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Primary Immunodeficiency Diseases in Singapore – the Last 11 Years

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ABSTRACT

Objectives: To describe the clinical features, disease complications, treatment modalities and overall outcome of 39 local patients with Primary Immunodeficiency Diseases (PID) in Singapore over the last 11 years.

Methods: Paediatric and adult patients who presented to the The Children's Medical Institute, National University Hospital, Tan Tock Seng Hospital and KK Women's and Children's Hospital between January 1990 and December 2000 were identified. Their diagnoses were categorised into six groups according to the IUIS (International Union of Immunological Societies, affiliated to World Health Organisation) classification: antibody deficiencies, combined immunodeficiencies, immunodeficiencies associated with other major defects, congenital phagocytic defects, complement deficiencies and other well-defined immunodeficiency syndromes. Patients were selected from screening of inpatients with discharge diagnoses associated with primary immunodeficiency and of patients undergoing tests for immunodeficiency. Patient data were collated from case files and compiled using a standard questionnaire.

Results: There were 39 Singaporean patients diagnosed and treated for PID during the study period. The age at diagnosis ranged from three weeks to 69 years. Antibody deficiency (41%) was the most common form of PID. Seven patients had a family history of PID. Recurrent bacterial respiratory tract infections were the most common clinical manifestation. Associated conditions included autoimmune diseases, allergies and malignancies. Infection was the commonest cause of mortality. Eighteen patients (46.2%) with antibody or combined deficiencies received regular intravenous immunoglobulin (IVIG) as the primary treatment modality. Two children successfully received sibling-matched haematopoietic stem cell transplantation (HSCT).

Conclusions: Antibody deficiencies are the most common form of PID in Singapore. Treatment with antibiotics, IVIG and HSCT are the main therapeutic modalities currently available. Early referral to an immunologist is needed to achieve good outcomes.

Keywords: Epidemiology, intravenous immunoglobulin, haematopoietic stem cell transplantation, gene therapy

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INTRODUCTION

Primary immunodeficiency diseases (PID) are rare inherited conditions that predispose individuals to infections that are recurrent or due to unusual organisms[1-3]. PIDs are also often associated with autoimmune, haematological and malignant disorders[4-8]. These conditions require specialised immunological services for diagnosis and management. Although they occur infrequently, they carry significant morbidity and mortality[1-3]. In recent years, tremendous advances have been made in the management of these patients. Early diagnosis and treatment have been shown to improve morbidity and mortality[9,10]. Identification of precise genetic mutations has also made antenatal diagnosis possible[11,12]. Most developed countries, including Australia and Japan have developed registries to estimate the prevalence of PID in their own countries[13,14]. However, we currently do not have any local data on PID in Singapore. The aim of this study was to describe the clinical features, disease complications, treatment modalities and overall outcomes of patients with PID in Singapore.

METHODS

Patient enrolment

Patients who presented to The Children's Medical Institute at the National University Hospital (NUH), KK Women's and Children's Hospital (KKWCH, from its inception in May 1997) and Tan Tock Seng Hospital (TTSH) from January 1990 to December 2000 were included in this study. The Children's Medical

Institute, NUH and KKWCH are the two main paediatric referral centres in Singapore. The Department of Rheumatology, Allergy and Immunology, TTSH is the major referral centre for adult patients with immunological disorders in Singapore. Although these are the major referral centres in Singapore for children and adults with PID, it is possible that patients with milder or organ-specific diseases may have been treated at other institutions, both in the private and public sectors, under organ-specific specialties. However, these are likely to be few.

Data collection

The inpatient discharge diagnoses of the different hospitals were screened for the following International Classification of Diseases, 9th revision (ICD-9) diagnosis codes: 279-279.9 (Disorders involving the immune system), 288.1 (Functional disorders of the polymorphonuclear neutrophils), 288.2 (Genetic anomalies of leukocytes), 334.8 (Ataxia-telangectasia), 238.7 (Other lymphatic and haemopoietic tissues) and 277.2 (Other disorders of purine and pyrimidine metabolism). Patients who had undergone immunological tests for immunodeficiency in the immunology laboratories of The Children's Medical Institute, NUH and TTSH were also identified and those with results confirming a clinical diagnosis of PID were included.

The case records of these patients were retrospectively reviewed and clinical information collected using a standardised questionnaire. The information collected included symptoms at presentation, age at presentation, family history of illnesses or PID, haematological and immunological laboratory findings, diagnosis, disease progression, treatment modalities used and outcome. These patients were classified as paediatric patients if they were <16 years old at the time of diagnosis. Their diagnoses were categorised according to the IUIS (International Union of Immunological Societies, affiliated to World Health Organisation) classification: antibody deficiencies, combined immunodeficiencies, immunodeficiencies associated with other major defects, congenital phagocytic defects, complement deficiencies and other well-defined immunodeficiency syndromes[1]. The incidence of PID was calculated by dividing the number of new cases born between 1990 and 2000 by the number of live births in that same period. Consanguinity was defined as first-degree relations. The data were analysed using SPSS 10 statistical software.

RESULTS

Case Ascertainment

There were 262 cases that fulfilled the criteria according to the ICD codes and 166 patients who underwent immunological investigations. Of these patients, 56 were diagnosed with PID during the period of the study. Thirty-nine[39] were Singaporeans and the remainder were foreigners who sought treatment in this country. Only the characteristics of the Singaporean patients were studied and will be described.

Patient Characteristics

The age at presentation ranged from three weeks of life to 69 years of age. There were no antenatal diagnoses made. There were 23 (58.9%) males and 16 (41.1%) females, giving a male-female ratio of 1.4:1. Fourteen of these patients were born in the 11-year period of observation from January 1990 to December 2000. This would correspond to an estimated occurrence of 1 in 37,000 live births and an incidence of 2.65 per 100,000 live births[15,16].

Distribution of PID cases

The distribution of local PID cases seen during the study period is shown in Table I. The antibody deficiencies predominated in both children and adults. Seven patients had a family history of PID (Table II). There was no consanguinity in these families.

Diagnosis

The most common presentation among the paediatric patients with PID were bacterial septicaemia (six cases, 27%), skin infections (five cases, 23%), pneumonia (three cases, 14%) and bronchiectasis (three cases, 14%). Among the adults with PID, the most common presenting conditions were recurrent pneumonia (nine cases, 62.9%), bronchiectasis (six cases, 35.3%) and chronic sinusitis (five cases, 29.4%). Some patients had more than one clinical feature at presentation. Apart from the distinctive clinical features and the quantitative and qualitative laboratory findings traditionally used to diagnose PID, the exact molecular or genetic defects were mapped in six patients (Table I). This information has important implications with regard to carrier testing, genetic counselling and antenatal diagnosis.

Types of infections

Recurrent infections occurred in all subjects except one, who was the sole case of ataxia-telangiectasia. Bacterial sino-pulmonary infections in the form of chronic sinusitis, bronchiectasis or pneumonia were the most common. *Haemophilus influenzae, Pseudomonas aeruginosa, Staphylococcus aureus,* Klebsiella species and Salmonella were common pathogens. Patients also suffered from opportunistic infections that are commonly associated with their respective conditions – both subjects with Hyper-IgM

Table I. Spectrum of PID in Singaporean patients.

Primary Immunodeficiency	No. of cases	Percentage of total	Male (Age)	Female (Age)	No. (n) of patients with genetic or molecular diagnosis
Antibody deficiencies	16	41.0			
IgG subclass deficiency	2		18 years	19 years	
IgA deficiency	4		5 months, 66 years	19 years, 40 years	
Common variable immunodeciency (CVI)	6		5 months, 3 years, 19 years	29 years, 30 years, 39 years	
Hypogammaglobulinemia (type not known)	4		7 months, 10 years	18 years, 59 years	Ring chromosome 18 (1)
Combined immunodeficiencies	4	10.3			
Severe combined immunodeficiency (SCID)	2		1 month	4 months	IL2 receptor gene mutation (1)
Hyper IgM (X-linked)	2		6 months, 3 years		CD 40 ligand deficiency (2)
Immunodeficiencies associated with other major defects	5	12.8			
Wiskott-Aldrich syndrome (WAS)	2			1 month, 9 months	
DiGeorge anomaly	1		Day 1		22q11.2 <D22S75> 46XX deletion
Ataxia telangiectasia	1		2 years		
Chediak-Higashi syndrome	1			2 weeks	
Phagocyte defects	6	15.4			
Chronic granulomatous disease (CGD)	2		6 months	3 months	P47phox cytosol factor deficiency (1)
Severe congenital neutropenis	1		1 month		
Cyclical neutropenia	3		7 months, 1 year	10 months	
Other well-defined immunodeficiencies	7	17.9			
Hyper IgE syndrome (Job's syndrome)	2		6 months, 18 years		
Chronic Mucocutaneous Candidiasis	1			25 years	
Immunodeficiency with thymoma	4		51 years, 64 years, 69 years	61 years	
Complement deficiencies	0	0			
Immunodeficiencies not elsewhere classified	1	2.6			
Immunodeficiency with T-cell defect	1			3 months	
Total	39	100			

syndrome had *Pneumocystis carinii* pneumonia, the patient with DiGeorge syndrome suffered from parainfluenza, adenovirus and rotavirus infections, one patient with Wiskott-Aldrich Syndrome (WAS) had disseminated cytomegalovirus infection and the patient with autosomal recessive chronic granulomatous disease (CGD) had an episode of Aspergillus pneumonia.

Table II. Patients with family history.

Patient	Disease	Number of family members involved
1	Common variable immunodeficiency (CVI)	1 brother, 1 cousin*
2	Common variable immunodeficiency (CVI)	1 sister, 1 cousin*
3	Common variable immunodeficiency (CVI)	2 cousins*
4	Hyper IgM syndrome	1 uncle
5	IgG subclass deficiency	1 uncle
6	Wiskott-Aldrich syndrome (WAS)	1 brother
7	Cyclical neutropenia	3 mothers and 2 siblings

*The three patients with CVI were related to each other: two were siblings (brother-sister) and the remaining one was their first cousin.

Associated diseases

Autoimmune diseases (systemic lupus erythematosus, seronegative arthritis and autoimmune polyglandular syndrome) were seen in seven patients (five children and two adults). Twelve (seven children and five adults) had concomitant asthma, eczema or allergic rhinitis. Only one paediatric patient in our cohort developed a malignancy. This was an eight-month-old child with common variable immunodeficiency who developed chronic myelo-monocytic leukaemia. The associated diseases are summarised in Table III.

Therapy

The primary treatment modalities were mainly supportive measures. Infections were treated aggressively with antimicrobial agents. Eighteen patients with antibody deficiencies received intravenous immunoglobulin IVIG on a monthly basis of which 5 (27.8%) had hypogammaglobulinaemia, 5 (27.8%) common variable immunodeficiency (CVI), 4 (22.2%) immunodeficiency with thymoma, 2 (11.1%) X-linked Hyper-IgM, 1 (5.6%) severe combined immunodeficiency (SCID) and 1 (5.6%) IgG subclass deficiency. Granulocyte-colony stimulating factor (G-CSF) was given to three patients with neutropenia (either severe congenital or cyclical). One patient with autosomal recessive CGD was also given a short course of gamma interferon. Two paediatric patients with WAS and CGD respectively underwent successful haematopoietic stem cell transplantation (HSCT) at NUH. The patient with WAS underwent a bone marrow transplant with a 6/6 HLA matched sibling donor in 1992 at the age of four years old. He achieved engraftment on 21 days post-transplant and on follow-up, there was no evidence of acute or

Table III. Diseases associated with PIDs.

Associated Diseases	No.	PID phenotype	Number of paediatric cases	Number of adult cases
Systemic Lupus Erthematosus	3	Selective IgA deficiency	1	–
		Chronic mucocutaneous candidiasis	–	1
		Chronic granulomatous disease	1	–
Seronegative arthritis	3	Common variable immunodeficiency	–	1
		Hyper IgM syndrome	1	–
		Chronic granulomatous disease	1	–
Autoimmune polyglandular syndrome	1	IgG subclass deficiency	1	–
Nephrotic syndrome	2	Hypogammaglobulinemia	–	1
		IgG subclass deficiency	1	–
Malignancy	1	Common variable immunodeficiency	1	–
Atopy (Asthma, Allergic Rhinitis or Eczema)	12	Hper IgE syndrome	1	1
		Hyper IgM Syndrome	1	–
		IgG subclass deficiency	–	1
		Selective IgA deficiency	–	1
		Common variable immunodeficiency	1	1
		Wiskott-Aldrich Syndrome	2	–
		Severe combined immunodeficiency	1	–
		Ataxia-Telangiectasia	1	–
		Immunodeficiency with thymoma	–	1

Table IV. Comparison with other PID registries.

	Singapore	Japan[11]	Australia[3]	Sweden[6]	Italy[14]	Brazil[8]	Spain[7]
Time period	1990-2000	1966-1975	1990-1994	1974-1979	1977-1987	1981-1996	1980-1995
Age group	All	All	All	Paed.	All	Paed.	All
Number of cases	39	497	500	174	1214	166	1069
Incidence (per 100,000)	2.65	NR	2.82	8.4	NR	Nr	1.04*
Sex Ratio	1.4:1	2.52:1	1.8:1	2:1	NR	1.34:1	NR
Composition (%)							
Antibody deficiency	41%	53%	71%	45%	75%	61%	71%
Combined disorders	10.3%	9%	5%	7%	5%	5%	7%
Associated with other major defects	12.8%	19%	8%	13%	9%	10%	6%
Phagocytic disorders	15.4%	13%	3%	22%	7%	12%	5%
Other PIDs	17.9%	3%	2%	12%	2%	6%	4%
Complement deficiency	0%	1%	7%	1%	2%	6%	6%

NR = not reported.

Paed. = paediatric patients.

* Projected PID prevalence from 1990 to 1994.

Antibody deficiencies: Agammaglobulinemia (all types), selective immunoglobulin (Ig) deficiency, Ig heavy chain deletions, common variable immunodeficiency, non X-linked hyper IgM syndrome, transient hypogammaglobulinemia of infancy.

Combined immunodeficiencies: SCID (all types), Adenosine Deaminase (ADA) deficiency, Purine Nucleoside Phosphorylase (PNP) deficiency, MHC class II deficiency, CD3 deficiency, X-linked hyper IgM.

Immunodeficiencies associated with other major defects: WAS, attaxia-telangiectasia, DiGeorge anomaly, Chediak-Higashi syndrome, Griscelli syndrome, X-linked lymphoproliferative syndrome.

Phagocytic defects: Severe congenital neutropenia, cyclic neutropenia, leucocyte adhesion defect, specific granule deficiency, Shwachman syndrome, CGD, myeloperoxidase deficiency.

Other PIDs: Hyper IgE, chronic mucocuaneous candidiasis, congenital asplenia, ID with thymoma, ID with short-limbed dwarfism, cartilage-hair hypoplasia.

chronic graft versus host disease (GVHD). He is currently eight years post-transplant and has no evidence of eczema, thrombocytopenia or recurrent infections. The second child suffered from X-linked CGD and received a 6/6 HLA matched sibling donor peripheral blood stem cell transplant (PBSCT) in the year 2000 when he was 18 months of age. He engrafted 11 days post-transplant and had no complications. He now has normal neutrophil function and has not suffered from any recurrent infections since the transplant.

Mortality

Four of the PID patients died. Three of these patients (two with SCID) suffered from T-cell defects and all died of overwhelming sepsis during infancy. One 13-year-old child with cyclical neutropenia died of sepsis and pulmonary haemorrhage. Of the adult patients, there were no deaths. However, three were lost to follow-up.

DISCUSSION

This is the first comprehensive study of PID in Singapore. Although these conditions are uncommon, failure to diagnose and treat early may lead to substantial morbidity and mortality[1-3]. Moreover, as most of these conditions are inherited, making a precise diagnosis is important for genetic counselling of the immediate and extended family[17-19]. The incidence of PID is our series is estimated to be 2.65 per 100,000 live births from January 1990 to December 2000. This is similar to that of Australia, where an incidence of 2.82 per 100,000 has been reported, but much lower than that reported in Sweden (8.4/100,000)[20] (Table IV). However, our data probably under-estimates the disease burden in Singapore as it did not include all the paediatric outpatients or those with asymptomatic IgA, IgG subclass or complement deficiencies. Moreover, it is possible that some patients with severe

immunodeficiencies died of sepsis before a definitive diagnosis was made.

The spectrum of PID in Singapore is similar to that of other countries for both paediatric and adult patients[13,14,20-23]. Antibody deficiencies are the most common followed by phagocytic disorders. It is likely that there are many asymptomatic people with undiagnosed antibody deficiencies and they are usually diagnosed incidentally[24]. There were no patients with complement deficiencies reported. This is consistent with the overall low prevalence of these deficiencies in about 0.03% of the general population[25], 3 in 10,000 prevalence of SLE in Singapore, and 0.3% prevalence of rheumatoid arthritis in Asia[26]. However, it is possible that such cases have been under reported locally. Patients with SCID may be under-represented as these patients often die, undiagnosed, in infancy[27]. As PIDs are usually inherited in an autosomal recessive or X-linked recessive fashion, it is not surprising that seven of our patients had a family history of PID, although none of the patients had parental consanguinity. No patients were diagnosed antenatally in this series, but advances in molecular and genetic testing are expected to lead to widespread availability of antenatal testing[11,12]. Carrier testing was performed in the mother of one of our paediatric patients with X-linked CGD and an antenatal diagnosis was made during her subsequent pregnancy. She chose to terminate that pregnancy.

Patients with PID usually present with recurrent infections or infections with opportunistic organisms[28]. In general, a child who within 12 months has ≥8 ear infections and/or >2 serious episodes of sinusitis, pneumonia, or deep-seated infections should alert the care-provider of the possible existence of immunodeficiency[29]. The other indications for immunologic evaluation include[30]:

- Infections: of prolonged duration, unusual severity, failure to respond as expected to antibiotic therapy, or with uncommon organisms.
- Reaction following transfusion of appropriately matched blood or blood products.
- Systemic illness following live vaccines.
- Clinical findings that may be part of immunodeficiency syndromes including failure to thrive, unusual rash, or persistent diarrhoea, abscesses, periodontitis, or unusual wound healing.
- Abnormal routine laboratory findings, e.g. lymphopaenia, neutropaenia, thrombocytopaenia, hypo- or dysgammaglobulinaemia.
- Infants with a family history of immunodeficiency or of deaths during early childhood.

The commonest presentation in our patients was that of recurrent bacterial infections, consistent with the finding that antibody deficiency is the commonest form of PID. These included chronic sinusitis, chronic pneumonia and bronchiectasis. Therefore, patients who present with recurrent infections or with opportunistic infections should be screened for possible immunodeficiency. There are also genetic conditions with multiple congenital anomalies (e.g. Ataxia-Telangiectasia, DiGeorge Syndrome) in which immunodeficiency is a major presenting symptom. In this group of patients with syndromic PID, the determination of an accurate diagnosis can have implications for treatment of the immunodeficiency and for determination of other organ system involvement as well as prognosis and recurrence risk[31].

A high index of suspicion and early diagnosis are of utmost importance in the successful management of PID. Early diagnosis leads to early treatment and this has been shown to improve prognosis tremendously[9,10]. Diagnosis in our patients was enhanced by both immunological profiling and definition of the molecular abnormality. The ability to define the exact molecular defect has many implications, especially the provision of the physician with the ability to prognosticate accurately. In SCID, molecular defects with poorer prognosis would warrant early HSCT[32]. When the precise molecular defect is known, carrier and prenatal testing can be performed[12,13]. Moreover, defining the genetic defect has led to the exciting advent of gene therapy[33,34].

Since the first descriptions of PIDs in the 1920s[35], the discovery of new therapeutic modalities has significantly improved the morbidity and mortality of these patients. The early and aggressive treatment of infections is an important aspect in the treatment of PID. This avoids life-threatening complications as well as prevents the development of organ damage (e.g. bronchiectasis) and improves overall prognosis[36]. Nine patients in our series had already developed bronchiectasis at the time of diagnosis. The management of patients with antibody defects has been revolutionised by the advent of IVIG. Eighteen (46.2%) of our patients receive IVIG on a regular basis. Early treatment with IVIG in patients with antibody deficiencies has been shown to decrease the incidence of recurrent infections and hence decrease the incidence of chronic sinusitis and irreversible bronchiectasis[37,38]. However, for patients with severe T-cell defects, the only hope of cure is through HSCT[39-43] or gene therapy[33,34]. Two patients have received HSCT in the last 10 years; one with CGD and the other with WAS. However,

the two patients with SCID died within the first year of life. Currently, patients with SCID have a hope of cure with the advent of HSCT[39-41], if diagnosed early. In 2002, a four-month-old boy with SCID was successfully transplanted at the Children's Medical Institute, NUH (unpublished data). He was diagnosed at three months of age and received a transplant three weeks after diagnosis. However, the future of PIDs may possibly lie in foetal stem cell transplantation[44,45] and gene therapy[46].

CONCLUSION

Based on the findings of this study, there is a need to clearly define the molecular abnormalities in Singapore patients to enhance prenatal diagnosis and improve overall morbidity and mortality of PID. The cornerstones of successful management of this special group of patients include a high index of suspicion, early referral, precise diagnosis and appropriate treatment. This is especially important in patients with SCID because if they are unrecognised, most will die in infancy. However, if recognised early, they can be cured by HSCT. In patients with less severe deficiencies, early and aggressive treatment will improve their overall prognosis.

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