one-fifth of patients (187 patients, 20.1%). The other common presentation were diarrhea (127 patients, 13.7%), sinusitis (96 patients, 10.3%), otitis media (89 patients, 9.6%), ataxia (in 72 patients with ataxia-telangiectasia, 7.7%), lymphadenopathy (69 patients, 7.4%), superficial abscesses (63 patients, 6.8%), mucocutaneous candidiasis (62 patients, 6.7%), and other cutaneous manifestations (59 cases, 6.3%). The less frequent presenting features were oral ulcers, urinary tract infections, omphalitis, septic arthritis, sepsis, septic meningitis, osteomyelitis, deep abscesses, angioedema, telangiectasis, and disseminated BCG. Some patients had more than one clinical complaint at presentation. One patient was diagnosed as a sibling of a PID patient without any complications. Although respiratory and gastrointestinal tracts are most common systems for presenting illness, lymphadenopathy was the most common manifestation in the group of combined T- and B-cell immunodeficiencies; and superficial abscesses and lymphadenopathy were most common in the group of congenital defects of phagocyte number and/or function.

Clinical Features

Infections were the most common complications in PID patients during the course of disease, which were seen in 883 patients (94.9%). These infections were seen especially in respiratory system (681 patients, 73.2%), cutaneous system (404 patients, 43.4%), and gastrointestinal system (376 patients, 40.4%), followed by central nervous system (130 patients, 13.9%), musculoskeletal system (111 patients, 11.9%), and urinary tract system (72 patients, 7.7%) (Fig. 3). All types of infections were seen in all groups of PID. Respiratory and gastrointestinal manifestations were the most common problems in general, particularly in the groups of predominantly antibody deficiencies and combined T- and B-cell immunodeficiencies, while cutaneous manifestations were most common in the patients with congenital defects of phagocyte number and/or function (Fig. 4).

Seven hundred and forty-six patients (80.2%) had multiple sites of infections. Although approximately half of the patients had infections in two to four organs (460 cases, 49.5%), 286 patients (30.8%) had infections in more than four organs. Pneumonia was the most common infection

Table II. The Age Distribution in Different Types of PID

Category	Disease	Current age (years)	Onset age (months)	Diagnosis age (months)	Diagnosis lag (months)
Combined T- and B-cell immunodeficiencies	T^-B^+ Severe combined immunodeficiency	3.0 (1–8)	2.0 (1–9)	5.0 (3–115)	3.0 (1–114)
	T^-B^- Severe combined immunodeficiency	3.0 (1–8)	4.0 (1–36)	8.0 (2–145)	4.0 (1–118)
	Omenn syndrome	1.0 (1–2)	3.0 (1–130)	7.0 (5–131)	4.0 (1–23)
	CD40 ligand deficiency	5.5 (4–13)	8.5 (1–58)	60.0 (37–75)	29.0 (2–66)
	MHC class II deficiency	11.0 (1–29)	5.5 (1–120)	36.0 (4–227)	25.0 (3–165)
	Total	3.0 (1–29)	3.0 (1–130)	8.5 (2–227)	4.0 (1–165)
Predominantly antibody deficiencies	Severe reduction in all serum Ig isotypes with absent B cells	12.0 (2–36)	11.0 (1–228)	49.0 (10–372)	30.5 (1–204)
	Severe reduction in at least 2 serum Ig isotypes with normal or low numbers of B cells	15.5 (1–82)	9.0 (1–588)	89.0 (2–638)	44.0 (1–477)
	Severe reduction in serum IgG and IgA with increased IgM and normal numbers of B cells	11.0 (6–31)	11.5 (1–132)	54.0 (25–300)	51.5 (1–216)
	Isolated IgG subclass deficiency	13.0 (8–28)	12.0 (1–168)	80.0 (52–236)	54.0 (24–208)
	IgA with IgG subclass deficiency	10.5 (9–20)	4.0 (2–6)	90.0 (90–96)	88.0 (84–92)
	Selective IgA deficiency	13.0 (1–40)	6.0 (1–300)	41.5 (2–336)	12.0 (1–154)
	Specific antibody deficiency with normal Ig concentration	23.0 (20–42)	6.0 (5–6)	12.0 (12–18)	7.0 (6–12)
	Transient hypogammaglobulinemia of infancy	5.5 (2–17)	3.0 (1–7)	26.0 (24–29)	23.0 (18–25)
	Total	14.0 (1–82)	8.0 (1–588)	63.5 (2–638)	35.0 (1–477)
Other well-defined immunodeficiency syndromes	Wiskott–Aldrich syndrome	7.0 (3–22)	2.0 (1–36)	15.0 (3–144)	10.0 (2–140)
	Ataxia-telangiectasia	17.0 (7–33)	13.0 (1–109)	85.0 (2–210)	60.0 (1–209)
	Nijmegen breakage syndrome	5.0 (3–9)	1.0	43.0 (30–50)	42.0 (35–49)
	Thymic defects Di George syndrome	1.5 (1–2)	2.5 (2–3)	8.0 (4–12)	5.5 (1–10)
	Hyper-IgE syndrome	17.0 (8–29)	1.0 (1–36)	86.5 (20–176)	80.0 (19–164)
	Chronic mucocutaneous syndrome	13.0 (6–31)	10.0 (1–72)	40.0 (8–228)	19.0 (2–216)
	Total	15 (1–33)	11.5 (1–109)	83 (2–228)	51.5 (1–216)
Diseases of immune dysregulation	Chediak–Higashi syndrome	9.5 (3–28)	5.0 (1–130)	29.5 (6–136)	20.5 (3–45)
	Griscelli syndrome, type 2	6.5 (6–7)	24.0 (12–36)	66.0 (60–72)	42.0 (36–48)
	X-linked lymphoproliferative syndrome (XLP)	8.0	4.0	152.0	148.0
	Autoimmune lymphoproliferative syndrome (ALPS)	11.5 (10–13)	54.0 (48–60)	126.0 (108–144)	72.0 (48–96)
	Total	8.0 (3–28)	12.0 (1–130)	48.0 (6–152)	30.0 (3–148)

Table II. Continued

Category	Disease	Current age (years)	Onset age (months)	Diagnosis age (months)	Diagnosis lag (months)
Congenital defects of phagocyte number, function, or both	Severe congenital neutropenia	6.5 (1–10)	4.0 (1–22)	16.0 (2–65)	8.0 (1–64)
	Kostman syndrome	5.5 (2–10)	1.0 (1–24)	31.0 (5–61)	18.5 (4–60)
	Cyclic neutropenia	11.0 (2–29)	3.0 (1–66)	25.0 (5–313)	20.5 (1–312)
	Leukocyte adhesion deficiency type 1	9.0 (2–25)	1.0 (1–72)	19.0 (2–168)	17.0 (1–144)
	Papillon–Lefevre syndrome	5.0 (4–6)	30.0 (24–36)	60.0 (48–72)	30.0 (24–36)
	Specific granule deficiency	18 (17–21)	9.0 (1–36)	38.0 (36–108)	35.0 (29–72)
	Shwachman–Diamond syndrome	9.5 (2–19)	1.0 (1–28)	34.0 (13–77)	33.0 (12–76)
	Chronic granulomatous disease (CGD)	13.0 (1–58)	7.0 (1–204)	58.5 (2–650)	26.0 (1–485)
	IL-12p40 deficiency	12.0	108.0	312.0	204.0
	IFN-gamma receptor 1 deficiency	18.0	2.0	10.0	8.0
	Total	12.0 (1–58)	4.0 (1–204)	37.0 (2–650)	24.0 (1–485)
Complement deficiencies	C4 deficiency	18.5 (12–27)	107.0 (6–120)	174.0 (119–240)	72.0 (1–222)
	C2 deficiency	23.5 (22–27)	114.0 (108–120)	210.0 (180–240)	96.0 (72–120)
	C3 deficiency	15.0	60.0	144.0	84.0
	C6 deficiency	18.0	120.0	184.0	64.0
	C1 inhibitor deficiency	24.0 (10–45)	121.0 (25–481)	368.0 (37–505)	120.0 (12–246)
	C1q deficiency	25.0 (22–28)	206.0 (120–292)	260.5 (240–293)	60.5 (1–120)
	C1r deficiency	22	108.0	240.0	132.0
	Total	21 (10–45)	119.0 (6–481)	240.0 (37–505)	84.0 (1–246)

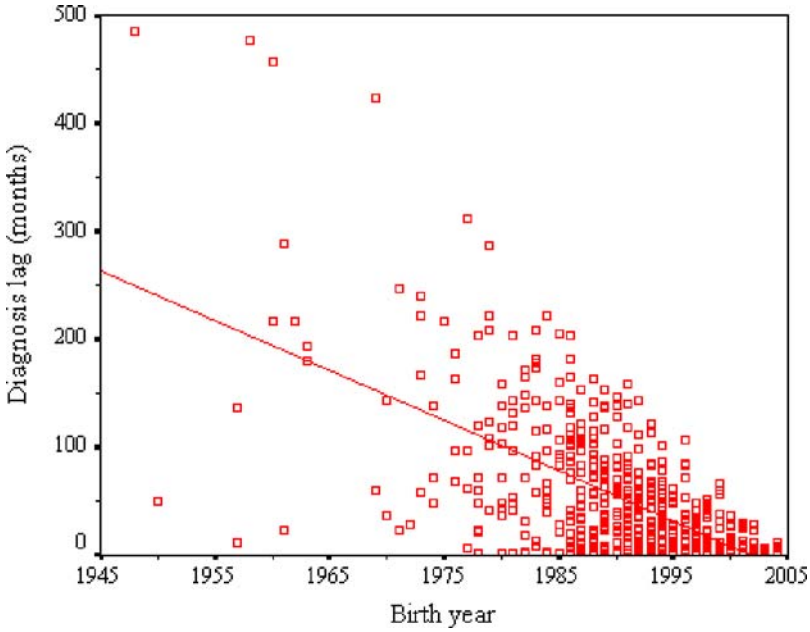

Fig. 3. Association between year of birth and diagnosis lag.

in PID patients (511 patients, 54.9%), followed by diarrhea (376 patients, 40.4%), sinusitis (345 patients, 37.1%), and otitis media (329 patients, 35.4%) (Table III). Although these infections were the most common features of patients with predominantly antibody deficiencies, mucocutaneous candidiasis and lymphadenopathy, in addition to pneumonia and diarrhea, were most common in patients with combined T- and B-cell immunodeficiencies. Superficial abscesses, pneumonia, and lymphadenopathy were the most common manifestations in the patients with congenital defects of phagocyte number and/or function (Table III).

Mortality

Among our 930 patients, 160 patients (97 male and 63 female) died (17.2%) because of recurrent and severe infections. Six hundred and twenty-six patients were still alive, and the remaining 144 patients are unavailable and could not be located during last 3 years. Ninety-five patients died during childhood (59.4%), including 51 cases who died within their 6 years of life (31.9%). The mortality rate was much higher in the group of combined T- and B-cell immunodeficiencies, including omenn syndrome and severe combined immunodeficiency, in which more than half of the patients died during their follow-up (Table I). Respiratory failure due to pneumonia and bronchiectasis, sepsis, and disseminated BCG were the most common causes of death in these patients.

DISCUSSION

Construction of the PIDR is important, not only for its epidemiological aspect but also for its role in increasing the physician's knowledge about such disorders (1). In this paper, an update report of PIDR in Iran has been presented; the number of 930 cases registered during three decades from 16 collaborating centers, with cumulative incidence rate of 11.9 in 10^6 population during last 10 years and an estimated occurrence of 6 per 100,000 live births. This rate is much lower than the incidence rate of PID all over the world, in general (2), while it is much higher than that in some Asian countries like Singapore (22), Taiwan (23), and Australia (17), and similar to that in some European countries like Sweden (24). It should be emphasized that this number does not necessarily reflect the actual prevalence and incidence of PID in Iran because the registry is hospital based, and there is no referral center in some states, especially in the western Iran. Although these are the major referral centers in Iran, it is possible that patients with milder or organ-specific diseases may be treated by private practitioners or at other centers; so, there are still many undiagnosed patients in our country. In contrast, it seems that many patients, especially severe forms of PID, remain undiagnosed if death occurred in early infancy (26).

The distribution of PID in Iran is similar to other countries. Predominantly antibody deficiencies were the most common, which is in agreement with other studies (19,

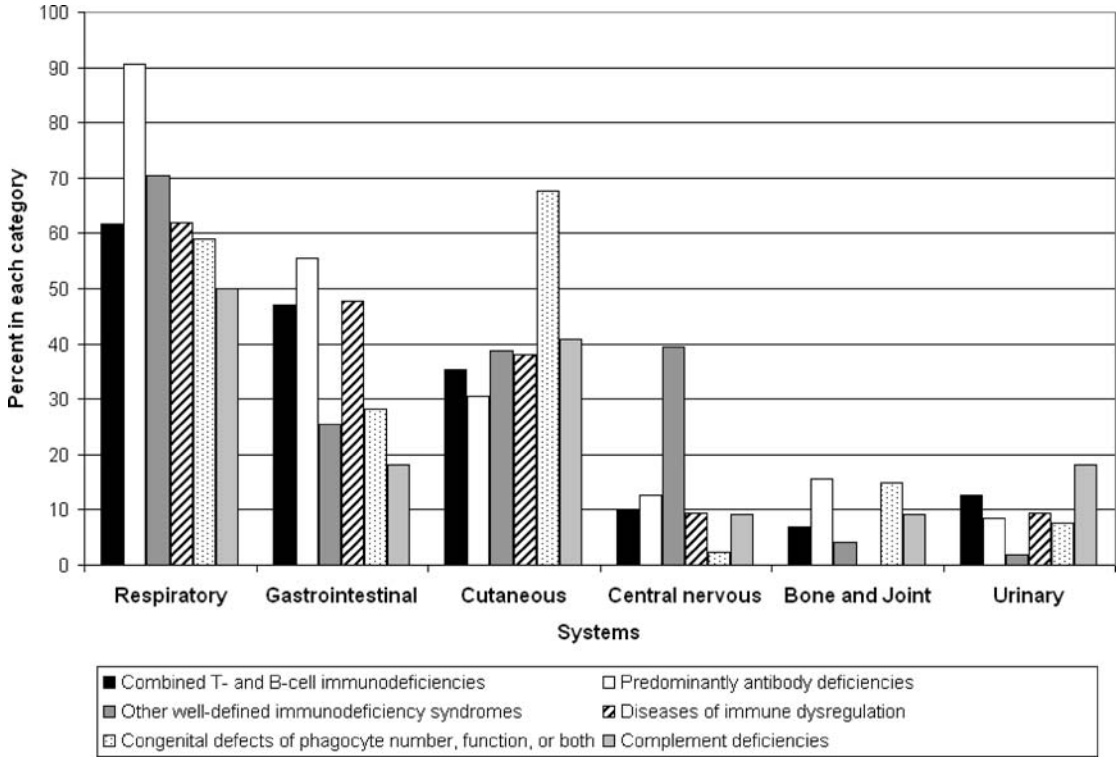

Fig. 4. The frequency of infectious manifestations in different organs in different categories of PID.

27, 13–24). However, congenital defects of phagocyte number and/or function was the second most common PID in our study, instead of combined T- and B-cell immunodeficiencies in other studies (13–25). Recent data from the European Society for Immunodeficiency (ESID) show that 1824 PID patients are registered in Europe based on 29 reports till July 2006 (27). The majority of these patients (66.9%) suffer from predominantly antibody deficiencies, which is much higher than our registry. Other well-defined immunodeficiency syndromes, T- and B-cell immunodeficiencies, and congenital defects of phagocyte number and/or function are other common disorders in Europe in order of frequency (27). Complement deficiencies are one of the less common PID disorders in Iran, which is in agreement with the overall low prevalence of this group of disorders in the general population (28).

Common variable immunodeficiency, chronic granulomatous disease and ataxia-telangiectasia were the most frequent disorders in our registry. Although these disorders can be easily diagnosed, the high frequency of these disorders could be due to the genetic backgrounds and the high consanguinity rate in Iranian population (29). The overall rate of consanguineous marriages in our PID patients was 68.5%, which is much higher than the rate in normal population. As it was predictable, consanguineous marriages were most common in the patients with autosomal recessive inheritance such as Kostman syndrome, Chediak–Higashi syndrome, severe combined immunodeficiency, ataxia-telangiectasia, and Shwachman–Diamond syndrome. In our country, where the consanguinity is common, there is an urgent need for public education programs and providing the facilities for genetic counseling and reproductive risk assessment (29).

The results of some European PID registries show the higher proportion of selective IgA deficiency in comparison with common variable immunodeficiency (13, 15). However, the low number of selective IgA deficiency in IPIDR is consistent with other studies from Japan and Australia (17, 18). It may be because asymptomatic IgA deficiencies were not included in these registries; moreover, there may be several patients with mild form of selective IgA deficiency who are treated by private practitioners without referral to medical centers, but this is not true for CVID patients, who were treated with immunoglobulin replacement therapy.

The proportion of male patients compared to females was 1.7:1, which could be due to the presence of several X-linked disorders like CD40 ligand deficiency, btk deficiency, and Wiskott–Aldrich syndrome; this finding is in

Table III. The Frequency of Common Manifestations in Different cAtegories of PID

	Combined T- and B-cell immunodefi-ciencies	Predominantly antibody deficiencies	Other well-defined immunodefi-ciency syndromes	Diseases of immune dysregulation	Congenital defects of phagocyte number, function, or both	Complement deficiencies	Total
Sinusitis	17 (16.7%)	**206 (57.7%)**	**62 (37.6%)**	6 (28.6%)	47 (17.9%)	**7 (31.8%)**	**345 (37.1%)**
Otitis media	22 (21.6%)	**181 (50.7%)**	48 (29.1%)	4 (19%)	65 (24.7%)	**9 (40.9%)**	**329 (35.4%)**
Pneumonia	**55 (53.9%)**	**262 (73.4%)**	**75 (45.5%)**	**11 (52.4%)**	**101 (38.4%)**	**7 (31.8%)**	**511 (54.9%)**
Bronchiectasis	7 (6.9%)	61 (17.1%)	10 (6.1%)	–	8 (3%)	–	86 (9.2%)
Diarrhea	**48 (47.1%)**	**198 (55.5%)**	42 (25.5%)	**10 (47.6%)**	74 (28.1%)	4 (18.2%)	**376 (40.4%)**
Mucocutaneous candidiasis	**45 (44.1%)**	66 (18.5%)	42 (25.5%)	2 (9.5%)	65 (24.7%)	4 (18.2%)	224 (24.1%)
Mucocutaneous ulcer	8 (7.8%)	14 (3.9%)	14 (8.5%)	2 (9.5%)	60 (22.8%)	–	98 (10.5%)
Eczema	27 (26.5%)	72 (20.2%)	**56 (33.9%)**	4 (19%)	59 (22.4%)	**7 (31.8%)**	225 (24.2%)
Superficial abscess	13 (12.7%)	37 (10.4%)	35 (15.2%)	6 (28.6%)	**129 (49%)**	5 (22.7%)	215 (23.1%)
Deep abscess	3 (2.9%)	8 (2.2%)	16 (9.7%)	–	36 (13.7%)	–	63 (6.8%)
Cojunctivitis	3 (2.9%)	37 (10.4%)	13 (7.9%)	–	8 (3%)	–	61 (6.6%)
Meningitis	10 (9.8%)	45 (12.6%)	5 (3%)	2 (9.5%)	5 (1.9%)	2 (9.1%)	69 (7.4%)
Arthritis	1 (0.9%)	48 (13.4%)	5 (3%)	–	19 (7.2%)	2 (9.1%)	75 (8.1%)
Osteomyelitis	6 (5.9%)	8 (2.2%)	1 (0.6%)	–	22 (8.4%)	–	37 (3.9%)
Urinary tract infection	13 (12.7%)	30 (8.4%)	3 (1.8%)	2 (9.5%)	20 (7.6%)	4 (18.2%)	72 (7.7%)
Hepatomegaly	18 (17.6%)	75 (21%)	16 (9.7%)	4 (19%)	40 (15.2%)	–	153 (16.5%)
Splenomegaly	20 (19.6%)	88 (24.6%)	13 (7.9%)	**11 (52.3%)**	39 (14.8%)	–	171 (18.4%)
Lymphadeno-pathy	**35 (34.2%)**	69 (19.3%)	23 (13.9%)	4 (19%)	**95 (36.1%)**	2 (9.1%)	228 (24.5%)

agreement with other previous reports (4, 16, 18, 24, 30, 31).

As PID are congenital disorders, they often been diagnosed in childhood. More than half of our registered patients are in pediatric age groups, which is in agreement with ESID registry (27). Although our registry covered both pediatric and adult centers and 40% of our patients are in adult age now, the main proportion of these patients experienced the first symptoms in the childhood, especially in the first 2 years of their life. As PID are relatively rare disorders and physician' knowledge about such disorders are poor, patients with PID often are diagnosed later than expected, and they are complicated by several manifestations before the definite diagnosis is made. Thus, these patients do not receive appropriate treatment for several years, and this can lead to morbidity and mortality (1, 10, 11, 12, 32). Recurrent pneumonia leads to bronchiectasis in these patients, which is the main cause of deaths in our PID patients. The median diagnosis delay of PID patients was more than 2.5 years. This diagnosis lag has been significantly decreased in the recent years (after the year 2000). It can show the role of this registry as well as related educational programs in increasing the awareness of medical staff about such disorders. Moreover, it could be due to recent developments and greater access to diagnostic techniques in our country (1, 2, 4). Disseminated BCG was another common cause of death in our PID patients, especially in the group of combined T- and B-cell immunodeficiencies. Although BCG vaccine is given routinely to all Iranian children, this vaccine and other live vaccines should be prohibited in the PID cases and also in their families who may have PID (33).

Infections were the most common manifestation in PID patients. All types of infections were seen in all groups of PID, and more than four-fifth of these patients have multiple sites of infections. The majority of PID patients present recurrent or chronic respiratory infections. However, infections in other systems such as diarrhea, abscesses, septic arthritis, osteomyelitis, sepsis, and septic meningitis are common as well (2, 3). These infections were most common in respiratory, cutaneous, and gastrointestinal system in our study. Although recurrent bacterial infections in the first year of life could suggest predominantly antibody deficiencies, severe infections in association with mucocutaneous candidiasis and lymphadenopathy could suggest combined T- and B-cell immunodeficiencies. Superficial and visceral abscesses could also suggest congenital defects of phagocyte number and/or function in susceptible patients (2, 3, 33–36). Unfortunately, culture analysis to determine the causative organisms of the various infections was not performed before empiric therapy in many patients. However, it should be considered that 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

(1, 10, 11, 12, 32). Early treatment of predominantly antibody deficiencies with immunoglobulin replacement therapy decreases the incidence of recurrent infections and hospitalization in these patients (37–43).

CONCLUSION

IPIDR has provided useful data on PID for further research and also provided effective treatment for PID patients during recent years. Increased awareness of Iranian physicians about such disorders and this registry, and also construction of more referral centers in the west of Iran could help IPIDR to register more patients in the near future. With continuous PID patients registering in Iran, it will be possible to provide accurate prevalence and distribution of PID disorders.

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