Distribution of Primary Immunodeficiency Disorders Diagnosed in a Tertiary Referral Center, Tehran, Iran (2006-2013)

Payam Mohammadinejad[1], Babak Mirminachi[1], Bamdad Sadeghi[1], Masoud Movahedi[2], Mohammad Gharagozlou[2], Javad Mohammadi[3], Hassan Abolhassani[1], Nima Rezaei[1,4], Asghar Aghamohammadi[1*]

[1]Research Center for Immunodeficiencies, [2]Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, [3]Department of Life Science, Faculty of New Science and Technology, Tehran University, [4]Molecular Immunology Research Center, and Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Background: Primary immunodeficiency disorders (PID) are a group of hereditary disorders characterized by an increased susceptibility to severe and recurrent infections, autoimmunity, lymphoproliferative disorders, and malignancy. **Objective:** To evaluate the demographic and clinical data of PID patients diagnosed in a referral pediatric hospital. **Method:** All PID cases with a confirmed diagnosis, according to the criteria of International Union of Immunological Societies, who were referred to the Children's Medical Center in Tehran, Iran, between March 2006 and March 2013 were enrolled in this retrospective cohort study. **Results:** Three-hundred and seven PID patients were investigated. Predominantly antibody deficiencies were the most common group of PID observed in 118 cases (38.4%), followed by the well-defined syndromes with immunodeficiency in 52 (16.9%), congenital defects of phagocyte in 45 (14.7%), combined immunodeficiencies in 36 (11.7%), autoinflammatory disorders in 34 (11.4%), immune dysregulation in 11 (3.6%), complement deficiencies in 7 (2.3%), and defects in innate immunity in 3 (1%). Selective IgA deficiency was the most prevalent disorder which affected 46 individuals (14.9%). The median diagnostic delay was 15 months. **Conclusion:** Increased awareness and availability of diagnostic tests could result in the better recognition of more undiagnosed PID cases and a decrease in diagnostic delay.

Mohammadinejad P, et al. Iran J Immunol. 2014; 11(4):282-291

Keywords: Diagnosis, Prevalence, Primary Immunodeficiency Disorders

---

*Corresponding author: Dr. Asghar Aghamohammadi, Children's Medical Center Hospital, Tehran, Iran, Tel: (+) 98 21 6642 8998, Fax: (+) 98 21 6692 3054, e-mail: aghamohammadi@sina.tums.ac.ir

INTRODUCTION

Primary immunodeficiency disorders (PID) are a heterogeneous group of hereditary diseases resulting in impaired function and/or development of the immune system (1). PIDs are characterized by severe and recurrent infections as well as an increased susceptibility to malignancies and autoimmune or lymphoproliferative conditions (1). Nowadays, more than 220 types of PIDs have been identified and categorized into 8 main groups of disorders by the International Union of Immunological Societies (IUIS) (2).

In the recent years, better understanding of the human immune system has resulted in the development of more accurate and effective diagnostic methods (3,4). However, it is well known that most physicians are not well aware of the clinical features of PID as well as the appropriate diagnostic approaches and therapeutic methods. This lack of awareness and knowledge causes an increase in the morbidity and mortality rates (3,5). Although PIDs are considered to be rare disorders, it is most likely that the true prevalence of such disorders is highly underestimated since many PID patients may remain undiagnosed and even die before receiving an appropriate treatment (3).

There are variations in the prevalence and characteristics of PIDs amongst reported studies from various regions of the world (6-8). Children's Medical Center located in Tehran, Iran, serves as a referral pediatrics hospital for both the diagnosis and treatment of suspected PID patients. A previous report in 2005 described an approximate number of 250 PID patients who were diagnosed in this center over a 20 year period (9).

Herein the current study, we present the demographic and clinical data of 307 PID patients who were referred to Children's Medical Center between March 2006 and March 2013.

MATERIALS AND METHODS

Medical records of all PID patients diagnosed between March 2006 and March 2013 in Children's Medical Center have been retrospectively reviewed. Secondary causes of immunodeficiency were ruled out in all patients and cases without confirmed diagnostic criteria were excluded from this study. Diagnosis was made according to the IUIS classification (2) by evaluating the compatibility of the clinical manifestations with immunologic and genetic evaluations. Informed consents were obtained from all patients, or their parents/legal guardians permitting the publication of this data without the identification of the individuals.

Laboratory evaluations were performed as indicated for each case, considering the probable diagnosis including complete blood count, peripheral blood smear, immunoglobulin serum levels, IgG subclasses serum level, isohemagglutinin tests, assessment of post-vaccination serum antibody response such as anti-tetanus, anti-diphtheria and anti-pneumococcal, flowcytometry evaluation of lymphocyte subtypes, lymphocyte transformation test (using tuberculin purified protein derivative, mitogens phytohemagglutinin, concanavalin A, lipopolysaccharide E. coli), granulocyte function tests (chemotaxis, opsonization, oxidative burst, nitro blue tetrazolium dye test, phagocytosis, and killing), complement component and hemolytic titration of complement components (C3, C4, CH50), and DNA sequencing to confirm the diagnosis (10). All mandatory data including clinical features, laboratory data, and

paraclinical findings of the patients as well as the follow-up information were entered in our online database (www.rcid.tums.ac.ir) with the ability to convert all the desired parameters to Microsoft Excel 2010 data files (Microsoft, USA).
Approval for this study was obtained from the institutional ethical review boards of the Tehran University of Medical Sciences.
Statistical Analysis. Data was then converted for analysis using SPSS statistical software package version 21 (IBM corporation, USA). Mann-Whitney U test was performed to compare the diagnostic delay between patients who referred with infectious or non-infectious first presentations since this variable was not normally distributed. A p value less than 0.05 was considered as statistically significant.

RESULTS

A total of 307 PID patients were enrolled in this study (185 males and 122 females). Predominantly, antibody deficiencies were the most common group of PID, observed in 118 cases (38.4%), followed by well-defined syndromes with immunodeficiency in 52 (16.9%), congenital defects of phagocyte in 45 (14.7%), combined immunodeficiencies in 36 (11.7%), autoinflammatory disorders in 34 (11.4%), immune dysregulation in 11 (3.6%), complement deficiencies in 7 (2.3%), and defects in innate immunity in 3 (1%) (Figure 1).

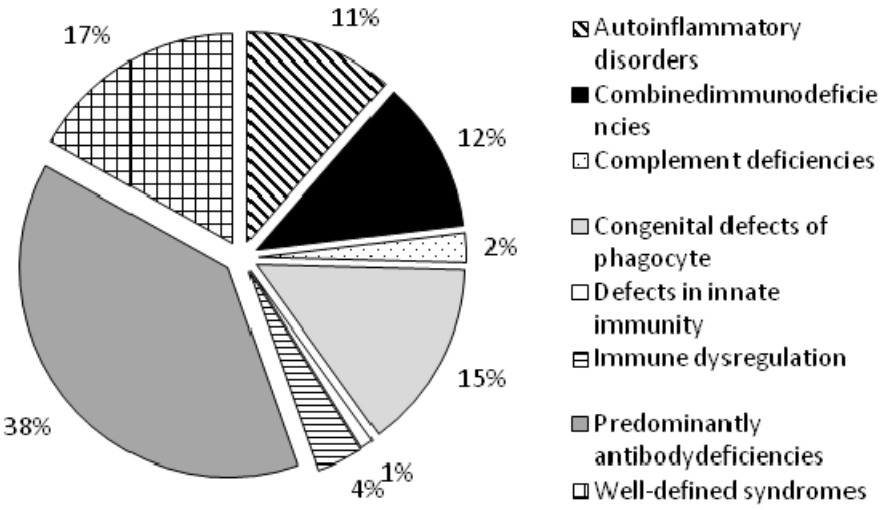

Figure 1. Prevalence of different groups of primary immunodeficiency disorders among 307 cases diagnosed at Children's Medical Center according to the classification of International Union of Immunological Societies (IUIS).

A majority of the patients were among the pediatric age group, mostly under 13 years old at the time of diagnosis (73.6%). The median age of the patients at the time of the study was 8 years with a minimum of 1 month and a maximum of 56 years.

The median diagnostic delay, defined as the time interval between the onset of symptoms and the diagnosis, was 1.25 year, with a minimum of 1week and a maximum of 28 years, for the whole study group, and as follows for most common types of PID: 2 years in selective IgA deficiency (SIgAD), 4.5 years in common variable immunodeficiency (CVID), 2 years in familial Mediterranean fever (FMF), and 2 months in severe combined immunodeficiency (SCID). Figure 2 compares diagnostic delay among various groups of PID.

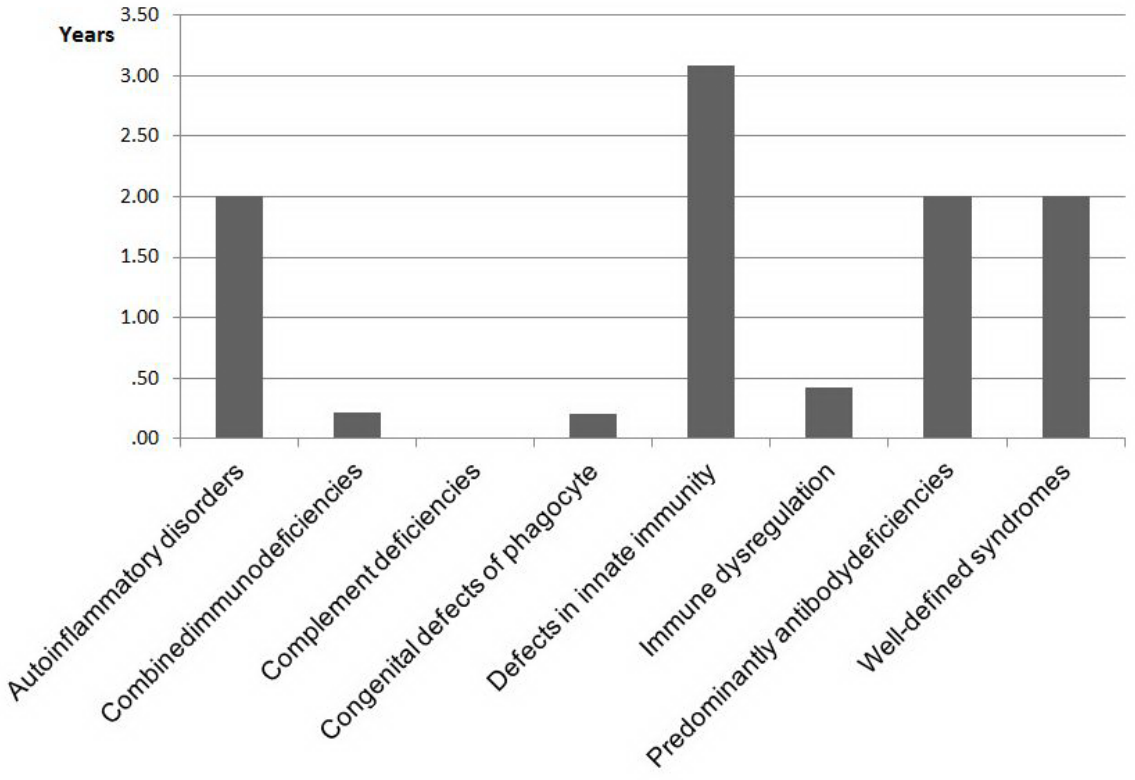

Figure 2. Median diagnostic delay by the category of 304 primary immunodeficiency disorders patients

From 307 patients, 14 (4.6%) individuals died and 84 (27.4%) patients could not be accessed for their last follow-up. Demographic data of the study population is presented in Table 1.

Table 1. Frequency and demographic data of 304 primary immunodeficiency disorders patients.

Disease category	Number	Percent	Age of diagnosis (range)	Male	Female	Consanguinity (%)
Combined immunodeficiencies	36	11.7	1m-13y	20	16	83.3
Severe combined immunodeficiency	34	11.1	1m-8y	18	16	82.4
MHC II deficiency	2	0.7	6y-13y	2	0	100
Well-defined syndromes with immunodeficiency	52	16.9	8m-42y	28	24	71.2
Ataxia-telangiectasia	19	6.2	2y-14y	10	9	84.2
Hyper IgE syndrome	27	8.8	1y-42y	12	15	74.1
Bloom syndrome	1	0.3		1	0	100
Wiskott–Aldrich syndrome	5	1.6	8m-7y	5	0	0
Predominantly antibody deficiencies	118	38.4	6m-57y	89	29	50.8
Common variable immunodeficiency	35	11.4	3y-57y	22	13	57.1
Hyper IgM syndrome	17	5.5	2y-21y	13	3	76.5
X-linked agammaglobulinemia	18	5.9	1y-26y	18	0	38.9
Selective IgA deficiency	46	15	1y-24y	34	12	39.1
µ Heavy Chain deficiency	2	0.7	6m-4y	1	1	100
Diseases of immune dysregulation	11	3.6	1y-11y	4	7	100
Chediak higashi	4	1.3	4y-11y	2	2	100
Griscelli syndrome	5	1.6	1y-6y	2	3	100
Hemophagocytic lymphohistiocytosis	2	0.7	4y-5y	0	2	100
Congenital defects of phagocyte number, function, or both	45	14.7	5m-17y	19	26	57.8
Chronic granulomatous disease	21	6.8	1y-17y	7	14	61.9
Cyclic neutropenia	3	1	4y-15y	1	2	100
Severe congenital neutropenia	11	3.6	3y-16y	7	4	27.3
Leukocyte adhesion deficiency	10	3.3	5m-10y	4	6	100
Defects in innate immunity	3	1	2y-6y	2	1	33.3
Chronic mucocutaneous candidiasis	1	0.3		0	1	0
NEMO deficinecy	1	0.3		1	0	0
WHIM syndrome	1	0.3		0	1	100
Autoinflammatory disorders	35	11.4	5y-44y	20	15	37.1
Familial Mediterranean fever	35	11.4	5y-44y	20	15	37.1
Complement deficiencies	7	2.3	3y-48y	3	4	42.9
C1 inhibitor deficiency	7	2.3	3y-48y	3	4	42.9
Total	**307**	**100**	**1m-56y**	**185**	**122**	**59**

Consanguinity: consanguineous marriage of parents, m: month, y: year, MHC: major histocompatibility complex, IgE: immunoglobulin E, IgM: immunoglobulin M, NEMO: NF-κB essential modulator, WHIM: Warts, Hypogammaglobulinemia,Infections, and Myelokathexis syndrome

Predominantly, antibody deficiencies were the most frequent disorders diagnosed in 118 cases (38.4%) including SIgAD in 46 cases, CVID in 35 cases, X-linked agammaglobulinemia (XLA) in 18 cases, and hyper-IgM syndrome (HIGM) in 17 cases. Mucosal infections, mostly severe and recurrent, were observed in almost all cases with this group of disorders. All patients with HIGM, XLA and μ heavy chain deficiency presented infections except for 1 XLA patient who first presented Kawasaki disease. However, 7 SIgAD and 3 CVID cases experienced non-infectious manifestations as the first presentation of disease, including various types of allergies in 7 cases in addition to malignancy, failure to thrive, and non-specific gastroenteropathy, each symptom was observed in a single patient. As expected, the most common infectious manifestation of CVID patients was pneumonia followed by diarrhea, otitis media, and upper respiratory tract infections, respectively. While most of SIgAD patients experienced infections of gastrointestinal and upper respiratory tracts at the onset of the disease, 7 patients (16.7%) only presented allergic manifestations without a notable history of infection. XLA patients suffered more severe infections including serious and/or recurrent respiratory infections, diarrhea, flaccid paralysis due to polio vaccination, meningitis, and septic arthritis specially before starting of treatment with intravenous immunoglobulin.

Well-defined syndromes with immunodeficiency involved 52 cases (16.9%) including 27 hyper IgE syndrome (HIES) and 19 Ataxia-telangiectasia (AT) patients. Dermatological features, most specifically eczema, were reported as the first presentation in almost all HIES cases. One patient, father of a HIES patient with STAT3 deficiency (Autosomal dominant-HIES), was diagnosed without any significant clinical features during the investigation of patient's family members by genetic testing.

Congenital defects of phagocytosis were observed in 45 (14.7%) individuals including chronic granulomatous disease (CGD) in 21 and leukocyte adhesion deficiency (LAD) in 11 cases. All patients with LAD had consanguineous parents; Moreover, family history of all patients revealed serious and/or recurrent infections in at least one of their first degree family members. The median diagnostic delay was 6 months and 3 months in CGD and LAD cases, respectively, which was considerably lower than other types of PID in this study.

Combined immunodeficiency involved 36 cases (11.7%) including 34 SCID cases who suffered a mortality rate of 29.4%, the highest mortality rate in the study population. Moreover, 38.2% of total cases in this group could not be accessed for further follow-ups.

Autoinflammatory disorders consisting of 35 cases with FMF and complement disorders with 7 cases of hereditary angioedema were the 2 groups of PIDs without infections as the major clinical feature of disease. Episodes of abdominal pain and the fever, and swelling in various parts of the body were observed as the clinical presentation of disease in these 2 groups, respectively.

Infections were the major manifestation of PID in our study group. However, non-infectious features as the first clinical presentation were observed in approximately one-third of the patients. Although cases without infectious manifestations at the onset of disease experienced a longer diagnostic delay, this difference was not statistically significant (median 2 years *vs.* 1 year, p=0.06). Common infectious of study group are shown in Table 2.

Table 2. Prevalence of frequent infections in various types of 304 patients with primary immunodeficiency disorders.

Disease Category	Pneumonia	Otitis media	Sinusitis	Diarrhea	Osteomyelitis	Septic arthritis	Meningitis/ Encephalopathy	Superficial abscess	Deep abscess	Candidiasis	BCGosis
Combined immunodeficiencies (n=36)	21 (58.3%)	3 (8.3%)	1 (2.7%)	14 (38.9%)	0 (0%)	0 (0%)	0 (0%)	3 (8.3%)	5 (13.9%)	13 (36.1%)	10 (27.8%)
Severe combined immunodeficiency (n=34)	20	2	0	14	0	0	0	3	5	13	10
Well-defined syndromes with immunodeficiency (n=52)	17 (32.7%)	8 (15.4%)	4 (7.7%)	9 (17.3%)	0 (0%)	0 (0%)	1 (1.9%)	10 (19.2%)	0 (0%)	6 (11.5%)	0 (0%)
Ataxia-telangiectasia (n=19)	7	3	3	4	0	0	0	1	0	0	0
Hyper IgE syndrome (n=27)	8	2	1	2	0	0	1	8	0	6	0
Predominantly antibody deficiencies (n=118)	57 (48.3%)	32 (27.1%)	43 (82.7%)	32 (27.1%)	2 (1.7%)	7 (5.9%)	3 (2.5%)	5 (4.2%)	0 (0%)	8 (6.8%)	1 (0.8%)
Common variable immunodeficiency (n=35)	28	15	15	12	2	3	1	4	0	0	0
Hyper IgM syndrome (n=17)	8	7	6	7	0	1	0	1	0	4	0
X-linked agammaglobulinemia (n=18)	9	4	3	6	0	2	0	0	0	0	0
Selective IgA deficiency (n=46)	12	6	19	6	0	0	1	2	0	4	1
Diseases of immune dysregulation (n=11)	3 (27.2%)	0 (0%)	0 (0%)	4 (36.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (9%)	0 (0%)
Congenital defects of phagocyte number, function, or both (n=45)	12 (26.7%)	4 (8.9%)	0 (0%)	7 (15.5%)	3 (6.7%)	3 (6.7%)	1 (2.2%)	11 (24.4%)	8 (17.8%)	3 (6.7%)	1 (2.2%)
Chronic granulomatous disease (n=21)	7	0	0	5	3	3	1	7	7	0	1
Severe congenital neutropenia (n=11)	1	1	0	1	0	0	0	2	0	0	0
Leukocyte adhesion deficiency (n=10)	3	2	0	1	0	0	0	1	1	2	0
Defects in innate immunity (n=3)	2 (66.6%)	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)
Autoinflammatory disorders (n=35)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Complement deficiencies (n=7)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total (n=307)	112 (36.5%)	47 (15.3%)	48 (15.6%)	67 (21.8%)	5 (1.6%)	11 (3.6%)	5 (1.6%)	29 (9.4%)	13 (4.2%)	32 (10.4%)	12 (3.9%)

n: number, IgA: immunoglobulin A, IgE: immunoglobulin E, IgM: immunoglobulin M,

DISCUSSION

In this report, we investigated the demographic and clinical data of 307 PID patients who were diagnosed and categorized based on the last IUIS classification (2) at our referral pediatric hospital over a period of 7 years. In addition to providing epidemiologic data, one of the major aims of this study was to attract the attention of health care providers regarding the underestimated prevalence of PID by showing the increasing trend in new PID case recognition over the recent years. Moreover, increasing awareness among the physicians regarding the probability of PID, as an underlying disorder in patients with or without classic manifestations of these disorders, was another main goal in this report. This study also provides data to investigate the effect of increased awareness and feasibility in providing advanced diagnostic methods on the detection of new PID cases and reduction of the diagnostic delay in a single center.

In a previous study on the distribution of PID cases referred to Children's Medical Center by Farhoudi *et al* in 2005, a total number of 247 PID patients were reported over a 20 years period (12.3 patients/year *vs.* 43.8 patients/years in this report) (9). A slight portion of this increase in the number of diagnosed cases is due to the enrollment of some disorders such as FMF (35 cases in the current report), in the latest IUIS classification, which were not considered as PID at the time of the previous report (2).

This achievement in diagnosing more PID cases is probably due to several factors; First, publications of various reports on the prevalence of PID in Iran including 2 reports of Iranian Primary Immunodeficiency Registry (IPIDR) in 2002 and 2006 (10, 11), as well as several single center reports which increased the awareness of medical personnel and health care providers about the prevalence and burden of these disorders(12); Second, hosting the IPIDR and contributions to scientific projects in collaboration with several divisions of other medical centers in the country helped better promote our hospital as a referral center for PID.

There were several considerations regarding the frequency of specific types of PID in comparison with other reports. Predominantly, antibody deficiencies were the most common disorders with 38.4% of total cases, a finding that was also observed in previous reports on PID in Iran as well as other countries (9,10,13-16). SIgAD was the most prevalent type of PID in most registry reports of other countries except for Iran, Japan, and Australia in which CVID was more frequency observed (9,10,13-16). It was suggested that this difference was mainly due to the fact that many SIgAD patients may be asymptomatic and not enrolled in the hospital-based registries (9). However, in the current report, SIgAD was the most prevalent type of PID with 46 cases diagnosed in 7 years. This is much higher than the previously reported 20 cases from our center during a 20-year period probably because of the screening programs in patients with allergic and autoimmune disorders during the recent 7 years (9). Other most prevalent types of PID were CVID and FMF both with 35 cases. Although a high frequency of CVID is in agreement with other studies (9,10,13-16), FMF, an autoinflammatory disorder, which was recently added into the classification of PID by IUIS, is considered to be a rare disorder worldwide expect for the regions around the Mediterranean Sea (17). In fact, only 2% of registered PID patients in ESID database are considered to suffer from autoinflammatory disorders including FMF, meaningfully lower than 11.4% of PID cases in the current report which is mainly due to the genetic background of the Iranian population and the rate of parental consanguinity in this region (17). High rates

of consanguineous marriage in the current study would most probably explain lower onset and diagnostic age of PID patients in the current study compared to other studies (3).

An increasing trend in recognizing new patients was also observed among SCID patients. Thirty-four patients with a confirmed diagnosis of SCID were enrolled in this report. This is much higher than 6 cases which were previously reported from the Children's Medical Center (9). Moreover, diagnostic delay was considerably lower in these patients (median of 2 months) mostly due to the severe and devastating nature of the disease as well as better awareness of it.

Even though we expected to observe the diagnosis of Mendelian susceptibility to mycobacterial diseases in some cases, this was not seen. It should be noted that Iranian children routinely undergo vaccination with bacillus Calmette-Guérin (BCG) vaccines (18). Hence, it is not surprising that 12 cases (3.9%), mostly SCID cases, had BCG-osis.

The median diagnosis delay in our study group was 15 months similar to the reports of several European studies (19,20) and lower than other reports from Asian countries indicating an increased trend towards prompt diagnosis in our center (8,13,16,21). The median diagnostic delay was 2 years in patients with non-infectious first presentations, 1 year longer than those with classic presentation of infections. Although this difference was not statistically significant, most probably due to the size of the study population, it is likely that PID patients without classic infectious presentations remain undiagnosed for a longer period of time due to the lack of awareness among physicians about other phenotypes of such disorders.

In conclusion, increased knowledge and awareness regarding PID, in addition to feasibility in accessing sophisticated diagnostic tests, will result in an increased number of diagnosed PID patients as well as reduced diagnostic delay. These advances will help physicians treat patients at early stages and reduce the morbidity and mortality rate while increasing the quality of life in the affected population.

ACKNOWLEDGEMENTS

We would like to thank Dr. Ali Mirhosseini for the English editing of the manuscript. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

REFERENCES

1. Bonilla FA, Geha RS. 12. Primary immunodeficiency diseases. J Allergy Clin Immunol. 2003; 111:571-581.
2. Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, Cunningham-Rundles C, et al. Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. Frontiers in immunology. 2014; 5:162.
3. Rezaei N, Mohammadinejad P, Aghamohammadi A. The demographics of primary immunodeficiency diseases across the unique ethnic groups in Iran, and approaches to diagnosis and treatment. Ann N Y Acad Sci. 2011; 1238:24-32.

4. Bousfiha AA, Jeddane L, Ailal F, Benhsaien I, Mahlaoui N, Casanova JL, et al. Primary immunodeficiency diseases worldwide: more common than generally thought. J Clin Immunol. 2013; 33:1-7.
5. Nourijelyani K, Aghamohammadi A, Salehi Sadaghiani M, Behniafard N, Abolhassani H, Pourjabar S, et al. Physicians Awareness on Primary Immunodeficiency Disorders in Iran. Iran J Allergy Asthma Immunol. 2012; 11:57-64.
6. Aghamohammadi A, Mohammadinejad P, Abolhassani H, Mirminachi B, Movahedi M, Gharagozlou M, et al. Primary immunodeficiency disorders in Iran: update and new insights from the third report of the national registry. J Clin Immunol. 2014; 34:478-490.
group CTFPs. The French national registry of primary immunodeficiency diseases. Clin Immunol. 2010; 135:264-272.
7. Rhim JW, Kim KH, Kim DS, Kim BS, Kim JS, Kim CH, et al. Prevalence of primary immunodeficiency in Korea. Journal of Korean medical science. 2012; 27:788-793.
8. Farhoudi A, Aghamohammadi A, Moin M, Rezaei N, Pourpak Z, Movahedi M, et al. Distribution of primary immunodeficiency disorders diagnosed in the Children's Medical Center in Iran. J Investig Allergol Clin Immunol. 2005; 15:177-182.
9. Rezaei N, Aghamohammadi A, Moin M, Pourpak Z, Movahedi M, Gharagozlou M, et al. Frequency and clinical manifestations of patients with primary immunodeficiency disorders in Iran: update from the Iranian Primary Immunodeficiency Registry. J Clin Immunol. 2006; 26:519-532.
10. Aghamohammadi A, Moein M, Farhoudi A, Pourpak Z, Rezaei N, Abolmaali K, et al. Primary immunodeficiency in Iran: first report of the National Registry of PID in Children and Adults. J Clin Immunol. 2002; 22:375-380.
11. Abolhassani H, Aghamohammadi A, Abolhassani F, Eftekhar H, Heidarnia M, Rezaei N. Health policy for common variable immunodeficiency: burden of the disease. J Investig Allergol Clin Immunol. 2011; 21:454-458.
12. Kirkpatrick P, Riminton S. Primary immunodeficiency diseases in Australia and New Zealand. J Clin Immunol. 2007; 27:517-524.
13. Leiva LE, Zelazco M, Oleastro M, Carneiro-Sampaio M, Condino-Neto A, Costa-Carvalho BT, et al. Primary immunodeficiency diseases in Latin America: the second report of the LAGID registry. J Clin Immunol. 2007; 27:101-108.
14. Cerutti A, Rescigno M. The biology of intestinal immunoglobulin A responses. Immunity. 2008; 28:740-750.
15. Ishimura M, Takada H, Doi T, Imai K, Sasahara Y, Kanegane H, et al. Nationwide survey of patients with primary immunodeficiency diseases in Japan. J Clin Immunol. 2011; 31:968-976.
16. Salehzadeh F, Emami D, Zolfegari AA, Yazdanbod A, Habibzadeh S, Bashardost B, et al. Familial Mediterranean fever in northwest of Iran (Ardabil): the first global report from Iran. Turk J Pediatr. 2008; 50:40-44.
17. Norouzi S, Aghamohammadi A, Mamishi S, Rosenzweig SD, Rezaei N. Bacillus Calmette-Guerin (BCG) complications associated with primary immunodeficiency diseases. The Journal of infection. 2012; 64:543-554.
18. Gathmann B, Binder N, Ehl S, Kindle G. The European internet-based patient and research database for primary immunodeficiencies: update 2011. Clin Exp Immunol. 2012; 167:479-491.
19. The French national registry of primary immunodeficiency diseases. Clin Immunol. 2010; 135:264-272.
20. Lim DL, Thong BY, Ho SY, Shek LP, Lou J, Leong KP, et al. Primary immunodeficiency diseases in Singapore--the last 11 years. Singapore Med J. 2003; 44:579-586.