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ORIGINAL ARTICLE

Continuous 6-Year Follow-Up Study of Sensitization to Japanese Cedar Pollen and Onset in Schoolchildren

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ABSTRACT

Background: Intra individual longitudinal data has been lacking for IgE-mediated seasonal allergic rhinitis (SAR), especially in young children. Little is known about the development and natural course of SAR in terms of prevalence and incidence rates in schoolchildren.

Methods: In May or June each year from 1994 to 2007, schoolchildren were assessed for serum Japanese cedar pollen (JCP)-IgE and house dust mite (HDM)-IgE levels, and surveyed regarding nasal symptoms.

Results: Among the 220 children initially assessed in the first grade, 69 (31.4%) were already sensitized to JCP at first grade and 119 (54.1%) did not develop JCP sensitivity during the 6-year study at all. In the first grade children who were HDM-sensitized but JCP non-sensitized, JCP-IgE level was significantly elevated compared to the JCP and HDM non-sensitized group. This seems to indicate that HDM sensitization was very strongly associated with JCP sensitization.

Conclusions: Elevated serum IgE is a consequence of specific sensitization to HDM and HDM sensitization appeared to develop prior to the start of primary school which distinguishes HDM sensitization from JCP sensitization.

KEY WORDS

allergic sensitization, children, epidemiology, Japanese cedar pollinosis, serum IgE antibody

INTRODUCTION

Allergic diseases are increasing worldwide and Japanese cedar pollinosis (JCPS) is an important allergic rhinitis in Japan during spring. The prevalence of JCPS is linked to the seasons and the amount of pollen dispersed in the environment. The amount of dispersed Japanese cedar pollen (JCP) has increased in Japan since the 1980s. In addition, several environmental factors that may affect allergic sensitization have changed in Japan in recent decades.[1-5]

The positive rate of JCP-IgE was increased in school children[6] and the prevalence rate of JCP was 17.1% among junior high school students during 1992 to 1994.[7] However, intra individual longitudinal data has been lacking for IgE-mediated seasonal allergic rhinitis (SAR), especially in large samples of subjects and in young children. Little is known about the development and natural course of SAR in terms of prevalence and incidence rates in school-age children. Studies that included a follow-up of the same children over several years are rarely performed.[8-10]

The present study involved a continuous 6-year follow-up observation of schoolchildren in order to identify factors that may prevent sensitization to JCP and development of JCPS.

METHODS

STUDY SUBJECTS

This study examined children from primary and junior-high schools in a rural town in the southern Kyoto Prefecture of Japan; most children in the town attended those schools. First-grade children were enrolled and examined every year from 1994 to 2007.

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SYMPTOM QUESTIONNAIRES

The children's parents were asked about their child's health conditions and environments using a self-administered questionnaire at each visit over the 6 years of the study. Symptoms of allergic rhinitis were defined as the presence of the following criteria: sneezing, nasal discharge, nasal obstruction, itching of nasal mucosa, itching of conjunctiva, watering eyes, and eye irritation. The children's parents were also asked whether symptoms lasted 3 weeks or longer. Symptoms that lasted longer than 3 weeks were definite symptoms, and 3 weeks or less were suspicious symptoms.

MEASUREMENT OF SERUM LEVELS OF TOTAL AND SPECIFIC IgE

We also analyzed the relationship between total and allergen-specific IgE to confirm the effect of antigen on the production of total IgE. Additionally, we examined the effect of HDM sensitization occurring prior to JCP sensitization during primary school.

Serum levels of allergen-nonspecific and allergen-specific IgE antibodies against JCP and house dust mite (HDM) were measured in May or June every year using the Pharmacia CAP System at SRL, Inc., (Tokyo, Japan) from 1994 to 2001, and at the Osaka Medical College from 2002 to 2007. JCP sensitization was examined each year to confirm the rate of sensitization to JCP and its onset during this 6-year follow-up study. Serum levels of allergen-nonspecific and -specific IgE were measured to evaluate the effect of HDM exposure for the development JCPS during the primary school years. Children were defined as sensitized if allergen-specific IgE levels were ≥0.7 IU/ml [CAP radioallergosorbent test (RAST), class 2].

DIAGNOSIS OF JCPS

Reported seasonal symptoms had to be associated with seasonal sensitization to JCP in order to be diagnosed as having JCPS. Therefore, subjects positive for JCP-IgE with JCPS symptoms were diagnosed as having JCPS. The relationship between the presence of JCPS and the degree of allergen-specific IgE CAP RAST Score was examined.

The childrens' parents were informed of the purpose of the survey and blood examination, and their written consent was obtained. These procedures were in accordance with the principles embodied in the Declaration of Helsinki of 1995. This study was approved by the Ethical Board of Kyoto Prefectural University of Medicine and Osaka Medical College.

STATISTICAL ANALYSIS

The Kruskal-Wallis method was employed to test the increments of symptom prevalence according to the CAP RAST score. In addition, this method was also adopted for analyzing the numbers of children with each CAP RAST score as they advanced through grades in school, and for determining significant differences in symptom prevalence between grades.

At the initial visit in the first grade, the children were divided into groups according to their JCP and HDM sensitization status (+ or -) to create 4 groups: JCP+/HDM+, JCP-/HDM+, JCP-/HDM+, and JCP-/HDM-. This group designation did not change throughout the study. Then serum levels of specific IgE in the HDM+ groups were compared to the HDM- groups at every grade by the Mann-Whitney test, and the Fisher's exact test was used to observe increased susceptibility to cedar pollinosis in the children who were positive for HDM in the first grade.

RESULTS

SUBJECTS

Two-hundred twenty school children entered this examination every year from first through sixth grade. There were no children who dropped-out of the study. There were 108 (49.1%) boys and 112 (50.9%) girls. Sixty-nine (31.4%) children were positive for JCP IgE (≥0.70 IU/ml) in the first grade, 32 (14.5%) developed JCP sensitivity, and 119 (54.1%) did not become sensitive to JCP during the 6-year study (Fig. 1).

RELATIONSHIP BETWEEN CAP RAST SCORES AND SYMPTOM QUESTIONNAIRE RESULTS

There was a high prevalence of children who were positive to JCP (Fig. 2). According to the questionnaire, 38% in the CAP-score 0 group had definite and suspicious symptoms. The prevalence of symptoms in the CAP score 0 group tended to increase as the children got older (data not shown). The prevalence of symptoms at each JCP CAP RAST score is shown in Figure 2. A significant effect was found on the prevalence of JCP symptomatic children by CAP RAST scores (Chi square test $p < 0.001$).

SERUM LEVELS OF SPECIFIC IgE

The number of children in each grade who were positive for specific IgE antibodies to JCP is shown in Figure 3. The number of children positive for JCP-IgE (CAP RAST ≥2) increases with grade. HDM-specific IgE antibody levels were measured similarly to JCP-specific IgE antibody levels, but HDM-specific IgE was not correlated with school grade (data not shown).

PREVALENCE OF JCP SYMPTOMS

The prevalence of symptoms at each grade is shown in Figure 4 and there was no difference in the prevalence of JCP-symptomatic children between grades. Thirty percent of the children had definite symptoms in the first grade compared to 40% of the children in sixth grade. As the children got older, their tendency to have definite symptoms did not increase. In our

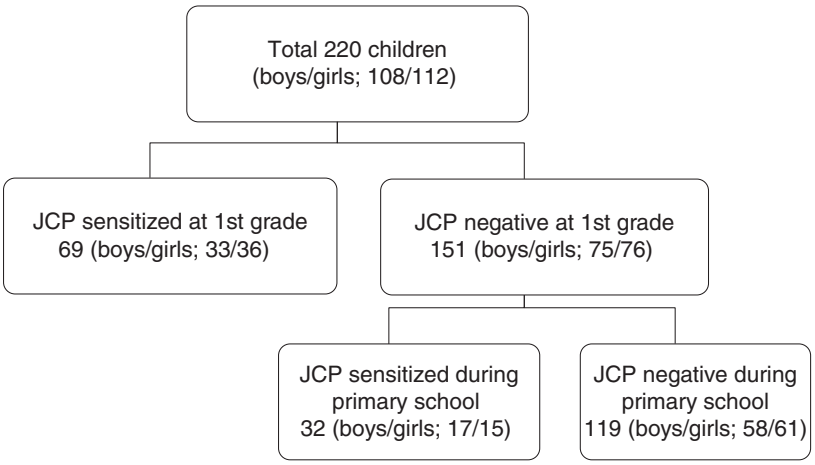

Fig. 1 A total of 220 children were examined repeatedly every year from first to sixth grade. Sixty-nine children (31.4%) were already sensitized to Japanese cedar pollen (JCP) in the first grade, 32 (14.5%) became sensitized to JCP, and 119 (54.1%) were not sensitized to JCP during the 6-year study at all.

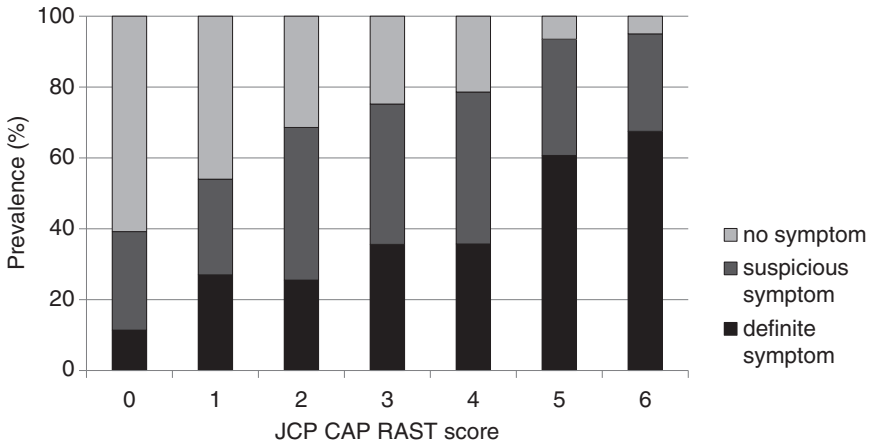

Fig. 2 Relationship between Japanese cedar pollen sensitization and Japanese cedar pollinosis (JCPS) prevalence. The x-axis demonstrates the CAP-RAST score and the y-axis is the prevalence of children having symptoms of JCPS.

study, JCPS (symptoms and sensitization) developed in 15.8% of the school children and the questionnaire identified 22.0% of subjects as having symptoms suggestive of JCPS.

RELATIONSHIP BETWEEN JCP AND HDM STATUS

The subjects were divided into four groups in the first grade as defined in the Statistical analysis section. The subjects remained in their initial groups as they moved through grades. The JCP-/HDM+ group tended to show more of an increase significantly in JCP-IgE as they got older compared to the JCP-/HDM- group (Fig. 5a). HDM status (+ or -) did not affect the increase of JCP-IgE in the JCP+ groups (Fig. 5b).

THE INFLUENCE OF HDM SENSITIZATION ON JCP SENSITIZATION

We analyzed whether prior sensitization to HDM (HDM+) was closely associated with the development of JCP sensitization during primary school. Of the 16 children who were HDM+ but JCP- in the first grade, 9 of them (56%) developed JCP sensitivity sometime over the next 6 years. In contrast, JCP sensitization developed in only 23 (15%) of the 135 children who were HDM- before school age. HDM+ status had a statistically significant effect on the development of JCP sensitization after the 2nd grade (Fisher's exact probability test $p = 0.001$) (Fig. 6).

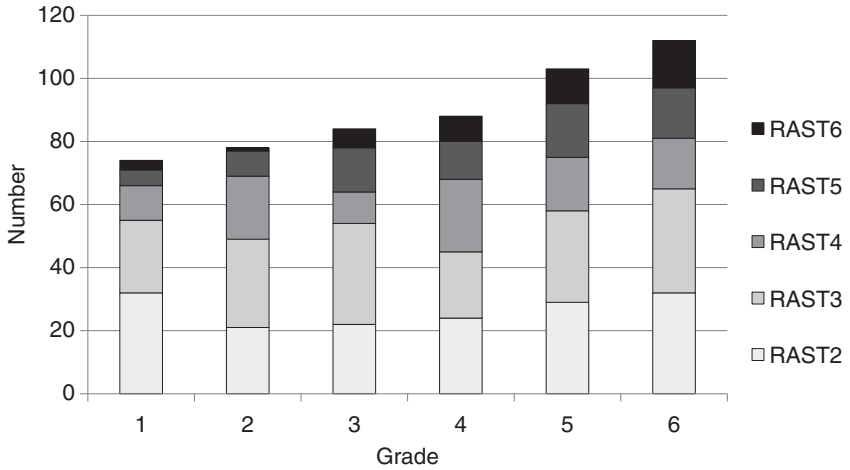

Fig. 3 Relationship between grade and the number of children with JCPS symptoms. The x-axis shows the grade in school and the y-axis is the number of children with JCPS symptoms.

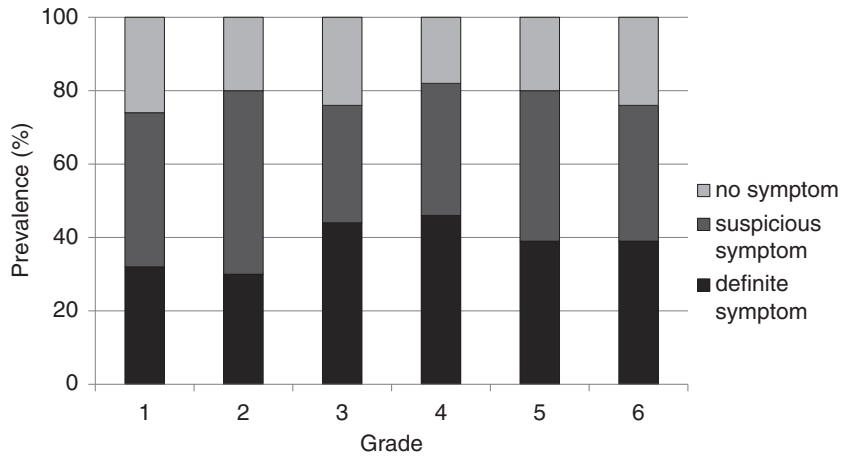

Fig. 4 Relationship between grade and prevalence of Japanese cedar pollinosis. The x-axis is the grade in school and the y-axis is the prevalence of Japanese cedar pollinosis.

DISCUSSION

We examined JCP sensitization and its onset in a continuous 6-year follow-up study of Japanese schoolchildren. This study showed that JCP sensitization may depend on prior sensitization to HDM and that HDM sensitization may be an important risk factor for developing JCPS.

The prevalence of JCP in the general population was estimated at 28.7% in metropolitan areas and 24.5% in urban areas in the year 2004. It has been reported that the prevalence of JCP increased 2.6-fold between 1980 and 2000.[1] Although the prevalence of JCPS is linked to the amount of dispersed pollen and the seasons, it has been suggested that a number of other environmental factors which have changed in Japan over recent decades may have also contributed to enhancing allergic sensitization, such as air pollution, urban lifestyle, and less exposure to a microbial environment.[1-5]

We described the development of seasonal allergic rhinitis (SAR) in a large cohort of primary students. In previous studies, results were mostly based on cross-sectional data in school-aged children[11-20] and sensitization status was not determined consecutively. Also, clinical studies on pollinosis have been performed employing placebo-controlled, double-blind, comparative and field techniques. Accurate evaluation is difficult because the scattering pollen count and climatic conditions vary between years and regions, leading to a bias in the results.[21-23] Environmental factors such as regional and climate factors,

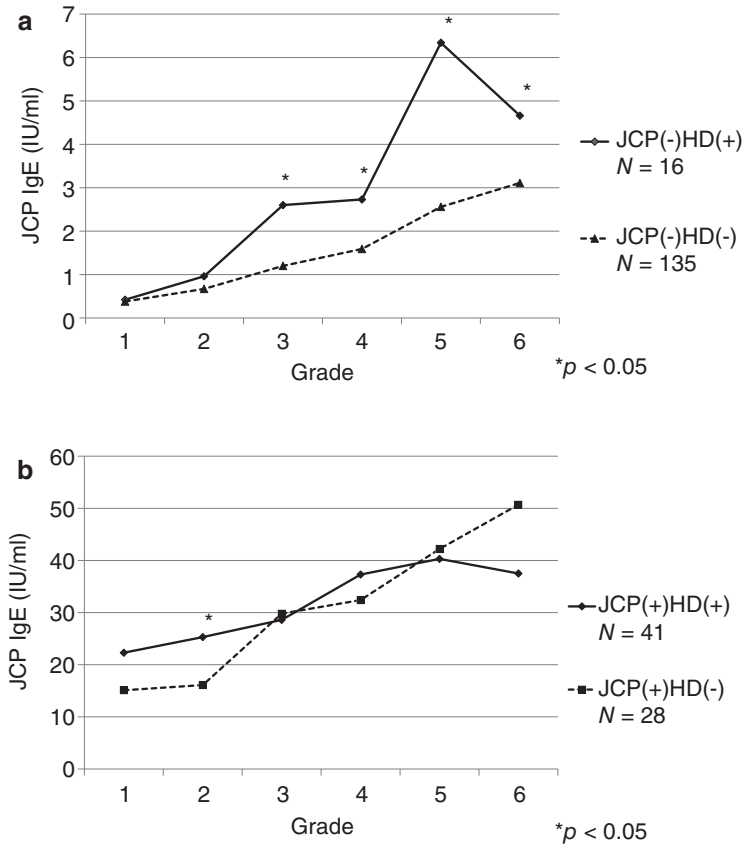

Fig. 5 Relationship between house dust mite (HDM) sensitization and Japanese cedar pollen (JCP) sensitization. The x-axis is the grade in school and the y-axis shows the level of JCP-specific IgE. **a**) JCP-/HDM+ versus JCP-/HDM, **b**) JCP+/HDM+ versus JCP+/HDM-.

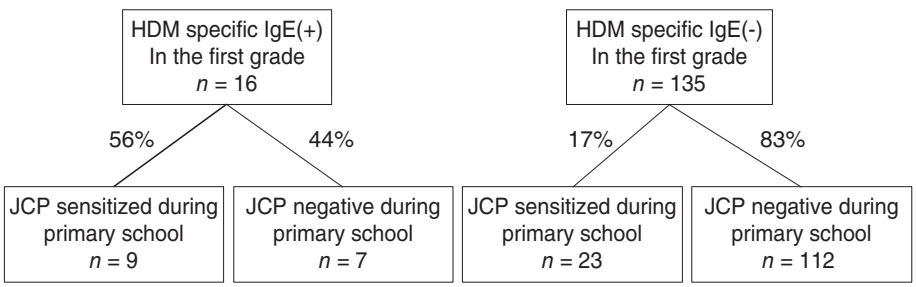

Fig. 6 The effect of HDM status on the development of JCP sensitization. Fisher's exact probability test was used to test for differences in the preceding HDM sensitization.

as well as family history, complications, and living habits, are thought to contribute to antigen sensitization. Our study was conducted in a rural town in southern Kyoto Prefecture, Japan, and most children in the town attended the same school. Under these conditions we were able to examine the same subjects over 6 years, in the same geographic area so that allergen exposure pattern and climatic conditions were the same for all the children. However, it is exceedingly difficult to conduct an epidemiological study that completely eliminates such environmental factors.

Infantile allergic disease has been described as the allergic march. It is believed to begin with atopic dermatitis accompanied by infantile asthma with subsequent progression to HDM-induced perennial allergic

rhinitis (PAR). SAR occurs from around primary school age onwards.[24] Despite the lack of definite evidence, a younger age of SAR onset has recently become a problem in Japan.[25] The JCP-specific IgE antibody levels of students in the JCP-/HDM- group gradually increased as children progressed through the school grades, but the change was not significant. In comparison, students in the JCP-/HDM+ group had significantly higher JCP-specific IgE antibody levels in the higher school grades.

These findings suggested that HDM sensitization may be an important risk factor for developing JCPS.

It is generally recognized that sensitization to any allergen is an important risk factor for developing allergic disease.[26] Our data indicated an important role for HDM in sensitization to JCP. A significantly higher prevalence of sensitization to JCP was observed in HD+JCP- group during primary school.

Because school children develop SAR with diverse symptoms, it is often difficult to make a diagnosis of SAR. Almost all studies investigating the prevalence of allergic sensitization use a skin prick test which is likely to be susceptible to variation and errors in measurement techniques.[27] IgE-mediated disease is usually defined by the presence of symptoms and by the presence of specific IgE. In this study, parents of the children were asked whether nasal symptoms, such as sneezing, nasal discharge, nasal obstruction, itching of nasal mucosa last for longer than 3 weeks in March or April of the surveyed year. Although previous reports on the prevalence of seasonal allergic nasal symptoms ranged from 4.4% to 42% in school-aged children and adolescents,[9,15] their reliability may be open to question. Moreover, although the prevalence rate of 38% in the CAP-score 0 group was very high, this high prevalence was thought to be shown because if any one of the seven symptoms on the questionnaire used in this study was present for even one day, it was judged to be a suspicious symptom. It is possible that the diagnosis of suspicious symptoms was inappropriate, and in the future it will probably be necessary to amend these criteria. The rates in our study cannot be compared with other findings because the others lack data on the prevalence and incidence of nasal symptoms and specific sensitization over a consecutive follow-up during the primary school years. Our findings suggest that the diagnosis of SAR in school children under different conditions may not be accurate.

A high proportion of children with definite symptoms were observed according to their CAP RAST score. The proportion of subjects with JCPS symptoms seems to be reflected by JCP-IgE levels. In the highly sensitized group (CAP RAST ≥5), the prevalence of JCPS was also related to the child's grade (Fig. 3). These results indicate that the high prevalence of JCPS reflects the high prevalence of elevated JCP-IgE antibody levels due to the accumulation of the pollen. It was anticipated that the prevalence rate would rise together with the elevation of JCP specific IgE antibodies as children progressed though the school grades, but the prevalence did not increase in our investigation.

In this study we did not look at whether or not students had received medical interventions or avoided antigen exposure. It may have been that an elevation in the prevalence rate was not seen because the frequency of medical intervention increased or students avoided antigens as they reached the higher grades of primary school.

In conclusion, elevated JCP-IgE is a consequence of specific sensitization to HDM that is the primary risk factor for JCPS. HDM sensitization appeared to develop prior to commencement of primary school, and this factor distinguished HDM sensitization from JCP sensitization.

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