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RAPID COMMUNICATION



Analysis of allergic reaction in IgG4-related disease

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ARTICLE HISTORY

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It is reported that allergic disorders are often complicated to immunoglobulin (Ig)G4-related diseases (IgG4-RD) [1]. High expression of type 2 helper T (Th2) cytokines has been confirmed in the involved organs of this disease [2]. However, it is unknown whether allergic reactions to any allergen are the causes of IgG4-RD. Therefore, in this study, we investigated the involvement of allergic reactions in the pathogenesis of IgG4-RD by evaluating specific IgE for several allergens in patients and analyzing the relationship between levels of serum IgG4, IgE, and peripheral counts of eosinophils.

The cases comprised 281 subjects with IgG4-related dacryoadenitis and sialadenitis (IgG4-DS) who visited Sapporo Medical University Hospital between April 1997 and December 2017. All subjects satisfied the comprehensive diagnostic criteria for IgG4-RD [3].

At the first visit, we interviewed the subjects regarding their allergic symptoms, determined the peripheral eosinophil counts, measured the levels of serum IgG, IgG4, and IgE, and performed screening for IgEs against specific allergens. We used the following enzyme-linked immunosorbent assay (ELISA) kits: Human IgG ELISA Kit (ab100547, Abcam, Cambridge, UK) and IgG4 Human ELISA Kit (BMS2095, Thermo Fisher Scientific K.K., Yokohama, Japan). The levels of serum IgE were measured using the radioimmunosorbent test. For the screening, IgEs against specific allergens were measured using the radioallergosorbent test. The following allergens were evaluated by fluorescence Enzyme Immunoassay: birch pollen, cedar pollen, moth scales, *Dermatophagoides pteronyssinus*, Poaceae pollens, weed pollens, food allergens, grain allergens, animal epithelia, and mold allergens. We measured specific IgEs using CAP system (Phadia 1000TM, Thermo Fischer Scientific Inc., Uppsala, Sweden). We analyzed for correlations between the laboratory data, including the peripheral eosinophil counts and the levels of serum IgG4 and IgE. We also compared the clinical features between the patients with IgEs against specific allergens (the positive group) and

the patients without IgEs against specific allergens (the negative group).

Student's *t*-test was used to compare continuous variables between groups. *p* Values <.05 were considered to be significant. Pearson's correlation coefficient was used to examine the statistical relationships between the laboratory data. All statistical analyses were performed using Multivariate Analysis for Mac version 3 software (ESUMI Co., Ltd., Tokyo, Japan).

The subjects consisted of 143 males and 138 females; 160 cases with IgG4-DS; 83 cases with IgG4-related sialadenitis; and 38 cases with IgG4-related dacryoadenitis. The mean ($\pm$ standard deviation) of the age at the time of diagnosis was 61.8 ± 11.4 years.

By medical interview, 165 cases (58.7%) of IgG4-DS were found to have allergic disorders, including 140 cases (49.8%) with rhinitis, 56 cases (19.9%) with conjunctivitis, 25 cases (8.9%) with bronchial asthma, and 5 cases (1.8%) with urticarial. The laboratory data from the first visit showed that the mean peripheral eosinophil count was $325.2 \pm 883.4/\mu\text{L}$, and the mean level of serum IgG, IgG4, and IgE was $2160.9 \pm 1179.8 \text{ mg/dL}$, $658.3 \pm 613.9 \text{ mg/dL}$, and $444.0 \pm 1263.2 \text{ IU/mL}$, respectively. A correlation was found between the peripheral eosinophil count and the level of serum IgG4 ($r = 0.34$, $p < .01$). However, no correlation was found between the level of serum IgG4 and the level of serum IgE, nor the peripheral eosinophil count and the level of serum IgE (Figure 1). We were able to perform the screening for IgEs against specific allergens in 257 cases with IgG4-DS; 163 (63.4%) of these cases had IgEs against some specific allergens, including: birch pollen in 66 cases (40.5%); cedar pollen in 26 cases (16.1%); moth scales in 83 cases (51.2%); *D. pteronyssinus* in 91 cases (56.2%); Poaceae pollens in 52 cases (32.1%); weed pollens in 33 cases (20.4%); food allergens in 28 cases (17.3%); grain allergens in 22 cases (13.6%); animal epithelia in 25 cases (15.4%); and mold allergens in 35 cases (21.6%).

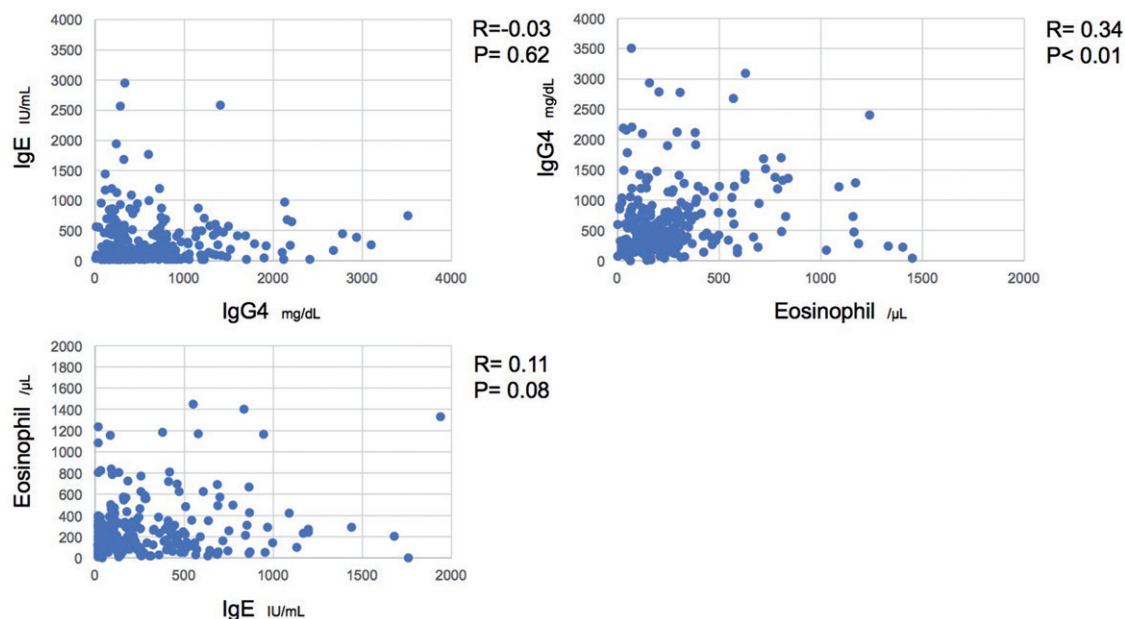


Figure 1. The correlations between the laboratory data. There was a correlation between the peripheral eosinophil counts and the levels of serum IgG4.

Table 1. Clinical characteristics of the cases with IgG4-DS with or without IgEs against specific allergens.

	Positive group	Negative group	
N (Male:Female)	163 (86:77)	94 (48:46)	n.s.
Age at diagnosis (y.o.)	60.20 ± 11.42	64.55 ± 11.01	$p < .005$
Prevalence of allergic disorders (%)	82.82	31.91	$p < .001$
Mean numbers of OOI	0.93	1.11	n.s.
Peripheral eosinophils count (/mL)	289.75 ± 475.60	271.84 ± 307.38	n.s.
Serum IgG (mg/dL)	2112.50 ± 1221.81	2165.36 ± 1049.45	n.s.
Serum IgG4 (mg/dL)	606.28 ± 568.74	697.62 ± 602.30	n.s.
Serum IgE (IU/mL)	612.66 ± 1604.96	201.18 ± 285.91	$p < .05$

OOI: other organ involvements.

Analysis of the clinical features of the IgG4-DS cases revealed that the age at the time of diagnosis was higher in the negative group than in the positive group. There was no significant difference between the two groups in the peripheral eosinophil count or the level of serum IgG or IgG4. Only the level of serum IgE was significantly higher in the positive group than in the negative group (Table 1).

IgG4 has been proposed to act as a blocking antibody against IgE, and the levels of serum IgG4 increases in immunologic desensitization [4]. We previously reported that the levels of serum IgG4 transiently increased when some cases with IgG4-DS were exposed to seasonal allergens [5]. These findings suggest that IgG4-RD and allergic inflammation are closely associated. However, Saeki recently analyzed the clinical symptoms and laboratory data of cases with IgG4-RD with or without allergic conditions, and reported results: the mean age at the time of diagnosis of IgG4-RD in the cases without allergic symptoms was significantly higher than that in the cases with allergic symptoms; among the IgG4-RD cases without allergic symptoms, males were more predominant; and there was no significant difference in the laboratory data, including the peripheral eosinophil counts and the level of serum IgG4 or IgE, between the two groups [6]. Our results were similar: the mean age at the time of diagnosis of IgG4-DS was significantly higher in

the cases without IgEs against specific allergens than in the cases with IgEs against specific allergens, and we did not find a significant difference between the peripheral eosinophil count and the levels of serum IgG4 and IgE. There was no tendency to be consolidated into specific allergens even in the positive group for IgEs for allergens. There was no difference between usual allergic rhinitis [7] and IgG4-DS in allergen screening. There was no correlation between the presence or the absence of other organ involvement, and the numbers of them and with/without allergen-specific IgE. Although allergic conditions may modify the pathogenesis of IgG4-DS, the existence of an allergic disease or IgEs against specific allergens was not important in the pathological mechanism of IgG4-DS. In other words, IgG4-DS occurs regardless of the presence or the absence of complicated allergic disorders and IgE. This raises the important question: what are the true players in IgG4-DS?

Recently, the relationship between autoimmune diseases and immune senescence is discussed [8]. Caruso et al. analyzed the cytokine production pathway in the elderly. Mitogen-stimulated cultures of mononuclear cells (MNC) from human beings were assessed for cytokine-producing capacity. A significant decrease in IFN γ and IL-2 production by MNC cultures from elderly individuals was observed. No significant difference was instead observed between cultures

from elderly individuals and those from young ones as regards IL-4, IL-5, and IL-6 production. Mitogen or antigen-stimulated cultures of MNC from aged mice also displayed a significant decrease in IFN γ and IL-2 production as well as TNF β . Instead IL-4 and IL-5 production significantly increased in these cultures [9]. Our results showed that there was no significance in the peripheral counts of eosinophils, the serum levels of IgG and IgG4 between the patients with and without antigen-specific IgE. It was suggested that IL-4, IL-5, and IL-6 was produced in the antigen-specific IgE negative group, affected by some factors just like the positive group. As we described above, there was a significant difference in the age at the time of diagnosis of IgG4-DS between the groups with and without IgEs against specific allergens. So we are considering immune senescence as one of factors. The influence of immune senescence on this disorder remains unclear. A sufficient number of Th2 cells is required for the development of allergic disorders, and the conditions required for inducing allergic inflammation may be fulfilled even in young populations. In addition, there is a shift to Th2 cytokine production [10], and the conditions for disease onset may be fulfilled even in elderly populations without allergic disorders. Further studies are needed to determine how much allergic conditions and immune senescence affect the pathogenesis of IgG4-RD.

Conflict of interest

None.

Patient consent obtained

Study participants provided written informed consent for inclusion in this study.

Ethics approval

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All study-related recruitment and procedures were approved by the Sapporo Medical University Hospital Institutional Review Board.

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