Primary Immunodeficiency Diseases in Oman: Five Years' Experience at Sultan Qaboos University Hospital

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Background: Primary immunodeficiency diseases (PIDs) are considered rare but are generally assumed to be more common in Middle Eastern countries. The prevalence and characteristics of PIDs are unknown in Oman.

Methods: Sultan Qaboos University Hospital is the national referral center for PID in Oman during the study period. Patients were diagnosed and classified according to the clinical and laboratory criteria of PID reported by the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. A registry was created, and patient data were analyzed between July 2005 and July 2010.

Results: Over a 5-year period, there were a total of 90 patients, with an estimated prevalence of 4.5 cases per 100,000. The most common form of immunodeficiency was phagocyte disorders (42%), mainly chronic granulomatous disease, followed by predominantly antibody disorders (18%), other well-defined PID syndromes (13%), and combined immunodeficiencies (12%). The median age of onset of symptoms was 9 months. The median age of diagnosis was 24 months. Consanguinity was present in 81% of patients. The most common infectious presentation was pneumonia (42%), followed by deep abscess (27%) and BCGosis (12%). A total of 25% of patients required intravenous immunoglobulins treatment, 4% required gamma interferon therapy, and 11% underwent bone marrow transplantation. Of all PID patients, 90% survived treatment, whereas 10% did not.

Conclusions: The estimated minimum prevalence of PID in Oman is 4.5 cases per 100,000, with a predominance of phagocyte disorders. Consanguinity is a significant factor; pneumonia and deep abscesses were the main infectious presentations. The overall survival rate was 90%. Strategies are needed to improve the care for PID patients and to increase the awareness among parents and physicians.

Key Words: immunodeficiency, immunodeficiency diseases, primary infectious disorders, recurrent infections, Oman

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Primary immunodeficiency diseases (PIDs) are considered rare. With increasing knowledge of basic immunology, and advancements in technical abilities in molecular biology, plus numerous genetics studies over the last 2 decades, many underlying causes of these diseases have become known, which has helped in firm diagnosis and the creation of certain management plans.[1] Because PIDs are rare and phenotypically variable, and many primary physicians are not familiar with these disorders, many patients arrive at immunology specialists too late for proper diagnosis and treatment; often there are complications secondary to manifestations of the disease, which are associated with a compromised quality of life, increased morbidity, and mortality.[2]

To foster a better understanding of these disorders, registries have been created in different centers around the globe, where valuable information is being collected. To date, more than 120 distinct genes have been identified, whose abnormalities account for more than 150 different forms of PID. The study of these diseases has provided essential insight into the functioning of the immune system. The complexity of the genetic, immunological, and clinical features of PID have prompted the need for their classification, with the ultimate goal of facilitating diagnosis and treatment.[3]

Most registries from Western countries have reported a predominance of antibody production defects over other forms of PID.[4–7] Additionally, there are a few reports from Arabian countries and the Middle East. A group from Tunisia reported 152 patients with PID over a period of 8 years, with a mortality of 24%.[8] One center in eastern Saudi Arabia found that over a period of 6 years, 31 patients were diagnosed with humoral immunodeficiency.[9] Kuwait reported 76 patients with PID between 2004 and 2006, of which 98% presented in childhood with 77% consanguinity.[10] An Egyptian study reported 64 patients with a higher prevalence of combined immunodeficiency over other forms and 62% consanguinity and a mortality of 23%.[11] The Iranian Primary Immunodeficiency Registry reported 440 patients with PID seen over a period of 20 years. There was a predominance of antibody production and phagocytic defects over other PID as compared with other registries, and only 3 patients with complement deficiencies were identified.[12] In other Asian countries, like Taiwan, over a 20-year period, 37 patients were diagnosed with PID. Antibody production defects and phagocytic function defects predominated over other forms of PID, and no patients were identified with complement deficiencies.[13]

Specific registries for certain kinds of PID have been established in certain countries. In the United States, there are registries for chronic granulomatous disease (CGD) and

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X-linked agammaglobulinemia that have provided important information for physicians.[14,15] The European Society of Immunodeficiency Registry has recently answered specific questions on the quality of life of patients receiving gamma globulin therapy for common variable immunodeficiencies, favoring the subcutaneous route over the intravenous route, which has been debated recently among immunologists.[16]

Because PIDs are genetic disorders and mostly inherited in an autosomal recessive form, they are expected to be more prevalent in societies where consanguineous marriage is prevalent. It is important to have registries of PIDs from different countries to understand the magnitude of the problem and illustrate any particular features that would help in managing these patients and performing effective counseling. This also would help in strategic planning for health care policy makers. A registry of PID in Oman was established by the Immunology Unit at Sultan Qaboos University Hospital (SQUH), the national referral center for primary immunodeficiency patients in Oman.

METHODS

Oman, located in the southeastern Arabian Peninsula, has a population of about 2 million Omani nationals and is divided into 9 governorates and regions. The majority of people living in Oman are of Arab ancestry. The health system in Oman is mainly public with primary and secondary health care available in all governorates and regions. Tertiary care is available in Muscat, the capital of Oman, with SQUH being the second largest tertiary care hospital in Oman. It is the referral center for patients who are suspected of having PID. Patients from different regions of the country are referred for consultation, investigation, and management, including stem cell transplants.

A registry for patients who are diagnosed with PID was established by the Immunology Unit at the Department of Child Health. The aim of this registry is to determine the prevalence and frequency of different PIDs in Oman, to identify clinical presentation patterns, consanguinity rates, treatment patterns, natural history, morbidity and mortality, and to determine if, in general, there is any particular pattern for this group of inherited disorders. This information will improve physicians' knowledge about PID in Oman and will also help with early detection, ultimately improving quality of life and survival rates. Allocation of resources and better, more strategic decision making will also result.

Patients were diagnosed and classified according to the clinical and laboratory criteria of PID as reported by International Union of Immunological Societies (IUIS) Primary Immunodeficiency Diseases Classification Committee.[3] Data were entered in Microsoft Access Datasheet and included patient demographic data, clinical presentation, infectious presentation, family history of PID, presence of consanguinity, previous death in the family related to PID, diagnosis, treatment, and survival. PID patients who were seen starting from July 2005 until January 2010 were included in the data. At the time of analysis, data were exported to a Statistical Package for the Social Sciences file and an analysis was performed. The study was approved by the ethical and scientific research committees of the College of Medicine at SQUH.

RESULTS

Ninety patients were seen during the study period who received a diagnosis of primary immunodeficiency: 55 males and 35 females, with an estimated prevalence of 4.5 cases per 100,000. According to the international classification of primary immunodeficiency, the most common type of immunodeficiency was phagocytic disorders (42%), followed by predominantly antibody disorders (18%), other well-defined PID syndromes (13%), combined immunodeficiency (12%), complement deficiencies (6%), unclassified PID (6%), and immune dysregulation syndromes (3%) (Fig. 1, Table 1). In the phagocytic disorders category, the commonest disease was CGD, representing 31 (82%) of 38 patients with phagocytic disorders, making it the commonest PID in Oman (34% of all PID diseases).

The age of onset of symptoms varied between the first month of life to 12 years of age, with a mean of 20.1 months and a median of 9 months. The age of diagnosis ranged from the first week of life to 16 years of age, with a mean of 35.5 months and a median of 24 months. Consanguinity was present in 81% of patients; 10% of patients' parents were from the same tribe, and only 9% of patient's parents were not related. A family history of PID was present in 42% of the patients. History of death of a previous child was present in 49% of the patients. The majority of patients (96.6%) showed pattern of autosomal recessive inheritance, only 3 patients (3.3%) showed X-linked pattern.

The most common infectious presentation was pneumonia; it was present in 42% of cases, followed by deep abscesses in 27% of patients and then by BCGosis (12%), chronic diarrhea (10%), superficial abscesses (8%), otitis media (7%), osteomyelitis (3%), candidiasis (3%), septic arthritis (1%), and meningitis (1%) (Fig 2).

Other clinical presentations of the study group include the following: 12% were diagnosed by screening because of a family history, 8% presented with recurrent nonpruritic angioedema without urticaria, 6% presented with ataxia, and 7% presented with dysmorphic features. Other features

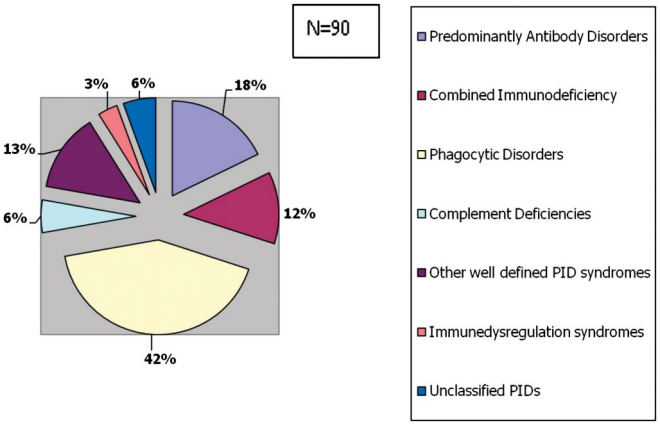

FIGURE 1. Types of primary immunodeficiency in Oman.

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TABLE 1. Types of Immunodeficiency, Diagnosis, and Number of Patients

Type of Immunodeficiency	Diagnosis and No. Patients
Predominantly antibody disorders, 16 patients	X-linked agammaglobulinemia, 3 Agammaglobulinemia, 4 Common variable immunodeficiency, 5 Hyper IgM syndrome, 2 Selective IgA deficiency, 1 Transient hypogammaglobulinemia of infancy, 1
Combined immunodeficiency, 11 patients	Severe combined immunodeficiency, 5 Major histocompatibility Class II deficiency, 2 Combined immunodeficiency, 4
Phagocytic disorders, 38 patients	CGD, 31 Interferon gamma receptor II deficiency, 2 Severe congenital neutropenia, 2 Leukocyte adhesion defect type-1, 1 Pearson syndrome (infections due to neutropenia), 1 Severe neutrophil defect, granules defect, 1
Complement deficiencies, 5 patients	Complement 3 deficiency, 1 Complement 7 deficiency, 1 C1 Esterase inhibitor deficiency type-1, 2 C1 Esterase inhibitor deficiency type-2, 1
Other well defined PID syndromes, 12 patients	Ataxia telangiectasia, 6 Di-George syndrome, 1 Cartilage hair hypoplasia, 1 Chronic mucocutaneous candidiasis, 1 Autosomal recessive hyper-IgE syndrome, 2 Nijmegen breakage syndrome, 1
Immune dysregulation syndromes, 3 patients	Chediak–Higashi syndrome, 2 Autoimmune lymphoproliferative syndrome, 1
Unclassified PIDs, 5 patients	4 patients presented with nonpruritic angioedema without urticaria but C1 esterase inhibitor was normal, and one patient presented with recurrent infections but investigations were normal

included failure to thrive, hepatosplenomegaly, lymphadenopathy, and skin ulcers. Of the total, 60% required regular prophylactic antimicrobial therapy, 25% required intravenous immunoglobulins (IVIG) treatment, 4% required gamma interferon therapy, and 11% underwent bone marrow transplantation (Fig. 3). A total of 81% of patients are alive and doing well, 9% are alive but with disabilities related to PID, and 10% of patients have since died (Fig. 4).

DISCUSSION

The estimated prevalence of PID in Oman is about 4.5 cases per 100,000, which is a higher incidence than the reported prevalence in European countries.[17] The rate of occurrence could be even higher because some patients die undiagnosed because of a progressive course of infections before arrival to tertiary care. Additionally, patients with hemophagocytic lymphocytic histiocytosis were not included in our registry because they are cared for by the Hematology Unit.

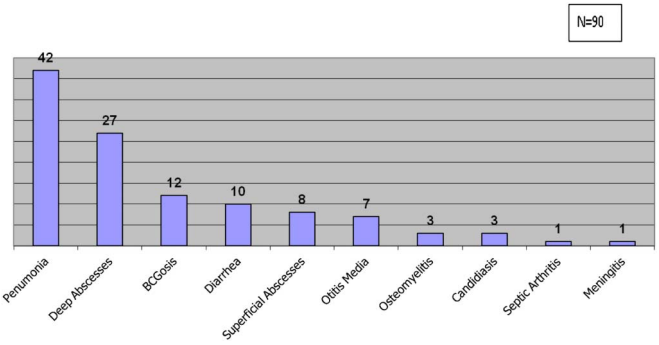

FIGURE 2. Infectious presentation of PID patients, percentage values from total number.

Oman's PID registry revealed a different pattern of types of PID as compared with other countries in the region. In Oman, phagocytic disorders were the most common type. In this group of PID, CGD represented the most common disorder, making it the most common form of immunodeficiency in Oman. Curiously, reported registries from different countries, even in the same region as Oman, identified antibody deficiency as the predominant type.[8–10] Although we could assume that PID is underdiagnosed, it would be unlikely that this is only reflected in the diagnosis of certain types of PID, so the finding that phagocytic disorder is the most common type of PID is likely to be true.

There is an overall delay in diagnosis by 15.4 months from the time of onset of symptoms, although there is less of a delay when compared with other registries.[10] This could be because many treating physicians do not think of immunodeficiency as an underlying cause of illness until there have been many recurrences of infections, which eventually lead to growth failure, or patients requiring longer stays in hospital. Pneumonia was the most common infectious presentation as seen in other registries and was seen in all types of PID. It was followed by deep abscesses (mainly recurrent lymphadenitis), which is a key presentation of CGD.[18]

Oman has one of the highest immunization coverage rates in the world,[19] and the BCG vaccination is part of the routine expanded program of immunizations because of endemic tuberculosis.[20] Except when there is a family history of immunodeficiency, the BCG vaccine is given after birth and before discharge to all newborns in Oman. Eleven patients

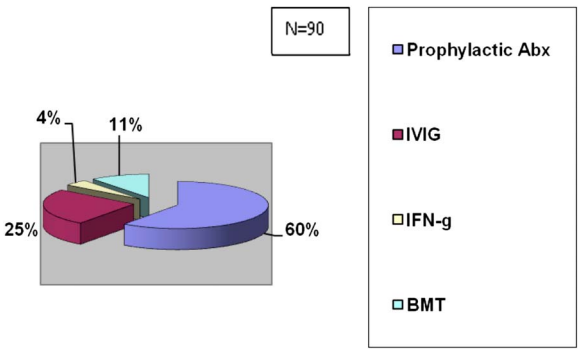

FIGURE 3. Treatment of PID patients.

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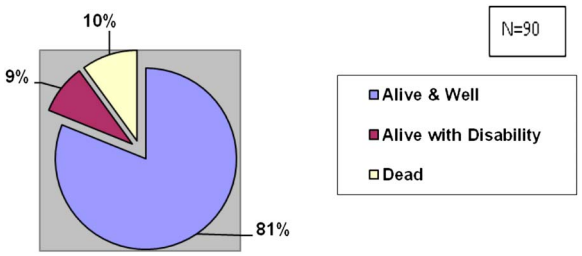

FIGURE 4. Survival rate of PID.

presented with BCGitis, which is a very difficult infection to treat in PID patients and associated with great morbidity and mortality in its disseminated form.[21] Oman has been polio free since 1993[22]; none of our patients presented with polio-related disease attributed to the vaccine. This could be because of protective maternal polio IgG passed to infants before delivery. The inactivated polio vaccine is available for immunodeficient children and children pending evaluation because of family history of PID and is now set to replace oral polio vaccine (OPV) in routine immunizations.

Consanguineous marriages are still customary in Oman,[23] and 81% of our patients were born to consanguineous parents. This number may be higher because some were from the same tribe but were not consanguineous. This represents a risk factor not only for PID but all genetic disorders and, naturally, autosomal recessive immunodeficiency disorders are more common in Oman and other Middle Eastern countries as compared with Western countries. The finding that 49% of PID patients have previous infant/child death makes it an important clinical feature.

All World Health Organization essential drugs are available in Oman, and treatment of PID is based on the type and severity of the underlying immunodeficiency disease. Acute infections require antimicrobial drugs that are readily available in all hospitals. In their usual status, PID patients may require prophylactic antimicrobial therapy to prevent recurrent infections and IVIG for antibody and combined immunodeficiencies. The Bone Marrow Transplant Unit at SQUH has 2 beds, and recently, 2 more beds have been added. It is the only unit in the country for children and adult allogeneic stem cell transplant (SCT), which is performed for hematological malignancy, hemoglobinopathy, primary immunodeficiency, and other inborn errors of metabolism. Ten patients with PID received stem cell transplants during the study period; all survived except one patient with severe combined immunodeficiency, who came in with an advanced disseminated stage of BCG-related infection.

The overall mortality rate for all PID patients was 10%, which is lower than reported rates in similar registries.[8,10,11] This could be due to the availability of IVIG and SCT for PID patients in Oman. Some of the PIDs are incurable by SCT and are associated with other systems' involvement, such as neurodegeneration and the development of malignancies, which contribute to morbidity and mortality. Some of our patients are alive but have disabilities because of unavoidable complications associated with PID.

CONCLUSIONS

The estimated minimum prevalence of PID in Oman is 4.5 cases per 100,000, higher than that in European countries. The predominant type is phagocytic disorders, mainly CGD. The commonest presentation was pneumonia and deep abscess with median delay of diagnosis of 15.4 months from onset of symptoms. Consanguinity and presence of previous infant/child death were significant factors. Although the survival rate is very good, further reduction in the delay of diagnosis should improve survival rates; this could be done by increasing the awareness of risk factors and the clinical presentations of PID among the public and physicians. Furthermore, development of fully specialized/integrated immunology units with physicians, nurses, dietitians, social workers, and proper isolation facilities is essential for patients to receive a high standard of care. In addition, specialized immunological laboratory tests should be readily available in the country to facilitate early diagnosis and management of PID patients. Resources for genetic research in primary immunodeficiency should be encouraged to identify the genetic causes of PID in Oman and establish a baseline genetic information for future customized genetic testing, gene therapy, and better counseling for families to prevent the occurrence of PID.

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