Mortality in Primary Immunodeficient Patients, Registered in Iranian Primary Immunodeficiency Registry

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ABSTRACT

Primary immunodeficiencies (PID) are a group of disorders, characterized by an unusual susceptibility to infections. Delay in diagnosis results in increased morbidity and mortality in affected patients. The purpose of this study was to determine the mortality rate of Iranian immunodeficient patients referred to Children Medical Center Hospital affiliated to Tehran University of Medical Sciences over a period of 20 years.

In this study, records of 235 (146 males, 89 females) patients with immunodeficiency who were diagnosed and followed in our center, during 22 years period (1979-2001) were reviewed. The diagnosis of immunodeficiency was based on the standard criteria. The cause of death was determined by review of death certificates.

Antibody deficiency was the most common diagnosis made in our patients. The overall five-year survival rate was 22.7% in our studied patient group; this was greatest in antibody deficiency. During the 22 year period of study, 32 patients died. As some of the patients could not be located, the true mortality rate ranged between 13.6% and 17.5%. The main leading cause of death were lower respiratory tract involvement in 14 cases (44%). The most common pathogenic microorganisms causing fatal infections were psudomonas and staphylococcus in 9 cases (28.1%) followed by *E. coli* in 7 (21.9%), tuberculosis in 13 (40.6%) and salmonella in 1 (3.1%).

Based on our study, delay in diagnosis in patients with PID results in tissue and organ damage and several complications. Mortality and morbidity are increased in undiagnosed patients.

Keywords: Chediak Higashi syndrome, Combined immunodeficiency, Common variable immunodeficiency, Mortality, Primary immunodeficiency, X-linked agammaglobulinemia, X-linked lymphoproliferative syndrome, Wisckot-Alderich syndrome.

INTRODUCTION

Primary immunodeficiencies are a group of disorders, characterized by an unusual susceptibility to infections.[1-2] Untreated patients or unrecognized primary antibody deficiency cases suffer from recurrent infections mainly affecting the respiratory and gastrointes-

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tinal systems.[3-13] In addition to an increased susceptibility to infections, a number of other diseases such as autoimmunity and malignancies can be involved in the clinical presentation. The main complication of these disorders is infections, involving mostly the respiratory and gastrointestinal systems.[5,7,12,14]

Early diagnosis and management are important in prognosis and outcome of these patients and a high index of suspicion and prompt diagnosis can lead to lifesaving treatment and significant improvement in the quality of life.[3,6,15]

Failure to provide adequate therapy results in tissue and organ damage and several complications.[3,4] Mortality rate among these patients varies from 10% - 20%[3] and is related to the type and severity of immunological defects, onset of symptoms, delay in diagnosis, management and quality of support.[3,6]

The most common etiology of death in these patients is respiratory infections.

The purpose of the present study was to determine mortality rate in Iranian patients with PID referred to our center over a period of 20 years.

PATIENTS AND METHODS

Patients

In Iran, an Iranian Primary Immunodeficiency Registry (IPIDR) has been active since 1997 and 440 cases with a variety of primary Immunodeficiency diseases were registered at the end of 2001.[2] Among the registered patients, the antibody deficiencies were the most common type of diagnosed immunodeficiencies (n= 202). In order to determine the mortality rate among the diagnosed immunodeficiency patients, 235 patients who were diagnosed and followed in Children's Medical Center Hospital, affiliated to Tehran University of Medical Sciences (TUMS), during 22 years period (1979-2001) were included in this study. The criteria of immunodeficiency diagnosis were based on standard criteria.[2,16]

Method

A two-page questionnaire was prepared to record all necessary information obtained from date of presentation until date of study in each patient in

Table 1. The characteristics of patients with primary immunodeficiency disorders.

Type of disease	No. of patients	Current age/yrs Median (Range)	Age at onset of disease Median (Range)	Delay in diagnosis Median (Range)	Follow up Median (Range)
Common variable immunodeficiency (CVID)	65	11.7 (2-44.8)	2 (.3-40)	5 (0-38.7)	3.4 (0-16.6)
X-Linked Agamma -globulinemia (XLA)	29	11.4 (5-28)	3.2 (.1-11)	3.4 (0-14)	4.9 (.1-17.2)
Hyper IgM Syndromes	4	7.9 (5.6-11.8)	3.2 (.1-11)	4.1 (2.1-6)	3.8 (1-8.1)
IgG Subclass deficiency	8	13.7 (7.1-22.8)	2.4 (.1-14)	6.3 (.9-17)	5.2 (.8-12.6)
Ataxia-Telangiectasia(AT)	35	10.5 (4.3-17.7)	2 (.1-9.1)	4.5 (0-12.2)	6.7 (1.3-21.3)
Chediak Higashi Syndrome(CHS)	4	17.1 (8.3-21.8)	.8 (.1-1.5)	5.7 (.7-17.8)	9.4 (3.6-20.3)
IgA deficiency	19	9.6 (.5-17.6)	2.2 (.1-15.3)	3.4 (0-13.4)	6.3 (0-41.1)
Hyper IgE Syndrome	8	12.7 (8.7-76.5)	.5 (.1-2)	4.6 (1.5-8.9)	8.5 (2.6-17.6)
Leukocyte Adhesion Defect Syndrom(LADs)	11	5.4 (1.3-10.3)	.3 (.1-2)	1.7 (0-5.6)	4.2 (.6-8.3)
Shwachman Diamond Syndrome	4	14.6 (8.9-20.3)	.5 (.1-1.7)	3.6 (1.9-6.3)	4.7 (2.6-6.8)
Combined Immunodeficiency disorder (CID)	3	.8 (.4-1.25)	.2 (.1-.3)	.7 (0-2)	5.8 (1-12.6)
Severe Combined Immuno-deficiency disorders(SCID)	6	1.3 (.2-2.58)	.6 (.3-.9)	.4 (.1-.7)	1 (0-2)
Wiscott-Aldrich Syndrome (WAS)	5	7.9 (2.4-15.3)	.7 (.1-3)	3.3 (.1-11.7)	7.4 (1.7-14.9)

Table 2. Mortality rate in different groups of immunodeficiency.

Disease type	No. of dead patients	Percentage
Common Variable Immuno-Deficiency	11	26.8%
Chronic Granulomatous Disorder	2	4.9%
Ataxia-Telangiectasia	3	7.3%
IgA deficiency	2	4.9%
Leukocyte Adhesion Defect	1	2.4%
Schawchman Diamond	1	2.4%
X-Linked Agammaglobulinemia	4	9.8%
Wiscott-Aldrich Syndrom	2	4.9%
Combined & Severe Combined Immuno-Deficiency	4	9.8%
Hyper IgM	1	2.4%
Hyper IgE	1	2.4%

Table 3. The cause of death in primary immunodeficienct patients.

Death causes	No. of cases	Percentage of deaths
Respiratory infections	14	43.8
Hematological involvement	10	31.3
GI complications	3	9.3
ENT involvement	3	9.3
CNS involvement	2	6.3
Total	32	100

Children's Medical Center Hospital. For those who had died, the cause of death was determined by review of death certificates.

Statistical Methods

Data analysis was done using Statistical Package for the Social Sciences software (version 11.0 for Windows). A linear regression to determine the association between onset date and delay in diagnosis was used. One-way ANOVA was used to compare mortality rate among different groups of PID.

RESULTS

From 1979 to 2001, 235 patients with PID diagnosed and followed up in Children's Medical Center Hospital, including 146 (62.1%) males and 89 (37.9%) females.

There were 125(53.2%) antibody deficiency, 47 patients (20%) with T cell immunodeficiency (most of them were Ataxia-Telangiectasia patients), 57 patients (24.3%) with phagocytic deficiency, and 6 patients (2.6%) with complement defect (Table 1).

The median age of patients at the time of study was 10.3 years (0.2-42), and the median age at the time of disease onset was 1.8 years (0.8-34). The mean duration of delay in diagnosis was 4.1 years (0-22) and this was greatest in antibody deficiencies (0.4-6.6).

The total follow up period was 824 patient-years and the mean follow up period for each patient was 4.9 years (0-22). During the 22 years period of study, 32 patients died, 52 patients could not be located and 151 patients were alive with a mean age of 7 years (0.08-34). The overall five-year survival rate was 22.7% in our studied patient group; this was 81% in antibody deficiency, 43.5% in cellular immunodeficiency (it was near 0 in SCID), and 28.6% in phagocytic deficiency.

Excluding the 52 patients, who could not be located, the mortality rate was estimated 17.5% (32 of 183). If 52 patients who could not be found is considered as dead patients, the mortality rate for the group would be 13.6% (32 of 235). Thus the true mortality lies between 13.6% and 17.5%.

The male to female ratio in dead patients was 1.9 (21 to 11) and the mean age of patients at the time of death was 8.4 years (0.16-21). The median age of onset of disease in dead patients was 0.5(0.08-11) years. Of 32 dead patients 18 had antibody deficiency, 6 had cellular immunodeficiency and 5 had phagocytic defect. Mortality rate in the group of patients with antibody deficiency was 14.4% (18 out of 125), in cellular immunodeficiency was 10.6% (5 out of 47), 16.6% (1 out of 6) in combined immunodeficiency and 10% (5 out of 57) in phagocytic immunodeficiency (Table 2).

The main leading death causes was lower respiratory tract involvement in 14 cases (44%); others were as is shown in Table 3.

The most common pathogenic microorganisms causing fatal infections were psudomonas and staphylococcus in 9 cases (28.1%) followed by *E. coli* in 7 (21.9%), tuberculosis in 13 (40.6%) and salmonella in 1 (3.1%). Viral and fungal infections were seen in 2 of the dead patients (6.3%).

The mean delay in diagnosis was 2.5 years (0-9) in dead patients.

DISCUSSION

Primary immunodeficiencies are a group of disorders, characterized by an unusual susceptibility to infections.[1-2] In this study 235 immunodeficient patients who were diagnosed, treated and followed up in Children's Medical Center Hospital were evaluated.

The median age of patients and median age at the time of disease onset show that our patients are younger than in other studies which might affect the mortality rate.

A severe infection was the leading cause of death in our patient group, which is congruent with other published data.[3-13] Therefore it can be concluded that patients with recurrent infections should have a full assessment of their immune systems. Early detection of antibody deficiency syndromes is of vital importance for prevention of recurrent and chronic infections often causing tissue damage in the respiratory tract. Immunoglobulin treatment is essential, but in some patients with late diagnosis, immunoglobulin replacement therapy does not eradicate ENT infections, possibly because of structural damage caused to the mucociliary system.

In our patient group mortality rate was not the same in different groups and it was greater in antibody deficient patients and among these patients it was greater in CVID patients; However, most of SCID patients were dead before referring to our center therefore SCID mortality rate is low in our patients. Previous studies have shown the same, and for example their reported mortality rate was 20%-30% in CVID patients (4,18) and 17% in XLA patients (19). 5-year survival was greatest in antibody deficiency and it was near zero in SCID. Therefore it can be concluded that one of the factors that affect mortality rate of patients is type of disease.

Another study by Hemans reported the mortality rate of 22% in 4.2 years follow up.[4] In Sweden a study, which was conducted from 1974-9, the mortality rate was 18.4% with predominance in patients with CID.[20]

The report from Brazil in 166 patients with PID who were followed for 15 years the mortality rate was 12.7%.[21] In one study in Japan the mortality rate in PID patients was 625 times that of general population.[22]

A study on 85 children with CID (53 male and 32 female) in a period of 5 years follow up at Great Ormod Street Children Hospital showed that 19% of the patients died because of infections and 9% after BMT.[5]

In Neker Hospital in Paris on 117 patients with CID, the main etiology for death was respiratory and GI infections. The pathologic agents were psudomona. Ecoli, staphylococci. Also in immunocompromised patients with bcgiosis the prevalence of death are high.[24]

In the study by Cunningham and Randles, 103 patients with CVID were followed for 13 years (1973-1987) and the mortality rate was 22% and the causes of death were cardio-respiratory insufficiency, lymphoma and cancers.[17]

The mortality rate of our patient group was between 13.6% and 17.5% which was similar to other studies although the follow up period was much less than in those studies. Therefore it shows that management and control of our patients had been worse than the other studies that in longer period have the same mortality rates as ours.

None of the dead patients had SCID. This is because patients with SCID had died before referral for diagnosis or treatment to our center.

The mean delay in diagnosis was greater in dead patients and the median age of onset was lower in them. These indicate that severity of disease and the time of onset and delayed diagnosis affect survival and prognosis of patients with primary immunodeficiency. Therefore early diagnosis, adequate therapy and good control will improve their condition.

Like our study, several studies have shown that mortality rate has decreased through the time which could be due to a better understanding of these disorders by physicians, development of registries and referral systems, improvement in diagnostic procedures and better therapies such as intravenous immunoglobulin.[3,6,15,17,24,25]

The complications of PID are heterogeneous diseases including several pathogens and poorly controlled inflammation leading to additional organ damage.

It is important to consider immunodeficiency in any patient, with a history of recurrent infections at different organ systems, and patients should have a full assessment of immune system including measurement of serum immunoglobulin levels, IgG sub-classes levels, antibody function evaluation, B and T-cell subsets enumeration. Diagnostic delay results in morbidity and complications in untreated patients. Failure to provide adequate therapy results in tissue and organ damage and several complications.

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