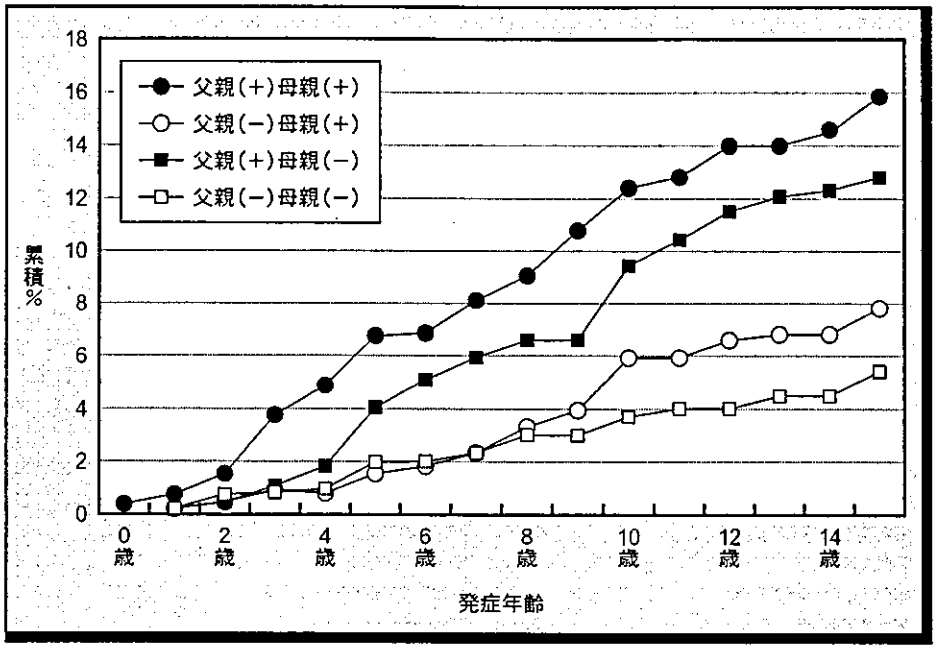

図2　アレルギー性鼻炎発症年齢（親と子の関係）－アレルギー性鼻炎305例中－
父親，母親がアレルギー性鼻炎がそれぞれある場合，ない場合におけるそれぞれの群の子どもの累積発症率を示す．父母ともアレルギーがある場合のアレルギー性鼻炎の発症が最も早い．

花粉症は見逃される傾向にあり，その子たちは抗原防御をしないため特異的IgE（immunoglobulin E）が徐々に増加する。このため成人になってからのQOL悪化につながってくると考えられる。以上からQOLが低下しない小児からの鼻アレルギー診療ガイドラインに沿った治療をする事がQOLの低下する成人への移行を抑制することが示唆される。

Ⅲ．長期予後を左右する治療について

薬物治療では，一般的に経口薬と点鼻薬を中心に小児に処方している。経口薬では，ケミカルメディエーター遊離抑制薬や第2世代抗ヒスタミン薬などのドライシロップタイプを主に用いている。薬剤の飲みやすさと，抗ヒスタミン薬服用による眠気の副作用の影響が少ないことを考慮して薬剤を選択する。また小児期に抗アレルギー薬を服用すると次のアレルギーに発展しないことが飯倉らによって証明されている[1]。経口ステロイド薬の処方は極力避けるべきと考えられ，ステロイドとしては点鼻薬を中心的に処方する。点鼻薬では患児によって好き嫌いが激しく，1度でも点鼻薬がいやになったらその後は決して服用しない場合も多い。患児がはじめて点鼻薬を服用するときは，小児に薬剤の使い方について具体的に説明して理解させることが重要である。成人用の点鼻薬服用により液だれする場合については注意が必要である。一般的に小児アレルギー性鼻炎の治療の目

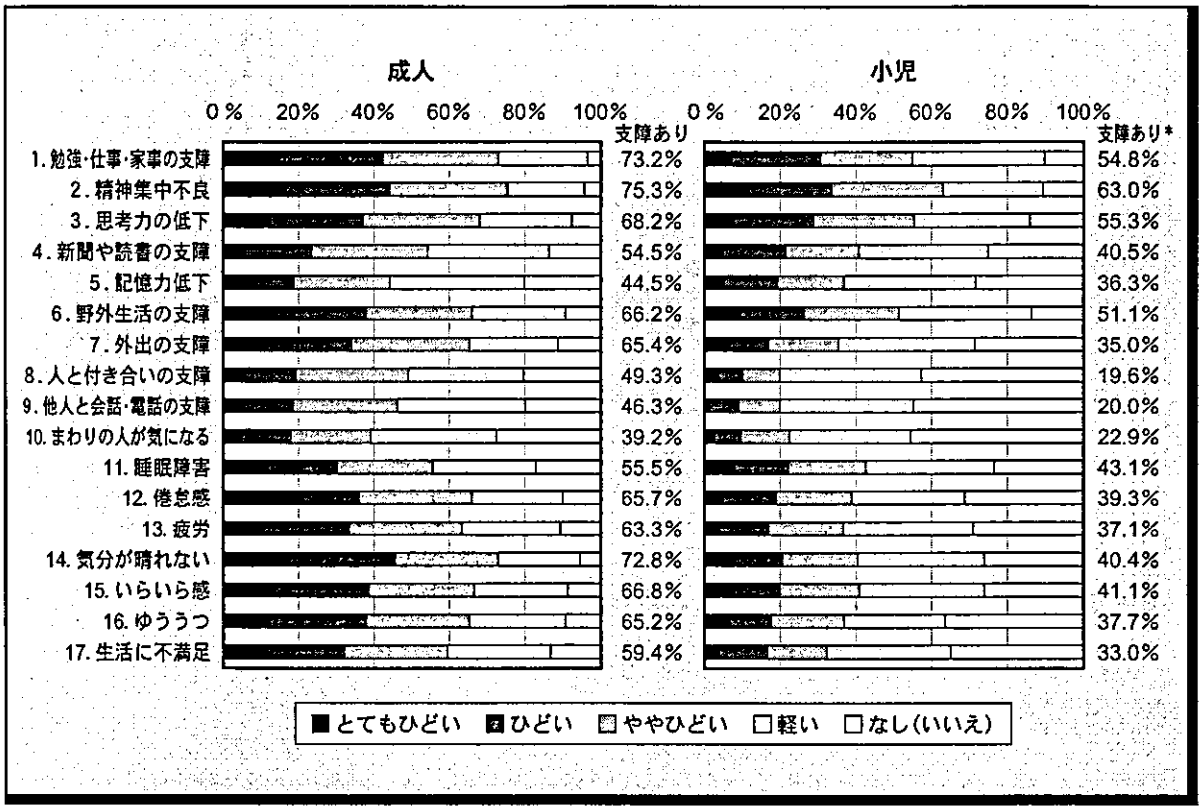

図3　アレルギー性鼻炎によるQOLへの影響
小児は成人と比較し，QOLの低下は少ないが，日常生活の領域ではほぼ同等に悪化する．

標はなるべく医師の手が離れる期間を多くすることであり，医師の手から離れられれば治療は成功と考えてよい。このときに重要なのは学校生活や，学業におけるQOLの低下はできる限り避けることであり，漫然とした薬物治療も避けなければならない。これらの観点から幼児～学童のスギ花粉症の場合を考えると現在一般的になりつつある初期治療はすべての症例に当てはまるとは考えにくい。前年度の症状が中等症以上で，生活に支障のあった症例が初期治療の適応となる。しかし小児特に幼児の場合，アレルギー性鼻炎(花粉症)の4大症状である「くしゃみ」,「鼻水」,「鼻づまり」,「目のかゆみ」のうち，はっきりと症状が分かるのはよく擦るため「目のかゆみ」のみである。くしゃみも外から見えるが，咳と区別が出来ないことがある。鼻水では重症度の決定に鼻をかむ回数が示されているが，幼児で鼻をかめる子供を見つけることは現在ではたやすいことではない。鼻づまりも通年性と合併しているような症例では細かい症状を言うことは出来ないであろう。このように幼児の場合には症状を訴える能力が少なく，保護者が注意して観察しなければならない。また前述のデータから両親がど

ちらかでもアレルギーを持っている場合のハイリスク児は十分観察し発症を早期に知らなければならない。ハイリスク児がもし発症した場合には花粉症の悪化を防ぐ意味でも初期治療の適応と考えてよいのかもしれない。

アレルギー性鼻炎(花粉症)の長期予後を最終的に最も左右するのは抗原回避・除去と考えられる。抗原の曝露量の増加はIgE産生の増加につながり，症状を悪化させる因子になることは自明の理であるが，エビデンスはほとんどない。ただ花粉症も年を追うごとに花粉量が同じであれば症状が悪化してゆくことを考えると患児に対する抗原の除去は必要と考えられる。これだけアレルギー疾患が増加するとハイリスク小児では発症前からも抗原回避除去を考える必要が将来的に出てくる可能性がある。

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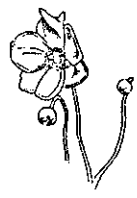

Clin Exp All Rev 2004; 4:31–34

Prevalence of Japanese cedar pollinosis in children aged under 15 years throughout Japan

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Summary
The prevalence of childhood allergic rhinitis is increasing steadily in Japan. Affected children are sensitized mainly by house dust mites; however, the prevalence of Japanese cedar pollinosis (JCP) in children is also on the rise. To ascertain the prevalence and current status of JCP in Japanese children, a retrospective analysis of a nationwide cross-sectional random sampling study was conducted. The survey, conducted shortly after the peak pollen season, was performed by self-evaluation questionnaire in 2001. Data from children aged under 15 years were collected and analysed. In these subjects, the response rate was 75.1%. The prevalence of JCP was 10.2% in children. Rhinorrhoea was the severest symptom reported; 19.5% had severe or moderate interference with daily activities and consulted physicians. Few children used prescribed drugs and some took measures to avoid contact with allergens.

Keywords children, epidemiology, Japanese cedar pollinosis, prevalence, allergic rhinitis

Introduction

Japanese cedar pollinosis (JCP) is a common allergic disease in Japan caused by inhalation of the pollen of Japanese cedar (*Cryptomeria japonica*) [1]. This disease is a major public health problem in Japan because of the severity of symptoms, high prevalence, poor spontaneous recovery rate and the cost of controlling the disease. Moreover, the prevalence in children is believed to have gradually increased in recent years [2]. According to a survey by Okuda et al. [3], the age-adjusted prevalence of JCP is 17.3% in the Japanese population as a whole, reduced to 13.1% after correction for possible biasing factors. However, although these data are useful, clearer understanding of the disease prevalence, variation in severity, limitations on activities of daily living and efficacy of current treatment and prevention strategies is needed for health-care policy planning and development of new treatment modalities and drugs in children with JCP.

Hence the present study was conducted to determine the current epidemiological prevalence of JCP in Japanese children using a cross-sectional random sampling method applied to the data from Okuda's survey.

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Method

Subjects

For the analysis, Japan was divided into 12 regional zones. Two-step stratified random sampling was performed in each zone. First, 390 of 3370 Japanese cities, towns and villages were selected randomly by the probability proportional sampling method in proportion to the overall population with respect to age (3–79 years) and sex on the basis of the National Census Report 1995. Following this, two subjects in each of the seven age/sex groups (14 subjects in total for each factor) were sampled randomly from the residents registration lists of the aforementioned 390 locations, and a list of 10 920 subjects was generated as reported previously [3].

Questionnaires

Self-evaluation questionnaires were mailed to all 10 920 subjects between 20 April and 2 May 2001. The questionnaire (see Appendix I) comprised 12 questions on symptoms (runny nose, sneezing, stuffy nose and eye itching) and their severity, changes after treatment (worse/improved/none), occurrence during each year, seasonal variability, frequency of JCP in the family, physician visits and clinical diagnosis, types of anti-JCP drugs used and their efficacy, degree by which JCP interferes with daily activities, methods used to avoid pollen and average duration of daily outdoor activities. Details of age and sex were also requested. Adult subjects were requested to

complete the questionnaires themselves; children were asked to respond with the assistance of a parent or guardian.

Diagnostic criteria

In the questionnaire-based diagnosis of JCP, definite JCP was diagnosed in subjects reporting ≥ 2 of a total of three nasal and one eye severe symptoms, with recurrence during February–April for more than 2 years or aggravation during this time if subjects reported perennial symptoms. Subjects whose symptoms had decreased to 'mild' or 'no symptoms' after treatment or occurred for the first time during 2001 were also deemed as having JCP. Suspected JCP was diagnosed in subjects who had ≥ 2 severe symptoms during the pollen season with occasional recurrence throughout the year as well as in those who had recurrence during the pollen season but whose symptoms were mild before treatment [3].

Results

Response rate

Fifty-four of the 10920 questionnaires mailed out were returned to sender as the subjects were no longer at the addresses. Of the remaining 10866 questionnaires, 5836 subjects (53.7%) responded. Of these returned questionnaires, 238 were discarded due to different age reporting from that given in the original mailed list or not specifying age or sex. Hence the usable response rate was 52.6% (5598 of 10628), among which 1303 (23.3%) were children aged < 15 years. Of the usable responses from those questionnaires returned from children aged < 15 years, 655 were from male subjects and 648 from female subjects. Two hundred and two questionnaires were answered by the children themselves, 1090 by parents, and 11 unknown. The severity of each symptom in these responders is shown in Table 1.

Prevalence

The crude prevalence of JCP was estimated at 17.3% (966 of 5598) in the total population. Adjusting for the 53.7% response rate, the prevalence was presumed 12.2% (95% confidence interval: 7.6–16.8%) for a 100% response. The prevalence in those aged under 15 years was estimated at 10.2% (133 of 1303 responders). With regard to sex, the prevalence of JCP in male subjects (12.4%) was higher than in female subjects (8.0%) in that age group. The prevalence rates generally increased with age (Fig. 1). Stratified by age, the prevalence was 4.5%, 10.5%, 12.1% and 15.1% in those aged 3–5, 6–9, 10–12 and 13–15 years, respectively (Fig. 2).

Table 1. Positive rate of symptoms in 1303 children aged < 15 years throughout Japan

Symptom	No response	Severe	Mild	None
Sneezing, *n* (%)	24 (1.8)	105 (8.1)	290 (22.3)	884 (67.8)
Rhinorrhoea, *n* (%)	17 (1.3)	187 (14.1)	318 (24.4)	781 (59.9)
Nasal obstruction, *n* (%)	24 (1.8)	173 (13.3)	288 (22.1)	818 (62.8)
Eye itching, *n* (%)	30 (10.1)	131 (10.1)	240 (18.4)	902 (69.2)

Current status of JCP

The current status of JCP was analysed in 133 affected children who conformed to the study criteria (questionnaire-diagnosed JCP). Recurrence in each year was seen in 78.9% of the subjects, whereas 21.1% had JCP for the first time during the year of completion of the questionnaire. In terms of the pollen season, 51.9% of the subjects had symptoms only between February and April. In contrast, 48.1% had perennial symptoms with aggravation during the pollen season, suggesting that those with allergic rhinitis had symptoms precipitated by house dust mites or other allergens in association with JCP.

Of 133 children with questionnaire-diagnosed JCP, 66.9% had sought medical advice from physicians. Among these subjects, 62.4% were prescribed drugs from physicians and 17.0% took over-the-counter medications (first-generation antihistamines). These rates are higher than those observed in the total population [3]. With respect to the degree of JCP interference with daily activities, 23.3% reported severe interference, 27.8% moderate difficulty and 34.6% mild problems. Among subjects who received drug therapy, interference with daily activities was severe in only 5.5%, moderate in 18.2% and mild in 37.4%.

The most frequently used measures to evade pollen exposure were gargling (removal of pollen from throat; 48.1%), avoiding exposure of mattresses to sunshine (32.3%) and keeping windows and doors closed (25.6%). Wearing facemasks (18.0%) and eye washing (3.8%) were less common strategies for avoiding pollen in children.

Discussion

The prevalence of JCP in children aged under 15 years throughout Japan was investigated by a cross-sectional population analysis with use of random sampling. Recently, Baba reported the national prevalence of JCP at 16.2% in a household study of otolaryngologists conducted by mailed questionnaires [4]. However, this nonrandomized family study did not sample from the general population, unlike our randomized study. Baba's study found prevalence rates of 1.7% and 7.5% in 0–4- and 5–9-year-old children, respectively [4]. These rates are a little lower than those revealed by our random sampling method. The different contents of the respective questionnaires may have affected the results and led to the difference in estimation of prevalence.

Internationally, many questionnaires pertaining to allergic rhinitis have been made available, including those of

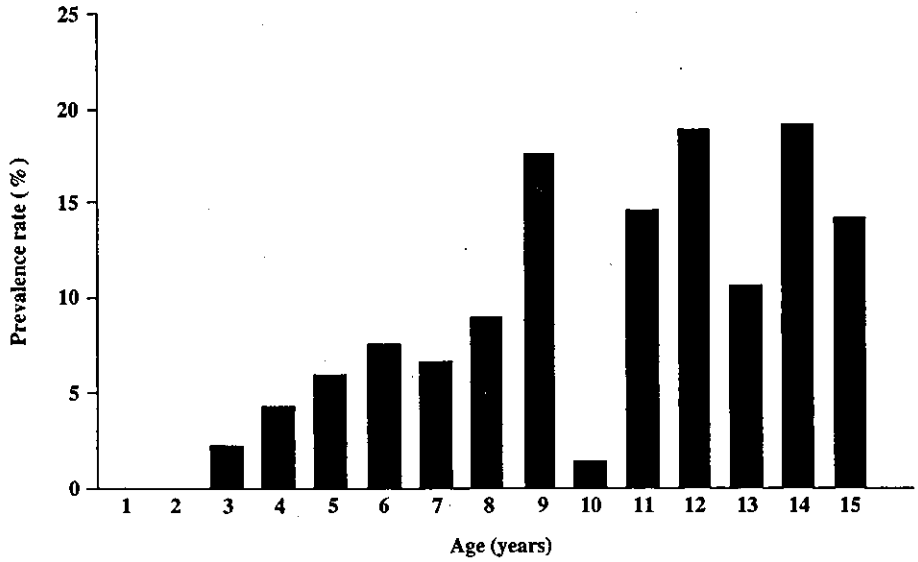

Fig. 1. Prevalence rate of JCP in children.

the International Survey of Asthma and Allergies in Childhood (ISAAC) formulated by the British Medical Research Council, the European Community Health Survey Questionnaire, the South London Survey, the American Thoracic Society questionnaire, and the Swiss Community Survey [5, 6]. According to these studies, allergic rhinitis prevalence rates in their respective populations were around 16–20%. However, none of these studies were conducted on a national basis. In Japan, surveys of JCP have been compiled by the Tokyo Metropolitan Government in addition to those conducted by Tanihara et al. [7], Sakakura and Ukai [8], Kozasa and Takenaka [2], and Okuda [9]. In general, all of these questionnaires had similar contents. However, the results varied considerably due to differences in sample size and year of study. The current study was conducted between April and July 2001, just after the peak pollen season when the subjects' perception of the severity of their symptoms was likely to be most accurate. During that period, the major airborne pollen in Japan was derived from the Japanese cedar tree, although small amounts of cypress pollen were also detected.

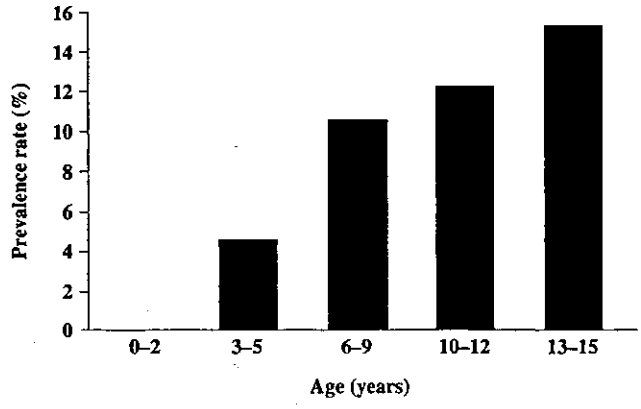

Fig. 2. Prevalence rate of JCP in children stratified by age.

The prevalence rates for JCP were low in the age groups comprising of subjects younger than 5 years old. No substantial differences in JCP prevalence were noted between the sexes in the total population, although male outnumbered female responders in the group aged < 15 years. This national survey revealed that patients had symptoms affecting both the nose and eyes. Nasal symptoms were more troublesome than eye symptoms in most children with JCP. The rate of medical treatment given was 18.2% of the total 5598 responders. On the other hand, 8.6% of 1303 responders aged < 15 years were treated by clinicians. Among those who received pharmacotherapy, the number of subjects experiencing severe interference in daily activities was less than the number of subjects experiencing mild or moderate interference in daily activities. This suggests that pharmaceutical intervention is effective in improving quality of life. Among those with questionnaire-diagnosed JCP aged < 15 years, the frequency of experiencing severe or moderate interference with daily activities before and after drug treatment was 51.1% and 23.7%, respectively. The relief of JCP symptoms is difficult, although patients may prevent symptoms altogether by avoiding the allergen. In the current study, gargling and keeping windows closed were often used as prophylactic measures. Although pollen masks have been shown to exclude approximately 60% of pollen inhaled from a pollen chamber [10], our children were not accustomed to seek prophylaxis by wearing masks and glasses.

Conclusion

The current study clearly demonstrates that JCP is a common disease in Japanese children and hence a public health problem because of its high prevalence (> 10% of Japanese children affected) and morbidity (causing severe or moderate interference with daily activity in 51.1% of patients).

Nevertheless, drug therapy and pollen avoidance seem very effective for symptomatic relief. Encouragingly, almost 66.9% of those affected visited physicians.

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Appendix 1

Self-evaluation questionnaire for Japanese cedar pollinosis

Japanese cedar pollinosis is a common allergic disease in Japan caused by inhalation of Japanese cedar pollen. It is characterized by symptoms such as sneezing, runny nose, stuffy nose and eye itching, especially during the season February to April, and usually recurs annually. At present, the disease presents considerable health problems because of its high incidence rates and severe symptoms, but the numbers of people affected in the country as a whole are unknown. This national survey is designed to clarify the status of Japanese cedar pollinosis in Japan.

1 Please fill out the questionnaire and send it back to us as soon as possible.
2 Please note that we are asking you about the condition of your nose and eyes during February through April of this year when you did not have a cold or flu.
3 Please answer each question by checking the appropriate number in each item.

Q1a: Symptoms. Did/do you have the following symptoms during February through April of this year when you did not have a cold or flu? (Please check the severity of each symptom.)
(See Table 1 for list of symptoms and severity)

Q1b: Treatment effect. (Please answer only when you did not have any severe nose or eye symptoms.)

Did you have any severe symptoms before treatment that changed to mild or no symptoms after treatment?

1 Yes
2 No
3 Other

(Please proceed to Q8 if you had/have no symptom and checked 'no' for all symptoms.)

Q2: Recurrence. Do your nose/eye symptoms occur repeatedly almost every year?

1 Almost every year
2 Manifested for the first time this year
3 Some years, not every year
4 Other

Q3: Season. What is/was the most frequent season for your symptom(s) to appear?

1 February to April alone
2 Perennial, but worsens in February to April
3 Worse in another season or perennial
4 Other

Q4a: Consultation with a physician. Did you visit a physician this year for your symptoms?

1 Yes
2 No

Q4b: Physician's diagnosis. What was the physician's diagnosis?

1 Japanese cedar pollinosis
2 Pollinosis due to a plant other than cedar
3 Dust mite rhinitis
4 Other allergic rhinitis
5 Non-allergic rhinitis
6 Other/undefined

(Q5 through Q10 are not included in this Appendix because they are not crucial for the diagnosis of Japanese cedar pollinosis.)

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Allergic rhinitis in children: association with asthma

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Summary

The incidence of allergic rhinitis in paediatric bronchial asthma patients was about 80% according to a questionnaire survey. Watery nasal discharge and nose rubbing were common symptoms of paediatric allergic rhinitis, while nasal congestion and sneezing increased with age. Although there were slight differences depending on the age of patients, one-third to nearly half were believed to have nasal symptoms and asthma attacks. The first wheezing episode preceded nasal symptoms in the majority of patients, but onset of allergic rhinitis occurred > 1 year before asthma in a little over 10%. The age of onset of allergic rhinitis was 1 year in these patients, which was clearly earlier than that observed in patients who first developed asthma (4 years). Furthermore, the incidence of cedar pollinosis was higher in patients who developed allergic rhinitis first than in those who developed asthma first, suggesting that asthma patients who develop allergic rhinitis first exhibit pronounced nasal hypersensitivity. Allergic inflammatory cells are present in the nasal mucosa of asthma patients who do not exhibit distinct allergic rhinitis symptoms, so nasal sensitization does not necessarily lead to allergic rhinitis symptoms, suggesting the existence of some other factor that induces nasal hypersensitivity. On nasal smear, the appearance of mast cells preceded a positive radioallergosorbent test (RAST), and the appearance of eosinophils and basophils was consistent with the degree of sensitization. Anti-allergic agents appear efficacious in patients' mast cells positive on nasal smear cytology with negative house dust mite RAST, suggesting that nasal smear cytology may be useful when beginning medication.

Keywords allergic march, allergic rhinitis, asthma, cedar pollinosis, cytology, questionnaire, nasal swab, RAST, wheezing

Introduction

Many children with bronchial asthma also have allergic rhinitis [1]. When allergic rhinitis is very active, airway hyperresponsiveness increases, often aggravating the symptoms of bronchial asthma. Furthermore, the onset of allergic rhinitis sometimes precedes bronchial asthma, and onset of bronchial asthma may be prevented by successful treatment of allergic rhinitis [2]. Recently, the concept of 'one way, one disease' has drawn attention to the relationship between allergic rhinitis and bronchial asthma in terms of the mechanism of airway inflammation, selection of medication and when to start treatment.

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Prevention of asthma onset by successful treatment of allergic rhinitis using drugs or allergen-specific hyposensitization therapy has been reported overseas [3, 4]. The relative timing of allergic rhinitis and asthma onset, association between allergic rhinitis and aggravation of asthma and seasonality of allergic rhinitis in asthma patients are important issues when considering early asthma intervention. However, there are few relevant reports of studies conducted in children in Japan [5]. Hence we conducted a randomized questionnaire survey of bronchial asthma patients at medical institutions associated with our institution to investigate the incidence of paediatric bronchial asthma and allergic rhinitis and the relative timing of onset of either disease. In addition, we performed nasal smear cytology as a marker of inflammation in paediatric bronchial asthma patients who did not exhibit distinct nasal symptoms to assist in determining the most appropriate anti-allergic inflammation therapy, and observed allergic inflammatory cell dynamics in nasal mucosa.

Patients and methods

Questionnaire survey of paediatric bronchial asthma patients

The questionnaire consisted of four questions covering the following: (1) whether patients experience sneezing, nose rubbing, watery nasal discharge, or nasal congestion for ≥2 weeks in the absence of having a cold; (2) when their first wheezing episode and nasal symptoms appeared; (3) seasonality of nasal symptoms; and (4) the relationship between their nasal symptoms and asthma. Subjects were the guardians of paediatric bronchial asthma patients aged 1–18 years.

Nasal smear cytology

Subjects were 39 paediatric bronchial asthma patients aged 1–12 years and not exhibiting distinct allergic rhinitis symptoms. Nasal smear cytology and grading of cell counts were performed using previously reported methods [6].

Results

Questionnaire survey

A total of 248 subjects completed questionnaires. Of these, 205 subjects responded in the affirmative for having ≥1 of sneezing, watery nasal discharge, nasal congestion and nose rubbing. Of these, patients with nasal congestion alone were excluded from the analysis since they may have had a different disorder such as sinusitis, leaving a total of 199 patients (80.2%) believed to have allergic rhinitis. The overall breakdown of nasal symptoms was as follows: 72%, 70%, 62% and 56% experienced nasal congestion, watery nasal discharge, nose rubbing and sneezing, respectively (including multiple responses) (Fig. 1). By age bracket, nose rubbing and watery nasal discharge were most common in younger children, while nasal congestion was most common in those in junior high school and older (data not shown). Looking at the association between nasal symptoms and asthma attacks by the age groups 0–3, 4–6, 7–12 and 13+ years, there was little correlation in the 0–3-year group, but 40–50% of respondents in the other age groups tested reported asthma attacks occurring when nasal symptoms were present (Fig. 2). Regarding the seasonality of nasal symptoms, two-thirds of patients were believed to have perennial allergic rhinitis and one-third cedar pollinosis. By age group, there was no major difference in terms of the perennial nature of nasal symptoms, but older patients were more likely to respond positively for 'perennial and particularly bad from February to April' and 'bad only from February to April', and the presence of cedar pollinosis was suspected in about 50% of patients aged ≥13 years and in about 10% of those aged 0–3 years (Fig. 3).

To analyse the age of onset of wheezing and nasal symptoms, we compared the age of onset of the first wheezing episode and that of nasal symptoms in the 60 patients (of a total of 179 who gave this information) who were free of fever during the first wheezing episode.

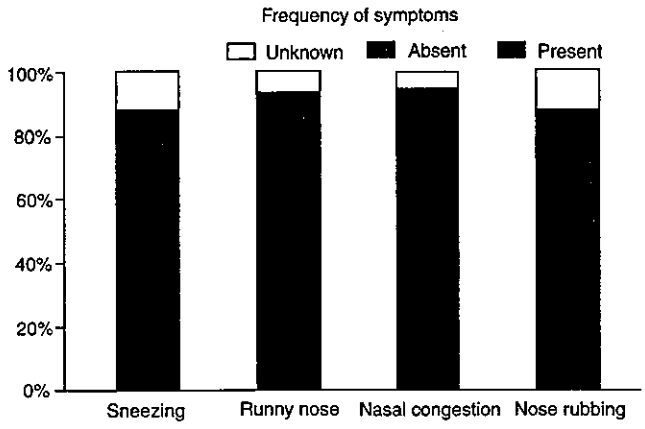

Fig. 1. Nasal symptoms in allergic rhinitis patients aged 1–18 years (n=199).

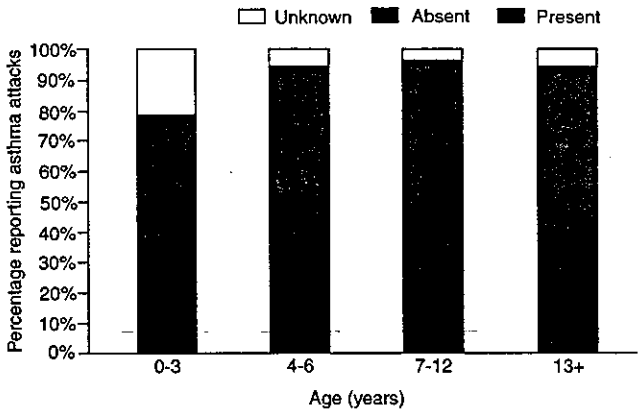

Fig. 2. Presence of experiencing asthma attacks concurrently with having nasal symptoms by age group.

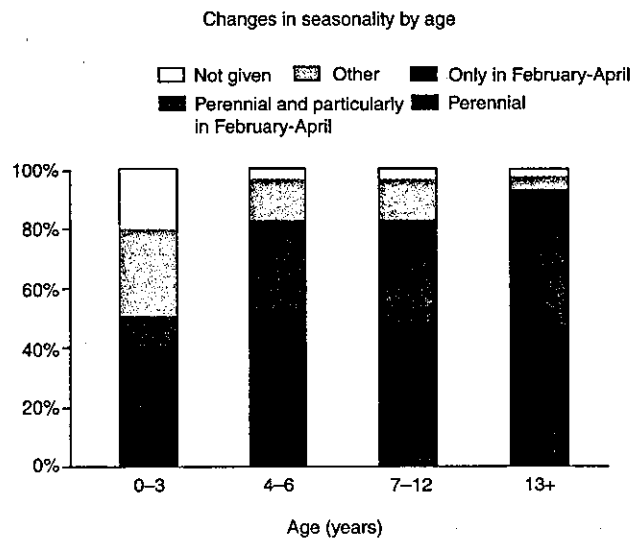

Fig. 3. Seasonality of nasal symptoms by age group.

Twenty-three patients experienced wheezing ≥1 year before the appearance of nasal symptoms; 10 experienced nasal symptoms ≥1 year before the appearance of wheezing; and the remaining 27 patients experienced both nasal symptoms and wheezing within <1 year of each other. Overall, wheezing preceded nasal symptoms in most patients (Fig. 4). Similarly, of a total of 119 patients who had fever of ≥38.5°C during the first wheezing episode, very few experienced allergic rhinitis before wheezing (results not shown). The average age of onset of asthma was 2 years in patients who developed asthma first and 3.5 years in those who developed allergic rhinitis first or both simultaneously. Nasal symptoms appeared at about age 1 year in patients who developed allergic rhinitis first (Fig. 5). Approximately 70% of patients who developed allergic rhinitis first ($n=10$) had symptoms of cedar pollinosis, much higher than the number of subjects who developed asthma first (Fig. 6).

Nasal cytology

We performed nasal smear cytology in paediatric bronchial asthma patients who did not exhibit distinct nasal symptoms and analysed mast cell, eosinophil and basophil

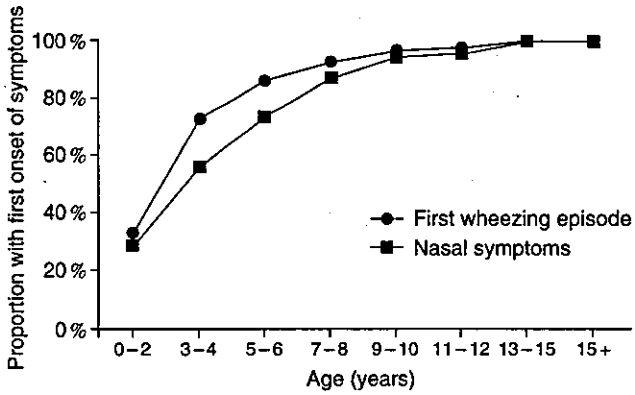

Fig. 4. Age of onset of first wheezing episode and nasal symptoms in patients free of fever during the first wheezing episode ($n=60$).

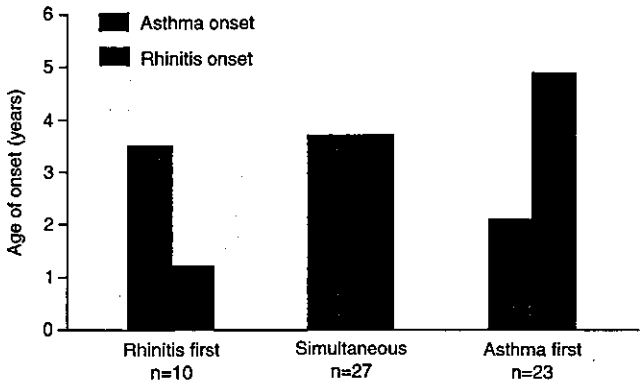

Fig. 5. Relationship between relative timing of allergic rhinitis and asthma onset and age of onset of each disorder in patients with no fever during first wheezing episode ($n=60$).

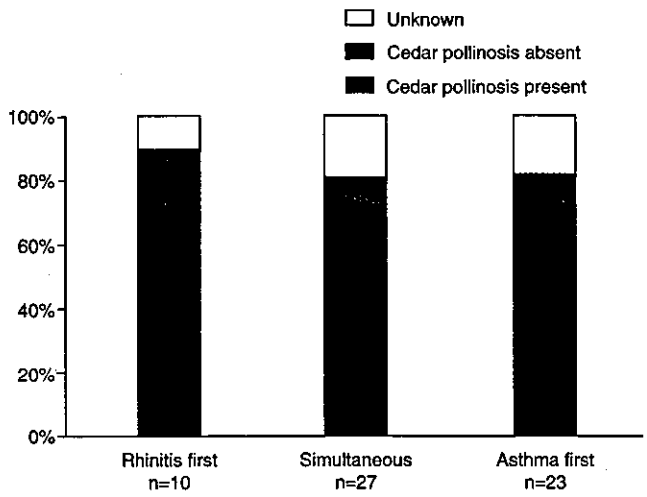

Fig. 6. Relationship between timing of allergic rhinitis and asthma onset and incidence of cedar pollinosis in patients with no fever during first wheezing episode ($n=60$).

counts and rates of positive *Dermatophagoides pteronyssinus* radioallergosorbent tests (RAST). Even though nasal symptoms were absent, allergic inflammatory cells were found in the nasal mucosa. Looking at the association with house dust mite sensitization, while mast cells were detected by nasal smear in the majority of asthma patients even if house dust mite RAST was negative, very few eosinophils and basophils were detected. On the other hand, when house dust mite RAST was positive and there was definite sensitization, both eosinophils and basophils appeared on nasal smear. Mast cells also increased with sensitization (Fig. 7). Results obtained in a typical patient are shown in Fig. 8.

Patients with only mast cells present on nasal smear but exhibiting negative house dust mite RAST who were given ketotifen (0.06 mg/kg/day) for 2 years, eosinophil count disappeared after increasing temporarily. Figure 9a shows the results from one such patient. However, treatment with oxatomide (1 mg/kg/day for 2 years) did not result in any change in eosinophil count in those patients with strongly positive RAST and continuous presence of eosinophils. Results from a typical patient are shown in Fig. 9b.

Discussion

In the present questionnaire survey, 80% of paediatric bronchial asthma patients also had symptoms of allergic rhinitis. This result is very close to the conventionally accepted incidence of allergic rhinitis in paediatric asthma patients in Japan based on diagnoses by doctors [1], suggesting good reliability of the results of this questionnaire. The survey also suggests that, unlike overseas [7], there are few paediatric asthma patients in Japan who develop allergic rhinitis before asthma. The reason for this is not clear, but

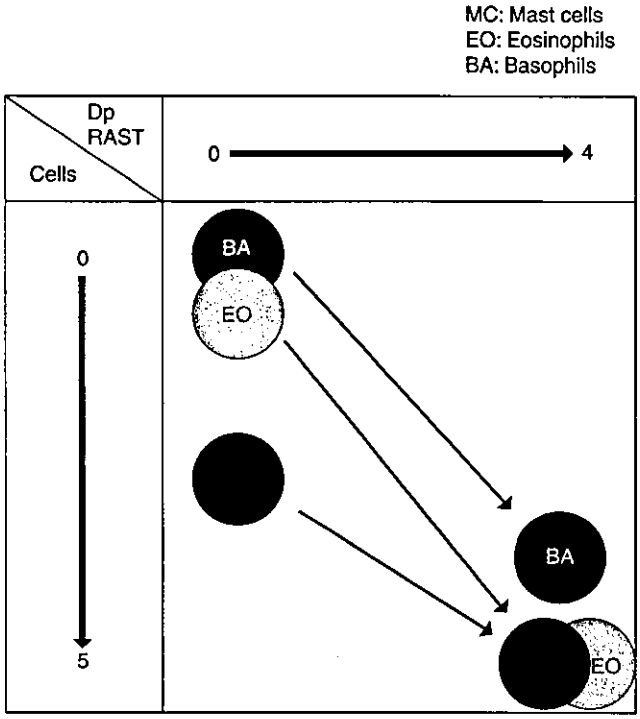

Fig. 7. Changes in house dust mite RAST antibodies and nasal smear cell groups.

the allergens in asthma patients overseas may differ from the main allergen in Japan, house dust mites. In Japan, house dust mites are a major allergen common to both allergic rhinitis and asthma. The allergic rhinitis symptoms in two-thirds of the paediatric asthma patients in the present study were perennial, suggesting that house dust mites are involved to a large extent.

An interesting result of this survey was that while allergic rhinitis symptoms began at around age 1 year in patients who developed allergic rhinitis first, nasal symptoms first appeared after 4 years of age in those who developed asthma first. Given that a higher percentage of patients who developed allergic rhinitis first had cedar pollinosis compared with among those who developed asthma first,

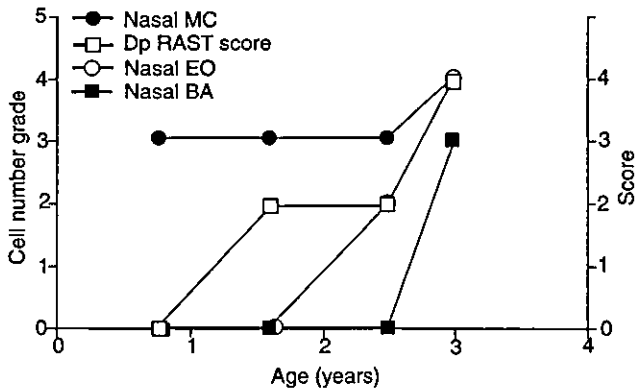

Fig. 8. Changes in house dust mite RAST antibodies and nasal smear cell groups over time in a typical asthma patient.

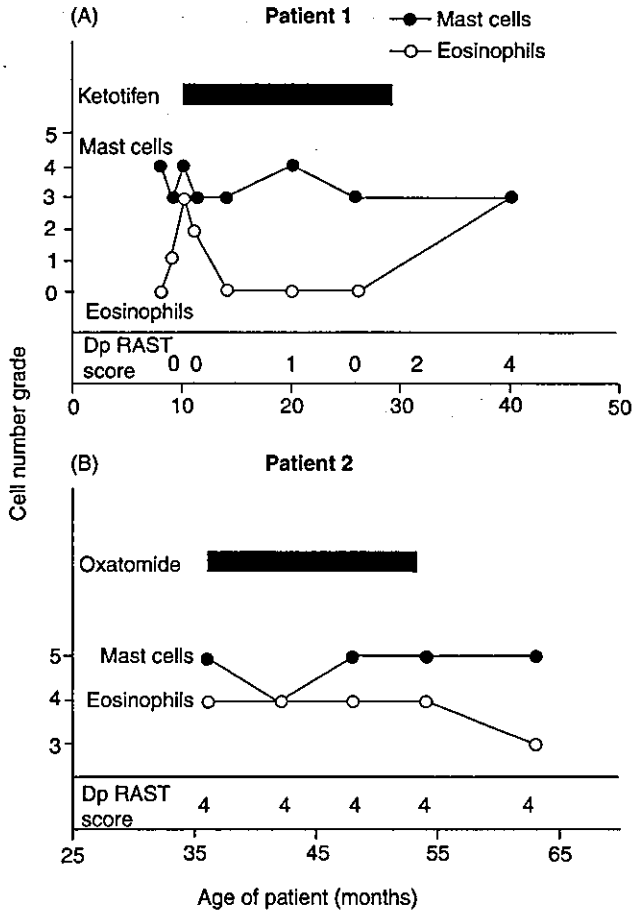

Fig. 9. Changes in house dust mite RAST antibodies and nasal smear cell groups (mast cells and eosinophils) over time in two bronchial asthma patients given (a) ketotifen (0.06 mg/kg/day for 2 years) and (b) oxatomide (1 mg/kg/day for 2 years).

the more pronounced the nasal hypersensitivity, the earlier the onset of allergic rhinitis occurred, indicating a possible susceptibility to cedar pollen sensitization. Additionally, the observation that >90% of paediatric bronchial asthma patients are sensitized to house dust mites and many have perennial allergic rhinitis suggests that the incidence of cedar pollinosis may increase when house dust mite-induced allergic rhinitis is present.

There are two possible explanations for the presence of mast cells, eosinophils and basophils on nasal smear in bronchial asthma patients who do not have distinct nasal symptoms. One is that these individuals have mild allergic rhinitis without clear clinical symptoms, and the other is that they are sensitized but develop only asthma and not allergic rhinitis. In support of the latter explanation, a big difference in nasal hypersensitivity has been observed between paediatric bronchial asthma patients with and without allergic rhinitis (A. Konno, personal communication 2003). In future, hypersensitivity testing of the nasal mucosa of asthma patients both with and without pronounced nasal symptoms needs to be carried out, together with analysis of the types and numbers of allergic

inflammatory cells and cellular activation. Our initial results suggest that nasal smear cytology may be an indicator of local sensitization, and this may in turn help determine when to give the patient anti-allergic agents. However, further investigation with a larger sample of patients is necessary to clarify this assumption.

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特集 花粉症の発症予防と治療

小児スギ花粉症の有症率，感作率の年次推移と今後の展望*

島　正之**

Key Words : Japanese cedar pollinosis, serum IgE antibody, prevalence, children, epidemiology

はじめに

花粉症は，1960年頃までわが国では稀な疾患であるとされていたが，1961年にブタクサによる花粉症，1964年にスギによる花粉症が報告されて以来，年々増加傾向にあり，とくにスギ花粉症は著しく増加している[1]．

スギ花粉症は毎年2～4月頃に飛散するスギ花粉に対する季節性アレルギー疾患であり[2]，わが国でスギ花粉症が増加した原因として，第二次世界大戦後に植林されたスギが花粉を飛散させる樹齢に達したことがあげられる[3]．一方，花粉飛散数の多い山間部だけでなく，都市部における有症率が増加していること，実験的研究ではディーゼル自動車の排気中に含まれる微粒子(diesel exhaust particles；DEP)に花粉に対する特異IgE抗体産生亢進作用が認められること[4]などから，自動車排出ガスをはじめとする大気汚染の影響を示唆する報告もある．

小児スギ花粉症の有症率，感作率と，それらに影響する因子を明らかにするためには疫学的な検討が必要である．わが国におけるスギ花粉症およびアレルギー性鼻炎の有症率については多くの報告があるが，対象や調査方法等が統一されておらず，報告者によってかなり大きな差が認められている．ここでは，わが国で行われた小児のスギ花粉症に関する疫学研究を紹介し，あわせて今後の展望について述べたい．

自覚症状の調査による疫学研究

欧米諸国を中心として56か国155地域の13～14歳児46万人を対象に行われたThe International Study of Asthma and Allergies in Childhood (ISAAC)[5]では，アレルギー性鼻結膜炎症状の有症率は，国や地域により1.4～39.7%と大きな差が認められている．これには地域により，アレルゲンや環境因子が異なることが影響しているためと考えられる．

最近，わが国においても調査票を用いて全国的に実施された大規模な疫学調査の結果が報告されている．1998年に全国の耳鼻咽喉科医師とその家族を対象に行われた郵送による質問紙調査(解析対象者17,301名)では，スギ花粉症の有症率は全体で16.2%であり，年齢別には0～4歳では低く，5～9歳，10歳代と加齢とともに有症率の増加が認められている[6]．通年性アレルギー性鼻炎の有症率は全体で19.8%であり，5～9歳で急激に上昇し，スギ花粉症よりも若年者での発症が多かった．

2001年に全国民から二段階無作為抽出した10,920

* Annual change and perspectives of the prevalence of Japanese cedar pollinosis among children.

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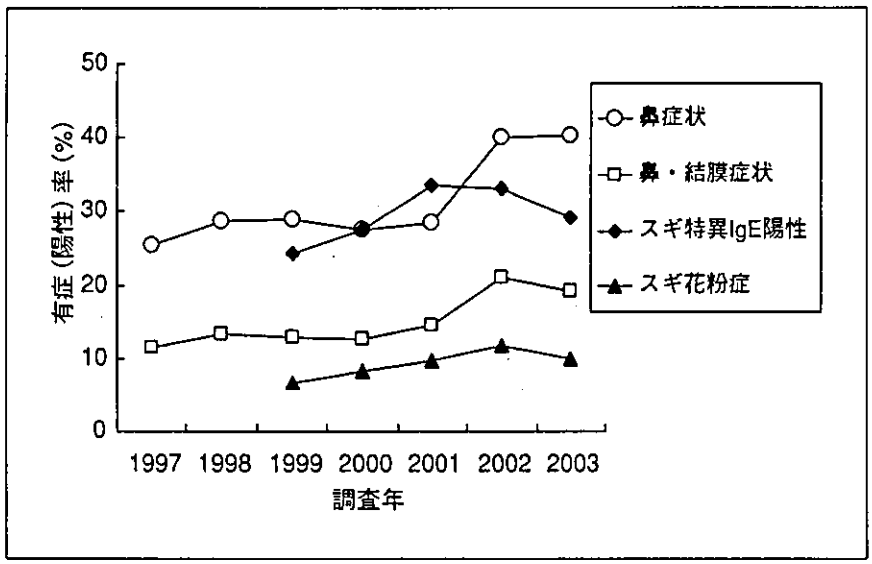

図1　スギ花粉症有症率・スギ特異IgE陽性率の年次推移

名を対象に実施された郵送による質問紙調査(有効回答率51.5%)では，スギ花粉症の有症率は17.3%であった[7]．年齢別には，3～9歳で男子12.8%，女子9.7%であり，10～19歳ではそれぞれ20.2%，18.8%に上昇している．

疫学研究では，集団として把握しやすいなどの理由により，小中学生を対象に実施されたものも多い．伊藤ら[8]は，1987年と1991年の岐阜県付知町と名古屋市瑞穂区の中学生を対象とした耳鼻科検診の結果を比較し，スギ花粉症有症率は付知町では1.5倍に増加したが，瑞穂区では増加がみられないとした．その理由として，この間に付知町では自動車交通量が約4倍に増加し，大気汚染濃度が高くなったが，瑞穂区では変化がなかったことをあげている．

楠ら[9]は，1996～1997年にかけて，京都・滋賀地域において小・中学生50,086人を対象に，厚生省アレルギー総合研究事業疫学班の作成した調査票を用いた疫学調査を行った．スギ花粉症有症率は全体で5.2%であり，年齢が高くなるほど上昇した．農村部の多い京都府下北部地域よりも都市部の多い南部地域でスギ花粉症有症率が明らかに高く，大気汚染をはじめとする都市環境がスギ花粉症の発症に影響を与える可能性を示唆している．

スギ特異IgE抗体検査を含めた疫学研究

これまで紹介したように，花粉症に関する疫学研究は質問紙によって自覚症状を調査したものが多い．客観的な評価を行うために，スギ特異IgE抗体，皮内反応検査等の検査を加えた調査も実施されているが，小児を対象とした疫学研究でこれらの検査を行っているものは限られている．

Ozasaら[10]は，1995～2001年まで毎年5～6月に，京都府南部の町の小・中学生407～510名を対象に，血清スギ特異IgE抗体の測定と鼻・結膜症状に関する調査を行い，スギ特異IgE抗体価1.5IU/ml以上であり，3～4月に鼻・結膜症状が3週間以上持続したものをスギ花粉症とした．実施年によってスギ花粉症の有症率は13.8～22.9%，スギ特異抗体1.5IU/ml以上の割合は39.0～50.1%であった．いずれも実施した年の花粉飛散数と関連があり，大量のスギ花粉への曝露が抗体価および有症率を高めることを報告している．

スギ花粉の大量飛散がみられた1995年6月に千葉県安房郡丸山町の小・中学生292名を対象に行った血清スギ特異IgE抗体測定と質問紙調査では，スギ花粉に対する感作率は44.9%であり，そのうちの40.5%は花粉症症状を有していた[11]．さらに，スギ花粉飛散数が少なかった翌年6月には，同じ中学生135名のうち多くのものでスギ特異抗体価は前年よりも低下していたが，有症率の低下はみられないとしている．

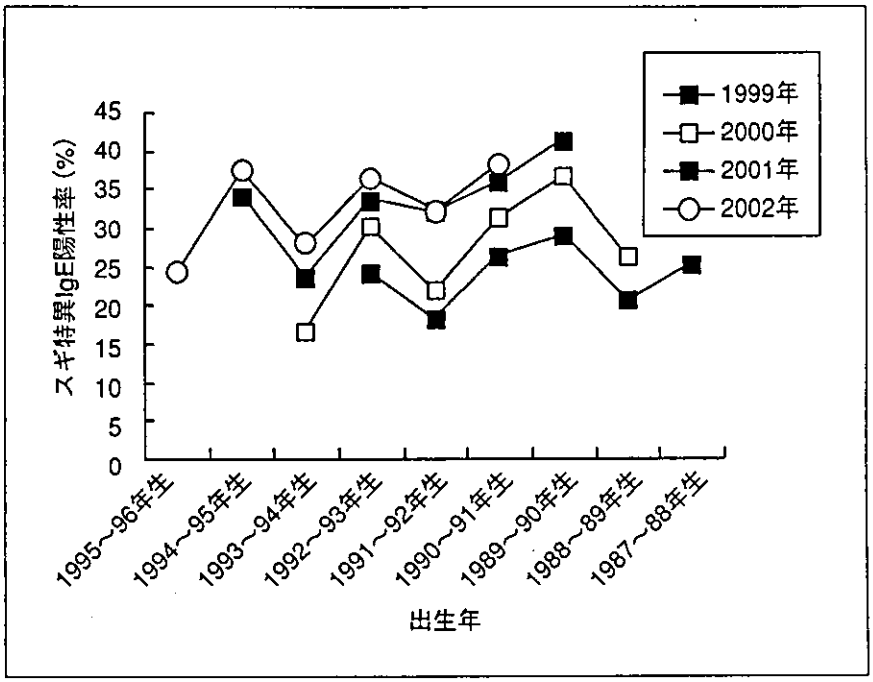

図2　学年(出生年次)別スギ特異IgE陽性率

千葉県における小学生を対象とした疫学研究

スギ花粉症の有症率および感作率は，調査方法や年ごとのスギ花粉飛散状況の違いによって差が認められるため，それらの年次推移を明らかにするためには，同一地域で同じ方法によって経年的に調査を行うことが有用である．

1．スギ特異IgE抗体陽性率および花粉症有症率の年次推移

筆者は，千葉大学在任中の1997～2003年までの7年間にわたり，千葉県君津市の3小学校の児童(対象者数1,183～1,478名)を対象に疫学研究を実施した[12]．毎年9～10月に，ISAAC[13]に準拠したアレルギー症状に関する質問紙を配布して両親に回答してもらい，鼻症状は「最近12カ月間に風邪でないのにくしゃみ，鼻水，鼻閉があった」もの，鼻・結膜症状は「これらの症状と同時に眼のかゆみ，流涙があった」ものとした．保護者の承諾が得られたものは血清スギ特異IgE抗体を測定し(受診率86.9～88.8%)，クラス2以上を陽性とした．調査年の2～4月に鼻・結膜症状があり，スギ特異IgE抗体が陽性のものをスギ花粉症とした．

鼻症状の有症率は1997年25.5%，2001年28.4%であり，この間に大きな変化はみられなかったが，2002年には40.0%と上昇した(図1)．スギ特異IgE抗体陽性率は，1999年24.3%，2000年27.5%，2001年33.6%と年々増加していたが，2002年以降は低下した．スギ花粉症の有症率も1999年から2002年まで増加したが，2003年には低下がみられた．こうした年次推移はそれぞれの年のスギ花粉飛散状況を反映したものと考えられる．

学年(出生年次)別・年度別のスギ特異IgE抗体陽性率は，全体として高学年となるほど高かったが，いずれの年にも出生年次による差が認められた(図2)．同一集団を経年的に比較すると，成長とともに陽性率が高くなっていた．出生早期に大量のスギ花粉に曝露されると，成長後にスギ花粉に感作されやすくなることが報告されている[14][15]．1994年4月から1995年3月に出生したものの陽性率は高く，1995年のスギ花粉飛散数が多かったことが影響している可能性が考えられた．

2．スギ特異IgE抗体およびスギ花粉症に影響を及ぼす因子

2001年に，花粉飛散数や大気汚染濃度の異なる千葉県市川市の3小学校の児童も対象として，君津市における調査と同様の調査を実施した(両市を合わせた対象者数2,539名，血液検査受診率

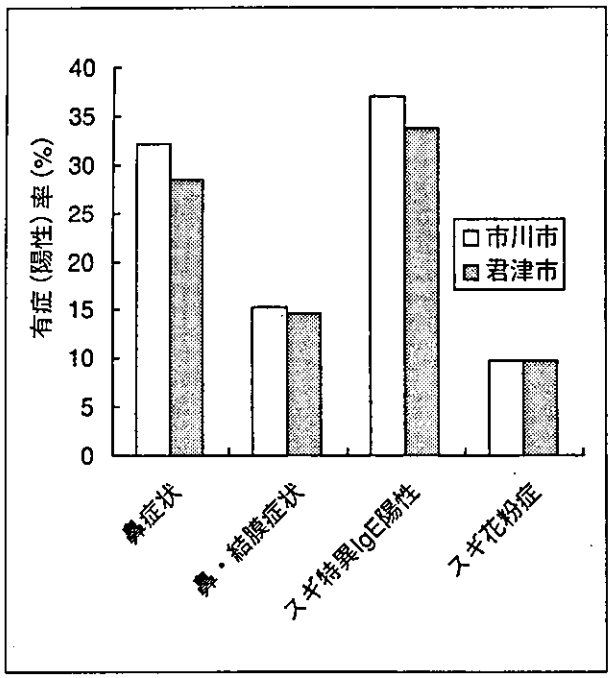

図3　地域別鼻症状等有症率・スギ特異IgE陽性率(2001年10～11月)

82.6%)[16]．鼻症状，鼻・結膜症状の有症率およびスギ特異IgE抗体陽性率は，いずれも花粉飛散数が少なく大気汚染濃度が高い市川市の方が花粉飛散数が多く，大気汚染濃度が低い君津市よりも高率であり(図3)，地域間の差は花粉飛散数の違いだけによるものではないことが示された．スギ花粉症有症率は両市ともに9.7%であった．

多重ロジスティック回帰分析では，スギ特異IgE抗体陽性は，学年(高学年)，性別(男子)，両親のアレルギー性疾患の既往，居間における加湿器使用，寝室でのじゅうたん使用，兄弟姉妹数(2名以下)との関連が認められ，対象児の出生後最初の花粉飛散期の飛散数との関連も有意であった(表1)．学校間の比較では，花粉飛散数の多い君津市A校のオッズ比(陽性率のもっとも低いC校を1としたとき2.06)がもっとも大きく，市川市の2校のオッズ比も有意であった．スギ花粉症についても，学年，両親のアレルギー性疾患の既往，居間における加湿器使用，寝室で

表1　スギ特異IgE抗体およびスギ花粉症に関連する因子(多重ロジスティック回帰分析)

	スギ特異IgE抗体陽性		スギ花粉症	
	オッズ比	95%信頼区間	オッズ比	95%信頼区間
学年				
6年生/1年生	2.10	1.59～2.78	2.19	1.40～3.44
性				
女子/男子	0.83	0.69～1.00	0.77	0.57～1.04
両親のアレルギー				
あり/なし	1.58	1.29～1.94	3.50	2.32～5.50
加湿器(居間)				
使用/非使用	1.38	1.13～1.69	1.78	1.30～2.43
ペット				
あり/なし	0.86	0.71～1.03	0.93	0.68～1.27
じゅうたん(寝室)				
あり/なし	0.77	0.62～0.95	0.47	0.31～0.68
兄弟姉妹数				
≦2名／≧3名	1.32	1.08～1.61	1.33	0.96～1.86
花粉飛散数				
1,000個/cm²増加あたり	1.07	1.03～1.13	1.11	1.02～1.20
学校				
君津市A校	2.06	1.50～2.83	2.30	1.36～3.88
君津市B校	1.05	0.87～1.26	1.05	0.78～1.42
市川市D校	1.19	1.05～1.36	1.02	0.82～1.26
市川市E校	1.12	1.00～1.25	1.06	0.89～1.26
市川市F校	1.02	0.94～1.11	0.94	0.81～1.09
君津市C校	1.00	—	1.00	—

解析対象は，2001年に千葉県市川市，君津市の小学生のうち，質問紙調査，血液検査のすべてに有効な結果が得られた2,093名．

のじゅうたん使用，出生後最初の花粉飛散数との関連が有意であった．学校間の比較では，君津市のA校のオッズ比が有意に大きかったが，そのほかの5校間に差はみられなかった．

性差について，浜野ら[17]は小児期の鼻アレルギーは男児が女児よりも多く，10歳を過ぎると女性の発症者が男性よりも多いことを報告し，女性ホルモンの影響を示唆している．また，兄弟姉妹数が少ないものにアレルギー性疾患が多いことは近年多数の報告があり[18)~20)]，乳幼児期の発育環境や母体内環境の関与が指摘されている[21)]．居間での加湿器使用，寝室でのじゅうたん非使用との関連も認められたが，花粉症症状のある児童の家庭がこれらの生活環境に配慮した結果である可能性も考えられる．喫煙等による室内空気汚染が小児の血清IgE値を増加させることも報告されており[22)]，生活環境因子と花粉症との関連についてはさらに検討する必要があろう．

3．同一対象者についての縦断的観察

君津市において，1997年の1,2年生のうち，2001年までの5年間の質問紙調査と血液検査のすべてに有効な結果が得られた175名を対象に縦断的な評価を行った[23)]．年度別のスギ特異IgE抗体陽性率およびスギ花粉症有症率は，いずれも年々増加していた(図4)．スギ抗体価の幾何平均値も年々増加していたが，とくに1999～2000年にかけて大きな増加がみられ(図5)，2000年にスギ花粉の大量飛散があったことが影響したと考えられる．

1997年に花粉症が認められなかった155名のうち，38名が2001年までに新規に花粉症を発症した．ロジスティック回帰では，1997年にスギ特異IgE抗体陽性であったものからの発症率が有意に高く(表2)，低学年でスギに感作されているものは，成長とともに花粉症を発症するものが多いことが明らかとなった．

今後の展望

わが国の小・中学生を対象に実施された疫学研究では，調査方法等の違いはあるものの，小学校低学年においてスギ花粉症症状を有するものが数～10%程度存在しており，成長とともに高率となることが示されている．われわれが千葉県で実施してきた疫学研究でも，小学生のスギ花粉症有症率，スギ花粉に対する感作率は，いずれも高学年になるに伴って増加していた．これらは，アレルギー素因とともに毎年のスギ花粉飛散による影響を受けることが示され，出生直後の花粉飛散期におけるスギ花粉曝露とも関連が認められた．花粉飛散数は気象条件等の影響によって年ごとに差があるが，スギ花粉に1度感作されれば，その後は花粉飛散数が少量で

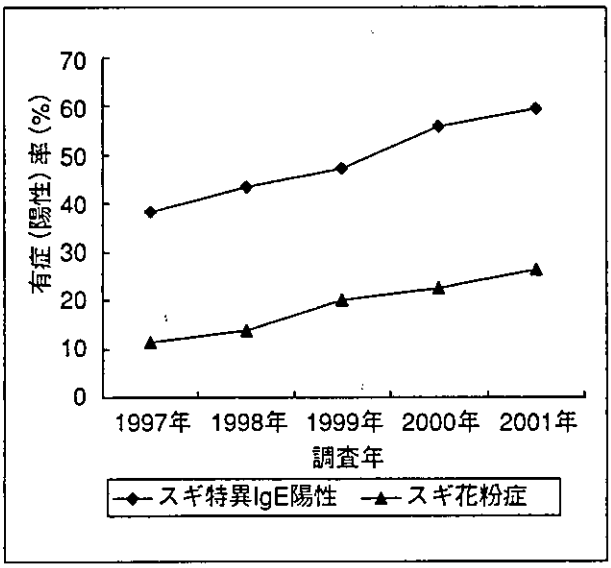

図4 スギ特異IgE陽性率・スギ花粉症有症率の年次推移
対象は，1997年の君津市の1,2年生のうち，2001年までの5年間の質問紙調査と血液検査のすべてに有効な結果が得られた175名．

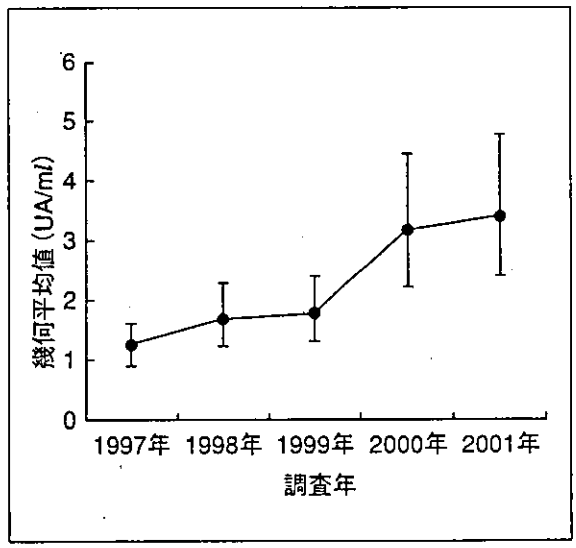

図5 スギ特異IgE抗体価幾何平均値の年次推移
対象は図4と同じ．幾何平均とその95%信頼区間．

表2　スギ花粉症の発症に関連する因子(多重ロジスティック回帰分析)

	オッズ比	95%信頼区間	p値
性			
女子／男子	0.57	0.23～1.35	0.210
生年			
1989年／1990年	1.63	0.69～3.98	0.272
スギ特異IgE抗体(1997年)			
陽性(クラス2以上)	4.45	1.28～15.7	0.019
疑陽性(クラス1)	4.26	0.68～26.9	0.113
陰性(クラス0)	1.00	—	—
居住地域			
山間部／臨海部	1.63	0.69～3.98	0.272

対象は，1997年の君津市の1,2年生のうち，2001年までの5年間の質問紙調査と血液検査のすべてに有効な結果が得られた175名．

あっても症状の改善には結びつかないようである．近年，大量のスギ花粉飛散が観察される年が多くなっていることから，今後も小児のスギ花粉への感作率および花粉症有症率は増加することが懸念される．

一方，スギ花粉への感作率や花粉症有症率は地域による差がみられるが，こうした地域間の差は花粉の飛散状況の違いだけで説明することはできない．近年，小児のアレルギー性疾患が世界的に増加傾向にあり，都市化を含めたさまざまな環境因子の変化が影響を及ぼしていると考えられる[24]．ディーゼル排気粒子等の大気汚染物質がアレルゲンによる鼻粘膜でのIgEやサイトカイン産生を増加させることが報告されており[4]，大気汚染をはじめとする環境因子との関連について，さらに詳細な疫学的検討が必要であろう．

これまで行われた疫学研究のほとんどは小学生以上を対象としているが，乳幼児期にすでに感作され，発症するものが相当数存在している．また，花粉症と気管支喘息がしばしば合併することが知られている[25]が，小児期における両疾患の関連性に関する知見は十分とはいえない．そのため，乳幼児からの気管支喘息，花粉症等のアレルギー性疾患の経過を明らかにするために，今後はさらに低年齢のものを対象とした疫学研究，とくにコホート研究の実施が望まれる．

おわりに

小児のスギ花粉症有症率およびスギ花粉への感作率について，主として国内で実施された調査とともに，筆者が千葉県で実施してきた疫学研究を紹介した．小児のスギ花粉症をはじめとするアレルギー性疾患は増加してきており，近年のスギ花粉飛散状況から，今後もさらに増加することが懸念される．花粉症にはスギ花粉への曝露のほかに，遺伝，ウイルス感染，居住環境等の多くの因子が関与していることから，乳幼児期からのコホート研究によって花粉症の発症に影響を及ぼす因子を明らかにし，予防対策を講じることが求められる．

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CD28 Costimulation Controls Histone Hyperacetylation of the Interleukin 5 Gene Locus in Developing Th2 Cells*

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Interleukin 5 (IL-5) plays a unique role in allergic inflammatory responses, and the understanding of molecular mechanisms underlying the generation of IL-5-producing cells is crucial for the regulation of allergic disorders. Differentiation of naive CD4 T cells into type-2 helper (Th2) cells is accompanied by chromatin remodeling including hyperacetylation of histones H3 and H4 in the nucleosomes associated with the IL-4, IL-13, and IL-5 genes. Histone hyperacetylation of the IL-5 gene displayed a delayed kinetics compared with that of the IL-4 and IL-13 genes, suggesting a distinct remodeling mechanism for the IL-5-gene locus. Here we studied the role of CD28 costimulation in the generation of IL-5-producing cells and the histone hyperacetylation of the IL-5 gene locus. CD28-costimulation selectively enhanced histone hyperacetylation of the IL-5 gene locus that appeared to be mediated through NF-κB activation and subsequent up-regulation of GATA3. The CD28 costimulation-sensitive histone hyperacetylation spanned almost the entire intergenic region between the IL-5 and RAD50 accompanied with intergenic transcript. Thus, this is the first demonstration that CD28 costimulation controls a chromatin-remodeling process during Th2 cell differentiation.

Upon antigen recognition by T cell receptor (TCR),[1] naive CD4 T cells differentiate into two distinct helper T (Th) cell subsets, Th1 and Th2 cells (1). Th1 cells produce IFNγ and tumor necrosis factor-β and initiate cell-mediated immunity against intracellular pathogens. Th2 cells produce IL-4, IL-5, and IL-13 and are involved in humoral immunity and allergic responses. The cytokine environment is crucial in controlling the direction of Th cell differentiation (2, 3). For Th1 cell differentiation, IL-12-mediated activation of signal transducer and activator of transcription (STAT) 4 is required, whereas IL-4-mediated STAT6 activation is important for Th2 cell generation (4–6). In addition, TCR stimulation events upon encounter with antigens are also indispensable for both Th1 and Th2 cell differentiation. We reported that efficient TCR-mediated activation of the $p56^{lck}$, calcineurin, and Ras-extracellular signal-regulated kinase mitogen-activated protein kinase signaling cascade is crucial for Th2 cell differentiation (7–9). Recent studies have identified several transcription factors that control Th1/Th2 cell differentiation (10). Among them, GATA3 appears to be a master transcription factor for Th2 cell differentiation. GATA3 is selectively induced in developing Th2 cells, and the ectopic expression of GATA3 induced Th2 cell differentiation even in the absence of IL-4 or STAT6 (11–14). For Th1 cell differentiation, T-bet was recently identified as a key transcription factor (15).

CD28 costimulation enhances Th2 responses significantly (16, 17). Upon anti-CD28 mAb stimulation, phosphatidylinositol 3-kinase is recruited to CD28 and activated, and then subsequent activation of NF-κB is induced (18–21). It has been reported that GATA3 induction was an outcome of the CD28-induced NF-κB activation in T cells (22, 23). This may be a mechanism by which Th2 responses were enhanced by CD28 costimulation. It is also known that IL-5 production and IL-5-dependent airway inflammation are dependent on NF-κB family members (24–26).

Chromatin remodeling of the Th2 cytokine gene loci (IL-4/IL-5/IL-13) occurs during Th2 cell differentiation (27). A highly conserved 400-bp noncoding sequence 1 (CNS1) was identified, and an important role in coordinate expression of Th2 cytokines was revealed (28, 29). More recently, a 3′ distal IL-4 enhancer (V_A) containing an inducible DNase I hypersensitive site was identified (30). Reiner and co-workers (31) report that demethylation of the intron 2 region of the IL-4 gene was associated with cell cycle progression and Th2 cell differentiation (31). We reported that demethylation of this region is regulated by *polycomb* group genes (32) that are known to

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[1] The abbreviations used are: TCR, T cell receptor; Th cells, helper T cells; IFN, interferon; STAT, signal transducers and activators of transcription; IL, interleukin; mAb, monoclonal antibody; ELISA, enzyme-linked immunosorbent assay; CNS1, conserved noncoding sequence 1; ChIP, chromatin immunoprecipitation; GFP, green fluorescent protein; EGFP, enhanced GFP; RT, reverse transcription; IRES, internal ribosome entry site; CREB, cAMP-response element-binding protein.