THE SPECTRUM OF PRIMARY IMMUNODEFICIENCY DISORDERS IN IRAN

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Abstract- ***Epidemiological studies have shown wide geographical and racial variation in the prevalence and patterns of immunodeficiency disorders. To determine the frequency of primary immunodeficiencies (PID) in Iran, the Iranian Primary Immunodeficiency Registry (IPIDR) was organized in 1999. The diagnosis of immunodeficiency in our patients was based on standard criteria. The patients' data were extracted, by using a uniform questionnaire from their hospital records. Three hundred and twenty eight patients with PID have been registered in our registry till 2000. Among these patients, the following frequencies were found: predominantly antibody deficiency in 48.48% of patients (n=159), T-cell disorders in 25.91% (n=85), phagocytic disorders in 24.7% (n=81), and complement deficiencies in 0.91% (n=3). Common variable immunodeficiency was the most frequent disorder (n=73), followed by chronic granulomatous disease (n=55), ataxia telangiectasia (n=39), x-linked agammaglobulinemia (n=35), selective IgA deficiency (n=34). This study reveals that antibody deficiencies are the most frequent diagnosed primary immunodeficiency disorder in our patients, which is similar to that observed in other registries. A comparative study shows some differences between our results and other registries.***

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Key Words: ***Primary immunodeficiency, national registry, Iran, diagnosis***

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INTRODUCTION

Primary immunodeficiencies are a group of disorders, characterized by an unusual susceptibility to infections. Since Bruton's first description of agammaglobulinemia in 1952 (1), about 80 different primary immunodeficiency disorders have been recognized (2). This increase in the recognition rate of more different types of primary immunodeficiency disorders is due to advances in our knowledge about the immune system and the novel progress in immunological and molecular techniques. Estimated occurrence of primary immunodeficiencies is about 1 per 10000 live births (excluding asymptomatic IgA deficiency) (3). Physicians and general practitioners are often poorly informed about the clinical presentation, diagnostic approach, importance, and health impact of primary immunodeficiencies; thus some patients may remain untreated for several years and this will lead to many complications for them (4-7). Epidemiological studies have shown wide geographical and racial variations in the prevalence and the pattern of immunodeficiency diseases (8-18).

In order to discover the frequency of the different forms of primary immunodeficiency, we organized the Iranian Primary Immunodeficiency Registry (IPIDR) in 1999. Our goal was to enhance the knowledge about these diseases among general practitioners and pediatricians, to emphasize the importance of early diagnosis and treatment, to determine the frequency of these diseases in Iran, to stress the importance of teaching the clinical immunology in the medical curriculum, and finally to promote research about primary immunodeficiencies in our country. This study provides data on Iranian patients with primary immunodeficiency diseases,

classified according to WHO criteria (2) and diagnosed between 1981 and 2000.

MATERIALS AND METHODS

Registry questionnaire

A four-page questionnaire was developed to contain all the patients' demographic informations including; name, date of birth, place of birth, the diagnosis of PID, first clinical presentation, age at the time of onset of symptoms, age at the time of diagnosis of PID, family history of immunodeficiency and/or recurrent infections, basic immunologic laboratory tests and follow-up information. This questionnaire was sent to the universities, participating in the IPIDR.

Participating centers

This initial survey, which included patients diagnosed from 1981 onward, covered six universities of medical sciences from four major states of Iran, including; Tehran, Mashhad, Isfahan, and Babol. The explanation for selecting these universities as participants in this registry was the existence of immunodeficiency clinics and immunologic laboratories in these regions.

Computer database program

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, recorded by the referring immunologist on the questionnaire, and also allows direct statistical analysis of data. Besides, it enables us to take different forms of reports and to export the data to other programs, like: Excel, Word, and SPSS....

Patients

The diagnosis of immunodeficiency in our patients was based on WHO criteria (2). Only patients with well-established immune deficiency and clinical manifestations, consistent with the diagnosis, were included. Laboratory analysis for our immunodeficient patients included blood smear, immunoglobulin levels, isohemagglutinins, Schick test, delayed cutaneous hypersensitivity reactions (Manteau test, Candidia skin test), T-cell and B-cell subpopulation enumeration, IgG subclasses titer, chemotaxis evaluation, nitro blue tetrazolium dye test, chemilluminescence, complement component and hemolytic titration of complement (CH50), as needed.

RESULTS

Three hundred and twenty eight patients with PID were reported to our center of registry. We had reviewed the patient's records for the last 19 years. All of the questionnaires were completed by the immunologists, involved in the care of the reported patients. These data were collected from six different centers, distributed in four major cities of Iran. Among our patients, predominantly antibody deficiencies were the most common, constituting 48.48% of our patients (n=159), followed by T-cell disorders 25.91% (n=85), phagocytic disorders 24.7% (n=81), and complement deficiencies 0.91% (n=3) (Fig. 1). Significantly, most of the registered cases were from Children's Medical Center, one of the affiliated hospitals to Tehran University of Medical Sciences (58.84%) (Table 1). Among our patients, male to female ratio was 1.68/1. Two thirds of the patients were in pediatric age range (70.7%). The average age of our patients at the time of study was 10.8 years, with the youngest patient, referred to our registry, being 2 months old and the oldest having 42 years. The onset age of clinical symptoms, the age of PID diagnosis, and the time elapsed between them were calculated for some of the primary immunodeficient patients (Table 2). Among our 328 patients, 43 patients (13.1%) expired. The detailed prevalence of immunodeficiency disorders is brought in table 3.

Antibody deficiencies

It can be seen in table 3 that antibody deficiencies are the most frequent immunodeficiency disorders, reported in 159 cases (48.48%). These patients suffered from upper and lower respiratory tract infections, including sinusitis, otitis, pharyngitis, and pneumonia. Common variable immunodeficiency (CVID) was the most frequently reported antibody deficiency (n=73), including 47 males and 26 females. X-linked agammaglobulinemia (XLA) was diagnosed in 35 boys, which constituted the second common humoral immunodeficiency. Their clinical manifestations included upper and lower respiratory tract infections, gastrointestinal infections, meningitis, and arthritis. Selective IgA deficiency was diagnosed in 34 patients and ranked the third among our humoral immunodeficiencies. The main symptoms, observed in these patients, were recurrent sino-pulmonary infections. There were 10 cases of selective IgG subclass deficiency, including 6 males and 4 females; all of them had presented with recurrent respiratory infections. There were also 5 cases of hyper-IgM syndrome and 2 cases of functional immunoglobulin deficiency.

T-cell disorders

T-cell deficiencies were the second frequent immunodeficiency disorders, reported in 85 cases

(25.91%) (Table 3). Ataxia telangiectasia was the most frequently reported T-cell disorders, constituting 45.88% of cases (n=39).

Table 1. The number and percentage of registered PID patients from different centers of Iran

Center name	No. of reported pts	percent
Children's medical center (Tehran University)	58.84	193
Daneshvari hospital (Beheshti University)	5.79	19
Alrasoul hospital (Iran University)	37	11.28
Isfahan	55	16.77
Mashhad	13	3.96
Babol	11	3.36
Total	328	100

Table 2. The onset age, diagnosis age, and the diagnostic delay of the primary immunodeficient patients

Disease	Onset Age/ years	Diagnosis Age/ years	Diagnostic Delay/ years
Common variable I.D.	2.5	7.7	5.2
X-linked agammaglobulinemia	1.6	5	3.4
IgA deficiency	1.8	5.2	3.4
IgG subclass deficiency	2.4	8.7	6.3
Hyper IgM syndrome	3.2	7.3	4.1
Ataxia-telangiectasia	2	7.1	4.7
Combined I.D.	0.16	0.8	0.56
Severe combined I.D.	0.2	0.56	0.35
Wiskott-Aldrich syndrome	0.73	4	3.31
Chronic mucocutaneous candidiasis	1.5	8.3	6.6
Chronic granulomatous disease	2.2	6.2	3.9
Leukocyte adhesion defect	0.3	2.1	1.7
Hyper IgE syndrome	0.4	5	4.6
Chediac-Higashi syndrome	0.8	6.5	5.7
Schwachmann syndrome	0.5	4.1	3.6

Table 3. Comparing data between Iranian primary immunodeficiency registry and other registries

	IPIDR*	Latin	Spain
X-linked agammaglobulinemia	35(10.67)	109(7.63)	49(4.6)
Common variable I.D.	73(22.25)	154(10.78)	213(19.9)
Selective IgA deficiency	34(10.36)	413(28.92)	394(36.9)
Selective IgG subclass deficiency	10(3.04)	39(2.73)	48(4.5)
Hyper IgM syndrome	5(l.52)	34(2.38)	23(2.1)
Functional Ig deficiency	2(0.61)	20(l.4)	2(0.2)
Predominantly Ab deficiency	159(48.48)		
Severe combined I.D.	8(2.44)	65(4.55)	61(5.7)
Combined immunodeficiency	12(3.65)	4(0.28)	
Wiskott-Aldrich syndrome	6(l.83)	34(2.38)	18(l.7)
Ataxia telangiectasia	39(11.89)	149(10.43)	29(2.7)
DiGeorge syndrome	2(0.61)	18(l.26)	19(l.8)
CD4 deficiency	7(2.13)		4(0.4)
Chronic mucocutaneous deficiency	11(3.35)		19(l.8)
T-cell deficiency	85(25.91)		
Leukocyte adhesion defect	8(2.44)	3(0.21)	4(0.4)
Chediac-Higashi syndrome	4(l.22)	43(3.01)	1(0.1)
Chronic granulomatous disease	55(16.77)	85(5.95)	32(3)
Myeloperoxidase deficiency	1(0.30)		
Schwachmann syndrome	2(0.61)	1(0.07)	
Hyper IgE syndrome	8(2.44)	63(4.41)	18(1.7)
Kostmann's disease	1(0.30)	14(0.98)	
Cyclic neutropenia	2(0.61)	11(0.77)	
Phagocytic disorders	81(24.7)		
Complement deficiency	3(0.91)	28(1.96)	65(6.1)
Total	328(100%)	1428	1069

*IPIDR: Iranian Primary Immunodeficiency Registry

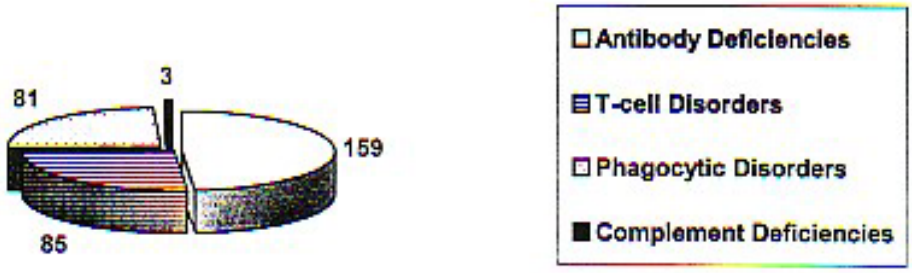

Fig. 1. Registered primary immunodeficient patients (n=328), according to the system involved

In this group, there were 18 males and 21 females. Apart from the presence of ataxia, which was necessary for diagnosis, recurrent respiratory infections constituted the predominant symptoms. The rest of T-cell disorders, in order of frequency, were as follows: combined immunodeficiency (CID) in 12 patients, chronic mucocutaneous candidiasis (CMCC) in 11 patients, and severe combined immunodeficiency (SCID) in 8 patients. We had also 7 cases of CD4 deficiency, 6 cases of Wiskott-Aldrich syndrome, and 2 cases of DiGeorge syndrome.

Phagocytic Disorders

Phagocytic disorders were reported in 81 out of 328 (24.7%) cases (Table 3). Chronic granulomatous disease (CGD) was the most frequent primary defect of phagocytes, with 55 patients (67.9%). Consanguinity was found in 27 families with CGD cases. Respiratory infections, including pneumonia, tuberculosis, aspergillosis, and pulmonary abscesses, made up the most frequent infections in these patients, followed by gasterointestinal tract infections, and musculoskeletal infections. We had registered also 8 cases of leukocyte adhesion defect (LAD), 8 cases of hyper-IgE syndrome, 4 cases of Chediac-Higashi syndrome, 2 cases of Schwachmann syndrome, 2 cases of cyclic neutropenia. We also documented Kostmann's syndrome and myeloperoxidase deficiency in one patient.

DISCUSSION

This is the first report of the Iranian Primary Immunodeficiency Registry (IPIDR). We have filled out the questionnaires for 328 patients with the diagnosis of primary immunodeficiency (PID) during a period of 19 years. This registry, being the first of its kind in Iran, is a collaboration of the major universities from all over the country and is supported by Tehran University of Medical Sciences. In fact, construction of such registry is much more important than merely its epidemiological aspect; it can show the health impact of PID and also increases the physicians' awareness about such disorder. All of our patients have been diagnosed in the affiliated hospitals of 6 universities. The explanation for selecting these universities, as a contributor of this registry was the existence of immunodeficiency clinics and immunology laboratories in these regions. However, it should be noted that the total number of patients with different PID diagnosis, reported in this study does not necessarily reflect the actual prevalence of these diseases, because some patients with severe forms of immunodeficiency, such as severe combined immunodeficiency (SCID) die in their early life, and they are not marked as immunodeficient patients. More than half of the patients were collected from Children's Medical Center, one of the hospitals of Tehran University of Medical Sciences. This hospital is a pediatric referral center and has a better equipped laboratory, where almost all of the immunologic tests can be performed.For convenience, we have divided the immunodeficiency disorders into 4 subgroups: antibody deficiencies, T-cell defects, phagocytic disorders and complement deficiencies. Humoral immunodeficiencies were seen in 48.48% of the patients, followed by T-cell defects, seen in 25.91%. In this study, antibody deficiency was seen in nearly one half of the patients, which is consistent with other studies. In table 3, the number and percentage of different primary immunodeficiency disorders, diagnosed in Iran and its comparison with other registries is shown (8-18). This comparison reveals that ataxia-telangiectasia (AT) and chronic granulomatous disease (CGD) are much more frequent in our registry than other ones. This finding can be due to the presence of non-sophisticated and easy tests for diagnosis of these two disorders; however, we should not forget the possible role of genetic backgrounds. This idea can be supported by comparing our results with those of our nearby countries, like Turkey, which have noted a high frequency of those two disorders (19). In contrast to other reports, we have not found severe combined immunodeficiencies with the same frequency as described. Many children with SCID die in their early years of life, before the diagnosis can be made. It may be due to lack of adequate knowledge in general pediatricians; so we believe that improvement of the pediatricians' knowledge about immunodeficiency disorders is a prerequisite for early diagnosis and hence, prevention of mortalities. In conclusion, the role of primary immuno-deficiency registries is fundamental, not only to obtain epidemiological data on these diseases, but

also, and perhaps more importantly to raise awareness within medical staff, to facilitate information concerning new immunodeficiency diseases and ensure access to diagnostic tests and updating of treatment. The registries can also promote collaborative work, which undoubtedly leads to a better understanding of primary immunodeficiency diseases. To keep the registry active, periodic contact must be maintained with all participants.

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