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The association of selective IgA deficiency and IgE hypogammaglobulinemia

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Key words: hypogammaglobulinemia; IgA; IgE; IgG subclasses.

Selective IgA deficiency has been associated with atopy and high serum IgE levels (1). Some small studies demonstrated its association also with low serum levels of IgE or IgE

hypogammaglobulinemia (2–7), which previously had been

noted to be associated with other primary immunodeficiencies such as common variable immunodeficiency and ataxia telangiectasia (8). The aim of the present study was to further explore combined IgA and

IgE deficiency in a larger cohort of patients with IgE hypogammaglobulinemia, and to describe its clinical presentation.

The database of the Clinical Immunology laboratory for 2001–2003 was searched to identify patients with serum IgE levels of < 10 IU/ml and serum IgA levels < 6.6 mg/dl, with normal IgG and IgM levels. For patients with combined deficiency, data were collected on age, gender, clinical diagnosis and serum IgG subclass levels. IgG subclass levels were compared with the normal range by age, as established in our laboratory. Levels below 2 standard deviations of the mean for age were considered low.

During 2001–2003, our laboratory performed 3287 tests for serum IgE, of which 532 (16.4%) yielded levels of < 10 IU/ml. Thirty-two of these patients had serum IgA levels of < 6.6 mg/dl. Seven of them had known primary immunodeficiencies (common variable immunodeficiency in five and X-linked agammaglobulinemia in two), and 19 were younger than 4 years, so that a diagnosis of selective IgA deficiency could not yet be made according to the criteria of the European Society for Immunodeficiency (9). The clinical features of the remaining six patients with selective IgA deficiency are presented in Table 1.

Table 2 summarizes the findings of previous studies of the association of selective IgA deficiency and IgE hypogammaglobulinemia. Our study included the largest number of patients with IgE hypogammaglobulinemia – 532 compared with 12 (6) and 44 (7) – most probably because of the large number of samples screened and our high cutoff of < 10 IU/ml relative to the 5 IU/ml (6) and 2.5 IU/ml (7) cutoffs in other studies. There is no established 'low level' for serum IgE, although Kjellman and Johansson found that serum IgE levels in healthy nonatopic children aged 0–14 years were > 5 IU/ml (10). Accordingly, three of six patients with concomitant selective IgA deficiency had serum IgE levels of 1–3 IU/ml, and in the other three patients, IgE levels were undetectable (Table 1).

The prevalence of selective IgA deficiency in our series of patients with IgE hypogammaglobulinemia was 1.12%,

lower than what was found in two previous studies of patients with IgE hypogammaglobulinemia (9–16.6%) (6, 7) (Table 2). In four other studies of patients with selective IgA deficiency, the prevalence of IgE hypogammaglobulinemia was 6.4–32% (2–5) (Table 2).

One possible explanation for the lower prevalence in our study is our exclusion of patients younger than 4 years, according to the criteria for selective IgA deficiency established by the European Society for Immunodeficiency (9), while other studies included also younger patients (Table 2).

Similar to previous studies, our patients with combined IgA–IgE deficiency had frequent upper and lower respiratory tract infections (patients 1, 4, 5 and 6) and bronchial asthma (patients 2 and 3). None had an autoimmune disease.

Two of our patients warrant special attention. Patient 4 had congenital heart disease and cleft palate, and cytogenetic analysis revealed a 22q11 deletion in 80% of the cells examined. The chromosome 22q11.2 deletion syndrome overlaps with DiGeorge syndrome (11), but the patient did not have any infection other than ear infections, and laboratory investigation did not reveal any evidence of cellular immune deficiency. Selective IgA deficiency has been described in patients with 22q11 deletion syndrome, but not in combination with IgG2, IgG4, and IgE deficiency (11).

Patient 6 had a more complicated course of pulmonary infections leading to bronchiectasis. His total serum IgG level was at the lower limit of normal. Further follow-up is needed to determine the future development of common variable immunodeficiency, as described previously in patients with selective IgA deficiency (12). Of the five patients with combined IgA–IgE deficiency who were tested for IgG subclass levels, four (80%) had concomitant IgG2–IgG4 subclass deficiency (Table 1). This finding is in accordance with previous studies wherein subclass deficiency rates in patients with IgA–IgE deficiency ranged from 15.3 to 50% (Table 2). In humans, the heavy chain for immunoglobulins is coded on chromosome 14 with IgA1, IgG2, IgG4, IgE and IgA2 in sequential order. Extensive multigene deletions have been

Selective IgA deficiency is present in 1.12% of 532 patients with IgE hypogammaglobulinemia.

Table 1. Clinical features and laboratory test results of six patients with IgA and IgE deficiency*

Patient no.	Sex/age (years)	Clinical diagnosis	IgE (IU/ml)	IgG (mg/dl)	IgA (mg/dl)	IgM (mg/dl)	IgG1 (mg/dl)	IgG2 (mg/dl)	IgG3 (mg/dl)	IgG4 (mg/dl)
1†	M/12	Chronic rhinitis; recurrent tonsillitis; past history of aseptic meningitis and pneumonia	2	1090	< 6.6	125	934	↓28	64	↓3.4
2	M/8	Bronchial asthma	Undetectable	672	< 6.6	117		Not done		
3	M/4	Bronchial asthma, eczema	3	968	< 6.6	52	629	↓55	58	↓4
4‡	M/11	Tetralogy of Fallot; pulmonary atresia; cleft palate; recurrent ear infections	Undetectable	1640	< 6.6	34	1400	↓61	82	↓1.4
5	M/30	Recurrent sinusitis and bronchitis	1	1380	< 6.6	129	913	320	119	24
6†	M/16	Recurrent pneumonia; bronchiectasis	Undetectable	526	< 6.6	81	362	↓45	95	↓< 1.4

*IgG, IgA, IgM and IgG subclass levels were compared with the normal range for age established in the laboratory.

†In patients 1, 4 and 6, blood tests were performed for T and B lymphocytes (percent and total) including CD4⁺/CD8⁺ ratio; all were within normal range.

‡Patient 4 was found to have 22q11 deletion in 80% of the cells examined.

Table 2. Comparison of present study with previous studies of association of IgE hypogammaglobulinemia and selective IgA deficiency

Study	Patients with selective IgA deficiency	Patients with IgE hypogammaglobulinemia	IgG subclass serum levels in patients with combined IgA–IgE deficiency	Clinical data
Stites et al. (2)	12 children and adults (4–60 years)	3 (25%) (< 10 IU/ml)	Not done	2 – recurrent respiratory infections
Kanok et al. (3)	31 children and adults (6–57 years)	2 (6.4%) (< 10 IU/ml)	Not done	Recurrent upper respiratory tract infections
Out et al. (4)	25 children and adults (3–60 years)	8 (32%) (< 10 IU/ml)	↓IgG ₂ in 4 (50%) ↓IgG ₄ in 4 (50%)	2 – asymptomatic; 2 – recurrent infections; 1 – celiac disease; 1 – Crohn's disease; 1 – arthralgia
Schottler et al. (6)	2 (16.6%)	12 children and adults (2–64 years) (< 5 IU/ml)	↓IgG ₂ in 1 (50%)	Recurrent sinopulmonary infections
De Laat et al. (5)	40 children (> 1 year)	13 (32.5%) (< 5 IU/ml)	↓IgG ₂ + ↓IgG ₄ in 2 (15.3%) ↓IgG ₄ in 4 (30%)	Recurrent respiratory infections 1 – celiac disease 1 – Crohn's disease
Smith et al. (7)	4 (9%)	44 adults (> 18 years) (< 2.5 IU/ml)	↓IgG ₄ in 1 (25%)	All – recurrent respiratory infections, increased prevalence of autoimmunity and nonallergic reactive airway disease
Present study	6 (1.12%)	532 children and adults (1–30 years) (< 10 IU/ml)	↓IgG ₂ + ↓IgG ₄ in 4 (66%)	3 – recurrent upper and lower respiratory tract infections 2 – asthma 1 – bronchiectasis

described in the immunoglobulin-heavy chain constant locus, and six different multigene deletion haplotypes have been identified, some of them encompassing the genes of IgA1, IgE, IgG2, and IgG4 (13).

In summary, IgE hypogammaglobulinemia was detected in 532 of 3287 patients (16%) of whom six (1.12%) had associated selective IgA deficiency. Concomitant IgG2–IgG4 deficiency was detected in four of

the six patients with the combined diseases. Further studies are needed to verify if these patients have multigene deletions in the immunoglobulin-heavy chain constant region on chromosome 14.

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Microwave radiation from cellular phones increases allergen-specific IgE production

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Key words: allergen-specific IgE production; atopic eczema dermatitis syndrome; cellular phone; microwave; Th1 and Th2 cytokine.

Exposure to microwave radiation caused neurological symptoms in humans, while it caused chromosomal instability in lymphocytes (1, 2). Microwave radiation from cellular phones enhanced allergic responses in patients with atopic eczema dermatitis syndrome (AEDS), while it failed to do so in normal subjects (3). Here, the effects of microwave radiation from cellular phones on allergen-specific IgE production were studied.

After obtaining informed written consent, 30 mild AEDS patients [mean SCORAD index 9 (95% CI: 8–10)] (15 women and 15 men, mean 28 years, range 22–32 years) were studied (4). AEDS patients were treated with application of mixture of pinetar (Yoshida

Pharmaceutical Co. Ltd, Tokyo, Japan) and zinc oxide ointment, but without oral medication. All of AEDS patients were positive for latex, but not to Japanese cedar pollen (JCP), by skin prick test and serum allergen-specific IgE. The serum levels of latex-specific IgE and JCP-specific IgE in AEDS patients were 27.4 and <0.34 IU/ml, respectively.

Randomly assigned 15 AEDS patients first viewed a weather information video, while putting cellular phones to the right ear for 30 min with transmitting but without sound (microwave radiation study). The model of cellular phone used was C5001T (Toshiba, Tokyo, Japan; specific absorption rate = 1.62). After 2 weeks, they viewed a weather information video while putting same cellular phones to the right ear for 30 min, but phone was turned off (control study). On the other hand, other 15 patients first conducted the control study, and after 2 weeks they conducted the microwave radiation study. None of the subjects were aware whether cellular phones had transmitting or not. Just before and immediately after each study, blood was sampled by medical staff who were blinded to the study.

Mononuclear cells from blood were separated, and they were cultured ($4 \times 10^4/0.2$ ml/well) with medium, and 0.1 ng/ml of latex or JCP (TORII PHARM, Co., Ltd, Tokyo, Japan) was added to each culture individually. After 14 days of culture, each allergen-specific IgE production was determined by commercial ELISA, while after 5 days of culture, cytokine production was determined by ELISA (R&D Systems, Inc., Minneapolis, MN) (4). Statistical analysis was performed ANOVA with Bonferonni's correction. This study was approved by the Ethical Committee of Ujitakeda Hospital.

Nonexposure to microwave radiation (control study) had no effect on allergen-specific IgE production, while exposure to microwave radiation (microwave radiation study) significantly increased allergen-specific IgE production (Table 1). This increase was selective to allergen to which AEDS patients were allergic, as exposure to microwave radiation increased

Microwave radiation from cellular phones increases allergen-specific IgE production in patients with AEDS.