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Analysis of factors influencing sensitization of Japanese cedar pollen in asymptomatic subjects

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ABSTRACT

Objective: Japanese cedar pollinosis is increasing rapidly in Japan. Although analysis has been made concerning the factors influencing the development of the cedar pollinosis, analysis concerning the risk factors influencing the sensitization in asymptomatic subjects has not been done.
Methods: Risk factors for sensitization to Japanese cedar pollen were analyzed among 73 subjects (32 men and 41 women) who do not develop symptoms of pollinosis at the time of Japanese cedar pollen scattering. Their ages ranged from 18 to 60 years with the mean of 34.1 years. Possible factors influencing sensitization were investigated through a written questionnaire and doctors' questioning. Japanese cedar-specific IgE titers and *Dermatophagoides pteronyssinus*-specific IgE titers in the serum were measured by CAP-FEIA (fluorescent enzyme immunoassay).
Results: Of the 73 subjects, 26 were sensitized to the Japanese cedar pollen, for a 36% sensitization rate. Among the eleven factors examined, only one factor was shown to significantly influence the sensitization rate to Japanese cedar pollen. It was sensitization to house dust mites (56.5% vs. 26.0% χ^2 value = 6.27, $p = 0.012$). The sensitization rate to the pollen did not correlate to the presence of other allergic diseases, history of rhinosinusitis, family history of Japanese cedar pollinosis, food preference, presence or absence of cedar trees in the surroundings, present living circumstances, childhood circumstances, age, sex, or smoking habits. We calculated odds ratios in order to estimate how much those factors influence the sensitization to Japanese cedar pollen. Significantly high odds ratio for sensitization to house dust mite (6.63; 95% confidence interval (CI): 1.76–32.2) was found.
Conclusion: The present study indicates that sensitization to the pollen in the subjects without pollinosis is influenced by sensitization to house dust mite.

1. Introduction

Japanese cedar pollinosis was first described by Saito [1] in 1964. Since then, the prevalence of pollinosis has been increasing. The prevalence of seasonal allergic rhinitis has increased over the past 10 years due to increased pollen exposure [2]. Sakashita et al. [3] found that the prevalence of allergic rhinitis in adults between 20 and 49 years of age has increased by nearly 10% during the last 10 years. The prevalence rate of pollinosis is 26.5% among Japanese people [4].

It has been reported that genetic factors [5–7], young age [2], fish intake [8], family history of pollinosis [3], and residence along a main street [3] influence the development of Japanese cedar pollinosis.

For people to develop pollinosis, they need to be sensitized. However, it is not clearly known what factors are influencing the sensitization to Japanese cedar pollen in patients without pollinosis. To decrease the prevalence of Japanese cedar pollinosis, it is very important to analyze what factors are playing roles in the sensitization in asymptomatic subjects. The purpose of this study is to elucidate the factors influencing the sensitization to Japanese cedar pollen.

2. Materials and methods

2.1. Study subjects

The subjects were 73 people (32 men and 41 women) who do not develop symptoms of pollinosis at the time of Japanese cedar pollen scattering. Those who have perennial allergic symptoms were not included in the subjects. Their ages ranged from 18 to 60 years with a mean age of 34.1 years. The age distribution is shown

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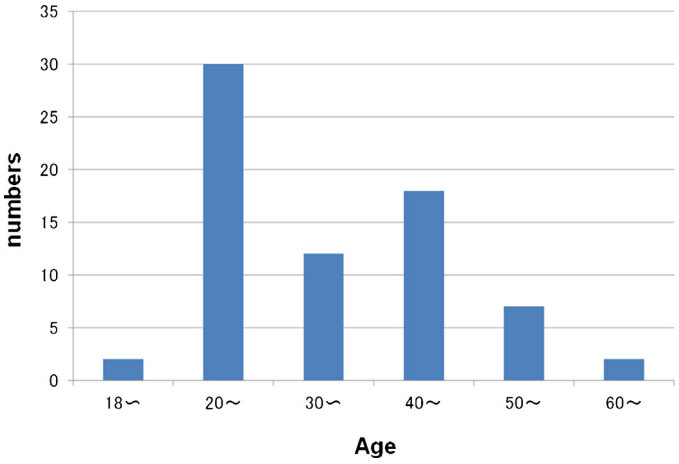

Fig. 1. Age distribution of the subjects examined.

in Fig. 1. In order to recruit subjects for the present study, we mounted posters and utilized Internet. We did not recruited subjects from patients in our outpatient clinic. Written informed consent was obtained from the subjects before their participation in the study. This study was approved by Mie University School of Medicine Ethical Committee (No. 2282).

2.2. Questionnaire

The following items were investigated by a written questionnaire and doctors' questioning.

- Past history of rhinosinusitis.
- Presence of other allergic diseases (allergic conjunctivitis, urticaria, drug allergy, food allergy, atopic dermatitis, bronchial asthma): information of the past history alone of other allergic diseases was not included.
- Family history of Japanese cedar pollinosis (siblings, parents, grandparents, children): presence of Japanese cedar pollinosis was defined as development of typical symptoms of nose and eyes at the time of cedar pollen scattering.
- Smoking habit: ex-smoking was not included.
- Food preference (whether they prefer meat or fish).
- Environment of the present residence (urban or rural).
- Environment of their childhood (urban or rural).

2.3. Laboratory analysis

Japanese cedar-specific IgE titers and *Dermatophagoides pteronyssinus*-specific IgE titers in the serum were measured by CAP-FEIA (fluorescent enzyme immunoassay). We examined the two IgE titers because cedar pollen and mites were the predominant allergen sources among seven aeroallergens in the Japanese population [3]. Sensitization was defined as serum allergen specific IgE titers with 0.70 UA/mL and over (IgE CAP score ≥ 2).

2.4. Statistical analysis

A chi-square test was used to compare sensitization rates to Japanese cedar pollen according to each factors examined in univariate analysis. The outcome variable of this study was sensitization to cedar pollen. Multivariate regression logistic test was used to assess putative relationship between the factors of interest and sensitization to cedar pollen. The factors of interest were sensitization to house dust mite, presence of other allergic diseases, age (less than 40 years vs. 40 years and over), family history of cedar pollinosis, history of rhinosinusitis, smoking habit, preference of eating (meat vs. fish), environment lived in childhood (in urban vs. in rural), environment currently living (in urban vs. in rural), exposure to cedar pollen (being surrounded by many cedar trees vs. none), and sex (female vs. male). The magnitude of the relation between these factors and sensitization to cedar pollen was expressed by odds ratios with 95% confidence intervals. To compare the means of Japanese cedar-specific IgE titers and scores between subjects sensitized to house dust mite, Student's *t*-test and Mann–Whitney's *U*-test were used respectively. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed with JMP version 5.1.1 (SAS Institute Inc., USA).

2.5. Determination of sample size

Prevalence of sensitization to house dust mite was defined as primary factor of interest. According to previous surveys assessed sensitization rate to various airborne antigens in certain populations in Japan, prevalence of sensitization to house dust mite in subjects who were not sensitized to Japanese cedar pollen ('controls') was estimated at about 20%. In this study, whether a subject was sensitized to cedar pollen could not be identified until titer of cedar pollen-specific IgE was measured. We assumed the ratio of subjects not sensitized ('controls') to subjects sensitized to cedar pollen ('cases') to be 2. We also assumed prevalence of sensitization to house dust mite in subjects not sensitized to cedar pollen ('controls') to be 20% and odds ratio of 4 for prevalence of sensitization to house dust mite in subjects sensitized to cedar pollen ('cases'). According to these assumptions, we calculated the sample size with 80% power of obtaining a significant difference at the 5% significance level. Required numbers of subjects sensitized to cedar pollen ('cases') and subjects not sensitized ('control') were 26 and 56, respectively. However, despite of maximum effort, a total of 73 subjects finally participated in this study.

3. Results

Of the 73 subjects, 26 were sensitized to Japanese cedar pollen (Fig. 2). The sensitization rate was 36%. The IgE titers in response to Japanese cedar pollen ranged from 0.34 to 84.7 UA/mL and the scores ranged from 0 to 5 (Fig. 2). The mean IgE score of this population was 1.12 and that of the sensitized subjects was 2.8.

Among the eleven factors examined, only one factor was shown to significantly influence the sensitization rate to Japanese cedar pollen. It was sensitization to house dust mites (Table 1).

The subjects who were sensitized to house dust mites had significantly higher sensitization to the Japanese cedar pollen than

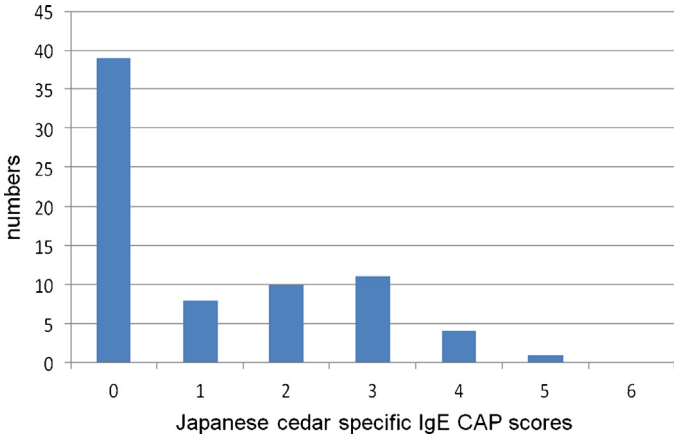

Fig. 2. Distribution of Japanese cedar-specific IgE CAP scores.

Table 1
Comparison of sensitization rates to pollen according to various factors.

Factors	Sensitization rate	χ^2 value	*p*-Value
Sensitized to house dust mite vs. unsensitized	56.5% vs. 26.0%	6.27	0.012
Other allergic diseases vs. none	52.4% vs. 28.9%	3.53	0.060
Age less than 40 years vs. 40 years and over	43.5% vs. 22.2%	3.48	0.062
Family history of cedar pollinosis vs. none	43.2% vs. 24.1%	2.84	0.092
History of rhinosinusitis vs. none	20.0% vs. 36.8%	0.622	0.430
Smoking habit vs. none	30.0% vs. 36.5%	0.163	0.684
Preference of eating (meat vs. fish)	39.1% vs. 29.6%	0.680	0.410
Lived in the city in childhood vs. in the country	29.4% vs. 37.5%	0.380	0.538
Now living in the city vs. in the country	40.0% vs. 34.0%	0.229	0.633
Surrounded by many cedar trees vs. none	42.8% vs. 32.8%	0.496	0.481
Sex (female vs. male)	36.6% vs. 34.4%	0.038	0.845

those without sensitization to house dust mites (56.5% vs. 26.0% χ^2 value = 6.27, $p = 0.012$). Those who were sensitized to house dust mite had significantly higher Japanese cedar pollen-specific IgE scores (Fig. 3) and significantly higher Japanese cedar pollen specific IgE titers (Fig. 4).

The sensitization rate did not correlate to presence of other allergic diseases, history of rhinosinusitis, family history of Japanese cedar pollinosis, food preference, presence of cedar trees in the surroundings, present living circumstances, childhood living circumstances, age, sex, or smoking habits (Table 1). We also examined the relationship between pollinosis and the family history of Japanese cedar pollinosis of siblings, parents, grandparents, and offspring, but no relationship was found.

We calculated odds ratios to estimate how much those factors influence the sensitization to Japanese cedar pollen using multivariate regression logistic test (Table 2). Significantly high odds ratio for sensitization to house dust mite (6.63; 95% confidence interval (CI): 1.76–32.2) was found. Odds ratios were high for association with preference of eating meat rather than fish (3.59; 95% CI: 0.93–17.8), age less than 40 years (2.58; 95% CI: 0.69–10.8), presence of other allergic diseases (2.37; 95% CI: 0.77–9.59), and family history of cedar pollinosis (2.09; 95% CI: 0.60–7.92), but they were not significant (Table 2).

4. Discussion

To the best of our knowledge, this is the first report on the analysis of factors influencing the sensitization rate to Japanese cedar pollen in asymptomatic subjects. The mean IgE score of this sensitized population was 2.8. This value is significantly lower than those of patients with pollinosis alone and those with pollinosis and who are allergic to house dust mites (data not shown). It is known that the percentage of development of pollinosis symptoms depends on the specific IgE titers [9]. Concerning the relationship between specific IgE titers and classes, Class 0 (0.34 UA/ml and under) and Class 1 (0.35–0.69) are considered to be negative (not sensitized). Classes 2–6 (0.79 UA/ml and over) are considered to be positive (sensitized). According to Ohtsuka [9], the rate of development of symptoms increases with increasing classes. For example, the percentage of developing symptoms are 100% in Class 6, 85% in Class 5, 50% in Class 4, 38% in Class 3, 13% in Class 2, 3% in Class 1, and 3% in Class 0.

The present study indicates that sensitization to the pollen of the subjects without pollinosis is influenced by their sensitization to house dust mite, not by their family history or their residential environments.

Among the 26 people sensitized to the pollen, 13 were also sensitized to house dust mites. Since it is clearly demonstrated that most of patients with Japanese cedar pollinosis were allergic to house dust mite in children [10], we have excluded those who had perennial allergic symptoms from the subjects in the present study. Although the reason why house dust mite sensitization alone leads to pollen sensitization is not clear, the result might simply show that they are predisposed to producing IgE antibodies to various antigens.

Although statistically not significant, the sensitization rate to cedar was higher in a younger population. Yonekura et al. [2] examined the natural history of seasonal allergic rhinitis and found that the sensitization rates to cedar pollen decreased with age in the same subject groups over 10 years.

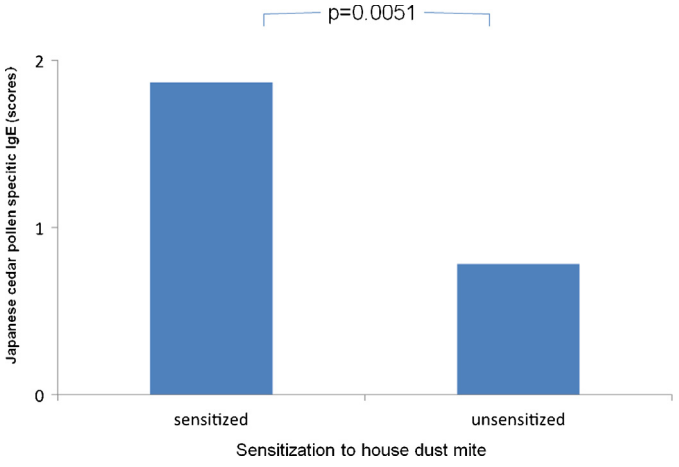

Fig. 3. Subjects sensitized to house dust mite had significantly higher Japanese cedar pollen-specific IgE scores.

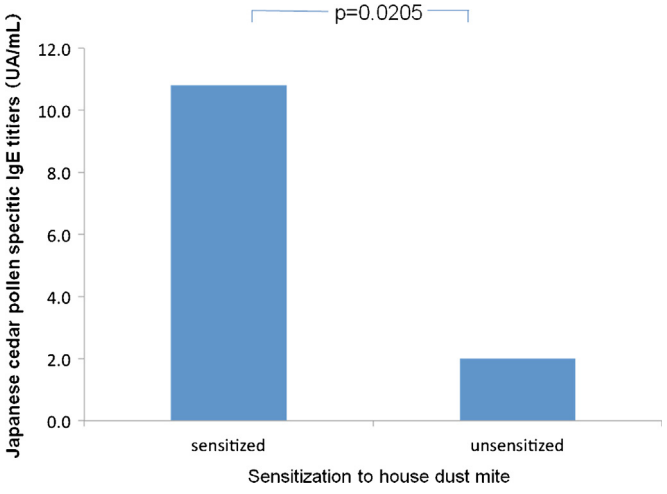

Fig. 4. Subjects sensitized to house dust mite had significantly higher Japanese cedar pollen-specific IgE titers.

Table 2
Risk factors influencing sensitization to Japanese cedar pollen.

Factors	Odds ratios	95% confidence interval	*p*-Value
Sensitized to house dust mite	6.63	1.76–32.2	0.009
Preference of eating meat (rather than fish)	3.59	0.93–17.8	0.082
Age less than 40 years	2.58	0.69–10.8	0.258
Other allergic diseases	2.37	0.77–9.59	0.124
Family history of cedar pollinosis	2.09	0.60–7.92	0.258
Surrounded by many cedar trees	1.59	0.33–7.44	0.551
History of rhinosinusitis	0.80	0.09–6.24	0.835
Lived in the city in childhood	0.64	0.14–2.62	0.541
Smoking habit	0.64	0.10–3.57	0.626
Sex (female)	0.57	0.15–2.06	0.399
Now living in the city	0.55	0.14–1.99	0.383

Although statistically not significant, the sensitization rate to the pollen was higher in the presence of other allergic diseases. Comparing patients with pollinosis to control subjects, Ozasa et al. [11] reported that significantly high odds ratios for a past history of allergic disease [8.80; 95% confidence interval (CI); 3.49–22.2], atopic dermatitis (9.00; 95% CI: 1.14–71.0), and a sibling history of allergic disease (3.25; 95% CI: 1.06–9.97) were found. The mechanism by which other allergic diseases increase the sensitization to pollen is not clear. One possibility is that other allergic diseases increase the interleukin-4 concentration in the blood, which increases the nasal permeability to the pollen [12]. Concerning the atopic dermatitis, it is reported that a null mutation of filaggrin increases the prevalence of both atopic dermatitis and allergic rhinitis [13].

The fact that a family history of pollinosis did not increase the sensitization rate to pollen was somewhat surprising. There are both positive and negative data concerning the relationship between a family history of pollinosis and the development of pollinosis. Ozasa et al. failed to demonstrate the association between the pollinosis of parents and siblings and the pollinosis of the examined subjects [11]. Conversely, Sakurai et al. [3] reported an increased prevalence of pollinosis with a family history of pollinosis.

Many reports concerning the association of pollinosis and gene polymorphisms suggest that Japanese cedar pollinosis may be inherited. Those genes include eosinophil peroxidase and interleukin-4 receptor alpha-chain [5], ADAM metallopeptidase domain 33 [6], and matrix metallopeptidase-9 [7]. However, such an inheritance might be a very weak factor compared with nongenetic factors.

Smoking habit showed no statistically significant relationship. According to Nagata et al. [14], when compared with those who had never smoked, current smokers at baseline were at a significantly decreased risk for cedar pollinosis after controlling for covariates in men (hazard ratio [HR]: 0.64; 95% CI: 0.50–0.83) as well as in women (HR: 0.64; 95% CI: 0.47–0.88). Ozasa et al. [11] reported that the odds ratio for passive smoking from 7 to 15 years of age as a result of the father's smoking habit (0.38; 95% CI: 0.17–0.86) was also significantly low. According to Kurosawa et al. [15], passive smoking was related to a significantly lower prevalence of Japanese cedar pollinosis (adjusted odds ratio: 0.81; 95% CI: 0.74–0.88). The reason why smoking or passive smoking is related to a lower prevalence of Japanese cedar pollinosis is currently unknown. Smoking was suggested to increase the level of antigen-specific IgE in serum [16]. However, smoking and passive smoking might have other effects of decreasing sensitization to Japanese cedar pollen and decreasing the development of cedar pollinosis.

Our study has limitations. First, the number of subjects was small. The sample size was determined by assuming sensitization to house dust mite as primary factor of interest. This study demonstrated that sensitization to house dust mite is an influencing factor in sensitization to Japanese cedar pollen, however the remains of the factors were not demonstrated to be significant. Some of non-significant factors might be true negative, or some might be false negative due to type II error because of the small sample size. Larger sample sizes are required to reduce type II error, enabling detect factors with slight differences. Second, the subjects' population lacked accurate representation of Japan's current population. This might result from small sample size and recruitment bias of subjects. According to the population estimates published by Ministry of Internal Affairs and Communications (http://www.stat.go.jp/english/data), the population aged between 18 and 60 years accounts for 52.5% of the population of Japan in 2011. Furthermore, in this study, subjects aged 20–29 years account for 41.1% of all the subjects, 30–39 years for 16.4%, 40–49 years for 24.7%, and 50–59 year for 9.6%, indicating different distribution pattern between the subjects of the study and age-matched Japan's current population. This difference reduces generalizability of this study.

In conclusion, the present study has shown that the sensitization of subjects without pollinosis is influenced by their sensitization to house dust mite, but not by family history or their environment. Further studies in larger populations are necessary.

Conflict of interest

None.

Acknowledgements

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