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ORIGINAL ARTICLE

Clinical characteristics and outcomes of primary antibody deficiency: A 20-year follow-up study

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Background/Purpose: Primary antibody deficiency is the most common disorder among primary immunodeficiencies. Recurrent infection and chronic lung change often lead to mortality and morbidity.
Methods: This study focused on the clinical presentation, molecular diagnosis, and outcomes of primary antibody deficiency in Taiwan pediatric group. Medical records of patients with primary antibody deficiency during the period 1990—2010 were retrospectively reviewed in one medical center.
Results: Among the 34 patients evaluated, X-linked agammaglobulinemia (XLA) (29.4%) and common variable immunodeficiency diseases (CVIDs) (29.4%) were the most common disorders presented with respiratory and skin infections. Some genotype/phenotype discordance was found in one family. Patients with XLA, CVID, and hyper-IgM syndrome without complications had higher trough and initial IgG levels, and shorter delays in diagnosis. Patients with trough IgG levels >700 mg/dL had less occurrence of bronchiectasis.
Conclusion: These results summarized clinical manifestations of primary antibody deficiency in pediatric group in Taiwan. Clinicians should strive to shorten delays in diagnosis and maintain higher trough IgG levels to decrease subsequent mortality and morbidity.
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Introduction

Primary immunodeficiencies are disorders resulting in increased susceptibility to uncommon pathogens, and recurrent and severe infections. Aside from infections, autoimmune diseases and malignancy might also be the associated disorders. The wide range of incidence, from 1/500 to 1/500,000, in the general population is due to a variety of subtypes that cause various symptoms.[1,2] Among the heterogeneous groups of primary immunodeficiencies, different incidence reports from different regions in the world show that antibody deficiencies are the most frequently diagnosed disorders, ranging from 50% to 70%.[3-5]

In general, selective immunoglobulin A (IgA) deficiency is the most frequent primary antibody deficiency but its clinical symptoms are obscure.[6] However, the incidence rate of selective immunoglobulin A (IgA) deficiency varies between Western and Eastern countries. For example, the prevalence of selective IgA deficiency is 1:223 to 1:1000 in the USA,[7] while it is about 1:3230 in China.[8] Selective IgA deficiency is more common in Caucasians. X-linked agammaglobulinemia (XLA) and common variable immunodeficiency diseases (CVIDs) are the two major groups wherein Ig replacement is used to prevent complications. Another group of antibody deficiencies, transient hypogammaglobulinemia of infancy (THI), is noted in children aged 1-2 years. The disease course is often benign as serum Ig levels increase with age. In Taiwan, one large cohort study has shown that primary antibody deficiency is the predominant group (36.3%) of primary immunodeficiency, and recurrent sinopulmonary infection is the most common presentation.[9]

Once primary antibody deficiency is diagnosed, intravenous immunoglobulin (IVIG) provides an effective treatment to improve survival and prevent infections,[10-13] with earlier institution of IVIG treatment providing better outcomes. Under regular IVIG replacement, the survival rate increases to more than 90%.[3,9] However, recurrent infections, bronchiectasis, and impaired lung functions are still major complications in spite of IVIG replacement, so many studies have focused on finding optimal serum IgG levels to prevent complications.

The current study focused on pediatric patients with primary antibody deficiency in a tertiary center and recorded initial Ig levels, trough IgG levels, diagnosed ages, initial presentations, and subsequent symptoms. The study also aimed at determining the relationship between Ig levels and outcomes.

Materials and methods

Data collection

The charts of the patients with suspected antibody deficiencies, indicated by the International Classification of Disease, Ninth Revision (ICD-9), in the Department of Pediatrics of National Taiwan University Hospital from 1990 to 2010 were screened and retrospectively reviewed. This study was approved by the institutional review board of National Taiwan University Hospital. The ICD-9 codes ranged from 279.00 to 279.09, which represented disorders of humoral immunity. Initially 232 patients were enrolled,

and we excluded those who did not meet the criteria of the World Health Organization Scientific Group, the Pan-American Group for Immunodeficiency, and the European Society for Immunodeficiencies.[14,15] Other secondary immunodeficiencies such as protein-losing enteropathy, chromosome abnormalities, drug-induced immunodeficiency, and prematurity were also excluded.

We recorded ages of onset, which were defined as the age at which the first episode of invasive infection or chronic course of sinusitis and otitis media occurred. Ages of diagnosis were also recorded when the final diagnosis was made in our hospital after a series of workups were done. Diagnosis delay time was presented as the duration from the time of disease onset to the time of diagnosis. Initial and subsequent episodes of infections of each patient were also recorded. Bacteremia and central nervous system infection were confirmed by documented pathogens from blood and cerebrospinal fluid cultures. Bronchiectasis was diagnosed by chest radiography and computed tomography. Lung function tests were done by standard spirometry. Each documented pathogen of infection was presented to see the specific distribution.

Immunologic studies and molecular analysis

All patients received immunologic tests by standard techniques, including complete blood count with differential count, serum Ig levels, functional antibody levels, and lymphocyte subsets by flow cytometry. Mitogen tests for lymphocyte proliferation assay, CH50, neutrophil oxidative burst assay, and chemotaxis assay were performed in some patients to exclude other immunodeficiencies. Bruton tyrosine kinase (BTK) genes were analyzed by polymerase chain reaction-direct sequencing. CD40/CD40 ligand was analyzed by flow cytometry and genomic DNAs of two patients were sent to the Queen Mary Hospital in Hong Kong for CD40 ligand sequencing.

Outcomes

Patients with XLA, CVID, and hyper-immunoglobulin M (IgM) syndrome were further divided into the complication and the noncomplication groups based on the subsequent symptoms and outcomes during follow-up. The complication group included patients with chronic sinusitis, otitis media, pneumonia, invasive bacterial infections, bronchiectasis, impaired lung function, failure to thrive, malignancy, and autoimmune diseases, or those with mortality. Patients in the non-complication group had no other morbidity or severe infections.

Statistical analysis

Data were expressed as mean ± standard deviation for age, laboratory data, and individual values with percentage for episodes of symptoms and infections. Data analysis was performed using the computer-based SPSS statistical software (version 17.0). Mann-Whitney U test was used to compare the diagnosis delay, age of onset, and initial and trough IgG levels in patients with and without long-term complications. Fisher's exact test was used to analyze the relationship between subsequent symptoms and trough IgG levels.

Results

Demographic characteristics of primary antibody deficiencies

Thirty-four patients who met the criteria of primary antibody deficiencies for the past 20 years in National Taiwan University Hospital were recruited. The most frequent disorders were CVID (10 patients) and XLA (10 patients), followed by THI (eight patients) and hyper-IgM syndrome (two patients). One patient had symptomatic selective IgA deficiency and three had selective IgG3 subclass deficiencies. Male (30 patients) to female (four patients) ratio was 7.5:1. No antenatal diagnoses were made.

Six patients from four unrelated families had family histories. Four had a family history of XLA. The other two patients, one with hyper-IgM syndrome and the other with XLA, had uncertain early death due to infections in their family. The age of onset on presentation ranged from 3 months to 9 years, and the age of diagnosis ranged from 4 months to 36 years. The diagnosis delay time varied from 0 to 33 years (Table 1).

Initial presentations and laboratory studies

Recurrent upper respiratory tract infection (15 patients, 44.1%) and recurrent sinopulmonary infection (16 patients, 47.1%) were the most common initial presentations. Skin infections, including cellulitis and recurrent folliculitis, were the third common manifestation (eight patients, 23.5%). Bacteremia was found only in patients with XLA and CVID (five patients, 14.7%). Recurrent gastroenteritis was present in two patients with CVID and one with THI. Only one patient with CVID initially presented with central nervous system infection by *Acinetobacter baumannii*. This patient also developed sepsis. Aside from infections, failure to thrive was also one of the initial presentations. There was at least one patient in each group of XLA, THI, hyper-IgM syndrome, and selective IgA deficiency (Table 1).

In terms of laboratory data, initial serum IgG levels were all <350 mg/dL in CVID, XLA, THI, and hyper-IgM syndrome. Initial serum IgG levels were extremely low (46.3 ± 7.1 mg/dL), especially in hyper-IgM syndrome. Serum IgA levels were usually below the detection limit in patients with XLA, CVID, THI, and selective IgA deficiency.

Molecular diagnosis

Fifteen patients from 11 unrelated families received genetic studies (44.1%), and genetic defects were found in the *BTK* genes (nine patients with XLA) and *CD40L* genes (one patient with hyper-IgM syndrome) (Table 2).

Table 1 Demographic data, initial presentations, and serum Ig levels.

Characteristics	CVID (n = 10)	XLA (n = 10)	THI (n = 8)	Hyper-IgM syndrome (n = 2)	Selective IgA deficiency (n = 1)	IgG subclass deficiency (n = 3)
Sex						
Male	8	10	8	2	0	2
Female	2	0	0	0	1	1
Age at onset (mo, mean ± SD)	36.6 ± 21.76	31.8 ± 32.21	6.4 ± 3.9	4.5 ± 0.7	49	26.7 ± 23.9
Age at diagnosis (mo, mean ± SD)	54.0 ± 32.9	90.9 ± 126.5	9 ± 4	20.5 ± 21.9	170	40.3 ± 38
Diagnosis delay (mo, mean ± SD)	17.4 ± 36.4	59.1 ± 120.5	2.6 ± 2.6	16 ± 22.6	121	19.7 ± 15.2
Presenting symptoms (n, %)						
Frequent URI	4 (40%)	6 (60%)	1 (12.5%)	1 (50%)	0	3 (100%)
Sinopulmonary infection	6 (60%)	5 (50%)	2 (25%)	2 (100%)	1	0
Skin infection	1 (10%)	3 (30%)	2 (25%)	1 (50%)	1	0
Gastroenteral infection	2 (20%)	0	1 (12.5%)	0	0	0
Osteomyelitis and arthritis	1 (10%)	3 (30%)	0	0	0	0
Bacteremia	2 (20%)	3 (30%)	0	0	0	0
CNS infection	1 (10%)	0	0	0	0	0
Failure to thrive	0	1 (10%)	1 (12.5%)	1 (50%)	1	0
Oral thrush	0	0	2 (25%)	0	0	0
Laboratory data (mean ± SD)						
IgG level(mg/dL)	305.1 ± 181.7	226.9 ± 217.6	288.8 ± 99.6	46.3 ± 7.1	1290	970.5 ± 352.8
IgA level (mg/dL)	Undetectable	Undetectable	Undetectable	5.3 ± 4.2	<10	80 ± 45.2
IgM level (mg/dL)	82.1 ± 50.5	22.8 ± 8.5	60.2 ± 29.5	101 ± 55.2	121	118.7 ± 11
WBC (K/μL)	8566 ± 2663.1	10,868 ± 4534	8019 ± 2661	15,000 ± 7778	16,880	9183 ± 1583
Hemoglobin (g/dL)	12.1 ± 1.1	12.9 ± 2.1	11.4 ± 1.2	12.4 ± 3.3	10.2	11.5 ± 0.6
Platelet (k/μL)	277.7 ± 97.2	390.9 ± 74	441.5 ± 175.3	672.5 ± 74.3	267	437.3 ± 96.6

CNS = central neural system; CVID = common variable immunodeficiency disease; Ig = immunoglobulin; SD = standard deviation; THI = transient hypogammaglobulinemia of infancy; URI = upper respiratory tract infection; WBC = white blood cell count; XLA = X-linked agammaglobulinemia.

Follow-up manifestation and outcome

Thirty-two patients were followed up for a mean duration of 8.0 ± 6.2 years. Two patients' data were lost to follow-up, including one with XLA and one with selective IgA deficiency. One patient with XLA with an initial IgG level of 164 mg/dL at the age of 14 months was lost to follow-up after bone marrow examination. A patient with selective IgA deficiency had serum IgA levels <10 mg/dL without low serum IgG levels. Recurrent sinusitis, pneumonia, and failure to thrive were noted since the age of 4 years. The patient was also lost to follow-up for several months, so the subsequent course was not clear.

The overall mortality rate was 12.5%, including patients with XLA (three) and hyper-IgM syndrome (one). Two patients with XLA expired due to severe respiratory failure caused by bronchiectasis, while the other two patients succumbed to severe septic shock. Severe respiratory complications, including bronchiectasis and impaired lung functions, accounted for 21.9%, mostly in patients with XLA, CVID, and hyper-IgM syndrome.

Failure to thrive was also noted in 15.6% of all patients. Three more patients (two with CVID and one with XLA) had failure to thrive on follow-up. All of them were followed up from childhood to adolescence, and their height and body weight gradually fell below the third percentile of age. The other two patients with initial failure to thrive did not catch up during follow-up.

Half of patients had allergic diseases, and only one, a patient with CVID, had an autoimmune disease diagnosed as inflammatory bowel disease. There was no malignancy in this series (Table 3).

Regarding subsequent infections, sinopulmonary infections were the most common complications. Recurrent sinusitis was found in 56.3% of all patients, followed by recurrent pneumonia (25%). Invasive bacteremia accounted for 18.8% (three XLA patients, one CVID, one hyper-IgM syndrome, and one IgG subclass deficiency). Documented infections existed mainly in patients with XLA, CVID, and hyper-IgM syndrome. The major pathogen in all 50 episodes of infection was *Haemophilus influenza* (38%) with the presentations of pneumonia and sepsis (Table 4). *Pseudomonas aeruginosa* (12%), also found in patients with XLA and hyper-IgM syndrome, was mainly cultured from sputum and ear discharge. We also found fungal infections with *Candida albicans* from sputum and urine culture, and *Cryptococcus* sp. from the culture of skin abscess. One patient with CVID had herpes zoster infection.

The initial IgG levels, age of diagnosis, diagnosis delay time, and trough IgG levels between those with severe/chronic complications and those without were compared. Patients in the complication group were older and had longer diagnosis delay time, but not statistically significant (Fig. 1). After IVIG supplementation, trough IgG levels were significantly higher in the noncomplication group than in the complication group (Fig. 2). In XLA, CVID, and hyper-IgM syndrome patients, incidences of recurrent infections, bacteremia, and failure to thrive in the group were low, with trough IgG levels being >700 mg/dL. They also had significantly less bronchiectasis and impaired lung functions ($p = 0.041$) (Table 5).

Table 2 Molecular findings and phenotypes.

No.	Gene	cDNA mutation	Exon	Codon mutation	Domain	Initial IgG levels (mg/dL)	B cell (%)	Presentation
1	*Btk*	c.1713T>G	17	Y571X	TK	59	0	Pneumonia with pleural effusion, otitis media, parasinusitis, failure to thrive, bronchiectasis, *Haemophilus* sepsis
2	*Btk*	c.569delC	7	P190fsX8	TH	3	0.2	Arthritis, repeated pneumonia, *Haemophilus* sepsis, positive family history, bronchiectasis
3	*Btk*	c.862C>T	10	R288 W	SH2	232	0.6	*P. aeruginosa* sepsis, oral ulcer, twin A
4	*Btk*	c.862C>T	10	R288 W	SH2	718	0.4	*P. aeruginosa* septic shock, oral ulcer, twin B
5	*Btk*	c.1000T>C	12	Y344H	SH2	180	1	Pneumonia, urinary tract infection with vesicoureteral reflux Grade III, positive family history
6	*Btk*	IVS11+6T>G	11	Splicing	SH2	33.1	1	Frequent upper respiratory tract infection and pneumonia
7	*Btk*	Unknown		Splicing	Unknown	275	0	Anal fistula, repeated pneumonia, bronchiectasis
8	*Btk*	c.1106 T->C	13	L369P	SH2	459	0.14	Frequent upper respiratory tract infection without severe infections, strong family history, mild bronchiectasis
9	*CD40L*	c.476 G->A	5	W140X	Intracellular	41.2	26.65	Pneumococcal pneumonia with pleural effusion and frequent otitis media, bronchiectasis

Btk = Bruton tyrosine kinase; CD40L = CD40 ligand; Ig = immunoglobulin.

**Table 3** Subsequent symptoms, outcomes, and trough IgG levels.

Characteristics	CVID (n = 10)	XLA (n = 9)	THI (n = 8)	Hyper-IgM syndrome (n = 2)	IgG subclass deficiency (n = 3)	Total (n = 32)
Follow-up years (mean ± SD)	9.8 ± 5.8	10.9 ± 6.2	2.8 ± 1.4	11.3 ± 4.7	5.6 ± 8.2	8.0 ± 6.2
IVIG use (n, %)	10 (100%)	8 (88.9%)	2 (25%)	2 (100%)	2 (66.7%)	24 (75%)
Trough IgG level (mean ± SD)	671.1 ± 161.2	666.7 ± 146.4	673.4 ± 191.1	442 ± 103.7	993.7 ± 402.6	656.3 ± 169.9
Follow-up symptoms (n, %)						
Recurrent otitis media	1 (10%)	2 (22.2%)	1 (12.5%)	0	0	4 (12.5%)
Recurrent sinusitis	7 (70%)	8 (88.9%)	1 (12.5%)	1 (50%)	1 (33.3%)	18 (56.3%)
Recurrent pneumonia	2 (20%)	4 (44.4%)	0	1 (50%)	1 (33.3%)	8 (25%)
Recurrent gastroenteritis	3 (30%)	1 (11.1%)	0	1 (50%)	0	5 (15.6%)
Recurrent UTI	0	0	0	0	0	0
Recurrent skin infection	1 (10%)	2 (22.2%)	0	0	0	3 (9.4%)
Recurrent arthritis	0	1 (11.1%)	0	0	0	1 (3.1%)
Bacteremia	1 (10%)	3 (33.3%)	0	1 (50%)	1 (33.3%)	6 (18.8%)
CNS infection	0	0	0	0	0	0
Bronchiectasis	2 (20%)	4 (44.4%)	0	1 (50%)	0	7 (21.9%)
Impaired lung function	2 (20%)	4 (44.4%)	0	1 (50%)	0	7 (21.9%)
Allergy	7 (70%)	0	4 (50%)	0	1 (33.3%)	16 (50%)
Autoimmune disease	1 (10%)	0	0	0	0	1 (3.1%)
Malignancy	0	0	0	0	0	0
Failure to thrive	2 (20%)	2 (22.2%)	0	1 (50%)	0	5 (15.6%)
Death	0	3 (33.3%)	0	1 (50%)	0	4 (12.5%)

CNS = central nervous system; CVID = common variable immunodeficiency disease; Ig = immunoglobulin; IVIG = intravenous immunoglobulin; THI = transient hypogammaglobulinemia of infancy; UTI = urinary tract infection; XLA = X-linked agammaglobulinemia.

Table 4 Documented pathogen and hypogammaglobulinemia.

| Pathogen	CVID	XLA	THI	Hyper-IgM syndrome	IgG subclass deficiency	Total
Bacteria						
Campylobacter coli	0	1 (2.8%)	0	0	0	1
Escherichia coli	2 (28.6%)	0	0	0	0	2
Enterobacter	0	1 (2.8%)	0	0	0	1
Enterococcus sp.	0	1 (2.8%)	0	0	0	1
H. influenza	0	18 (50%)	0	1 (16.7%)	0	19
Klebsiella sp.	0	3 (8.3%)	0	0	0	3
Moraxella sp.	0	1 (2.8%)	0	0	0	1
Staphylococcus aureus	0	3 (8.3%)	0	0	0	3
Pantoea agglomerans	0	1 (2.8%)	0	0	0	1
S. pneumoniae	2 (28.6%)	1 (2.8%)	0	1 (16.7%)	1	5
Proteus sp.	0	1 (2.8%)	0	0	0	1
P. aeruginosa	0	3 (8.3%)	0	3 (50%)	0	6
Salmonella sp.	1 (14.3%)	1 (2.8%)	0	0	0	2
Virus						
Herpes zoster	1 (14.3%)	0	0	0	0	1
Fungus						
Candida sp.	0	1 (2.8%)	0	1 (16.7%)	0	2
Cryptococcus neoformans	1 (14.3%)	0	0	0	0	1
Total episodes	7	36	0	6	1	50

CVID = common variable immunodeficiency disease; Ig = immunoglobulin; THI = transient hypogammaglobulinemia of infancy; XLA = X-linked agammaglobulinemia.
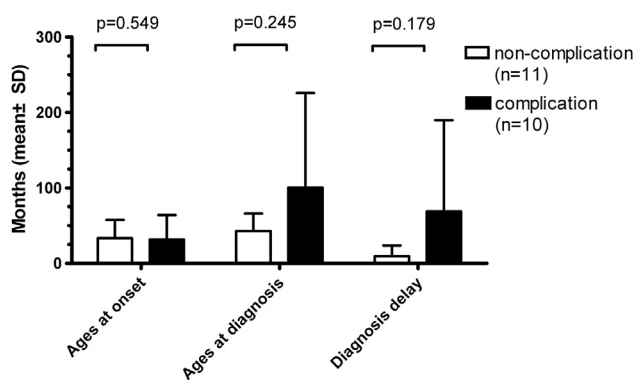
Figure 1 The ages at onset, ages upon diagnosis, and diagnosis delay time (in months) for patients with XLA, CVID, and hyper-IgM syndrome, who were divided into the non-complication and complication groups. Values were presented as mean ± SD. Ages upon diagnosis and diagnosis delay time were higher in the complication group than in the non-complication group, but without any significant difference. CVID = common variable immunodeficiency disease; Ig = immunoglobulin; SD = standard deviation; XLA = X-linked agammaglobulinemia.

Ig replacement therapy

Twenty-four (75%) patients received regular IVIG treatment with a dose interval of 400– 800 mg/kg every 3–4 weeks, according to infection status and trough IgG levels, and most had CVID, XLA, and hyper-IgM syndrome. Two patients with THI and two with IgG subclass deficiencies also received IVIG temporally due to frequent episodes of infections. They had reduced episodes of infections after IVIG treatment. Mean trough IgG levels increased to >660 mg/dL in all groups with initially low serum IgG levels. However, two patients with hyper-IgM syndrome still had low serum IgG levels (average, 442 ± 103.7 mg/dL) despite regular IVIG replacement therapy every 3–4 weeks (Table 4).
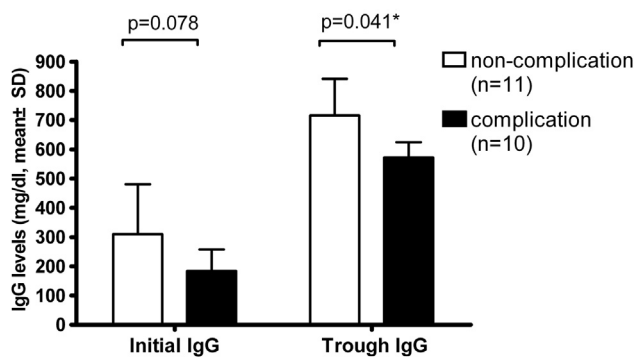
Figure 2 The initial and trough serum IgG levels for patients with XLA, CVID, and hyper-IgM syndrome. Values were presented as mean ± SD. Serum IgG levels increased significantly in both groups after IVIG replacement therapy. Trough IgG levels were significantly lower in the complication group than in the noncomplication group (p = 0.041). CVID = common variable immunodeficiency disease; Ig = immunoglobulin; IVIG = intravenous immunoglobulin; SD = standard deviation; XLA = X-linked agammaglobulinemia.

Discussion

The current study focuses on the disease course of primary antibody deficiency in a tertiary center in Taiwan and shows that CVID and XLA are the most common disorders, similar to the findings of other studies in Taiwan,[9,16] Singapore, and other registries from Norway and Ireland.[17–20] Male predominance, with male:female ratio of 7.5:1, is very significant, as in previous reports. In contrast, some studies show that specific antibody deficiencies, including those of IgG subclass or selective IgA deficiency, are the predominant disorders.[3,4,21] In Taiwan's pediatric groups, serum IgG/A/M and IgG subclass levels are checked for recurrent or invasive infections. Symptoms of selective IgA deficiency are usually subclinical, so it is often underestimated. In the current study, only one patient has been found with selective IgA deficiency due to recurrent infections and failure to thrive, which raises the clinicians' awareness regarding checking of serum Ig levels.

Molecular diagnosis was performed for patients with suspected XLA and hyper-IgM syndrome. Most patients with BTK gene mutation were compatible with their typical presentations and B-cell percentages. Interestingly, among them two were identical twins who shared the same BTK gene mutation and initial presentations (No. 3 and 4 in Table 2). However, twin B had nearly normal serum IgG levels (initial IgG levels: 718 mg/dL) upon diagnosis, unlike his twin A brother (initial IgG levels: 232 mg/dL). This difference of initial IgG levels in the same genetic background might have been caused by the differences in disease status of initial Pseudomonas infection and in nutritional status, which might have affected the catabolism of IgG. In addition to the external factors, there still were possibilities of a second mutation existing in an upstream or intron regulatory region of the btk gene between these twin brothers. On the other hand, other known or unknown regulatory factors might affect the translation of btk genes. Discordant phenotypes with varied serum IgG levels in affected family members with same btk mutation were also reported previously.[22,23] Another recent study on 62 Chinese XLA patients by Lee et al[24] supported the genotype/phenotype correlations of XLA in Chinese

Table 5 Relationship between trough IgG levels and following symptoms.

Symptoms	Trough IgG level		p
	700– (n = 13)	700+ (n = 8)	
Recurrent otitis media	2 (15.4%)	3 (37.5%)	0.325
Recurrent sinusitis	10 (76.9%)	6 (75%)	1
Recurrent pneumonia	6 (46.1%)	1 (12.5%)	0.174
Recurrent gastroenteritis	4 (30.7%)	1 (12.5%)	0.36
Recurrent skin infection	2 (15.4%)	1 (12.5%)	1
Bacteremia	5 (38.5%)	0	0.111
Bronchiectasis	7 (53.8%)	0	0.018*
Impaired lung function	7 (53.8%)	0	0.018*
Failure to thrive	5 (38.5%)	0	0.111
Frequent admission	6 (46.1%)	2 (25%)	0.4

* p < 0.05 between the two groups.

populations, but discordant phenotypes in affected members of the same family had been documented.

Graziani et al[25] and Conley et al[26] reported atypical presentations of XLA. In the current study, one patient (No. 8 in Table 2) with XLA mutation had a strong family history of early infant death and low circulating B cells with borderline low serum IgG levels. The patient only had a past history of frequent upper respiratory infections without any invasive infections or hospitalization, and was not diagnosed until the age of 35 years. During follow-up, chest computed tomography revealed that the patient had mild bronchiectasis. Although there are genotype/phenotype correlations in XLA,[24,27,28] discordant findings under the same background of genetic mutation or atypical presentations point to some epigenetic change or other regulatory factors that may influence the XLA phenotype.

In this cohort, recurrent sinopulmonary infections and bacteremia are the most common presentations in patients with primary antibody deficiencies, consistent with previous studies. In addition, skin infection is the third most common initial manifestations (23.5% of all patients). These skin infections include recurrent folliculitis and cellulitis. One patient even had prolonged varicella infection. Skin infections accounted for 15.5% of antibody deficiencies in a previous study in Taiwan[9] and 8.3% in a report on Thai children.[3] The recurrent skin infection may be one of the common presentations of antibody deficiencies, although skin infections are often associated with other cellular or well-defined immunodeficiencies.

Despite the high frequency of IVIG supplementation, recurrent sinopulmonary and airway infections are still the most frequent complications in patients with CVID, XLA, and hyper-IgM syndrome. *H. influenza* plays major roles in respiratory tract infections in the current study. This is also consistent with a previous report,[29] but its definite role in pneumonia is still in question because it is also a normal flora of the respiratory tract. In fact, *Streptococcus pneumoniae* is the most common pathogen of community-acquired pneumonia in Taiwan, and *H. influenza* accounts only for 4.8—9%.[30,31] The study of infections in CVID patients in France also supports this distribution of pathogens of pneumonia.[32] However, *H. influenza* is still the cause of most sepsis cases in the current study, while *P. aeruginosa* is the major pathogen of sepsis in other studies.[3,16]

In addition to bacterial infections, viral and fungal infections are rare, as found in previous reports.[9,·29,32] Most patients have the ability to recover from these infections due to the normal T-cell responses. In the current study, only one patient suffered from herpes zoster infection, two from *Candida* infections, and one from *Cryptococcus* infection. Complaints about frequent upper respiratory tract infection and sinusitis were very common during follow-up, but examinations of respiratory specimens were not performed. A recent study of 12 adult patients with hypogammaglobulinemia suggested that rhinovirus might cause prolonged and frequent respiratory tract infections.[33] Viruses may not be a major cause of severe mortality and morbidity, but their influence on chronic inflammation of the respiratory tract may be a factor in chronic lung changes. The role of viral infection warrants further investigation.

Patients with CVID, XLA, and hyper-IgM syndrome were further divided into two groups depending on the occurrence of recurrent or long-term complications. Initial and trough IgG levels were lower in the complication group. Delayed time of diagnosis was also longer in patients with complications, but without statistical significance. This is the first study focusing on the relationship between serum IgG levels and complications in Taiwan. The reason why serum trough IgG levels were not increased accordingly in complication group might be the different catabolisms of IgG under IVIG supplement. The patients' nutritional status, gastrointestinal losses, or numbers of infection during follow-up might affect the catabolism of IgG levels. Clinically, we need to further re-evaluate the patients' infection status, nutrition, and psychosocial conditions if the efficacy of IVIG is not satisfactory. However, the limitation exists in too few populations of these patients, and cross-area database should be established in the future to clarify the factors that influence the outcomes. With improved knowledge and awareness of immunodeficiency, delays in diagnosis decreases gradually,[3,34] leading to greater survival and outcomes.[35] On the other hand, initial serum IgG levels, upon diagnosis, may influence the disease course of the current study, even though few reports have focused on this issue.

One recent multicenter prospective cohort study in the Italian Primary Immunodeficiency Network (IPINET) database showed a higher risk of pneumonia in CVID patients with low basal IgG levels, IgA levels, and trough IgG levels.[36] In an *in vitro* mitogenic stimulation study, Ig secretion from B cells in pediatric patients with hypogammaglobulinemia was much lower than that of normal populations, even after the clinical Ig levels were corrected.[37] Lower initial IgG levels, along with delayed diagnosis, may cause patients to be more susceptible to infections and lead to some irreversible pulmonary destruction prior to IVIG replacement therapy. However, this hypothesis requires large and strict studies to be validated.

The trough IgG levels >700 mg/dL in patients can reduce the occurrence of bronchiectasis or chronic lung change significantly. Early and prolonged IVIG replacement therapies can improve the outcome of primary hypogammaglobulinemia,[13] shorten hospitalization,[38] and lessen pneumonia episodes.[36,39,40] Many studies are further focusing on the optimal serum IgG levels to prevent complications after IVIG replacement therapy. A randomized, double-blinded crossover trial in 43 patients with primary hypogammaglobulinemia further indicates that high-dose IVIG is associated with a significant reduction in complications of infection.[41] The overall consensus among clinical immunologists is to maintain serum IgG levels >500 mg/dL,[13,42,43] and set even higher IgG levels of >800 mg/dL to prevent bronchiectasis.[13] Another meta-analysis suggests that aggressive IVIG replacement that increases trough IgG levels up to 1000 mg/dL can reduce the risk of pneumonia.[39]

In contrast, a multicenter prospective cohort study in the IPINET database has shown no significant difference in the trough IgG levels between patients with and those without bronchiectasis.[36] It also shows that pneumonia is a risk factor for bronchiectasis and vice versa. The definite mechanism of IVIG in protecting against chronic lung

change remains inconclusive. According to the results here and in previous studies, higher trough IgG levels may prevent chronic lung damage by reducing the episodes of pulmonary infection, so the vicious cycle can be broken. However, since the results remain controversial, there may not be an absolute cutoff value of trough IgG levels for all patients. Regular IVIG replacement remains beneficial in all patients with primary hypogammaglobulinemia. Further, we assume that clinical symptoms signify whether they are sufficient or not, and suggest that the dosage of IVIG should be individualized to keep patients symptom free.

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