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

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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.

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 Immunodeficien-
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 0.7–137 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 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 | 1 (1.5) |
| 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) |

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.

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**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
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 presenta-
tion 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

| 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%)                     | 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%)                 | –                                               |

UR/ 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

| 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].
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 |
| Intravenous immunoglobulin | 10 (37.0%) | 15 (88.2%) | – | 2 (25%) |
| Prophylaxis medications | 11 (40.7%) | 5 (29.4%) | 5 (83.3%)<sup>a</sup> | 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%) |

<sup>a</sup> 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. violaceum 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).

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