Clinical-Epidemiological Pattern of Primary Immunodeficiencies in Malaysia 1987-2006 : A 20 year experience in Four Malaysian Hospitals

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SUMMARY

Aim of study: To determine the clinical and epidemiological characteristics of patients seen with primary immunodeficiencies referred at four Malaysian Hospitals between 1987 to 2007

Methods: Patient data were retrospectively obtained from patient records and supplemented by information from a standardized questionnaires taken at the time of diagnosis from 4 participating hospitals. The completed data were transferred to document records kept by the first author. The diagnoses made were based on criteria set by WHO Scientific Committee 1986.

Results:

Fifty one (51) patients with completed records satisfied the criteria of primary immunodeficiencies based on WHO Scientific Committee 1986. Predominant Antibody deficiency (40.4%) is the commonest of the class of primary immunodeficiency (based on modified IUIS classification) followed by phagocytic defect (17.3%), combined immunodeficiencies (15.4%) and other cellular immunodeficiencies (11.5%). The commonest clinical presentation is pneumonia (54%) . A positive Family history with a close family relative afflicted was a strong pointer to diagnosis for PID (52.6%) Primary immnodeficiencies are seen in all the major ethnic groups of Malaysia, predominantly among Malays. As observed in other patient registries, diagnostic delay remains the major cause of morbidity and mortality.

Conclusion: Primary immunodeficiencies is relative rare but is an emerging disease in Malaysia. Creating awareness of the disease, may reveal more cases within the community. It is sufficient to be a health issue in Malaysia as in other developing countries in the future.

KEY WORDS:
primary immunodeficiency , clinical patterns , diagnostic delay, Malaysia

INTRODUCTION

Primary immunodeficiency (PID), thought to be rare, does occur in the Malaysian population and is seen in increasing numbers since 1986 [1]. The prevalence in the general population is between 1: 500 and1:500,000 depending on diagnostic skills and medical resources available in the country [2]. In countries with established tertiary care, PID is less rare. The US has a prevalence rate of 1:1200 [3]. The first case reported in Malaysia was in 1977[4] and with raised awareness and appropriate medical resources more cases followed 4-13. We report the pattern of 51 cases with PID in Hospital Kuala Lumpur ,HKL, Hospital USM,HUSM, Hospital Kota Bharu, HKB and Hospital Serdang in Malaysia between 1987 - 2006.

MATERIALS AND METHODS

Patients with recurrent infections with diagnosis of PID seen between 1987- 2006 at HKL (1986-1993), HUSM, HKB(1994-2000), and Hospital Serdang (2003-2006) referred by pediatricians and physicians were included in the study. Diagnosis was made based on the World Health Organisation (WHO) criteria[14]. Patients data were retrospectively obtained from patient records and supplemented by information from a standardized questionnaires taken at the time of diagnosis from participating centres. The completed data were transferred to document records kept by the first author. Of the 71 patient records suspected as PID that were available, only 52 were considered as appropriately complete to assign a diagnosis of PID and suitable for reporting and to be classified according to 2003 modified IUIS classification of primary anf secondary immunodeficiencies[15]. The immunology laboratory investigations was carried out by the Institute for Medical Research, Kuala Lumpur and the Department of Immunology, Hospital University Sains Malaysia at Kubang Kerian , Kelantan. The immunology investigations include a full blood and differential count, evaluation of serum immunoglobulin G,A,M, assessment of IgM function (isohemeagglutinin titres A,B), enumeration of lymphocyte subsets, assessment lymphocyte function (in

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Table I: Frequency of various Primary Immunodeficiencies, sex distribution in the Major Ethnic Groups in Malaysia

CLASS	n	%	M , F	Malay	Chinese	Indian	Iban
Predominant Antibody Deficiency	**21**	**(40.38)**					
XLA	10	(19.2)	10, 0	5	1	4	0
CVID	3	(5.7)	2 1	1	1	1	0
HIGM	6	(11.53)	4 2	5	0	1	0
sIgA	1	(1.9)	1 0	1	0	-0	0
Undefined hypogammaglobulinemia	1	(1.9)	1 0	1	0	0	0
Combined immunodeficiency	**8**	**(15.38)**					
SCID	5	(9.6)	3 0	4	0	1	0
T cell defect	3	(6.7)	1 2	3	0	0	0
Other cellular immunodeficiency	**6**	**(11.5)**					
DGA	5	(9.6)	4 1	0	3	2	0
Ataxia Telangiectasia	1	(1.9)	0 1	1	0	0	0
Phagocytic defect	**9**	**(17.3)**					
CGD	4	(7.6)	3 1	4	0	0	0
LAD	1	(1.92)	1 0	0	1	0	0
Chronic neutropenia	3	(6.7)	1 2	2	1	0	0
MSMD	1	(1.92)	1 0	1	0	0	0
ID assoc lymphoproliferation	**1**	**(1.92)**					
Myelodysplasia	1	(1.92)	1 0	1	0	0	0
ID secondary /other diseases	**2**	**(3.8)**					
Chediak Higashi syndrome	2	(3.8)	1 1	1	0	0	1
Other defect	**5**	**(9.61)**					
Chronic mucocutaneous candidiasis	2	(3.8)	1 1	1	0	1	0
HIGE	3	(6.7)	0 1	1	0	2	0

[XLA ,X Linked Agammaglobulinemia; CVID ,common variable immunodeficiency;HIGM ,Hyper IgMsyndrome;SCID ,Severe combined immunodeficiency; DGA ,Di George anomald;CGD ,chronicgranulomatous disease; LAD ,Leukocyte adhesion molecule deficiency;MSMD ,Mendelian Susceptibility to mycobacterial diseases;; ID ,immune deficiency; HIGE ,Hyper IgE syndrome.

Table II: Delay in Diagnosis of Primary Immunodeficiencies

	n	mean sd
XLA	10	5.27 ± 3.99
HIGM	6	2.38 ± 2.63
SCID	5	0.38 ± 0.16
CGD	3	4.73 ± 3.75
CVID	3	13.67 ± 14.36
HIGE	3	4.00 ± 1.73

* delay is considered as age of diagnosis minus age of first symptom
[XLA, X Linked Agammaglobulinemia; CVID, common variable immunodeficiency; HIGM, Hyper IgMsyndrome; SCID, Severe combined immunodeficienc; CGD, chronicgranulomatous disease; HIGE ,Hyper IgE syndrome.

Table III: Comparison of Primary Immunodeficiencies From Registries of Other Countries

	Malaysia	Iran[19]	France[18]	Taiwan[23]
Time period ,year	1987-2006	1981-2001	2005-2009	1985-2004
Number of cases	52	247	3083	37
Male:Female ratio	2.1:1	1.6:1	1.42:1	3.6:1
Family history	52.63%	na	na	18.91%
Frequency (Diagnostic delay)				
XLA	*19.2%	*13.3%	*5.2%	16.0%
	5.27yr /(3.75 yr)	6.47 yr/ -	- /(1.0 yr)	na
Chronic granulomatous disease	*7.6%	*11.7	*5.15%	1.1%
	4.73 yr /(6.8yr)	3.5yr /-	- /(0.9 yr)	na
SCID	*9.6%	*2.4%	*7.1%	8.1%
	0.38 yr / (0.3yr)	na	- /(0.2 yr)	na
CVID	*5.7	*2.4%	*14.3%	*10%
	13.67 yr / (8yr)	6.18yr /-	- /(6.0 yr)	na

* proportion of pid class
Diagnostic delay. mean/(median)
Note: for delay of diagnosis Iran quote as mean while France as (median)
na - not available

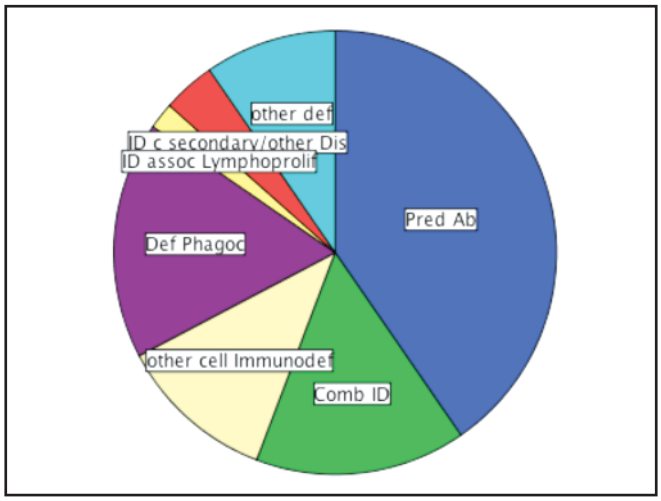

Fig. 1: Spectrum of Primary Immunodeficiency in Malaysian patients.
[Pred Ab, predominant antibody defect; Comb ID, combined immunodeficiency; other cell immunodef,other cellular immunodeficiency; Def Phagoc, defective phagocytosis; ID assoc lymphoprolif,immunodeficiency associated lymphoproliferation; ID c secondary/other dis ,immunodeficiency with secondary /other disease;, other deficiencies

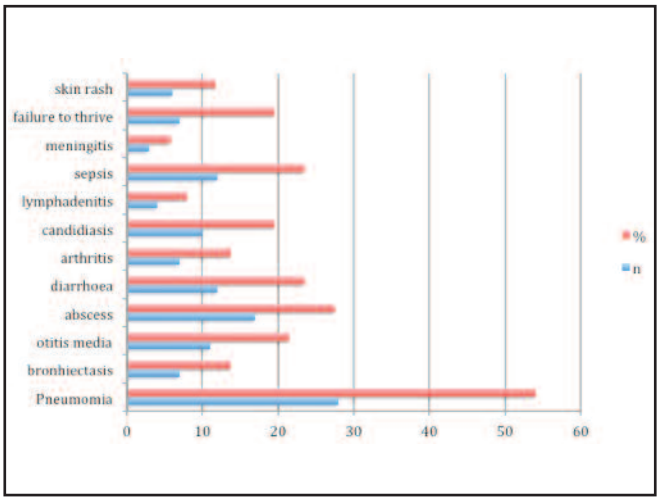

Fig. 2: Clinical Presentations of 52 Primary Immmunodeficiency Patients in Malaysia.

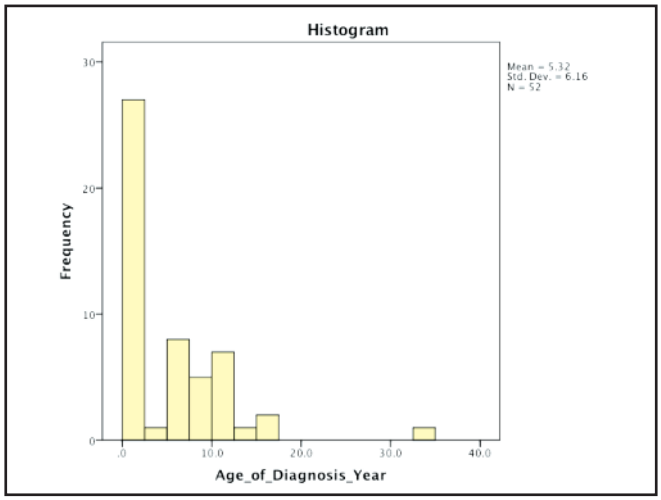

Fig. 3: Age at Diagnosis of Primary Immunodeficiency in Malaysia.

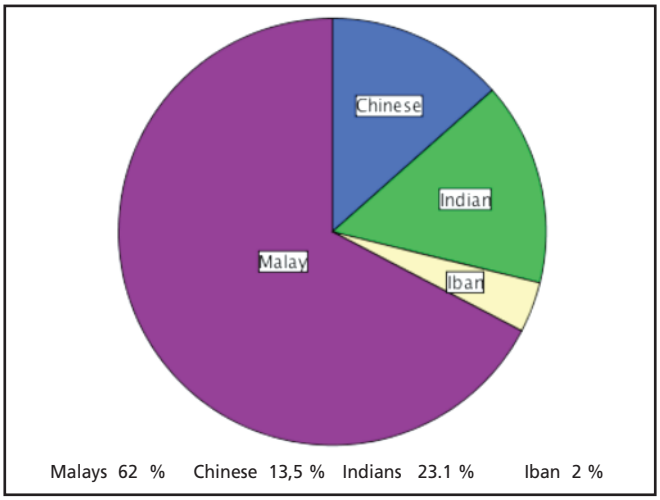

Fig. 4: Ethnic distribution of Pimary Immunodeficiencies in Malaysia.

vitro lymphocyte proliferation to mitogen) and assessment of neutrophil function (NBT, chemiluminescence assays). Assays for Complement components were not available and hence not included here.

RESULTS

Fifty two patients were diagnosed with primary immunodeficiency (PID) based on WHO criteria (1986)[14]. We grouped our patients applying the Modified International Union of Immunological Union of Immunological Societies (IUIS) Classification of Primary and Secondary Immunodeficiencies[15]. Predominantly antibody deficiencies were the most common (40.4%) followed by phagocytic defect (17.3%), combined immunodeficiency (15.4%) and the other cellular immunodeficiencies (11.5%) were less common (Fig 1).

The most common entity in our series is X linked agammaglobulinemia (,XLA) (n=10) followed by Hyper IgM syndrome (HIGM) (n=6) syndrome and severe combined immunodeficiency (SCID) (n=5). Fig 1

Clinical Presentations

The most frequent clinical presentations are recurrent pneumonia (54%), abscess (27.5%), followed by diarrhoea (23.5%), sepsis (23.5%), candidiasis (16.6%) and otitis media (13.7%).

Pneumonia remains the most common presentation in the 3 commonest PID category (XLA, HIGM, SCID); abscess in CGD; diarrhea and candidiasis in SCID see Fig 2

Diagnosis was made below the age of 10 years in 78.4 % of cases, most within the first 5 years of life (51.9 %). Only

19.1% were diagnosed above 12 years of age including one patient with CVID who was diagnosed at the age 33 years. See Fig 3

Ethnic distribution of PID in Malaysia
The majority of patients were ethnic Malays (67.3%) followed by Chinese (13.5%) and Indians (15.4 %) (Fig 4).

As a point of interest, although the Chinese community forms about 24.6% [27] of the Malaysian population, the frequency of PID (13.5%) is disproportionately lower than that in the Indians (15.4%) which forms 7.1% [26] of Malaysian population.

The frequency of specific PID for each ethnic group is seen in Table I.

Diagnostic Delays
We considered the interval between the age of diagnosis and the age when symptoms were first noticed as delay in diagnosis. The average delay in our 52 patients was 3.87 years. Individually CVID had the longest delays in diagnosis (13.67 years), followed by XLA (5.27 years) and CGD (4.73 years). SCID is diagnosed early in our series (0.38 years). (Table 2)

Gender There is a preponderance of males over females (M:F 35:17) in PID patients.
Family History
Family History is positive in 20 out of 38 patients (52.63%)

Intravenous immunoglobulin therapy
Nineteen (40.3%) patients required intravenous immunoglobulin (IVIg)mainly for antibody deficiencies (XLA 10, Hypogammaglobulinemia 1, CVID 3, HIGM 2, SCID 3).

Distribution of patients among states of Malaysia
PID patients were from almost all states of Malaysia. We considered where the patient reside according to the address that was documented on the records. From the available data on 35 patients. Selangor had the most patients, 8 (23%), Wilayah Persekutuan 5 (14%), with 4 in each of the states of Perak (11.4%), Negeri Sembilan (11.4%), and Kelantan (11.4 %), 3 for each for the states of Pahang (8.5%) and Sarawak(8.5 %), 2 (5.7%) for Kedah and 1 each for Malacca (2.8%) and Johore (2.8%). It appears that most of the patients were from states close to the capital, Kuala Lumpur where tertiary clinical immunology services is available

DISCUSSION

Primary Immunodeficiency is a disorder resulting from monogenic defects of the human immune system[16]. It is an emerging disease in Malaysia, not because it is a new entity, rather with increasing awareness and better diagnostic facilities more cases are being diagnosed. A large population of patients with recurring infections is undiagnosed or misdiagnosed. PID is more common than as previously estimated [16]. Delay in diagnosis is often the cause of severe morbidity and/or frequent mortality. As in many other countries, the diagnosis of PID is often delayed, optimum treatment missed and patients are only referred to the clinical immunologist when they have suffered critical events[17].

'The prevalence in the general population is between 1: 500 to 1:500,000 depending on diagnostic skills and medical resources available in the country'[1]. This may be applicable to Malaysia as in many other developing countries. Because of incomplete collection of data as in registries elsewhere (Spain, Australia, Latin America, Norway)[18], the true prevalence of symptomatic primary immunodeficiency is probably considerably higher than a frequency 1: 5000 population[26]. Malaysia has seen more cases in the last 5 years(2007-2011) due to increasing awareness and improved medical resources in the country (unpublished data). Similar increasing trend is also reported in other countries [16,18].

It is important to recognize and treat PID early, as failure to do so would lead to significant morbidity and mortality. This is especially pertinent as many of the immunodeficiency can be treated and even cured [17,18].

The relative distribution of primary immunodeficiencies in our series indicated that predominantly antibody deficiency is still the commonest (40%), followed by phagocytic defect (17.3%), combined immunodeficiency (15.38%) and cellular immunodeficiency (11.5%). The frequency of Antibody deficiency is similar to reports from Iran (52.6%)[19], Singapore (41%)[20], and the registries summarized by Affentranger and colleagues[21]. The prevalence of antibody deficiency appears more predominant in Australia (77%)[22].

Of the individual PID in our series, XLA, is the commonest (n= 10; 19.2%), followed closely by CGD (n=9; 17.3%), HIGM (n=6; 11.53%) and SCID (n=5; 9.6%). The frequencty of XLA constituting 19.2% of all our PID case , is similar to that seen in Iran (13.3%)[19] and Taiwan (16.5%)[23]. CGD in Taiwan (1.1%) occurs less frequently than in Iran (11.7) or Malaysia (7.6%). However frequency of SCID for Malaysia (9.6%) is similar to Taiwan (8.1%) but is less frequent in Iran (2.4%). SCID is especially relevant to Malaysia where it constitutes almost 10% of all PID cases. The medical practitioner must be sufficiently familiar with SCID, so as not to miss an early referral to tertiary PID centre for diagnosis and further management including Hemapoietic Stem Cell Transplant. (HSCT). It is crucial that a patient with SCID receives hemapoietic stem cell transplant early (within the first 3 months) as the survival rate is over 90%; without a transplant they will barely survive beyond 1 year of age, making SCID a pediatric emergency[24].

The use of replacement immunoglobulin therapy for 40% of all Malaysian PID cases is similar to the situation in France (42%)[18] but less than that in Australia (76.2%)[22]. This has implications for developing countries as use of commercial immunoglobulin is both expensive and life-long and will pose a financial strain on the family with it non compliance. Hence it is desirable for PID patients requiring Immunoglobulin therapy to receive subsidized treatment as in Malaysia.

Unfamiliarity with PID amongst practicing doctors often causes delays in diagnosis even in developed countries. The diagnostic delay as seen in the Malaysian series is compared to other countries. (Table 3).

Comparing Malaysia with Iran, the following mean diagnostic delay was noted: 13.67 years vs 6.18 years for

CVID and 4.73 years vs 3.5 years for CGD. However when comparing with a developed country like France,[17] the delay is more pronounced. The favourable French figures may be due to the availability of better facility as a result of the creation of the French National Centre of Primary Immunodeficiency (CEREDIH)[25] in 2005, constituting a network of pediatric and adult medical department in University Medical Centres which boasts of a registry of 3,083 patient between 2005-2009. The centre is believed to hold the largest national registry. Fifty eight (58) medical departments with experience in the care of both children and adult PID in 19 regional centres contribute to the present registry of PID[17]. Diagnostic delay can result in unnecessary morbidity in untreated disease and making complications of long standing disease difficult to treat [25]. The most common cause of delay is still the lack of awareness of individual advisers and diagnostic centres[17].

Family history is considered positive when a first degree relative is affected with PID or a sibling suffers an early death associated with infection . In our series, 52.6% of patients had a positive family history compared to 24% in the USA[3], 31.2% in Australia[22] and 18.7% in Taiwan[23]. The most plausible explanation is that patients with recurrent infections in Malaysiua are more likely to be referred to tertiary centres if there had been a previous affected close degree relative in the family by the attending doctor.

CONCLUSION

More primary immunodeficiency cases are being recognized in developing countries such as Malaysia, making it important to develop sufficient tertiary centres equipped with clinical expertise and laboratory facilities for better diagnosis. As PID is still a relative rare but emerging disease in Malaysia, the setting up of a credible registry acting as a tool that provide prospective and retrospective data for the medical community, health authorities, PID patients and families is highly desirable. A registry would improve access to good medical care and promote research and innovation.

More clinical epidemiological data on primary immunodeficiencies from developing countries are highly sought. Our data and others support the perception that clinical epidemiological pattern of primary immunodeficiency differs in various population and regions of the world.

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