J Clin Immunol (2009) 29:357–364
DOI 10.1007/s10875-008-9273-5

Clinical Characteristics and Outcomes of Primary Immunodeficiencies in Thai Children: An 18-year Experience from a Tertiary Care Center

P. Benjasupattananan · T. Simasathein · P. Vichyanond · V. Leungwedchakarn · N. Visitsunthorn · P. Pacharn · O. Jirapongsananuruk

Received: 20 November 2008 / Accepted: 31 December 2008 / Published online: 28 January 2009

Abstracts

Introduction Early diagnosis and treatment are keys to improve survival of patients with primary immunodeficiency diseases (PID). The clinical characteristics of these patients in Thailand were not well defined.

Objective This study aimed to determine the clinical characteristics and outcomes of patients with PID in Thailand.

Methods Medical records of PID patients in the past 18 years were reviewed.

Results Sixty-seven children were registered. Antibody deficiencies were the most common PID (52.2%), followed by combined T cell and B cell immunodeficiencies (25.4%), other well-defined immunodeficiency syndromes (11.9%), and phagocytic defects (10.4%). The most common presentations of antibody deficiencies, combined T cell and B cell immunodeficiencies, and phagocytic defects were infection in the upper respiratory tract (74.3%), gastrointestinal tract (82.4%), and skin (85.7%), respectively. The highest mortality rate (52.9%) was found in severe combined immunodeficiency.

Conclusion These results provide clinical features of PID in Thailand. Knowing these features will lead to prompt diagnosis and appropriate management.

P. Benjasupattananan · T. Simasathein · P. Vichyanond · N. Visitsunthorn · P. Pacharn · O. Jirapongsananuruk (✉)
Division of Allergy and Immunology, Department of Pediatrics, Siriraj Hospital Mahidol University,
2 Prannok Rd, Bangkoknoi,
Bangkok 10700, Thailand
e-mail: siojr@mahidol.ac.th

V. Leungwedchakarn
Department of Immunology, Siriraj Hospital Mahidol University, Bangkok, Thailand

Keywords Agammaglobulinemia · antibody deficiency · chronic granulomatous diseases · common variable immunodeficiency diseases · IgG subclass deficiency · other well-defined immunodeficiency diseases · primary immunodeficiency diseases · severe combined immunodeficiency diseases · Thailand

Abbreviations

BMT	bone marrow transplantation
CGD	chronic granulomatous disease
CVID	common variable immunodeficiency
GI	gastrointestinal
IVIG	intravenous immunoglobulin
PID	primary immunodeficiency diseases
SCID	severe combined immunodeficiency

Introduction

Primary immunodeficiency diseases (PIDs) are inherited disorders of the immune system resulting in increased susceptibility to unusual infections and predisposition to autoimmunity. The overall incidence was one per 10,000 live births [1]. The common presentations of PID patients were recurrent infections, especially in the respiratory and gastrointestinal tracts. Previous studies reported that PIDs were the cause of recurrent infections in 4.5–58% of patients [2–13]. Knowing the clinical features of PID will raise physician awareness of this condition which leads to prompt diagnosis and appropriate management.

Intravenous immunoglobulin (IVIG) and antibiotic prophylaxis were the conventional treatments which resulted in an increasing survival rate of PID patients [14–16]. The early treatment of PID resulted in better outcome. Antoine

et al. [17] reported that bone marrow transplantation (BMT) for immunodeficiencies provided a 3-year survival rate of 85% in children who were younger than 6 months old and 53% in children who were older than 12 months old. Therefore, early diagnosis and treatment of PID would improve the survival of these patients.

The morbidities of PID such as recurrent infections, chronic pulmonary diseases, autoimmunity, and malignancy affect the quality of life and produce economic burden [18–22]. The incidence of malignancy in common variable immunodeficiency (CVID) patients was five to 13 times higher than in the normal population [18–19]. The appropriate diagnosis and management would decrease health care cost and result in improved quality of life for these patients. The diagnosis of PID was confirmed by immunologic workup [23]. Recently, the World Health Organization (WHO) and the International Union of Immunological Societies reported more than 120 groups of PID [24–25]. The distributions of PID from several countries [26–34], including Thailand [35], showed the highest prevalence in antibody deficiency diseases. However, ethnic differences contributed to different prevalence for some PID. For example, selective IgA deficiency was found to be 1:369 in Finland whereas it was found to be 1:18,500 in Japan [26].

In Thailand, Simasathein et al. [36] reported cases of PID in the year 2003. The most common PID was antibody deficiency (46%) followed by severe combined immunodeficiency (SCID, 24%), other combined T cell and B cell defects (14%), chronic granulomatous disease (CGD, 8%), DiGeorge syndrome (6%), complement deficiency (1.3%), and chronic mucocutaneous candidiasis (1.3%). All patients presented with severe or recurrent infections.

At present, there are no systematic data regarding the long-term outcome of PID in Thailand. This study was performed to determine the frequency, characteristics, and clinical course of these patients. These data will help physicians to identify patients with PID and to provide a national database of PID in order to initiate a multi-institutional network to study PID in Thailand.

Methods

Subjects

The study was approved by the ethics committee, Siriraj Hospital Mahidol University, Thailand. Sixty-seven medical records of all patients diagnosed and treated for PID in the past 18 years at Siriraj Hospital were reviewed.

The patients were diagnosed and classified according to the WHO Scientific Group, Pan-American Group for Immunodeficiency, European Society for Immunodeficiencies, and the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee [24–25, 37]. Secondary immunodeficiency diseases such as human immunodeficiency virus infection, drug-induced immunodeficiency, congenital infection, nephrotic syndrome, protein-losing enteropathy, severe burns, lymphangiectasia, and recurrent pneumonia from gastroesophageal reflux were excluded by detailed history and appropriated testings, when these disorders were suspected.

Immunologic Studies

The immunological tests were performed using standard techniques and included complete blood count with peripheral blood smear evaluation, serum immunoglobulins, antibody response to pneumococcal vaccine, lymphocyte phenotype (T, B, and natural killer cells) by flow cytometry, lymphocyte proliferation test, dihydrorhodamine assay, and CH50. Mutation analysis using genomic DNA for interleukin (IL)-2R, IL-7R, Bruton tyrosine kinase (BTK), and cytochrome b-245, beta polypeptide (CYBB) genes were done by previously described methods [38–41]. For IL12RB1 gene, coding regions of the IL12RB1 locus were polymerase chain reaction (PCR)-amplified using exon-specific primers (primer sequences available upon request). The PCR products were directly sequenced in both the forward and reverse direction using BigDye (version 1.1) terminators (Applied Biosystems, Foster City, CA, USA). All identified mutations were confirmed by sequencing a second PCR product. The coding sequence was compared with RefSeq NM_005535.

Statistical Analysis

Data were expressed as individual values or the mean±SD for groups. Data analysis was performed using computer base and SPSS statistical software (version 11.0). A linear regression analysis was used to determine the association between birth date and diagnosis lag in months (duration from time of onset of disease to time of diagnosis). The Mann–Whitney U test was used to compare the diagnosis lag in months in the patients who were born before the year 1995 and since the year 1995.

Results

Demographic Characteristics and Distributions of PID

A total of 67 patients (44 males, 23 females) representing four classes of PID were registered. All patients were Thai. The most common group of PID was antibody deficiency diseases (52.2%), followed by combined T cell and B cell

Table I Distribution of Primary Immunodeficiency Diseases

Classification of primary immunodeficiency diseases	*n* (%)
Antibody deficiencies	35 (52.2)
Agammaglobulinemia	6 (9.0)
Common variable immunodeficiency	5 (7.5)
Selective IgA deficiency	2 (3.0)
IgG subclass deficiency	8 (11.9)
Specific antibody deficiency	11 (16.4)
IgG subclass deficiency + specific antibody deficiency	1 (1.5)
IgG subclass deficiency + transient hypogammaglobulinemia	1 (1.5)
IgG subclass deficiency + IgA deficiency	1 (1.5)
Combined T cell and B cell immunodeficiencies	17 (25.4)
Severe combined immunodeficiency	12 (17.9)
Hyper-IgM syndrome	5 (7.5)
Congenital defects of phagocyte number, function, or both	7 (10.4)
Chronic granulomatous disease	6 (9.0)
IL-12 receptor deficiency	1 (1.5)
Other well-defined immunodeficiency syndromes	8 (11.9)
DiGeorge syndrome	4 (6.0)
Hyper-IgE syndrome	1 (1.5)
Isolated CD4 deficiency	1 (1.5)
Chronic mucocutaneous candidiasis	1 (1.5)
Ataxia telangiectasia	1 (1.5)

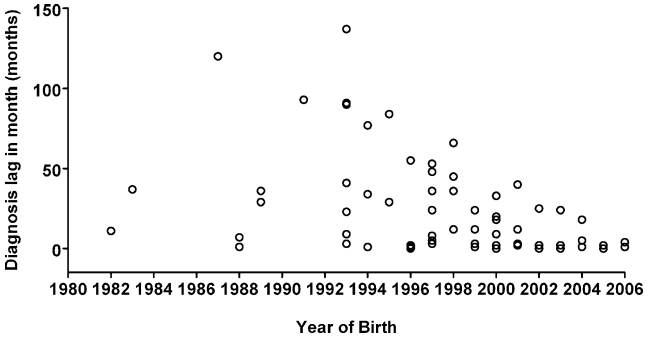

Fig. 1 Diagnosis lag in months and year of birth of PID patients. The diagnosis lag in months which were defined as the duration from time of onset of disease to time of diagnosis was plotted against year of birth. The diagnosis lag in months decreased from 44.28 months before the year of birth of 1995 to 29.46 months since the year of birth of 1995 (p=0.005)

immunodeficiency diseases (25.4%), other well-defined immune deficiency syndromes (11.9%), and congenital defects of phagocytes (10.4%). The distributions of specific PID in each classification were shown in Table I. The male-to-female ratio was 1.9 and males predominated in all classes of PID (Table II).

The family history of death at a young age was found in SCID and CGD (11 patients, 16.4%). A family history of PID was found in hyper-IgM syndrome and CGD (three patients, 4.5%). The consanguineous marriage was found in SCID and CGD (six patients, 9%). Overall, the onset of symptoms occurred at the mean age of 23.8±27.5 months (range newborn period–108 months old). The mean age at diagnosis was 48.5±42.7 months (range 1–168 months old). The mean duration from time of onset to time of diagnosis (diagnosis lag in months) in all groups was 25.2± 31.1 months (range 0.5–137 months). The age at onset, age at diagnosis, and diagnosis lag in months varied considerably for different types of PID (Table II). Of note, the combined T cell and B cell immunodeficiency diseases presented and were diagnosed at the youngest age and had the shortest diagnosis lag in months when compared to other groups. Ten percent of all PID patients were not diagnosed until they were older than 9 years old, especially in antibody deficiency diseases.

There was an increasing trend towards the early recognition of PID in the past decade. Seventy-six percent of all patients were diagnosed in the past 9 years (1999–

Table II Demographic Data and Diagnosis Lag in Months for Each Classification of Primary Immunodeficiency Diseases

Characteristics		Antibody deficiencies, n=35	Combined T cell and B cell immunodeficiencies, n=17	Phagocytic defects, n=7	Other well-defined immunodeficiency syndromes, n=8
Sex	Male	22	12	5	5
	Female	13	5	2	3
Age at onset, mean±SD, months (range)		35.8±28.6 (NB–108)	6±6.9 (1–30)	22.8±36.3 (2–95)	10±15.9 (NB–48)
Diagnosis lag months, mean±SD, months (range)		32.7±24.2 (NB–91)	3.9±3.5 (0.5–10)	36.3±55.4 (0.7–137)	30.6±48.0 (0.7–120)
Age at diagnosis, mean±SD, months (range)		68.5±31.3 (2–119)	10±7.2 (3–32)	52.1±57.7 (2–146)	39.5±61 (1–168)

NB newborn period

Table III Presenting Symptoms of each Classification of Primary Immunodeficiency Diseases

Presenting symptoms	Antibody deficiencies, $n=35$	Combined T cell and B cell immunodeficiencies, $n=17$	Phagocytic defects, $n=7$	Other well-defined immunodeficiency syndromes, $n=8$
URI	26 (74.3%)	–	–	–
LRI	12 (34.3%)	4 (23.5%)	3 (42.9%)	–
Chronic diarrhea	5 (14.3%)	14 (82.4%)	–	–
Sepsis	6 (17.1%)[a]	5 (29.4%)	5 (71.4%)	–
Skin infection	3 (8.6%)	3 (17.6%)	6 (85.7%)	4 (50%)
Failure to thrive	2 (5.7%)	14 (82.4%)	–	–
Pneumocystis jirovecii pneumonia	–	10 (58.8%)	–	–
Oral candidiasis	–	8 (47.1%)	–	–
Vaccine-related infection	–	3 (17.6%)	–	–
Osteomyelitis	2 (5.7%)	–	–	–
Oral ulcer	–	2 (11.8%)	–	–
Graft versus host disease	–	1 (5.9%)	–	–
Meningitis	1 (2.9%)	–	–	2 (25%)
Cardiovascular diseases	–	–	–	2 (25%)

URI upper respiratory tract infections (including recurrent sinusitis, chronic rhinosinusitis, and otitis media), *LRI* lower respiratory tract infections including pneumonia and bronchiectasis

[a] In agammaglobulinemia and common variable immunodeficiency disease

2007) while 24% were diagnosed before the year 1999. A reversed association between the year of birth and diagnosis lag in months was shown in Fig. 1. The diagnosis lag in months decreased from 44.3 months before the year of birth 1995 to 29.5 months since the year of birth 1995 ($p=0.005$)

Presenting Symptoms of PID

A diversity of presenting symptoms in each classification of PID was observed (Table III). Some patients presented with more than one manifestation. Although recurrent upper respiratory tract infection was the most common presentation in antibody deficiency diseases (74.3%), other groups did not present with this symptom. In the group of antibody deficiencies, sepsis was found only in agammaglobulinemia and CVID. Combined T cell and B cell immunodeficiency patients commonly presented with chronic diarrhea (82.4%), failure to thrive (82.4%), *Pneumocystis jirovecii* pneumonia (58.8%), and oral candidiasis (47.1%). In our study, *P. jirovecii* pneumonia, oral candidiasis, oral ulcer, graft versus host diseases, and vaccine-related infection were selectively found in combined T cell and B cell

Table IV Organisms Found in Each Classification of Primary Immunodeficiency Diseases

Organisms	Antibody deficiencies ($n=35$)	Combined T cell and B cell immunodeficiencies ($n=17$)	Phagocytic defects ($n=7$)	Other well-defined immunodeficiency syndromes ($n=8$)
S. pneumoniae	2 (5.7%)	–	–	–
S. aureus	–	–	1 (14.3%)	–
K. pneumoniae	1 (2.9%)	–	2 (28.6%)	–
P. aeruginosa	4 (11.4%)	1 (5.9%)	–	1 (12.5%)
Salmonella sp.	–	2 (11.8%)	2 (28.6%)	–
C. violaceum	–	–	3 (42.9%)	–
Mycobacterium sp.	1 (2.9%)	3 (17.6%)	2 (28.6%)	1 (12.5%)
Norcadia sp.	–	–	1 (14.3%)	–
Histoplasma sp.	–	–	–	1 (12.5%)
Candida sp.	–	8 (47.1%)	–	1 (12.5%)
P. jirovecii	–	10 (58.8%)	–	–
G. lamblia	1 (2.9%)	–	–	–
Herpes simplex virus	1 (2.9%)	1 (5.9%)	–	1 (12.5%)
Cytomegalovirus	–	–	1 (14.3%)	–

immunodeficiencies. Patients with congenital defect of phagocytes frequently presented with skin infection (subcutaneous abscess, 85.7%), sepsis (71.4%), and recurrent lower respiratory tract infection (42.9%).

The most common organism in antibody deficiency patients was *Pseudomonas aeruginosa* (11.4%) which caused sepsis in agammaglobulinemia and CVID patients (Table IV). *P. jirovecii* was the most common organism (58.8%) in combined T cell and B cell immunodeficiency patients and was not found in other group of PID. *Chromobacterium violaceum* was the most common organism (42.9%) in patients with congenital defects of phagocyte (CGD), followed by *Klebsiella pneumoniae*, *Mycobacterium* sp., and *Salmonella* sp. (28.6% for each organism). Patients with other well-defined immunodeficiency syndromes were infected with diverse organisms such as *Mycobacterium* sp., herpes simplex virus, *P. aeruginosa*, *Candida* sp., and *Histoplasma* sp.

Genetic Analysis

Genetic analysis was performed in ten patients (14.9%). The genetic defects were found in the *BTK* gene (four X-linked agammaglobulinemia patients), *CYBB* gene (three CGD patients), *IL-7R* gene (one SCID patient), *IL-2R* gene (one SCID patient), and *IL-12RB1* gene (one IL-12 receptor deficiency patient).

Treatment and Outcome of PID

Fifty-eight patients were followed for a mean duration of 40.2±46.6 months. There were incomplete data in nine patients. The mortality rate was 29.3% which was mainly found in the group with combined T cell and B cell immunodeficiencies (SCID, 52.9%, and hyper-IgM syndrome, 17.6%), followed by CGD (11.8%; Table V). The most common cause of death was sepsis which was found in combined T cell and B cell immunodeficiencies and congenital defects of phagocytes (Table VI). Patients who survived with complications were found in the antibody deficiency group (Table V).

A number of antibody deficiency patients received oral antibiotic prophylaxis (40.7%) and IVIG (37.0%; Table VII). All patients with agammaglobulinemia and CVID received IVIG which resulted in a high survival rate (80%). In ten patients with IgG subclass deficiencies and/or specific antibody deficiencies, decreasing rate of recurrent infection was observed after treatment with IVIG or prophylactic antibiotics in five patients (50%). Four patients received bone marrow transplantation (three SCID, one CGD) and three of these patients were doing well. Most patients with phagocytic defects received antibiotic and anti-fungal prophylaxis and their survival rate was 66.7%.

Table V Outcome of 58 Primary Immunodeficiency Patients

Outcomes	*n* (%)
Dead	17 (29.3)
Severe combined immunodeficiency	9 (52.9)
Hyper-IgM syndrome	3 (17.6)
Chronic granulomatous disease	2 (11.8)
Agammaglobulinemia	1 (5.9)
Common variable immunodeficiency	1 (5.9)
Isolated CD4 deficiency	1 (5.9)
Surviving	41 (70.7)
Surviving without complications	34 (82.9)
Antibody deficiency	
IgG subclass deficiency	3 (8.8)
Specific antibody deficiency	9 (26.5)
IgG subclass deficiency + specific antibody	1 (2.9)
Deficiency	
IgG subclass deficiency + IgA deficiency	1 (2.9)
Selective IgA deficiency	2 (5.9)
Agammaglobulinemia	2 (5.9)
Combined T cell and B cell immunodeficiencies	
Severe combined immunodeficiency	3 (8.8)
Hyper-IgM syndrome	2 (5.9)
Congenital defect of phagocyte number, function, or both	
Chronic granulomatous disease	3 (8.8)
IL-12 receptor deficiency	1 (2.9)
Other well-defined immunodeficiency syndromes	
DiGeorge syndrome	4 (11.8)
Hyper-IgE syndrome	1 (2.9)
Chronic mucocutaneous candidiasis	1 (2.9)
Ataxia telangiectasia	1 (2.9)
Surviving with complications	7 (17.1)
Agammaglobulinemia (hydrocephalus, chronic lung diseases)	3 (42.9)
Common variable immunodeficiency (bronchiectasis, chronic otitis media)	3 (42.9)
IgG subclass deficiency (chronic hepatitis B infection)	1 (14.3)

Discussion

Early diagnosis and treatment are keys to improve survival of PID. This study provided the clinical characteristics and outcome of PID for our institute. As in many studies, antibody deficiencies were found to be the most common group of PID [26–34, 42]. In our study, the most common disease in antibody deficiencies was IgG subclass deficiency and specific antibody deficiency which was supported by the report from Hong Kong [32]. In contrast, the PID registry from Ireland and Norway showed that CVID was the most frequent disorder among antibody deficiencies [30, 34]. SCID was found to be the most common disease in the group with combined T cell and B cell immunodeficiencies which was supported by the study of Lee et al. [31]. CGD was the most common phagocytic disorder which was supported by the study of Lam et al. [32].

Table VI Causes of Death of 17 Patients

Causes of death	Antibody deficiencies, n=2	Combined T cell and B cell immunodeficiencies, n=12	Phagocytic defects, n=2	Other well-defined immunodeficiency syndromes, n=1
ARDS	–	3 (25%)	–	–
PCP	–	3 (25%)	–	–
GVHD	–	3 (25%)	–	–
Sepsis	–	6 (50%)	1 (50%)	–
CNS infection	1 (50%)	–	1 (50%)	–
Pneumonia and respiratory failure	1 (50%)	–	–	1 (100%)

ARDS adult respiratory distress syndrome, *PCP Pneumocystis jirovecii* pneumonia, *GVHD* graft versus host disease, *CNS* central nervous system

A detailed family history was essential for early recognition of primary immunodeficiencies. In our study, a family history of consanguineous marriage and death at a young age, although found in low percentages, was the leading clue to the diagnosis of SCID and CGD. The family history of PID was found in hyper-IgM syndrome and CGD. Of note, these diseases were most commonly inherited through the X chromosome.

Patients with combined T cell and B cell immunodeficiency developed symptoms in the youngest age (6.0± 6.9 months) and were rapidly diagnosed in 3.9±3.5 months. The reason for the shortest diagnosis lag in months was the early onset and severe symptoms of these patients in the first year of life. Other groups of PID might have a long diagnosis lag of many months due to the mild presentations and onset after the first year of life. A number of patients with congenital defects of phagocyte presented their symptoms when reaching school age because two patients had autosomal recessive CGD and one patient had IL-12 receptor deficiency. These two diseases usually had mild symptoms and presented at school age.

The majority of PID patients presented with recurrent respiratory tract infections. However, septicemia, gastrointestinal tract infections, skin infections, and failure to thrive were common presentations as well. There were variations of presenting symptoms in each classification of PID. Recurrent upper respiratory tract infections, the most common presenting symptom in antibody deficiency, were the additional clue enabling increased recognition of this disorder. This was found in many studies [43–44]. In our study, 24 patients who presented with recurrent upper respiratory tract infections were diagnosed as IgG subclass disproportion (the proportion of each subclass was below normal proportion). These patients did not fulfill the standard diagnostic criteria for IgG subclass deficiency (the level of specific subclass less than two SD of the mean for age with normal or near-normal total IgG concentration). Their data were not included in this study. Nevertheless, these patients had the same presentations as IgG subclass deficiency and demonstrated a decreasing rate of infection after antibiotic prophylaxis. In this study, sepsis in antibody deficiency patients was found to be high (17%) compared to the previous study (10%) [45]. These patients had protracted infections and were treated in the primary hospitals before they were referred to our tertiary hospital. As a result, hospital-acquired infections from gram-negative bacteria such as *P. aeruginosa* and *K. pneumoniae* were reported.

Gastrointestinal infections and failure to thrive were the most common presentations in combined T cell and B cell immunodeficiency patients. *P. jirovecii* pneumonia infection was markedly high in combined T cell and B cell immunodeficiency patients. Our study found Bacillus Calmette-Guérin (BCG)-related infection in three SCID patients in contrast to reports from Singapore and Hong Kong [29, 32]. These patients received BCG vaccine despite the family history of consanguineous marriage and

Table VII Treatment and Survival Rate of 58 Primary Immunodeficiency Patients

Treatment	Antibody deficiencies, n=27	Combined T cell and B cell immunodeficiencies, n=17	Phagocytic defects, n=6	Other well-defined immunodeficiency syndromes, n=8
Treatment				
Intravenous immunoglobulin	10 (37.0%)	15 (88.2%)	–	2 (25%)
Prophylaxis medications	11 (40.7%)	5 (29.4%)	5 (83.3%)[a]	3 (37.5%)
Bone marrow transplantation	–	3 (17.6%)	1 (16.7%)	–
Survival rate	25 (92.6%)	5 (29.4%)	4 (66.7%)	7 (87.5%)

[a] Includes anti-fungal and antibiotic prophylaxis

death at an early age. Live vaccine administration should be delayed until the immunological statuses of these patients are identified.

Of interest, a number of the patients with congenital defect of phagocytes presented with *C. violace*um septicemia and subcutaneous abscess. *C. violaceum*, an atypical organism which was rarely found in a normal host, was associated with a high mortality rate. Infection with this organism led to a definite diagnosis in three CGD patients. This might be a distinct feature of CGD in tropical countries as almost all reported cases of *C. violaceum* septicemia occurred in tropical and subtropical regions [46–55]. Septicemia from this organism, in addition to *Salmonella* sp., in CGD was accounted for the high rate of sepsis (71%) in our phagocytic defect patients compared to the previous study (18%) [56].

Autoimmune diseases or malignancy was not found in any patients, neither in presenting manifestations nor in follow-up periods. These findings are not in agreement with previous report in other countries [29, 31–32]. It was possible that most of our patients were followed only in childhood and the follow-up periods were not long enough to detect autoimmune disorders.

In our study, the mortality rate was 29.3% and half of it occurred in patients with SCID. Severe sepsis was the major cause of death in these patients. These patients would not survive unless definite treatment such as BMT was done. In this report, two of three SCID patients who receive BMT were doing well. In contrast to SCID, the patients with agammaglobulinemia and CVID had a good survival rate (80%) by regular treatment with IVIG. This was comparable to the report by Winkelstein et al [45]. However, such morbidity as bronchiectasis and chronic otitis media were still high (12.1%) especially in agammaglobulinemia and CVID. All patients with CGD had fair survival with prophylactic antibiotic and anti-fungal which was reported by many studies [57–59] (interferon-γ is not available in Thailand).

Acknowledgements This study was supported by the Siriraj Grant for Research Development 361/2550. The authors wish to thank Julie E. Niemela, B.S., Thomas A. Fleisher, M.D., Mary E Conley, M.D., Duangrurdee Wattanasirichaigoon, M.D., Surapon Piboonpocanun, Ph.D., Vip Viprakasit, M.D., Ph.D., and Siribangon Boonchoo, B.S., for their contributions in genetic analysis.

References

1. Conley ME, Stiehm ER. Immunodeficiency disorders: general consideration. In: Steihm ER, editor. Immunologic disorders in infants and children. 4th ed. Philadelphia: Saunders; 1996. p. 201–52.
2. Lyall EG, Eden OB, Dixon R, Sutherland R, Thomson AF. Assessment of a clinical scoring system for detection of immunodeficiency in children with recurrent infections. Pediatr Infect Dis J 1991;10:673–6.
3. White AG, Raju KT, Abouna GM. A six-year experience with recurrent infection and immunodeficiency in children in Kuwait. J Clin Lab Immunol 1998;26:97–101.
4. Gross S, Blaiss MS, Herrod HG. Role of immunoglobulin subclasses and specific antibody determinations in the evaluation of recurrent infection in children. J Pediatr 1992;121:516–22. doi:10.1016/S0022-3476(05)81137-0.
5. Sanders LA, Rijkers GT, Tenbergen-Meekes AM, Voorhorst-Ogink MM, Zegers BJ. Immunoglobulin isotype-specific antibody responses to pneumococcal polysaccharide vaccine in patients with recurrent bacterial respiratory tract infections. Pediatr Res 1995;37 (6):812–9. doi:10.1203/00006450-199506000-00023.
6. Buckley RH, Dees SC, O'Fallon W. Serum immunoglobulins. II. Levels in children subject to recurrent infection. Pediatrics 1968;42:50–60.
7. Shapiro GG, Virant FS, Furakawa CT, Pierson WE, Bierman CW. Immunologic defects in patients with refractory sinusitis. Pediatrics 1991;87:311–6.
8. Quezada A, Norambuena X, Bravo A, Casro-Rodriguez JA. Recurrent pneumonia as warning manifestation for suspecting primary immunodeficiencies in children. J Investig Allergol Clin Immunol 2001;11:295–9.
9. Glassman M, Grill B, Gryboski J, Dwyer J. High incidence of hypogammaglobulinemia in infants with diarrhea. J Pediatr Gastroenterol Nutr 1983;2:465–71.
10. Perlmutter DH, Leichtner AM, Goldman H, Winter HS. Chronic diarrhea associated with hypogammaglobulinemia and enteropathy in infants and children. Dig Dis Sci 1985;30:1149–55. doi:10.1007/BF01314049.
11. May A, Zielen S, von Ilberg C, Weber A. Immunoglobulin deficiency and determination of pneumococcal antibody titers in patients with therapy-refractory recurrent rhinosinusitis. Eur Arch Otorhinolaryngol 1999;256:445–9. doi:10.1007/s004050050186.
12. Scadding GK, Lund VJ, Darby YC, Navas-Romero J, Sevmour N, Turner MW. IgG subclass levels in chronic rhinosinusitis. Rhinology 1994;32:15–9.
13. Ekdahl K, Braconier JH, Svanborg C. Immunoglobulin deficiencies and impaired immune response to polysaccharide antigens in adult patients with recurrent community-acquired pneumonia. Scand J Infect Dis 1997;29:401–7.
14. Buckley RH, Schiff RI. The use of intravenous immune globulin in immunodeficiency diseases. N Engl J Med 1991;325:110–7.
15. Chapel HM. Fortnightly review: consensus on diagnosis and management of primary antibody deficiencies. BMJ 1994;308: 581–5.
16. Stadtmauer G, Cunningham-Rundles C. Outcome analysis and cost assessment in immunologic disorders. JAMA 1997;278: 2018–23. doi:10.1001/jama.278.22.2018.
17. Antoine C, Muller S, Cant A, Cavazzana-Calo M, Veys P, Vossen J, et al. Long-term survival and transplantation of haematopoietic stem cells for immunodeficiencies: report of the European experience 1968-1999. Lancet 2003;361:553–60. doi:10.1016/S0140-6736(03)12513-5.
18. Kinlen LJ, Webster AD, Bird AG, Haile R, Peto J, Soothill JF, et al. Prospective study of cancer in patients with hypogammaglobulinemia. Lancet 1985;8423:263–6. doi:10.1016/S0140-6736(85)91037-2.
19. Cunningham-Rundles C, Siegal FP, Cunningham-Rundles S, Lieberman P. Incidence of cancer in 98 patients with common varied immunodeficiency. J Clin Immunol 1987;7:294–9. doi:10.1007/BF00915550.
20. Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA. A multiinstitutional survey of the Wiskott-Aldrich syndrome. J Pediatr 1994;125:876–85. doi:10.1016/S0022-3476(05)82002-5.
21. Markert ML. Purine nucleoside phosphorylase deficiency. Immunodefic Rev 1991;3:45–81.

22. Swift M, Morrell D, Massey RB, Chase CL. Incidence of cancer in 161 families affected by ataxia-telangiectasia. N Engl J Med 1991;325:1831–6.
23. Tangsinmankong N, Bahna S, Good RA. The immunologic workup of the child suspected of immunodeficiency. Ann Allergy Asthma Immunol 2001;87:362–70.
24. WHO Scientific Group. Primary immunodeficiency diseases: report of a WHO scientific group. Clin Exp Immunol 1997;109 (suppl 1):S1–28. doi:10.1046/j.1365-2249.1997.00439.x.
25. Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A, et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol 2007;120:776–92. doi:10.1016/j.jaci.2007.08.053.
26. Hayakawa H, Iwata T, Yata J, Kobayashi N. Primary immunodeficiency syndrome in Japan I. Overview of a national survey on primary immunodeficiency syndrome. J Clin Immunol 1981;1:31–9. doi:10.1007/BF00915474.
27. Fasth A. Primary immunodeficiency disorders in Sweden: case among children, 1974–1979. J Clin Immunol 1982;2:86–92. doi:10.1007/BF00916891.
28. Javier FC, Moore CM, Sorensen RU. Distribution of primary immunodeficiency diseases diagnosed in a pediatric tertiary hospital. Ann Allergy Asthma Immunol 2000;84:25–30.
29. Lim DL, Thong BY, Ho SY, Shek LPC, Lou J, Leong KP, et al. Primary immunodeficiency diseases in Singapore—the last 11 years. Singapore Med J 2003;44:579–86.
30. Abuzakouk M, Feighery C. Primary immunodeficiency disorders in the Republic of Ireland: first report of the national registry in children and adults. J Clin Immunol 2005;25:73–7. doi:10.1007/s10875-005-0360-9.
31. Lee WI, Kuo ML, Huang JL, Lin SJ, Wu CJ. Distribution and clinical aspects of primary immunodeficiencies in a Taiwan pediatric tertiary hospital during a 20-year period. J Clin Immunol 2005;25:162–73. doi:10.1007/s10875-005-2822-2.
32. Lam DST, Lee TL, Chan KW, Ho HK, Lau YL. Primary immunodeficiency in Hong Kong and the use of genetic analysis for diagnosis. Hong Kong Med J 2005;11:90–6.
33. Mansouri D, Adimi P, Mirsaedi M, Mansouri N, Tabarsi P, Amiri M, et al. Primary immune deficiencies presenting in adults: seven years of experience from Iran. J Clin Immunol 2005;25:385–91. doi:10.1007/s10875-005-4124-0.
34. Pedersen SA, Abrahamsen TG, Froland SS. Primary immune deficiency diseases in Norway. J Clin Immunol 2000;20:477–85. doi:10.1023/A:1026416017763.
35. Loleka S, Chulajata R, Sricharmon S. Primary immune deficiency diseases in Thailand. Ramatihibodi Med J 1978;1:17–28.
36. Simasathien T, Benjaponpitak S, Chatchatee P, Trakultivakorn M, Sangsupavanich P, Vichayanond P, et al. Primary Immunodeficiency Registry of Thailand. J World Allergy Org. 2003;15 (suppl 1):141, Abstract.
37. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Clin Immunol 1999;93:190–7. doi:10.1006/clim.1999.4799.
38. Niemela JE, Puck JM, Fischer RE, Fleisher TA, Hsu AP. Efficient detection of thirty-seven new IL2RG mutations in human X-linked severe combined immunodeficiency. Clin Immunol 2000;95:33–8. doi:10.1006/clim.2000.4846.
39. Butte MJ, Haines C, Bonilla FA, Puck JM. IL-7 receptor deficient SCID with a unique intronic mutation and post-transplant autoimmunity due to chronic GVHD. Clin Immunol 2007;125:159–64. doi:10.1016/j.clim.2007.06.007.
40. Wattanasirichaigoon D, Benjaponpitak S, Techasaensiri C, Kamchaisatian W, Vichyanond P, Janwityanujit S, et al. Four novel and three recurrent mutations of the BTK gene and pathogenic effects of putative splice mutations. J Hum Genet 2006;51:1006–14. doi:10.1007/s10038-006-0052-y.
41. Jirapongsananuruk O, Niemela JE, Malech HL, Fleisher TA. CYBB mutation analysis in X-linked chronic granulomatous disease. Clin Immunol 2002;104:73–6. doi:10.1006/clim.2002.5230.
42. Rezaei N, Aghamohammadi A, Moin M, Pourpak Z, Movahedi M, Gharagozlou M, et al. Frequency and clinical manifestation of patients with primary immunodeficiency disorders in Iran; update from the Iranian primary immunodeficiency registry. J Clin Immunol 2006;26:519–32. doi:10.1007/s10875-006-9047-x.
43. Ozkan H, Atlihan F, Genel F, Targan S, Gunvar T. IgA and/or IgG subclass deficiency in children with recurrent respiratory infections and its relationship with chronic pulmonary damage. J Investig Allergol Clin Immunol 2005;15(1):69–74.
44. Steim RE. The four most common pediatric immunodeficiencies. Adv Exp Med Biol 2007;601:15–26.
45. Winkelstein JA, Marino AC, Lederman HM, Jones SM, Sullivan K, Burks AW, et al. X-linked agammaglobulinemia. Report on a United state registry of 201 patients. Medicine 2006;85:193–202. doi:10.1097/01.md.0000229482.27398.ad.
46. Wilkey IS, McDonald A. A probable case of *Chromobacterium violaceum* infection in Australia. Med J Aust 1983;9:39–40.
47. Wu SH, Lin SJ, Tso HM, Liu CB, Tsai WC. Fatal septicemia due to *Chromobacterium violaceum*. Article Chin 1986;19:289–94.
48. Perera S, Punchihewa PM, Karunanayake MC, de Silva N. Fatal septicemia caused by *Chromobacterium violaceum*. Ceylon Med J 2003;48:26–7.
49. Manjunath M. Fatal septicemia due to *Chromobacterium violaceum*. West Indian Med J 2007;56:380–1.
50. Teoh AY, Hui M, Ngo KY, Wong J, Lee KF, Lai PB. Fatal septicemia from *Chromobacterium violaceum*: case reports and review of the literature. Hong Kong Med J 2006;12:228–31.
51. Hassan H, Suntharalingam S, Dhillon KS. Fatal *Chromobacterium violaceum* septicemia. Singapore Med J 1993;34:456–8.
52. Chang CY, Lee YT, Lui KS, Wang YL, Tsao SM. *Chromobacterium violaceum* infection in Taiwan: a case report and literature review. J Microbiol Immunol Infect 2007;40:272–5.
53. Shao PL, Hsueh PR, Chnag YC, Lu CY, Lee PY, Lee C, et al. *Chromobacterium violaceum* infection in children: a case of fatal septicemia with nasopharyngeal abscess and literature review. Pediatr Infect Dis J 2002;21:707–9. doi:10.1097/00006454-200207000-00022.
54. Moore CC, Lane JE, Stephens JL. Successful treatment of an infant with *Chromobacterium violaceum* sepsis. Clin Infect Dis 2001;32:e107–10. doi:10.1086/319356.
55. Sirinavin S, Techasaensiri C, Benjaponpitak S, Pornkul R, Vorachit M. Invasive Chromobacterium violaceum infection in children: case report and review. Pediatr Infect Dis J 2005;24:559–61. doi:10.1097/01.inf.0000164761.81491.3f.
56. Winkelstein JA, Marino MC, Johnston RB Jr, Boyle J, Curnutte J, Gallin JI, et al. Chronic granulomatous disease: report on a national registry of 368 patients. Medicine 2000;79:155–69. doi:10.1097/00005792-200005000-00003.
57. Liese J, Kloos S, Jendrossek V, Petropoulou T, Wintergerst U, Notbeis G, et al. Long-term follow up and outcome of 39 patients with chronic granulomatous disease. J Pediatr 2000;137:687–93. doi:10.1067/mpd.2000.109112.
58. Petropoulou T, Liese J, Tintelnot K, Gahr M, Belohradsky BH. Long-term treatment of patients with itraconazole for the prevention of *Aspergillus* infections in patients with chronic granulomatous disease. Mycoses 1994;37:64–9.
59. Gallin JI, Alling DW, Malech HL, Wesley R, Koziol D, Marciano B, et al. Itraconazole to prevent fungal infections in chronic granulomatous disease. N Engl J Med 2003;348:2416–22. doi:10.1056/NEJMoa021931.