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PRIMARY IMMUNODEFICIENCY DISORDERS IN SOUTHERN IRAN

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ABSTRACT:

Background: There are great diversities in the frequency of different types of Primary immunodeficiency disorders (PIDs) in between various races and geographic regions. This study was designed to gather epidemiologic information on PID patients from the Pediatric Immunologic Department and Clinic at the Shiraz University of Medical Sciences.

Methods and Materials: The medical records of 60 patients with diagnosis of PID over the past 20 years, were reviewed.

Results: The most common immunodeficiency disorders detected were; Combined Immunodeficiency with Associated or Syndromic Features (33.33%), Immunodeficiencies affecting cellular and humoral immunity (31.66%) and predominately antibody deficiency (23.33%). The most common specific immunodeficiency disorder severe combined immunodeficiency disorder (SCID), (30%). A consanguinity rate of 63.33% was found.

Conclusion: SCID is the most common immunodeficiency disease in our geographic region with a high associated consanguinity rate. Surging the necessity for further focus on PID screening health policies in the region.

Introduction:

Primary immunodeficiency disorders (PID) are a group of genetic defects involving the immune system, often resulting into chronic and serious life threatening infections [1, 2]. With advancements in molecular diagnosis and genetic sequences, PIDs now comprise more than 200 different genetic abnormalities, classified into nine different groups [2-4]. Although the exact global prevalence of PID is unclear, recent studies have estimated very higher rates of the disease, contrary to what was previously thought [5-9]. Prevalence as high as 86.3: 100,000 should suggest the effort to raise the awareness of PIDs among physicians, reducing morbidity and mortality [9]. On the other hand, there are great diversities in the frequency of different types of PIDs in between various races and geographic regions [9-14]. Therefore, gathering epidemiologic information regarding these disorders in different areas of the world will assist the better understanding of this rapidly growing medical field.

Up to now there have been three reports from the Iranian Primary Immunodeficiency Registry (IPIDR) established in 1999 [14-16]. This Study represents the epidemiologic information of PID patients from the Shiraz University of Medical Sciences- Southern Iran, as one of the 14 participant medical centers in the IPIDR. We are hopeful that these data will contribute to the better attention of our physicians and health care system to this concept.

Method and Materials:

Over a 20 year interval, we evaluated all pediatric patients (age <18 years), diagnosed with PID at the Pediatric Immunologic Department and Clinic, affiliated to the Shiraz University of Medical Sciences. Classification of PID was made according to the updated version of The International Union of Immunological Societies (IUIS) expert committee 2015 classifications [4]. The patients' medical charts were reviewed by a trained physician. Demographic data consisting of the patient's sex, gender, and area of residence, in addition to information regarding the patient's illness, such as the type of PID, clinical presentation, episodes of admission, history of received treatments and medications, and positive history of any type of PID or unknown cause of death in first degree family members, were all gathered in a designed data collecting sheet.

All participants were informed of the medical chart reviews, regarding research purposes.

Patients with secondary immunodeficiency disorders (eg. HIV), those with incomplete medical charts, and patients unwilling to share their medical information were considered to be excluded from the study.

Collected data were further coded, and analyzed using the SPSS program version 16.0 (SPSS software version 16.0 manufacture by IBM, United States of America).

Results:

Medical records of 60 PID patients were reviewed. All patients agreed to share their medical record information. Our PID patients were arranged into 5 categorizes according to the IUIS expert committee 2015 classifications: 1) Immunodeficiencies affecting cellular and humoral immunity 2) Combined Immunodeficiency with Associated or Syndromic Features 3) Predominately Antibody Deficiencies 4) Congenital Defects of Phagocyte Number, Function or Both 5) Defects of Innate Immunity. With an overall male to female ratio 1.5:1 (36 boys vs. 24 girls), the most common major category of immunodeficiency disorders detected were; Combined Immunodeficiency with Associated or Syndromic Features (33.33%) , Immunodeficiencies affecting cellular and humoral immunity(31.66%) and predominately antibody deficiency (23.33%)(Figure 1). Table 1 summarized the characteristics of the PID categories and their disease subgroups in our study. As it can be seen the most common specific immunodeficiency disorder in our study was severe combined immunodeficiency disorder (SCID), with 18 patients diagnosed.

We had one female Bruton's patient whom had been diagnosed at the age of 12 months due recurrent respiratory infections. The patient had low immunoglobulin levels and so CD flow cytometry was done which was in favor of absence of B cells. With knowing that Bruton's disease is mainly a X-linked disorder hover considering the fact that the parents of this child were relatives we believe there has been an autosomal recessive mode of transmission of the disease in this patient

The mean age of our patients at the end of the study period was 8 years (1 month – 18 years). The mean age at onset of symptoms was 7.2 months in Immunodeficiencies affecting cellular and humoral immunity, 20.11 months in Combined Immunodeficiency with Associated or Syndromic Features, 8 months in patients with Predominately Antibody Deficiencies, 30.5 months in the Congenital Defects of Phagocyte Number, Function or Both group, and 7 months in our patient with Defects of Innate Immunity. The mean age at diagnosis ranged from as early as 7 months in the defects of innate immunity group to as delayed as 58.35 months in the Combined Immunodeficiency with Associated or Syndromic Features category.

The most common presenting symptoms in our study population were prolonged fever (78.3%), recurrent pneumonia (66.7%), failure to thrive (36.7%), eczema (25%), chronic cough (25%), abscess formation (18.3%), lymphadenitis (15%), recurrent oral aphthous lesion (10%), and chronic diarrhea (10%). Fifty-five percent of our SCID patients had presented with disseminated BCGitis.

We found an overall consanguinity rate of 63.33% (n=38) in our study population. Table 2 shows the consanguinity rate in each PID group respectively.

A positive history of immunodeficiency in the patients' siblings was detected in 18 cases (30%) (7 SCID,6 Hyper-IgE, 2 CGD, 2 Chronic neutropenia, 1 hyperIgM)

A positive history of unknown cause of death in the patients' siblings was seen in 11 case (18%) (5 SCID, 2 CGD, 1 Hyper-IgE, 1 WAS, 1 Hyper-IgM, 1 Chronic neutropenia)

History of any kind of malignancy in first degree family members were seen in 7 cases (11.6%) (2 SCID,1 CVID, 1 Bruton's Disease, 1 WAS, 1 AT, 1 CMC)

Most patients (n=15) had at least one hospital admission and 16.7% (n=10) had more than 5 admissions. Forty percent of the patients had hospital stays of more than 14 days.

Regarding treatment, 70% (n=42) of the patients were receiving intravenous immunoglobulin (IVIG) therapy, and 31.7 % (n=19) were on prophylactic antibiotic therapy. At the time of this study 7 patients (11.66%) underwent hematopoietic stem cell bone marrow transplantation (HSCT). Table 2 shows the specific PID cases that received bone marrow transplantation in this study. The mortality rate following HSCT in these patients was 42.8% (n=3), which were all SCID patients.

The overall mortality rate in our PID patients was 21.66% (10 SCID, 2 HyperIgE, 1 chronic neutropenia).

Discussion

In the past decade many studies worldwide have proven the fact that PIDs are common illnesses in the human population, evolving the need for further attention and research in this field [5-9]. As these disorders occur on a genetic basis, it is apparent that different geographic areas with human genomic diversities, will definitely have various distributions of the disease categorizes [9-14]. For example, in areas with a greater prevalence of consanguineous marriages such as Northern Africa and the Middle East, there are higher incidences of autosomal recessive PIDs [12, 17].

In this study we evaluated the distribution and characteristics of PIDs in our area in Southern Iran and will further compare our results to researches from the Middle East region.

It is worthy to mention that despite all the efforts that have been made regarding PID awareness and diagnosis in our geographic area, still many patients remain undiagnosed, obscuring the true prevalence of the disease. Additionally, the lack of advanced genetic studies in our center impairs further diagnosis of the likely inheritance mode of the diseases.

In our study Combined Immunodeficiency with Associated or Syndromic Features, Immunodeficiencies affecting cellular and humoral immunity and predominately antibody deficiency were the most common PID categories detected. A report from the Kuwait national registry has also shown a similar distribution [21]. However other studies from the Middle East region are in contrary to our report. For example, the latest report from the IPIDR in 2014 showed predominantly antibody deficiencies (32.3 %) followed by Immunodeficiencies affecting cellular and humoral immunity (22.3 %), and congenital defects of phagocyte number, function, or both (17.4 %), as the most prevalent PIDs throughout Iran [14]. Also in a study by Ehlayel MS etal from Qatar, predominantly antibody deficiency (23.7 %), followed by Combined Immunodeficiency with Associated or Syndromic Features (22.9 %), and Immunodeficiencies affecting cellular and humoral immunity (19.1 %) were the most common PID types [18]. The discrepancy of our report from others in the area, could possibly be due to the fact that predominantly antibody deficiencies; due to their subtle symptoms and signs, are being underdiagnosed in our area, and on the other hand more severe entities such as SCID come in the spot light of diagnosis; still there is also a probability that the disease distribution in this geographic area, is merely different from elsewhere.

Nevertheless, the most common specific immunodeficiency disorder reported in our study was SCID, which is comparable to reports from other studies in the district [14,18]. Unfortunately, our center lacks the advanced laboratory facilities for a definite genetic diagnosis of our patients, therefore we have no information regarding the route of inheritance of the disease in our patients; however, regarding the high consanguinity rate (83.33%) and also the higher female acquisition of the disease (M: F ratio 0.8) we are mostly in favor of an autosomal recessive mode of transmission in our SCIDs patients. More than half of our SCID patients had presented with disseminated BCGitis following BCG vaccination prior to diagnosis. Vaccination for prevention of tuberculosis is part of the national vaccination protocol in Iran, which is inoculated to all newborns within the first 3 days after birth. Whereas SCID is the most common PID in the area, it raises the concern for further attention of national health policies towards newborn screening of PIDs and also the alternate timing of BCG vaccination until the newborns' immune status is well specified. The fact that about 40% of our SCID patients had given a positive history of a sibling with immunodeficiency and 30% positive history of death of unknown cause in a sibling, highlights the importance of a detailed history and physical exam in children prior to any type of vaccination.

The most common fact reported in all studies from the Middle East region regarding PID, is the high rate of associated consanguinity. In our study we reported an overall consanguinity rate of 63.33% in our PID patients, very similar to the percentages stated from Iran (63.1%), Qatar (61.1%), Kuwait (77%), and Oman (81%) [14, 18, 21, 22]. The concern of consanguineous marriages as a risk of various diseases have been widely discussed in different articles from the region [24,25, 26]. It has been suggested that especially autosomal recessive disorders are strongly associated with consanguinity [26]. This is why molecular studies on PID in the region, suggest a high autosomal recessive transmission mode of the diseases and some have even reported novel autosomal recessive gene mutations [29-32]. What researchers from the region suggest, is to warn the general population about the risks of consanguineous marriages [27,28].

As a chronic disease, PID patients require lifelong treatments and follow ups. Supportive managements in these patients can consist of immunoglobulin (Ig) replacement therapy, antibiotic and antifungal prophylaxis. Other treatment options for some patients include cytokine therapy, enzyme replacement. However, the definitive treatment pertinent for some patients depending on local availabilities, include hematopoietic stem cell transplantation

(HSCT), and gene therapy [33]. In our study 70% of the patients were on Ig replacement therapy. This is while in reports from Qatar 49.6 % received Ig therapy and those from Oman stated 25% Ig therapy in their patients.

At the present time the only definitive treatment modality for some PIDs in the region is HSCT. The performance of bone marrow transplantation for PID patients has been carried out in different centers in the Middle East region in the past decade [14, 19, 21-22, 34-35]. In this study a total of 11.66% of our patients underwent HSCT. This is comparable to reports from Oman (11.5%) and Kuwait (8%) [21-22]. Nearly half the patients who received HSCT in our study expired (42.8%). Studies from Jordan have reported a 28% mortality, those from Saudi Arabia 24%, and Oman 10% [22, 34-35]. Despite the improvements achieved in allogeneic HSCT at our center in the recent years, the mortality rate of this procedure still seems relatively high for our PID patients. This could be due to the fact that the PID patients transplanted at our center were mostly from the SCID category, whom due to the lack of a screening program in our country, are usually diagnosed after acquiring a life threatening infection and therefore go through a much severe courses of illnesses prior to transplantation, further deteriorating their medical condition, and increasing their risk of post- transplant complications.

Irrespective of all the advances in the field of PID there are still many challenges in our area. Although in its initial stages, hopefully the registration of our patients is being done through the IPIDR since 1999, it is worth pointing out that this registry is one of the only two PID registries (the other being Kuwait national immunodeficiency registry) out of the 10 Middle East countries. In the recent years great efforts have been made in increasing the awareness of PID among general physicians and specialists, through annual conferences and Continuing Medical Education short courses. However, at the present time the main concern at our center is the lack of specialized laboratory facilities at the level of molecular diagnosis. Needing collaboration with specialized laboratories elsewhere in the country and even abroad. In addition, the costs of such tests are mostly way over the family's economic capability, bring up the concern of special insurance coverage of these patients, as a health policy. These facts could delay diagnosis and further treatment of our patients, compromising their final outcome.

The high consanguinity rate found in our patients conveys a suitable condition for future studies with special focus on possible novel genetic mutations in the region.

Conclusion:

Severe Combined Immunodeficiency is the most common immunodeficiency disease in our geographic region with more than 80% associated consanguinity rate. This fact surges the necessity for further focus on PID screening health policies in the region. Also there is a need for increase in public awareness of the consequences of consanguineous marriages.

Table 1 Characteristics of the PID categories

Type of PID	Number of patients	Male to female ratio	Mean age at onset (months)	Mean age at diagnosis(months)	Number of deaths
1- Immunodeficiencies affecting cellular and humoral immunity					
Severe Combined immunodeficiency (SCID)	18 (30%)	8:10	4.9 (1-12)	6.76(1-14)	10(55.5%)
Hyper IgM Syndrome	1 (3.33%)	1:0	9.5 (7-12)	25.25(7-64)	0
2- Combined Immunodeficiency with Associated or Syndromic Features					
Hyper-IgE syndrome (HIES)	14 (23.33 %)	8:6	23.6 (1-96)	58.07(9-120)	2(14.28%)
Wiskott Aldrich Syndrome (WAS)	2 (3.33%)	2:0	6.5 (1-12)	78(60-96)	0
Ataxia telangiectasia	4 (6.66%)	3:1	30.25 (9-48)	39(24-60)	0
3- Predominately Antibody Deficiencies					
Bruton's Disease	10 (16.66%)	9:1	6.9 (1-16)	38.4(8-120)	0
Common variable immunodeficiency (CVID)	4 (6.66%)	1:3	9.25 (1-12)	51(36-72)	0
4- Congenital Defects of Phagocyte Number, Function or Both					
Severe Congenital Neutropenia	4 (6.66%)	2:2	24.5 (1-48)	24.5(1-48)	1(25%)
Chronic Granulomatous Disease	2 (3.33%)	1:1	36.5 (1-72)	36.5(1-72)	0
5-Defects of Innate Immunity					
Chronic mucocutaneous candidiasis	1 (1.66%)	1:0	7	7	0

Table 2 Consanguinity Rate of PID groups

Type of PID	Consanguinity Rate
Immunodeficiencies affecting cellular and humoral immunity	41.66%
2- Combined Immunodeficiency with Associated or Syndromic Features	34.5%
Predominately Antibody Deficiencies	90%
4- Congenital Defects of Phagocyte Number, Function or Both	62.5%
Defects of Innate Immunity	100%

Table 3PID syndromes treated by bone marrow transplantation

PID subgroup	Number of patients
SCID	5
WAS	1
HIES	1

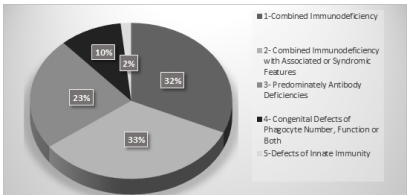

Figure 1 Disturbution of PID Major Categories

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