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Prevalence of Primary Immunodeficiency Diseases in Kerman, Southeast of Iran

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Abstract

Introduction

Primary Immunodeficiency Diseases (PID) are rare and heterogeneous congenital diseases leading to increased unusual susceptibility to developing infections and causing some malignancies and autoimmune diseases. This study was conducted to evaluate characteristics of these diseases in patients attending the clinic of immunodeficiency diseases in Kerman.

Materials and Methods

In a case series study from 2003 to 2014 in the clinic of immunodeficiency diseases in Afzalipour Hospital in Kerman, 32 patients with primary immunodeficiency disease were included. Data was analyzed by statistical software SPSS-19. The level of significance was considered $P<0.05$ in all cases.

Results

The mean age at the onset of symptoms was 4.45 ± 4.35 years. About 60% of patients had phagocytic disorders. Antibody deficiencies were seen in approximately 20% of patients. X-linked agammaglobulinemia was reported in about 6.5% of patients. About 75% of parents were relatives. Developing pneumonia was observed as the most common infection in about 70% followed by adenitis which existed in 47% of cases.

Conclusion

This study revealed that intra-family marriages can be a risk factor for the development of PID in children. So it is essential to recommend genetic counseling before marriage and pregnancy in addition to improving awareness of families with known disease.

***Key Words*:** Children, Infectious Diseases, Kerman, Primary immunodeficiency diseases.

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Introduction

Nowadays, the detection of primary immunodeficiency diseases (PID) is rapidly growing as a fascinating branch of science due to advances in medical science and immunology.

In these congenital diseases, a defect is created in the immune system leading to decrease or failure to produce or dysfunction in a part of immune system components. Hence, we are facing a collection of rare and heterogeneous diseases leading to increased unusual susceptibility to developing infections and causing some malignancies and autoimmune diseases (1-3).

So far, more than 200 types of disorders have been detected in this regard (4). Due to various clinical presentations and lack of relationship between clinical symptoms and genetic defects, the collaboration between experts in different fields is needed for diagnosis and treatment of these patients (5).

Since the mutation or deletion of a gene can cause a range of dysfunction to complete removal of the final product, various forms of the disease with various symptoms or abnormal cell phenotype may be seen with the same diagnosis among different individuals (6).

Today, diagnosis is based on immunologic tests and molecular genetic analysis in selected cases. If there is a positive family history, there is a possibility of prenatal diagnostic testing. Also in some countries, newborn screening programs are running as pilot projects with the aim of initiating appropriate treatment to prevent possible complications of diseases (5).

Many countries have attempted to develop a database of PID (7-10). These reports indicate widespread geographic and racial differences in the prevalence of different types of primary immunodeficiency diseases. Also, since 1999, the data recording system of patients with primary immunodeficiency has been formed and even the data for 20 years before 1999 was recorded in Iran (2).

The information in the database of immunodeficiency diseases showed that the diagnosis of these diseases was 5 to10 cases per 1,000,000 people until 2006 in Kerman, while the diagnosis in provinces such as Isfahan, Fars, Tehran and Qom was more than 20 cases per 1,000,000 people (2).

This study was conducted to evaluate the epidemiological characteristics of primary immunodeficiency diseases in patients attending the clinic of immunodeficiency diseases in Afzalipour Hospital from 2003 to 2014.

Materials and Methods

This study was performed by "case series" of patients during 2003 to 2014 in the clinic of immunodeficiency diseases in Afzalipour Hospital in Kerman, the capital of Kerman Province.

In all cases, after providing the necessary information and granting permission from the individuals or parents (of children) to participate, the subjects were evaluated. Since the clinic of immunodeficiency diseases has started its activities in 2003, some of the patients who were known cases before 2003 had been referred from Children Medical Center Hospital in Tehran-Iran.

In every case, after taking patient's medical history and examining his clinical symptoms, if necessary, additional tests were requested.

In cases that disease diagnosis had already been made, all tests were reviewed. Complete blood count (CBC) was performed by automated blood counting machine, the Sysmex XE-2100, Erythrocyte Sedimentation Rate (ESR)

was measured by Western Green Method, hemagglutinins measured by CA1600 and immunoglobulin levels measured by Elisa, reviewing Cluster of Differentiation (CD) markers done by flow cytometry, the level of serum complement components (C3, C4, CH50) measured by Elisa.

Patients were included if primary immunodeficiency disease was confirmed. Patients with Human Immunodeficiency Virus (HIV) infection, who had the history of using immunosuppressive medication, organ transplantation or radiotherapy, were excluded from the study. Finally, 32 patients with primary immunodeficiency disease were included.

We recommend monthly visits in the clinic for repeat prescription drugs. Laboratory tests were reevaluated every 3 to 6 months, based on the nature of disease. Further, telephonic follow up was performed if the patient did not refer for routine visits.

This study was approved by the Ethics Committee of the Medical University of Kerman. All the data were analyzed by statistical software SPSS-19. The level of significance was considered $P<0.05$.

Results

In this study, 32 patients (50% male) were evaluated. The mean age at the time of participating was 16.03 ± 9.74 years (from 2 to 35 years old).

The mean age at the onset of symptoms was 4.45 ± 4.35 years (from 1 month to 17 years old) and the mean age at the time of diagnosis was 7.55 ± 6.06 years (from 4 months to 22 years old).

This study showed that the first symptoms of the disease in 62.5% occurred at ages less than 5 years (75 percent of male patients and 50 percent of female patients).

Phagocytic disorders in 19 patients (59.4%) and antibody deficiencies in 7 patients (21.9%) were the most frequent deficiencies. While combined disorders were observed in only 5 patients (15.6%) and complement deficiencies in only one patient.

Table.1, demonstrates the frequency of different types of PID in the population studied in terms of gender. In 68.75% of all cases, parents were close relatives and in 18.75%, they were distant relatives.

The most common infections in these patients were pneumonia (68.7%), adenitis (46.9%), bronchiectasis (37.5%), recurrent cutaneous abscesses (31.2%) and tuberculosis (21.9%) respectively.

Table.2, shows the frequency of various respiratory infections in patients surveyed in terms of age when diagnosed.

In terms of developing autoimmune and malignant complications only hypothyroidism, diabetes, anemia, autoimmune thrombocytopenia, cerebral vasculitis, dermatitis, allergic colitis and Pyoderma Gangrenosum (PG) were observed sporadically.

Aggressive treatments were performed on six patients with Chronic Granulomatous Disease (CGD) including four liver abscess surgeries, one lung lobectomy surgery and one bone marrow transplant.

This study showed that in terms of infection two patients with CGD had died because of developing cor pulmonale and one patient with Ataxia-telangiectasia (AT) had died because of the septic shock.

Following up 29 other patients revealed that one patient with CGD developed cor pulmonale, but other patients with drug prophylaxis (cotrimoxazole and receiving interferon gamma as needed) had normal life.

Table 1: The frequency distribution of primary immune deficiency diseases diagnosed in the study population according to gender

Type of Primary Immunodeficiency Diseases		Gender		Total
		Female	Male	
Phagocytic Disorders	Numbers	10	9	19
	%	62.5%	56.3%	59.4%
Antibody Deficiencies	Numbers	4	3	7
	%	25.0%	18.8%	21.9%
Combined Immunodeficiency	Numbers	1	4	5
	%	6.3%	25.0%	15.6%
Complement deficiency	Numbers	1	0	1
	%	6.3%	.0%	3.1%
Total	Numbers	16	16	32
	%	100.0%	100.0%	100.0%

Table 2: Infectious pulmonary complications in patients surveyed according to the age diagnosed

Variables	Age of Diagnosis				Total	P -value
	< 5 Years	5-9 Years	10-14 Years	> 15 Years		
Pulmonary Tuberculosis	0	1	4	2	7	0.018
Bronchiectasis	1	4	4	3	12	0.019
Pneumonia	6	5	7	4	22	0.038

Discussion

In this study, only half of the patients were male. Since the pattern of inheritance of some primary immunodeficiency diseases is gender-related, the overall incidence of immunodeficiency diseases was reported 1.4 to 2.3 times more in males than females in other studies (11, 12). It seems that the main reason for the difference in the sex ratio of our patients is the relatively few cases investigated. The patients' mean age was 16 years; while in other epidemiological studies, the patients mean age was reported from 8 to nearly 17 years (1, 11, 13). This study showed that the patients mean age at the onset of symptoms was about 4 years; while in other studies, it was reported from 11 to nearly 21 months (14, 15). However, it should be considered that in all types of PID we can't expect the onset of the disease at early ages, for example, most patients with Common Variable Immunodeficiency (CVID) become symptomatic in the third decade of life (4, 16). Nevertheless, using new diagnostic techniques also play an important role, so

that in England after implementing active screening programs, the patients mean age at the time of diagnosis reached to 97 days (17).

This study revealed that 75% of male and 50% of female patients experienced their initial symptoms before their fifth birthday. This is consistent with the results of Ishimura (12) and Lee (18). The reason can be due to more cases of gender-related PID such as X-linked form of CGD in our study.

About 60% of patients had CGD (a phagocytic disorder). Phagocytosis defects as the most common PID in Oman were also reported in approximately 42% of patients (19). However, the rate of CGD has only been reported to be 4.33%, 8.6% and 11.9% in European countries, Latin American countries and Japan respectively (4, 12, 20).

Antibody deficiencies (including Immunoglobulin G subclass deficiency, X-linked agammaglobulinemia and CVID) were seen as the second PID in approximately 20% of patients as shown in Al-Tamemi (19). Meanwhile, antibody deficiencies have been reportedas the most common type of PID in approximately 53% of patients in Latin American countries (20). This study showed that CVID (one of antibody deficiencies) can be seen in about 12.5% of patients, which is consistent with the results of Ishimura (12); however, it was reported as the most common form of PID in 20.7% of European patients (4). It seems that inappropriate diagnosis of diseases such as CVID which are not usually symptomatic at childhood is the major cause of differences observed here. In the present study, X-linked agammaglobulinemia was reported in about 6.5% of patients which is consistent with the results of Gathmann (4). However, Ishimura (12) showed that this disorder was seen in about 15% of patients as the most common PID. The reason of the high prevalence in Japan apparently is the use of modern methods of genetic diagnosis in patients who did not have obvious symptoms (21).

About 75% of parents were relatives. Other studies in the Middle East have reported that 62-81% of parents were relatives (19, 22, 23). Since PID are often autosomal recessive genetic diseases, it is expected that they should be observed more in societies where marriage among relatives is common (19).

Developing pneumonia was observed as the most common infection in about 70% of our patients. Al-Herz (15) also showed that pneumonia, is the most common infectious complication (60%), however, the rate of pneumonia in other studies varies from 23 to 42% (19, 24).

The second most common infection in our patients was adenitis which existed in 47% of cases. Al-Tamemi (19), showed that deep abscess (mainly lymph node abscesses) are seen in about 27% of patients as the second most common infectious complication. Different studies show that the lymph nodes abscess can suggest phagocytic disorders such as CGD (25, 26). In our patients, roughly 90% of adenitis was seen in patients with CGD.

The development of bronchiectasis was seen in 37% of patients with prolonged pulmonary infections. This complication has been reported from 18% to 75% in other studies (17, 27, 28). Bronchiectasis is an important cause of morbidity in patients with CVID (29).

It seems that this complication is developed due to severe lung infections rather than repeated lung infections (16, 17). In our study, recurrent cutaneous abscesses were observed in approximately 30% of patients. However, the incidence rate of surface abscesses has been reported from 5% to 20% in other studies (13, 15, 19, 24).

Although it seems that respiratory tract infections are the most prevalent infections, it should be considered that the most common clinical presentation in the combined immunodeficiency, lymphadenopathy and the most common clinical presentation in phagocytic disorders is superficial abscesses and lymphadenopathy (30-32).

Autoimmune complications had a small prevalence and were reported sporadically in our survey. Some autoimmune and malignant complications are more seen in a certain group of PID (33, 34). However, the greatest risk of malignancy can be seen in patients with CVID, these complications may be developed in other types of immune deficiency disorders (34, 35). It seems that developing atopic dermatitis, allergic rhinitis, asthma, nonspecific colitis or autoimmune colitis is seen more than usualin patients with primary immune deficiencies (36-38).

A patient with CGD underwent bone marrow transplantation and is currently recovering. Bone marrow transplantation was performed in 8.5-11% in other reports (4, 19). Furthermore, immune system in some children will not retrieve its natural and full function even after successful stem cell transplantation or gene therapy (39). In our study, roughly 15% of patients with CGD needed surgical resection of liver abscess or lung lobectomy due to infectious complications of the disease. It seems that liver abscess occurs more in patients with CGD or hyper Immunoglobulin E (IgE) syndrome (28).

Approximately 85% of our patients had normal life after receiving antibiotic prophylaxis and treatment with intravenous immunoglobulin. Chronic complication in a patient with CGD existed in the form of cor pulmonale. Respiratory failure and cor pulmonale are the most common cause of morbidity in antibody deficiencies and may be created despite appropriate treatment and replacement of immunoglobulins (38, 39).

Twelve percent of patients in this study died following infectious complications. This is almost consistent with the results of Al-Tamemi (19). However, according to the latest information available from Iranian patients the mortality rate is about 19-21% which is much higher than our figures (15, 24). Nonetheless, the mortality rate in European countries is reported to be 8.5% (4). It should be considered that life expectancy is significantly different among various types of PID.

Conclusion

This study revealed that intra-family marriages can be a risk factor for the development of PID in children. So it is essential to recommend genetic counseling before marriage and pregnancy in addition to improving awareness of families with known disease.

On the other hand, in light of genetic background in most of these diseases, conducting epidemiologic research can be helpful in identifying regional variation of these diseases.

Conflict of interest: None.

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