J Microbiol Immunol Infect.
2009;42:271-275

Original Article

Serum immunoglobulin E levels in patients with primary hypogammaglobulinemia — experience from a tertiary hospital in Taiwan

Wen-Ju Tsai[1,2], Jeng-Yee Lin[2], Yao-Hsu Yang[1], Jyh-Hong Lee[1], Bor-Luen Chiang[1]

[1]Department of Pediatrics, National Taiwan University Hospital, Taipei; and [2]Graduate Institute of Clinical Medical Science, Chang Gung University, Taoyuan, Taiwan

Received: March 13, 2006 Revised: May 14, 2008 Accepted: July 31, 2008

Background and purpose: Primary hypogammaglobulinemia has been proposed to be associated with an increased incidence of allergic diseases, but the correlation between the clinical presentation and the serum immunoglobulin E (IgE) level has not been studied in this patient group. This study investigated the correlation of IgE levels and allergic condition in patients with primary hypogammaglobulinemia.

Methods: Thirty five patients with primary hypogammaglobulinemia were enrolled from September 2004 to March 2005. Serum IgE levels were measured at clinic follow-up. Information regarding the patient's history of allergic diseases, including atopic dermatitis, allergic rhinitis, allergic conjunctivitis, and asthma, were collected from chart review and clinic interviews.

Results: Significantly lower mean ± standard deviation serum IgE levels were found in allergic patients with primary hypogammaglobulinemia (123.9 ± 148.8 IU/mL) than in the healthy control group (376.2 ± 471.7 IU/mL) [$p < 0.005$] or in allergic patients without primary hypogammaglobulinemia (544.1 ± 309.1 IU/mL) [$p < 0.001$].

Conclusions: Serum IgE level is not a suitable diagnostic criterion or treatment guide for allergy in patients with primary hypogammaglobulinemia.

Key words: Agammaglobulinemia; Allergy and immunology; Immunoglobulin E

Introduction

Hypogammaglobulinemia may be caused by either B-cell immunodeficiencies or combined B-cell and T-cell deficiencies. B-cell immunodeficiencies might result from defects in signal transduction through Bruton's tyrosine kinase (X-linked agammaglobulinemia), leading to a selective or generalized failure to progress from the immature B-cell stage to the plasma cell stage (immunoglobulin A [IgA] immunodeficiency or common variable immunodeficiency [CVID]). 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 [1]. Many reports have documented a variety of abnormalities in concentrations of the 3 major Igs — IgG, IgA, and IgM — in patients with primary hypogammaglobulinemia [2]. The association between primary immunodeficiency diseases and allergic diseases has been well established. In Taiwan, allergic diseases are noted in 76% of patients with CVID [1]. In Hong Kong, morbidities such as autoimmune disease (6%) and allergic disease (20%) are common in patients with primary immunodeficiency diseases [3].

To the authors' knowledge, there have been no reports in the literature regarding IgE levels in allergic patients with primary hypogammaglobulinemia. This study was performed to investigate the serum IgE levels in allergic patients with primary hypogammaglobulinemia.

Methods

Thirty five patients with primary hypogammaglobulinemia were enrolled, and categorized according to

Corresponding author: Dr. Bor-Luen Chiang, Department of Pediatrics, National Taiwan University Hospital, Fl. 7, No. 7 Chung-Shan South Road, Taipei 100, Taiwan.
E-mail: gicmbor@ha.mc.ntu.edu.tw

the following diseases: X-linked agammaglobulinemia (3 boys), CVID (15 boys and 10 girls), transient hypogammaglobulinemia of infancy (1 boy), IgG subclass deficiencies (1 boy with IgG3 deficiency and 1 girl with IgG2 deficiency), and SCID (4 boys) [Table 1]. The diagnosis of primary hypogammaglobulinemia was confirmed by clinical manifestations and biochemistry data.

Hypogammaglobulinemia was defined as an IgG level 2 standard deviations below the mean level for the corresponding chronologic age. Quantifications of serum Igs were done by nephelometry in the central laboratory at the National Taiwan University Hospital, Taipei, Taiwan.

Twenty six of 35 patients with primary hypogammaglobulinemia (74%) had symptoms of allergic diseases (Table 1). Three patients had X-linked agammaglobulinemia, 21 had CVID, and 2 had selective immunodeficiencies.

Sixty two age-matched patients with allergic diseases were randomly selected from the clinic to serve as controls. Serum IgE levels were measured in all participants. Diagnoses of allergic diseases, including atopic dermatitis, allergic rhinitis, allergic conjunctivitis and asthma, were confirmed by medical chart review and clinic-based interviews.

Determination of total and allergen-specific serum immunoglobulin E levels

Total and allergen-specific serum IgE levels were measured using the Pharmacia CAP System (Pharmacia, Uppsala, Sweden) according to the manufacturer's instructions. Values are represented as mean ± standard deviation. The assay was calibrated against the World Health Organization standard for total serum IgE with a range of 0.35-100.00 kU/L for allergen-specific IgE and 2-2000 kU/L for total serum IgE. Titers were considered positive for sensitization when the observed allergen-specific serum IgE level was above 0.35 kU/L.

Data analysis

The comparison of IgE levels was statistically analyzed with a non-parametric Mann-Whitney test. A 2-tailed p value of <0.05 was considered statistically significant.

Results

Serum immunoglobulin E concentrations

The mean age of allergic patients with primary hypogammaglobulinemia was 12.5 ± 5.4 years. The mean age of non-allergic patients with primary hypogammaglobulinemia was 13.8 ± 6.2 years. Among the allergic control patients (40 boys and 22 girls), the mean age was 12.2 ± 4.6 years. The mean serum IgE concentration for all patients with primary hypogammaglobulinemia was 112.2 ± 136.7 IU/mL. The mean serum IgE concentration for allergic patients with primary hypogammaglobulinemia was 123.9 ± 148.8 IU/mL. The mean serum IgE concentration of non-allergic patients with primary hypogammaglobulinemia was 81.56 ± 11.26 IU/mL. Among the allergic control patients, the mean serum IgE concentration was 544.1 ± 309.1 IU/mL (Table 2).

Group comparisons

The mean IgE level of the allergic patients with primary hypogammaglobulinemia (123.9 ± 148.8 IU/mL) was significantly lower than that of allergic patients with-

Table 1. Demographic characteristics of patients with primary hypogammaglobulinemia.

Characteristic	X-linked agammaglobulinemia	Common variable immunodeficiency	Transient hypogammaglobulinemia of infancy	Immunoglobulin G subclass immunodeficiencies	Severe combined immunodeficiency	Total
No. of patients	3	25	1	2	4	35
Allergic	3	21	0	2	0	26
Non-allergic	0	4	1	0	4	9
Sex (male:female)	3:0	15:10	1:0	1:1	4:0	22:13
Allergic	3:0	11:10	-	1:1	-	15:11
Non-allergic	-	4:0	1:0	-	4:0	9:0
Age (years) [mean ± standard deviation]	14.0 ± 9.3	17.0 ± 3.5	1	11.0 ± 1.4	12.3 ± 5.5	12.9 ± 7.6
Allergic	14.0 ± 9.3	19.0 ± 2.6	-	11.0 ± 1.4	-	12.5 ± 5.4
Non-allergic	-	12.2 ± 3.5	1	-	12.3 ± 5.5	13.8 ± 6.2

Table 2. Serum immunoglobulin E level in different study populations.

	Patients with hypogammaglobulinemia	Allergic patients with hypogammaglobulinemia	Non-allergic patients with hypogammaglobulinemia	Allergic control patients
No. of patients	35	26	9	62
Mean immunoglobulin E level (IU/mL)	112.2 ± 136.7	123.9 ± 148.8	81.6 ± 11.3	544.1 ± 309.1

out hypogammaglobulinemia (544.1 ± 309.1 IU/mL; $p < 0.001$) [Fig. 1]. The mean serum IgE concentration of allergic patients with primary hypogammaglobulinemia (123.9 ± 148.8 IU/mL) was significantly lower than the mean serum IgE concentration of the age-appropriate controls (376.2 ± 471.7 IU/mL; $p < 0.005$) [Fig. 2]. The mean serum IgE concentration of the non-allergic patients with primary hypogammaglobulinemia (81.56 ± 11.26 IU/mL) was lower than the mean serum IgE concentration of the allergic patients with primary hypogammaglobulinemia (123.9 ± 148.8 IU/mL). The mean serum IgE concentrations between non-allergic and allergic patients with primary hypogammaglobulinemia showed no significant difference ($p = 0.792$) [Fig. 3].

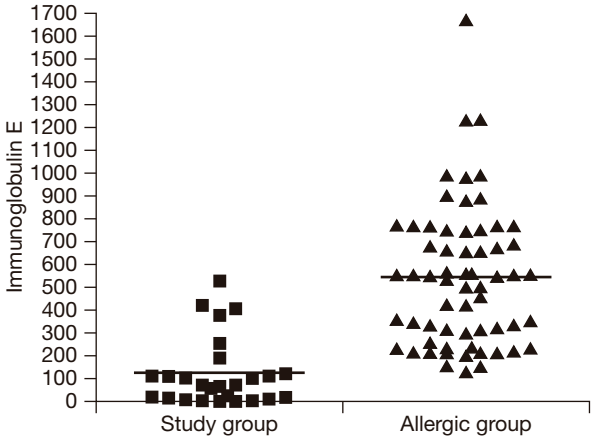

Fig. 1. Comparison of serum immunoglobulin E concentrations between allergic patients with primary hypogammaglobulinemia and allergic patients ($p < 0.001$).

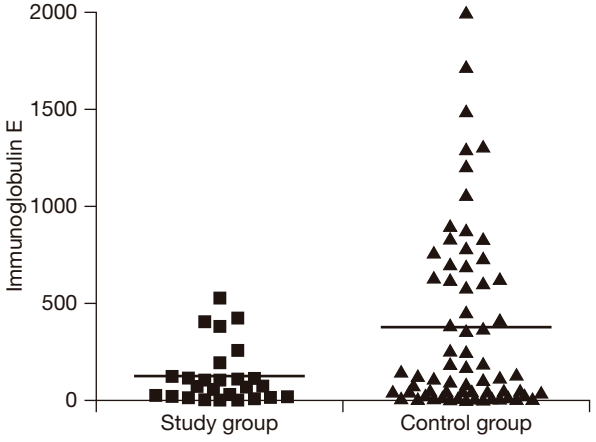

Fig. 2. Comparison of serum immunoglobulin E concentrations between allergic patients with primary hypogammaglobulinemia and controls ($p < 0.05$).

Relationship between primary hypogammaglobulinemia and allergic disease

Twenty six of 35 patients with primary hypogammaglobulinemia (74%) had symptoms of allergic disease [Table 3]. Three patients had X-linked agammaglobulinemia, 21 had CVID, and 2 had selective immunodeficiencies.

Nine of 35 patients with primary hypogammaglobulinemia (26%) had no symptoms of allergic disease [Table 3]. Four patients had CVID, 1 had transient hypogammaglobulinemia of infancy, and 4 had SCID.

Positive CAP results were found for 13 of 26 allergic patients with primary hypogammaglobulinemia (50%) [Table 4]. Twelve of these patients had CVID and 1 had selective immunodeficiency.

Discussion

Allergy can be divided into 2 distinct variants, the extrinsic or allergic variant and intrinsic or non-allergic

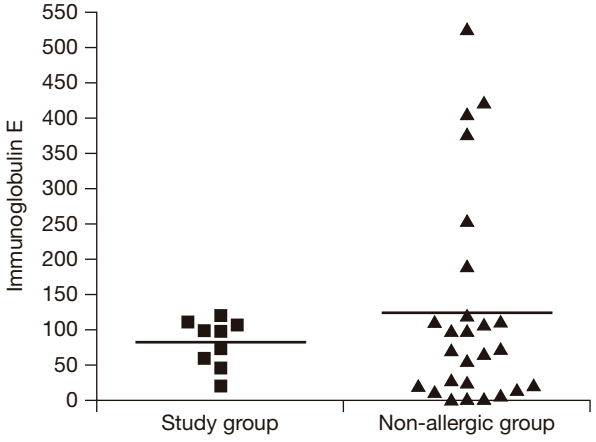

Fig. 3. Comparison of serum immunoglobulin E concentrations between non-allergic and allergic patients with primary hypogammaglobulinemia ($p < 0.792$).

Table 3. Positive allergic history in patients with primary hypogammaglobulinemia.

	X-linked agamma-globulinemia	Common variable immunodeficiency	Transient hypogamma-globulinemia of infancy	Immunoglobulin G subclass immuno-deficiencies	Severe combined immuno-deficiency	Total
Positive allergic history[a] No. (%)	3/3 (100)	21/25 (84)	0/1 (0)	2/2 (100)	0/4 (0)	26/35 (74)

[a]History of atopic dermatitis, allergic rhinitis, or asthma.

Table 4. Positive CAP findings in allergic patients with primary hypogammaglobulinemia.

	X-linked agammaglobulinemia	Common variable immunodeficiency	Immunoglobulin G subclass immunodeficiencies	Total
Positive CAP finding No. (%)	0/3 (0)	12/21 (57)	1/2 (50)	13/26 (50)

variant. The extrinsic variant occurs in the context of sensitization toward environmental allergens and is accompanied by elevated serum IgE levels. The intrinsic variant is known to have no detectable sensitization and low serum IgE levels. However, the exact pathophysiology of non-allergic atopic disease is not fully understood [4-6].

The percentage of positive allergic history in patients with primary hypogammaglobulinemia was 74% in this study, which is evidently higher than that of the healthy population. In addition, the percentage of positive CAP results in allergic patients with primary hypogammaglobulinemia was 50% in this study, which is higher than that usually observed in allergic patients. Therefore, allergic patients with primary hypogammaglobulinemia are more likely to have a non-allergic variant.

It is estimated that approximately 50% to 60% of patients with primary immunodeficiency disease have humoral immunity, 15% to 20% have combined humoral and cellular immunity, 10% to 15% have phagocytic immunity, and 1% to 3% have the complement system.

In this study, 21 of 26 allergic patients with primary hypogammaglobulinemia had CVID, which is the most prevalent human primary immunodeficiency. The etiology of CVID has not been well studied. There are several possible causes of CVID, including inducible costimulatory receptor deficiency, which accounts for less than 1% of patients. In addition, it has been reported that mutations in the tumor necrosis factor receptor family member transmembrane activator, calcium modulator and cyclophilin ligand interactor, which mediates isotype switching in B cells, have been found in 10% to 20% of patients with CVID [7,8].

Although deficient production of Ig by B cells is the immunologic hallmark of CVID, T-cell abnormalities are also present in a high proportion of these patients. Dendritic cells of patients with CVID have a significantly reduced capacity to secrete interleukin-12 (IL-12). Deficient dendritic cell function could lead to attenuated T-cell activation and defective immunization [9].

Some studies have demonstrated reduced secretion of IL-10 from T cells in CVID. Reduced IL-10 secretion by T cells may contribute to the deficient B-cell function in CVID [10]. More specifically, IL-10 and transforming growth factor-β secreted by allergen-specific type 1 regulatory cells skew the antibody production from IgE towards the non-inflammatory isotypes IgG4 and IgA [11]. This might explain why patients with CVID have a higher incidence of allergic disease but a lower IgE level.

In this study, allergic diseases were seen in 100% of patients with X-linked agammaglobulinemia or IgG subclass deficiencies, but in 0% of patients with SCID or transient hypogammaglobulinemia of infancy. However, it is hard to draw any conclusion from this observation due to the small sample size.

These results demonstrated that the mean serum IgE concentration of allergic patients with primary hypogammaglobulinemia was significantly lower than that of allergic patients. One reason may be the lower IgE level in the former patients, which may be attributed to the ubiquitous use of intravenous immune globulin (IVIG) therapy in patients with primary hypogammaglobulinemia.

In the past 20 years, IVIG therapy has become the standard treatment for antibody deficiency syndrome, and has significantly decreased the occurrence

of pneumonia in patients with agammaglobulinemia [12,13]. In this study, 20 of 26 allergic patients with primary hypogammaglobulinemia had regular IVIG therapy at the outpatient department to maintain a relatively high trough level of 700 mg/dL. Some papers have reported that IVIG therapy may suppress IgE production by inhibiting anti-CD40 and IL-4–stimulated B-cell proliferation. Diminution of IgE production in anti-CD40/IL-4–stimulated B cells by IVIG is due to inhibition proliferation and progression early in the cell cycle [14-17].

It remains difficult to determine the causal relationship between primary hypogammaglobulinemia and IgE deficiency from this study. The limitations of the study were the small number of patients and the confounding factor of IVIG therapy.

Nevertheless, the authors suggest that serum IgE level is not an appropriate reference for diagnosis or treatment guidelines for allergy in patients with primary hypogammaglobulinemia.

References

1. Wang LJ, Yang YH, Lin YT, Chiang BL. Immunological and clinical features of pediatric patients with primary hypogammaglobulinemia in Taiwan. Asian Pac J Allergy Immunol. 2004;22:25-31.
2. Buckley RH, Fiscus SA. Serum IgD and IgE concentrations in immunodeficiency diseases. J Clin Invest. 1975; 55: 157-65.
3. Lam DS, 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.
4. Novak N, Bieber T. Allergic and nonallergic form of atopic diseases. J Allergy Clin Immunol. 2003;112:252-62.
5. Bardana EJ Jr. Immunoglobulin E- (IgE) and non-IgE-mediated reactions in the pathogenesis of atopic eczema/dermatitis syndrome (AEDS). Allergy. 2004;59:25-9.
6. Schmid-Grendelmeier P, Simon D, Simon HU, Akdis CA, Wüthrich B. Epidemiology, clinical features, and immunology of the "intrinsic" (non-IgE–mediated) type of atopic dermatitis (constitutional dermatitis). Allergy. 2001;56:841-9.
7. Lim MS, Elenitoba-Johnson KS. The molecular pathology of primary immunodeficiencies. J Mol Diagn. 2004;6:59-83.
8. Castigli E, Geha RS. Molecular basis of common variable immunodeficiency. J Allergy Clin Immunol. 2006;117:740-6.
9. Cunningham-Rundles C, Radigan L. Deficient IL-12 and dendritic cell function in common variable immunodeficiency. Clin Immunol. 2005;115:147-53.
10. Holm AM, Aukrust P, Aandahl EM, Müller F, Taskén K, Frøland SS. Impaired secretion of IL-10 by T cells from patients with common variable immunodeficiency — involvement of protein kinase A type I. J Immunol. 2003;170:5772-7.
11. Taylor A, Verhagen J, Blaser K, Akdis M, Akdis CA. Mechanisms of immune suppression by interleukin-10 and transforming growth factor-β: the role of T regulatory cells. Immunol. 2006; 117:433-42.
12. Aghamohammadi A, Moin M, Farhoudi A, Rezaei N, Pourpak Z, Movahedi M, et al. Efficacy of intravenous immunoglobulin on the prevention of pneumonia in patients with agammaglobulinemia. FEMS Immunol Med Microbiol. 2004;40:113-8.
13. Lemieux R, Bazin R, Neron S. Therapeutic intravenous immunoglobulins. Mol Immunol. 2005;42:839-48.
14. Zhuang Q, Mazer B. Inhibition of IgE production in vitro by intact and fragmented intravenous immunoglobulin. J Allergy Clin Immunol. 2001;108:229-34.
15. Bayry J, Thirion M, Misra N, Thorenoor N, Delignat S, Lacroix-Desmazes S, et al. Mechanisms of action of intravenous immunoglobulin in autoimmune and inflammatory diseases. J Neurol Sci. 2003;24(Suppl. 4):S217-21.
16. Sigman K, Ghibu F, Sommerville W, Toledano BJ, Bastein Y, Cameron L, et al. Intravenous immunoglobulin inhibits IgE production in human B lymphocytes. J Allergy Clin Immunol. 1998;102:421-7.
17. Simon HU, Späth PJ. IVIG — mechanisms of action. Allergy. 2003;58:543-52.

