

Immunological and Clinical Features of Pediatric Patients with Primary Hypogammaglobulinemia in Taiwan

Ling-Jen Wang¹, Yao-Hsu Yang², Yu-Tsan Lin² and Bor-Luen Chiang²

Hypogammaglobulinemia may result from either B-cell immunodeficiencies or combined B-cell and T-cell deficiencies. The B-cell immunodeficiencies might result from defects in the signal transmission through the Bruton tyrosine kinase (X-linked agammaglobulinemia; XLA), a selective or generalized failure to progress from the immature B-cell stage to the plasma cell stage (IgA immunodeficiency or common variable immunodeficiency; CVID).¹ Severe combined immunodeficiency (SCID) consists of a group of genetic disorders characterized by profoundly defective T-cell differentiation, with or without abnormal B-cell differentiation.² Screening tests and numerous advances have increased the ability to identify and diagnose hypogammaglobulinemia in the early stage. Patients with delayed diagnosis or who are not treated aggressively may suffer sustained permanent complications or death. Due to the lack of data from Taiwan,

SUMMARY We retrospectively reviewed the clinical and immunological features as well as the outcome of children with a diagnosis of primary hypogammaglobulinemia, who were treated at the National Taiwan University Hospital between 1984 and 2001. A total of 33 patients were enrolled: seventeen patients with common variable immunodeficiency (CVID), six patients with selective immunoglobulin deficiencies (one subclass IgA and five IgG), four patients with severe combined immunodeficiency (SCID), three patients with transient hypogammaglobulinemia of infancy (THI) and three patients with X-linked (Bruton) agammaglobulinemia (XLA). In addition to recurrent sinopulmonary infections and prolonged fever, allergic diseases are noted in 76% of CVID patients and 100% of patients with selective immunodeficiencies. Immunoglobulin levels were extremely low in XLA and decreased in CVID patients. Three SCID patients had decreased mean absolute lymphocyte counts of 290/mm³. Long-term complications included bronchiectasis in 2 XLA patients, 2 CVID patients and 1 patient with selective immunodeficiency; short stature in one of each XLA, SCID, and CVID patients respectively; poor school performance in 2 SCID patients and 1 XLA patient; and hemolytic anemia in 1 CVID patient. We concluded that in addition to a thorough physical examination, a family history of early death from infection and past history of neonatal hyperbilirubinemia, are crucial in evaluating a patient with suspicious primary hypogammaglobulinemia. The associated symptoms of primary hypogammaglobulinemia, such as recurrent sinopulmonary infections, prolonged fever and allergic diseases, are also diagnostic clues. In the treatment of hypogammaglobulinemia, early and regular high doses of intravenous immunoglobulin (IVIG) supplement may avoid the development or decrease the severity of bronchiectasis.

this study investigated the clinical and immunological features as well as the outcome of pediatric patients with hypogammaglobulinemia treated at the National Taiwan University Hospital during a 17 year period.

From the ¹Department of Pediatrics, Shin Kong Wu Ho-Su Memorial Hospital, ²Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan.
Correspondence: Bor-Luen Chiang

PATIENTS AND METHODS

The clinical and immunological manifestations of children with hypogammaglobulinemia at the National Taiwan University Hospital from January 1984 to December 2001 were reviewed retrospectively. A total of 33 patients with X-linked agammaglobulinemia (3 boys), selective IgA deficiency (1 girl), IgG subclass deficiencies (2 boys: 1 with IgG3 deficiency, 1 with IgG2 and IgG4 deficiency; 3 girls: 2 with IgG3 and IgG4 deficiency, 1 with IgG2 and IgG4 deficiency), with common variable immunodeficiency (12 boys and 5 girls), transient hypogammaglobulinemia of infancy (THI) (2 boys and 1 girl), and severe combined immunodeficiency (2 boys and 2 girls) were involved in the study (Table 1). Patients were excluded if they had human immunodeficiency virus infection, secondary hypogammaglobulinemia, or post-infectious transient hypogammaglobulinemia. Hypogammaglobulinemia was defined as an IgG level which was 2 standard deviations below the mean level for that age, on 2 different specimen examinations. Quantifications of serum immunoglobulins were done by nephelometry in the central laboratory

of the National Taiwan University Hospital. Lymphocyte subsets were done at the pediatric immunology laboratory. Before 1992, T- and B-cell enumerations were done by E-rosetting and by demonstrating surface immunoglobulin, respectively. Thereafter cytofluorographic analysis was done with murine monoclonal antibodies against CD3, CD4, CD8, CD19, and CD20 (Becton Dickinson, IgG1-FITC/IgG1-PE 1388, CD3-FITC/CD19-PE 1384, CD45-RA-FITC/CD4-PE PN IM2762, CD3-FITC/CD8-PE 1383).

RESULTS

The mean age at diagnosis was 5 years for patients with XLA, 5 years in CVID, 2 years in selective immunodeficiency, 1 year and 4 months in THI and 6 months in SCID (Table 1). A family history of early deaths from infections was obvious in patients with XLA (2/3, 67%, all in the mother's pedigree) and SCID (2/4, 50%, all in the mother's pedigree) (Table 1). Past history of the illness as well as a past family history of early deaths from infections was noted in about 25% of all patients. The initial presentations for immunologic evaluation were recurrent sinopulmonary infections ($n = 18$, 54.5%), prolonged

fever ($n = 18$, 54.5%), failure to thrive ($n = 13$, 39.4%), allergic diseases (atopic dermatitis, allergic rhinitis, asthma) ($n = 12$, 36.4%), and chronic diarrhea ($n = 8$, 24.2%) (Table 2). The initial serum immunoglobulin concentrations were abnormal in all patients. IgG was 60 mg/dl in XLA, 659 mg/dl in selective immunodeficiency, 312 mg/dl in CVID, 403 mg/dl in THI, and 296 mg/dl in SCID (Fig. 1). IgA and IgM were extremely low in XLA (IgA: 9 mg/dl and IgM: 15 mg/dl). IgA was low in IgA deficiency (IgA < 23.2 mg/dl) and CVID (31 mg/dl), but was within normal range in the other types (selective immunodeficiency: 72 mg/dl, THI: 34 mg/dl, SCID: 23 mg/dl). IgM was decreased in XLA (15 mg/dl), THI (61 mg/dl) and CVID (100 mg/dl), normal in selective immunodeficiencies (118 mg/dl) and increased in SCID (137 mg/dl).

Leukocytosis at presentation was noted in 2 patients with XLA, 1 with selective immunodeficiency, and 2 patients with CVID (range, from 12,100 to 23,100 cells/mm³). Leukopenia was noted in 4 CVID patients (range, 1,190 to 2,790 cells/mm³), and lymphopenia was noted in 3 SCID patients with a mean absolute lymphocyte count of

Table 1 Clinical profiles of patients with hypogammaglobulinemia

	XLA (n = 3)	CVID (n = 17)	Selective (n = 6)	THI (n = 3)	SCID (n = 4)	All (n = 33)
Boys	3	12	2	3	2	22 (67%)
Girls	0	5	4	0	2	11 (33%)
Age in years at diagnosis	5	5	2	1.4	0.5	
Family history	2	3	1	0	2	8 (24%)
Past history of neonatal phototherapy	1	1	3	1	2	8 (24%)

XLA = X-linked (Bruton) agammaglobulinemia; CVID = common variable immunodeficiency; Selective = IgA and IgG subclass immunoglobulin deficiencies; THI = transient hypogammaglobulinemia of infancy; SCID = severe combined immunodeficiency.

290 cells/mm³ (range, 99 to 451 cells/mm³). Patients with XLA had no detectable B cells in their peripheral blood, while B cells were increased in CVID (18%), THI (31%), and SCID (28%). The T-cell count was elevated in XLA (86%), decreased in both THI (61%) and SCID (49%), and normal in CVID (75%). The NK cell count was elevated in SCID (34%) but decreased in the other types (XLA: 8%, CVID: 6%, and THI: 2%) (Fig. 2).

Except patients with IgA immunodeficiency, almost all patients (XLA: 3/3, CVID: 17/17, IgG subclass immunodeficiency: 2/4, SCID: 1/3) received supplemental intravenous immunoglobulin 400 to 700 mg/kg every 3 to 4 weeks in order to keep IgG levels above 700 mg/dl. Reactions to intravenous immunoglobulin were rare and only seen in three CVID patients: one with fever, one with headache and one with aseptic meningitis. IgG sub-

class immunodeficiency returned to normal values within 1 to 2 years in two patients who received intravenous immunoglobulin supplement and these patients were doing well 4 to 5 years after discontinuing the IVIG replacement. IgG levels returned to normal in all THI patients by 3 years of age. Two patients with SCID underwent bone marrow transplantation (BMT) at age 9 months and 11 months, respectively. One patient with SCID received a fetal thymus transplantation at 2

months of age but died at age 3 months due to *Pseudomonas* sepsis. Another patient did not match the HLA type of his family members, and received intravenous immunoglobulin supplement every month, but was lost to follow up at the age of 4 years. The two patients who received bone marrow transplantation developed acute graft-versus-host disease and chickenpox infection. One of these two patients developed polio-like myelitis one and a half years after bone marrow trans-

Table 2 Clinical presentations at diagnosis

	All patients (n = 33)	%
Recurrent sinopulmonary infections	18	54.5%
Prolonged fever	18	54.5%
Failure to thrive	13	39.4%
AD, AR, Asthma	12	36.4%
Chronic diarrhea	8	24.2%

AD = atopic dermatitis; AR = atopic rhinitis

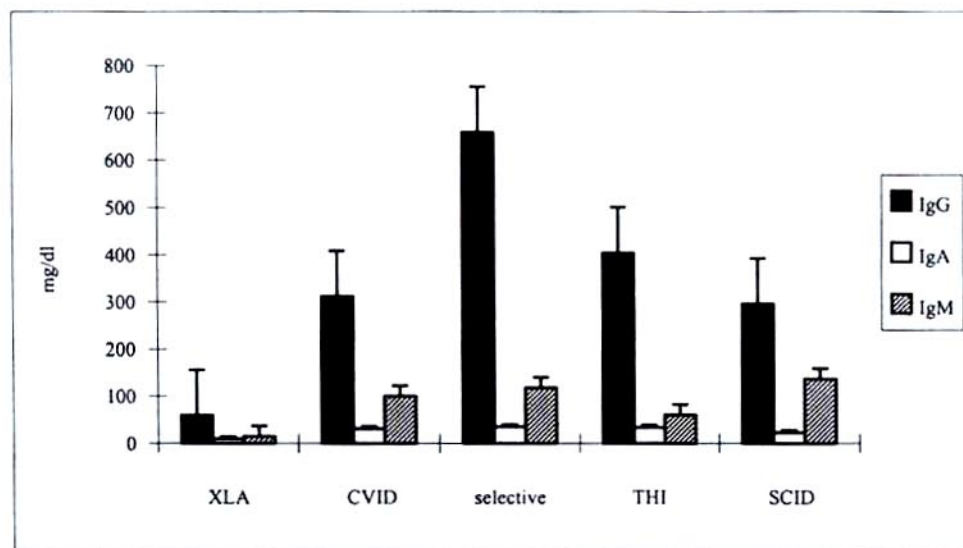


Fig. 1 Mean serum immunoglobulin concentrations (mg/dL) in XLA, CVID, selective immunodeficiencies, THI, and SCID. IgG, IgA and IgM were extremely low in XLA. IgA was low and IgM was decreased in CVID.

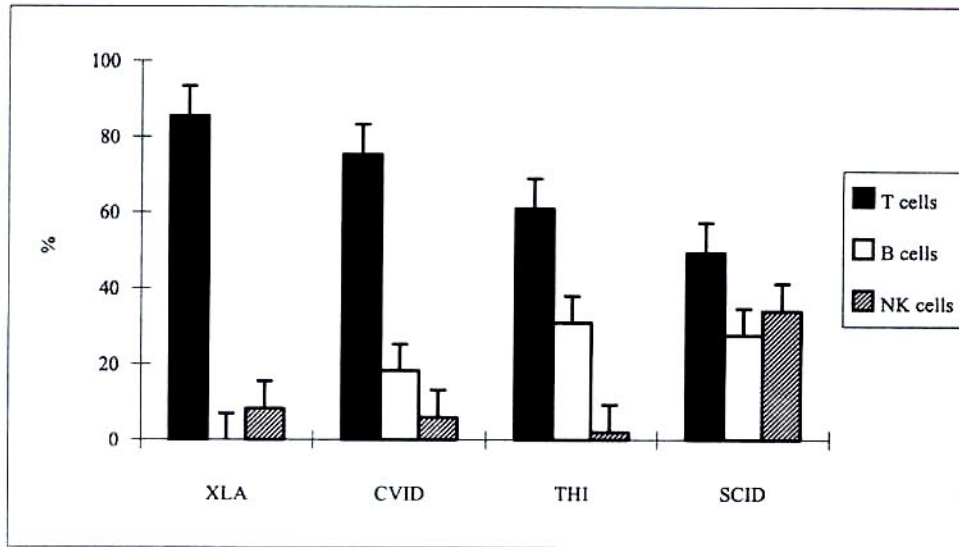


Fig. 2 Mean values of CD19+ B cells, CD3+ T cells, and CD16+ CD56+ NK cells at initial evaluation (%) in patients with XLA, CVID, THI, and SCID. B cells were not found in patients with XLA and were increased in patients with CVID, THI and SCID. T cells were increased in patients with XLA, and decreased in patients with THI and SCID. NK cells were elevated in SCID, and decreased in the other types.

plantation (Table 3), which led to short stature and physical disability and the need for braces due to bilateral short legs. Long-term complications consisted of bronchiectasis in 2 patients with XLA, 2 patients with CVID and 1 patient with selective immunodeficiency. Short stature was noted in one each of XLA, SCID, and CVID, patients. Poor school performance was reported in 2 patients with SCID and one patient with XLA. One CVID patient had associated hemolytic anemia (Table 4).

DISCUSSION

We retrospectively evaluated the clinical characteristics of 33 cases of hypogammaglobulinemia treated during a period of 18 years. Recurrent sinopulmonary infections or prolonged fever were noted at di-

Table 3 Complications of IVIG replacement and bone marrow transplantation

	XLA	CVID	IgG subclass	SCID
Fever	0	1	0	0
Headache	0	1	0	0
Aseptic meningitis	0	1	0	0
Acute GVHD				2
Polio-like myelitis				1

Table 4 Long-term follow-up

	XLA	CVID	IgG subclass	SCID
IVIG supplement	3/3	17/17	2/5	1/3
Bronchiectasis	1/3	2/17	1/6	0/3
Poor school performance	0/3	2/17	1/6	2/3
Short stature	1/3	1/17	0/6	1/3

agnosis in more than half of the patients. Nearly forty percent of the patients had the symptom of failure to thrive. A past history of neonatal hyperbilirubinemia was noted in about 25% patients, most of whom (75%) needed phototherapy. One third of the patients had allergic diseases, which were present in a significantly increased number of patients with selective immunodeficiency (6/6, 100%) and CVID (13/17, 76%). The mean age at diagnosis of XLA was 5 years whereas the mean age at the onset of symptoms was 3 years. Most XLA patients begin to suffer recurrent infections following the natural loss of transplacentally acquired maternal immunoglobulin between 4 and 12 months of age.³ A study from the United Kingdom found that 21% (9 of 44) of XLA patients developed medically significant symptoms for the first time as late as 3 to 5 years of age.⁴ One possible reason for the high rate of delayed diagnosis is the use of antibiotics and good hygiene.

Leukocytosis at evaluation may have been caused by concurrent pyogenic bacterial sinopulmonary infections, whereas leukopenia in CVID patients in mid-childhood may be the result of a viral infection acquired in a day-care center. Early recognition of SCID should be considered a pediatric emergency, because a diagnosis before the onset of opportunistic infections permits life-saving HLA-identical or T-cell-depleted haploidentical bone marrow transplantation.⁵ Absolute lymphocyte count (ALC) is the most useful screening test because lymphocytopenia is present in almost all patients with SCID from the time of birth.⁶ Lymphocytopenia was significant in our patients

with a mean ALC of $290/\text{mm}^3$, compared with the lower limit of the normal range which is $4,000/\text{mm}^3$ at 6 months of age. The positive family history of early deaths from infections in 50% of our SCID patients with maternal pedigree implies the X-linked nature of SCID, which is the most frequent form, accounting for 50-60% of the cases.⁷ The lymphocyte subset at the initial evaluation represents the characteristic features of each disease. There were no CD19+ B cells in our XLA patients as a consequence of a defect at the development stage from pre-B lymphocytes to B lymphocytes. Patients with XLA have pre-B lymphocytes in their bone marrow but have few if any B lymphocytes in their blood and lymphoid tissues.⁸ A profound deficiency of B cells and an arrest in B lymphocyte development resulting in severe hypogammaglobulinemia was characteristically seen in our patients with extremely low immunoglobulin levels (60 mg/dl).³ As expected, the T lymphocyte numbers were normal in patients with XLA. 25% to 30% of CVID patients had increased numbers of CD8+ lymphocytes and, as a result, reduced CD4/8 ratios.⁹ As much as 57% of our CVID patients had a CD4/CD8 ratio below 1. CD8+ T lymphocytes may have a suppressive effect on B cell differentiation and immunoglobulin secretion.¹⁰ In addition, intrinsic B cell defects, a defective interaction between T and B cells, defective T-helper function, and immunoregulatory cytokine abnormalities all contribute to variable and complex immune abnormalities in CVID.^{11,12} Data on selective immunodeficiencies were not available as almost all patients did not have data on lymphocyte subsets. In our patients,

combined T and B cell immunodeficiencies of SCID were reflected in the decreased numbers of T lymphocytes and very low immunoglobulin levels, while NK cell numbers were elevated. Variations in NK cell numbers and functions as well as variations in T and B cells numbers were noted in different genetic subtypes,⁵ and may be useful in subdividing these genetic subtypes. The existing data on lymphocyte subsets did not allow us to match patients with specific genetic subtypes.

In this series, all patients were supplied with 400 to 700 mg/kg intravenous immunoglobulin every 3 to 4 weeks in order to maintain a relatively high trough level of 700 mg/dl. This strategy appeared to result in a better quality of life as indicated by reduced rates of infections and hospital admissions. One boy with selective IgG3 immunodeficiency and 1 girl with selective IgG3 and IgG4 immunodeficiency discontinued IVIG after 1 to 2 years, and were doing well 4 to 5 years later. It is important to regularly reevaluate immunoglobulin levels and symptoms because of the high likelihood of outgrowing the need for supplementation with age. This developmental change may also reflect that IgG subclass deficiencies might be caused by a dysregulation of the immune response rather than a defect in immunoglobulin production. Bronchiectasis was the most common long-term complication in this series of patients with hypogammaglobulinemia, occurring in 2 patients with XLA, 2 with CVID, and one each with IgG3 and IgG4 immunodeficiency, respectively. The high prevalence of this complication may have been due to the lack of initial regu-

lar IVIG treatment, which was not covered under the National Health Insurance system prior to 1995. Although use of a portable oxygen supply was necessary in 1 of the CVID patients, regular IVIG supplement and aggressive pulmonary physiotherapy thereafter allowed him to live a relatively active lifestyle. To prevent the development of chronic lung disease and bronchiectasis, early diagnosis of antibody deficiency and initiation of prophylactic treatment with IVIG are before the age of 1 year of great importance.⁸ One study reported a significant association between bronchiectasis and trough IgG concentrations lower than the 10th percentile.¹³ Early diagnosis and high dose IVIG replacement therapy might avoid the complication of bronchiectasis. Patient education and aggressive physiotherapy are important factors affecting the outcome. Another long-term complication, malignancy, which is most commonly seen in the fourth and fifth decades of life, was not seen in our patients for all our patients were younger than thirty years old. However, close follow-up for early diagnosis of malignancy is necessary. HLA identical bone marrow transplantation was performed in two of our SCID patients, both of whom were free of hypogammaglobulinemia 1 year later. One patient received IVIG supplement only and was lost to follow-up. Such patients have a poor prognosis and may benefit from haploidentical BMT nowadays, which is nearly as successful as HLA-identical transplantations.¹⁴

We conclude that in addition to a thorough physical examination, a family history of early deaths from infections and a past

history of neonatal hyperbilirubinemia are crucial informations for the initial suspicion of hypogammaglobulinemia. Associated symptoms such as recurrent sinopulmonary infections, prolonged fever and allergic diseases are clues for the diagnosis of hypogammaglobulinemia. Patients with allergic diseases especially warrant an investigation for CVID and selective immunodeficiencies. Lymphocytopenia is an early diagnostic clue to identifying the pediatric emergency of SCID. In the treatment of hypogammaglobulinemia, early and regular high dose IVIG supplement may avoid the complication of bronchiectasis.

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