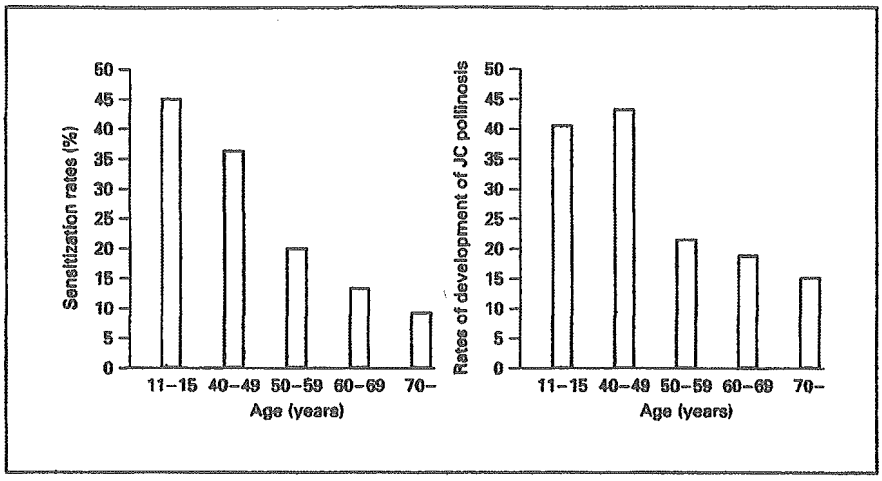

Fig. 1. Positive rates for serum IgE antibody to JCP (percentage of subjects with CAP RAST score of ≥2) and rates of development of JC pollinosis in subjects positive for the antibody (1995).

Subjects and Methods

As part of the medical examination of adult residents of the Maruyama Town, Awa-gun, Chiba Prefecture, located towards the southern tip of the Boso Peninsula, a questionnaire survey was conducted to determine whether they had developed JC pollinosis. This study was performed in June 1995. In this area, the JCP season is from early January to April. In 1995, the pollen count was high in this area. Among the local residents, 1,560 adults (647 men and 913 women) participated in the study; written informed consent was obtained after having adequately explained the objective of the study and its procedures. Serum IgE antibodies to JCP and to mites *(Dermatophagoides pteronyssinus)* were determined to investigate the sensitization rates of JC pollinosis and of mite allergic rhinitis to these antigens in all residents and any difference in the prevalence rate by age (cross-sectional research). Similar investigations were conducted with 292 children aged 11–15 years as part of the medical examination at elementary schools and junior high schools in the same district.

In June 1996, when the JCP count was low, medical examination, questionnaire survey and determinations of serum IgE antibody titer antibodies to JCP were conducted in the same 135 junior high school students who were examined in 1995, a year with a high pollen count.

In the same adult subjects who were examined in 1995, medical examination, questionnaire survey and measurement of serum IgE antibody titers to JCP and to mites were also conducted in 1999, 2000 and 2001 to investigate the changes in the above antibody titers as well as changes in rates of development of JC pollinosis and mite allergic rhinitis with aging (vertical-sectional research). Incidences of multiple sensitization to *Dactylis glomerata* and *Artemisia* were also examined in 2000.

Incidences of spontaneous remission and background factors of JC pollinosis were examined in subjects who had developed JC pollinosis symptoms in at least three successive seasons by 1995 and showed serum CAP (Pharmacia CAP System) radioallergosorbent test (RAST) score above 2 in 1995 and whose serum IgE antibody titers to JCP were measured more than once during the 3 years from 1999 to 2001. The specific antibody level (CAP RAST score) was classified as follows: score 6 = higher than 100 UA/ml; score 5 = 50.0–99.9 UA/ml; score 4 = 17.5–49.9 UA/ml; score 3 = 3.50–17.4 UA/ml; score 2 = 0.70–3.49 UA/ml; score 1 = 0.35–0.69 UA/ml; score 0 = less than 0.34 UA/ml. Generally a CAP RAST score of 2 or more is regarded as positive, a score of 0 is negative, and a score of 1 is equivocal.

A follow-up survey was conducted from 1995 to 2001 in subjects above the age of 40 who had a CAP RAST score to JCP of above 2 but did not develop JC pollinosis in 1995 during the period of the high JCP count to investigate the incidence and background factors of newly developing JC pollinosis after the age of 40 years in addition to the measurement of changes in serum IgE antibody titer to JCP.

Statistical Analysis

A significant difference was assessed by the Fisher exact test for categorical variables and the Mann-Whitney U test for continuous variables. Multiple logistic regression models were employed in order to analyze factors associated with remission and onset. Statistical analysis was performed with the JMP 5.0 (SAS Institute, Cary, N.C., USA).

Results

Changes in Serum IgE Antibody Titers to JCP and to Mites with Aging

Results of Cross-Sectional Research

Figure 1 shows positive rates for serum IgE antibody to JCP (CAP RAST score of ≥2) by age as well as rates of development of JC pollinosis by age in 292 elementary school and junior high school students aged 11–15 years measured after the JCP season in 1995. Sensitization rates reached 44.9% at this age. The rate of development of JC pollinosis in children with positive antibody to JCP reached 40.5%. Figure 1 indicates sensitization rates to JCP and rates of development of JC pollinosis compared

Table 1. Comparison of the number of children with JC pollinosis and serum IgE antibody titer to JCP in the same junior high school students between 1995 (high JCP count year) and 1996 (low JCP count year)

IgE antibody titer	Subjects	Mean serum IgE antibody titer to JCP (UA/ml)		Number of children with JC pollinosis	
		1995	1996	1995	1996
1995 ≥ 1996	121	9.31	5.42	30	43
1995 < 1996	14	2.72	4.35	3	8
Total	135			33	51

with each age group covering 10 years in 1,560 residents over the age of 40. A sharp decrease in sensitization rates with age was observed in subjects over the age of 40. The rate of development of JC pollinosis in subjects positive for IgE antibodies to JCP decreased rapidly over the age of 50 years.

Results of Vertical-Sectional Research

Chronological changes with age in serum IgE antibody titer to JCP were investigated in 162 adult subjects who showed a CAP RAST score ≥2 to JCP in 1995 and whose serum IgE antibody titers to JCP were measured in 1999, 2000 and 2001. In the Chiba Prefecture, the JCP count was high in 1995, low in 1999, moderate in 2000 and high in 2001. In subjects in their 40s, serum IgE antibody titers to JCP fluctuated depending on the pollen count and there was no effect of aging on the serum antibody titer to JCP. In subjects in their 60s and 70s, no correlation was observed between fluctuations of serum IgE antibody titers to JCP and the pollen count, while a variation of the antibody titer in subjects in their 50s was intermediate compared to subjects in their 60s and 40s (fig. 2).

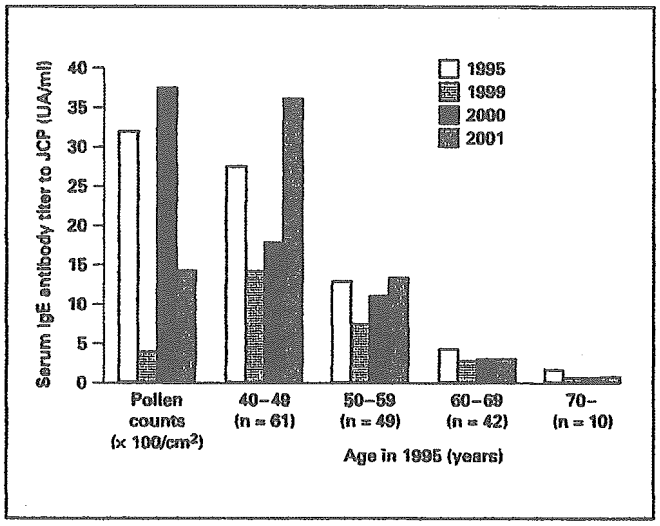

Fig. 2. Fluctuations of serum IgE antibody titer to JCP by age group over the 6 years from 1995 to 2001 in 162 subjects with a CAP RAST score to JC of ≥2 in 1995.

Because of the markedly decreased pollen count in 1996 compared to that in 1995, an increase of serum IgE antibody titer to JCP was observed in only 14 children and a decreased titer was seen in 121 of 135 junior high school students who were examined both in 1995, a year with a high pollen count and in 1996, a year with a low pollen count. Despite the above facts, JC pollinosis symptoms were observed in 1996 in all children except 1 of 33 who developed JC pollinosis symptoms in 1995, a year with a high pollen count. Moreover in 1996, 18 children newly developed JC pollinosis of 102 who did not develop the symptoms in 1995 (table 1).

Multiple Sensitization to Other Allergens in Subjects Positive for Serum IgE Antibody to JCP

In the investigation performed in 2000, children corresponding to 76.3, 59.3 and 16.9% of those who showed a CAP RAST score ≥2 to JCP were shown to have also been sensitized to mites, *D. glomerata* and *Artemisia*, with a CAP RAST score of ≥2 to each allergen. On the other hand, adult subjects aged over 40 years corresponding to 36.8, 54.7 and 23.6% of those who showed a CAP RAST score ≥2 to JCP were shown to have also been sensitized to mites, *D. glomerata* and *Artemisia* with a CAP RAST score of ≥2 to each allergen. Subjects who had been sensitized with 3 and 4 allergens including JCP were observed in 40.7 and 13.6% of children, respectively, and 25.7 and 10.4% of adults, respectively (fig. 3).

Spontaneous Remission of JC Pollinosis

Among 280 subjects aged over 40 years who showed a CAP RAST score ≥2 to JCP in the first examination performed in 1995, 56 subjects developed symptoms of JC pollinosis in more than three successive seasons including

Table 2. Background factors in subjects in whom spontaneous remission of JC pollinosis occurred compared with those who continue to have the disease

	Subjects with spontaneous remission (n = 9)	Subjects without spontaneous remission (n = 47)	p
Age (in 1995), years	61.1	48.7	0.002
Males	7/9	13/47	0.007
Age at the onset, years	50.8	40.2	0.027
Serum IgE antibody titer to JCP in 1995, UA/ml	4.7	40.7	<0.001
Complications by other allergic diseases	5/9	16/47	0.272
Predisposition	0/9	7/47	0.583

There were 280 subjects over the age of 40 in 1995 with a serum CAP RAST score to JCP of ≥2. Of these, 9 were asymptomatic in the last 3 successive pollen seasons (including 2001).

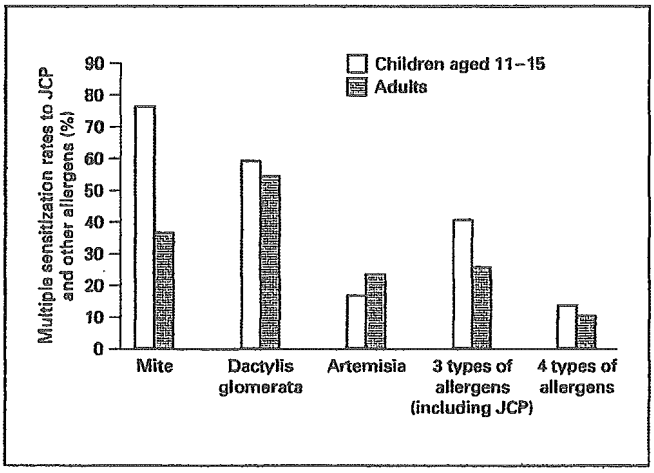

Fig. 3. Multiple sensitization rates (CAP RAST score of ≥2) in adult residents (n = 144/1,451) and children (n = 59/158) positive for JC antibody in 2000.

1995, and the serum IgE antibody titers to JCP were measured more than twice by 2001 in these 56 subjects. In 9 subjects among them, no JC pollinosis symptoms were observed during the last three seasons or more including 2001, a year with a high pollen count. These subjects were regarded as cases of spontaneous remission and examined regarding their background factors including age and serum IgE antibody titer to JCP at first examination, age at onset of JC pollinosis, age at disappearance of JC pollinosis symptoms, complications by other allergic diseases including perennial allergic rhinitis and their correlation with the incidence of predisposition (history of JC pollinosis in their parents, brothers and sisters). Serum IgE antibody titers to JCP in 1995 were 4.7 UA/ml in the spontaneous remission group and 40.7 UA/ml in the non-remission group. The comparison of their background factors with those of 47 subjects who continued to show JC pollinosis symptoms successively over the same periods of time demonstrated significant differences in sex, age at onset of JC pollinosis, age at first examination, and serum IgE antibody titer to JCP (table 2). In addition, the CAP RAST score was strongly associated with spontaneous remission in the multivariable model [odds ratio (OR) 48.99; 95% confidence interval (CI) 4.17–2,204.96]. In multivariate analysis, there was no significant effect on sex, age (in 1995) and age at the onset (table 3).

Onset of JC Pollinosis in Middle-Aged and Elderly Persons

Showing a CAP RAST score ≥2 to JCP in 1995, a year of an abundance of scattered JCP, 182 subjects over the age of 40 did not develop JC pollinosis. Among these subjects, serum IgE antibody to JCP was measured in a total of 151 subjects over the years 1999, 2000 and 2001, and 19 of these subjects developed JC pollinosis in the 6 years since 1995. Comparison of age, sex, complication, predisposition and serum IgE antibody titer to JCP of these subjects with those of subjects who did not develop JC pollinosis in these periods of time revealed that the mean age of the former is 50.7 years and that of the latter is 58.7 years, with the former age being significantly lower (table 4). In a multivariate analysis, age was associated with a lower risk of onset (OR 0.49 per 10 years; 95% CI 0.26–0.86). Predisposition was related to a higher risk (OR 5.06; 95% CI 0.94–22.80) (table 5). Since the number of

Table 3. Factors of spontaneous remission of JC pollinosis

Factor	OR	95% CI	p
Age (in 1995; per 10 years)	1.31	0.36–5.50	0.681
Male	9.49	0.90–286.80	0.097
Age at the onset (<40/≥40)	0.26	0.01–8.89	0.469
CAP RAST score (2/>2)	48.99	4.17–2,204.96	0.009
Complications by other allergic diseases	0.31	0.01–4.17	0.384

Table 4. Background factors in subjects who newly developed JC pollinosis after reaching 40 years of age compared with subjects positive for serum IgE to JCP who had not developed the disease

	Subjects who developed JC pollinosis (n = 19)	Subjects who did not develop JC pollinosis (n = 163)	p
Age (in 1995)	50.7	58.7	0.003
Males/females	10/19	99/163	0.622
Serum IgE antibody titer to JCP in 1995, UA/ml	24.5	4.8	0.118
Complications by other allergic diseases	0/19	9/163	0.008
Predisposition	3/19	7/163	0.073

There were 280 subjects over the age of 40 in 1995 with a CAP RAST score to JCP of ≥2. A total of 182 subjects had not developed symptoms of the disease by 1995. Of these, 19 subjects developed JC pollinosis in 1996 or thereafter.

Table 5. Factors of onset of JC pollinosis

Factor	OR	95% CI	p
Age (in 1995; per 10 years)	0.49	0.26–0.86	0.019
Male	1.03	0.33–2.95	0.963
CAP RAST score (2/>2)	0.55	0.18–1.73	0.296
Complications by other allergic diseases	4.08	0.91–17.09	0.057
Predisposition	5.06	0.94–22.80	0.040

subjects who newly developed the disease was larger than that of those in whom spontaneous remission occurred in their 40s, the prevalence rate of JC pollinosis in subjects positive for antibody to JCP increased with age. On the other hand, in subjects in their 60s or older, the incidence of subjects developing the disease newly decreased and the number of subjects in whom spontaneous remission occurred increased. Accordingly, a prevalence rate of JC pollinosis in subjects over the age of 60 positive for serum IgE antibody to JCP in 1995 decreased with age or remained low at the same level. The variation of the prevalence rate of JC pollinosis in patients in their 50s was intermediate in its pattern compared with that in patients in their 60s and 40s (fig. 4).

Discussion

In childhood, the sensitization rate to JCP and the prevalence rate of JC pollinosis increased with age, and subjects who developed the symptoms of JC pollinosis once continued to have it in the next pollen season even

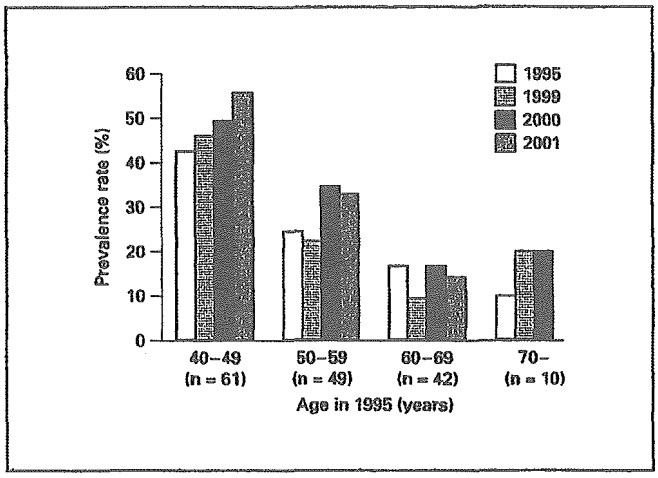

Fig. 4. Fluctuations of prevalence rates of JC pollinosis over a 6-year period in subjects with a serum CAP RAST score to JC of ≥2 by age group.

when the amounts of scattered JCP were remarkably reduced. Spontaneous remission hardly occurred at this age. In vertical-sectional research where the same adult subjects were followed up for 6 years, serum IgE antibody titer to mites significantly decreased with age in subjects over the age of 40 who were positive for serum IgE antibody to mites but this was not accompanied by double sensitization to JCP. It is considered that the potential of IgE production in B lymphocytes to mites antigen decreases with age from the age of 40 onward [6–9]. However in subjects with JC pollinosis serum IgE antibody titers to JCP did not decrease over a 6-year period in subjects in their 40s, and the IgE antibody titers to JCP are strongly influenced by the amount of pollens scattered. The difference in the variation of antibody titers to different antigens might have arisen from the difference in the amounts of antigen exposed and in the degree of their antigenic potency between patients with JC pollinosis and those with perennial allergic rhinitis due to mites. After the age of 60 years, differences in the amounts of JCP scattered did not affect the IgE antibody titer to JCP, while at the age of 50, the variation of the titer was intermediate in its pattern compared to those at the age of 60 and 40. The above data are in agreement with the fact that spontaneous remission of JC pollinosis was observed in subjects from the age of their late 40s and at the highest incidence in those in their 60s.

There have been very few reports on spontaneous remission of pollinosis, while there are large differences in the spontaneous remission rates given by different authors. From the results of a follow-up study in 738 university students with pollinosis conducted 23 years after graduation from the university, Greisner et al. [10] reported that the symptoms of pollinosis disappeared in 22.9% of the subjects, while they remained but were improved in 32%, remained unchanged in 33.3% and were exacerbated in 9.2%. For evaluating the results, however, changes in the environment as regards exposure to pollens due to changing their place of residence after graduation should be taken into consideration. Broder et al. [11] reported that spontaneous remission of pollinosis was observed in 5% of females and 10% of males during a 5-year follow-up period in examinations of 6,563 residents with a high incidence of spontaneous remission in subjects aged 45 years or more. On the other hand, Danielsson and Jessen [12] reported after their 12-year follow-up of 82 subjects that a disappearance of JC pollinosis symptoms was observed only in 1.2% (1/82), while the symptoms were improved, remained unchanged and worsened in 39, 39 and 21% of subjects, respectively. According to Smith [13], 10 (8.9%) of 112 children became asymptomatic 5 years later. Since there are significant differences in the incidence of spontaneous remission of allergic rhinitis for all types of antigen, the amount of antigen to which the subjects are exposed, age distribution, severity of the disease and the length of the follow-up period, and a consolidation of the definition itself of the term of spontaneous remission are considered necessary.

When the subjects studied were limited to those whose ages at first examination were over 40 and whose CAP RAST scores to JCP were more than 2, spontaneous remission was observed in 16.1% of subjects in the 6-year follow-up period. Although spontaneous remission rates of JC pollinosis are significantly higher in subjects over the age of 60, the overall rate in subjects including children was several percent lower than reported until now. Cases in which spontaneous remission cannot be expected will likely increase, as children with JC pollinosis and patients with a predisposition to JC pollinosis increase.

Since there might be large differences in environmental factors from childhood to the age of onset of pollinosis, including diet, residence and many other factors between patients with JC pollinosis aged 10–20 at present and those aged 60 or more, it is difficult to predict and compare future incidences of spontaneous remission in these two groups in a similar straight line. Further long-term vertical-sectional follow-up research is required to understand the natural history of JC pollinosis.

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Allergic rhinitis in children: environmental factors

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Summary
Increasing numbers of patients with allergic rhinitis are being noted on a global scale. Over 90% of Japanese patients with perennial allergic rhinitis show allergic reaction to the mite antigen and major pollen allergens such as Japanese cedar and Japanese cypress, which are carried long distances (> 100 km) by wind and hence can produce substantial harmful effects even in metropolitan areas. This situation is distinct from that in the West, where the most common anemophilous allergen, ragweed, travels much shorter distances of up to only several hundred metres. Environmental factors such as increased antigen, air pollution, diet, intestinal microflora, decreased incidence of infections, smoking, breastfeeding and vaccination may play important roles in the development and manifestation of allergic rhinitis in genetically predisposed subjects. In particular, in newborn infants, who carry the Th2 predominant state, environmental factors may greatly affect the development of balanced production of Th1 and Th2 cytokines. However, the contribution of any environmental factor to the postnatal development of allergic rhinitis has not been sufficiently determined. A better understanding of the processes involved may lead directly to better treatment or cure of allergic rhinitis.

Keywords air pollution, allergen, allergic rhinitis, dietary lifestyle, environmental factors, hygiene theory, intestinal microflora, parasite, tuberculin reaction, viral infection

Introduction

In recent years, many countries have experienced the problem of increasing prevalence of nasal allergy, with > 90% of patients with perennial allergic rhinitis showing allergic reaction to mite antigens [1]. The major pollinosis allergens in Japan are tree pollens such as sun tree (Japanese cypress) and evergreen tree (Japanese cedar), which can spread > 100 km from source and hence affect people living in metropolitan areas. This situation is distinct from that in the West, where the most common allergen is ragweed, which travels shorter distances of up to several hundred metres. Japanese cypress is widely distributed in Japan, predominantly to the west of the Kanto (Tokyo surrounding) region. Cedar pollen and cypress pollen share a common antigen and > 70% of Japanese patients with cedar pollen allergy also develop cypress pollinosis [1].

Although a well-controlled epidemiological study has yet to be conducted in Japan, questionnaire-based data suggest that cedar/cypress pollen allergy has a prevalence of 10–20/100 people nationwide. This figure varies considerably among the regions of the country, being lower than average in Hokkaido and Okinawa to the far north and far south, respectively [2, 3].

The age distribution curve of nasal allergy patients exhibits a bimodal pattern with two peaks: at ages 20s–40s affecting predominantly females and at approximately 10 years where males are more affected. It is generally regarded that the onset of perennial nasal allergy due to mite antigens begins in children and that of pollinosis is seen mainly in adult females. Recently, however, the age of onset of pollinosis appears to be decreasing.

A recent report by the Japan Ministry of Health, Welfare and Labor [4] has shown an increasing trend in the annual prevalence rate of allergic rhinitis among infants and children (Fig. 1). Furthermore, scratch tests of Japanese schoolchildren with nasal allergy indicate that besides mite antigens, children are also sensitized at high rates with many other allergens including Japanese cedar, cypress, orchard grass and ragweed pollen [3].

About 7% of patients with Japanese cedar pollinosis show spontaneous resolution of allergic reaction within a 10-year period after the onset of symptoms; elderly patients with initial symptoms after age 50 years are more likely to undergo spontaneous regression, whereas younger patients may not [5].

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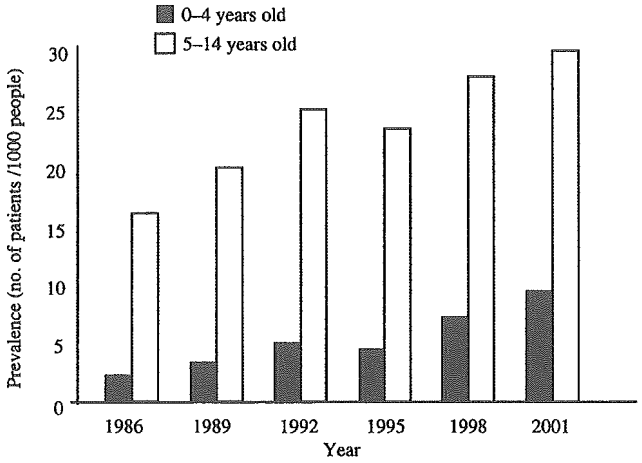

Fig. 1. Prevalence of allergic rhinitis (number of patients/1000 people) in Japanese children. Data from the Japan Ministry of Health, Welfare and Labor [4].

Onset of allergic rhinitis

As is seen with many other diseases, both genetic and environmental factors appear to be involved in the onset of allergic rhinitis. It is well known that family history is relevant to the onset of nasal allergy. For example, among identical twins concurrent onset is seen at high rates [6]. Furthermore, recent progress in genetic analysis has revealed the presence of genes regulating reactivity to leukotrienes [7] as well as cytokine-producing ability, both of which are involved in allergic responses. However, environmental factors appear to play a major aetiological role as even among identical twins the influence of genetic factors is calculated at < 70%, and nasal allergy prevalence rates are known to increase among immigrant populations moving from developing to developed countries. At least one report has stated that environmental factors play the most important role in the recent increase of allergic diseases [8].

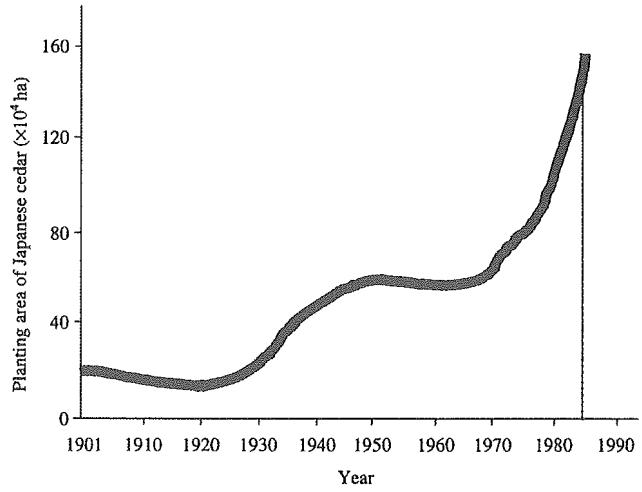

Fig. 2. Planting area of Japanese cedar aged > 30 years.

Table 1. Time-course of number of mites in house dust in Japan

Year	No. of mites (per g house dust)
1964	600
1976	1100
1983	1250

Environmental factors

Increase of allergens

Levels of environmental allergens are rising. In Japan, the amount of airborne Japanese cedar pollens has increased dramatically; after World War II, an extensive afforestation programme with Japanese cedar was initiated because of the fast growth rate of this species and its value as a building material. Figure 2 shows the planting area of Japanese cedar aged > 30 years, which produces the most pollen [9]. In addition, mites have also increased vastly in number in Japan (Table 1) due to the extensive use of concrete for houses, which provides high humidity and favourable temperatures for propagation [10].

Air pollution

Air pollution due to ozone, nitrogen oxides and sulphur oxides has been pointed out as contributing to morbidity due to allergic rhinitis [11–14]. Although not implicated directly in the development or enhancement of allergic sensitization, these environmental factors have been shown to aggravate allergic symptoms. More recently, discharge of diesel exhaust particles (DEP) from automobiles, rather than industrial soot and smoke, has attracted particular attention following reports that DEP challenge can lead to overproduction of IgE and increased permeability of the nasal mucosa membrane [15, 16]. Binding of DEP to cedar pollen grains during their long-distance travel has also been observed and may contribute to the promotion of cedar-specific IgE production.

Change of dietary lifestyle and intestinal microflora

Recently, consumption of fish rich in n-3 polyunsaturated fatty acid has been decreasing in Japan, whereas that of meat containing high amounts of n-6 polyunsaturated fatty acid is increasing [17]. Some studies have suggested that administration of n-3 polyunsaturated fatty acid improves symptoms in Japanese children with asthma [18]. However, the benefits of this treatment in allergic rhinitis have not been elucidated.

Lifestyle changes in diet tending towards high protein and fat intake also greatly affect the intestinal microflora, which in turn has significant effects on the body's immune reactions. For example, in germfree mice lacking intestinal microflora, IgE production was accelerated, whereas on normalization of intestinal bacterial flora IgE production was restored [19]. Another interesting study of the human

intestinal microflora reports that in Estonia, where the allergy prevalence rate is low, the human intestinal microflora mainly consists of eubacteria and enterococci [20]. However, in Sweden where high allergy prevalence is observed, the microflora comprises mainly *Bacteroides* and *Clostridium* species whereas 35 years ago both the microflora and prevalence were similar to those currently seen in Estonia [20]. This suggests that increases in allergy prevalence in Sweden may reflect changes in gut microflora.

Infectious diseases

Infectious diseases may also play a role in the aetiology of allergic rhinitis. Th2 cytokines such as interleukin (IL)-4 and IL-5 are involved in the stimulation of IgE production as well as migration and activation of eosinophil leucocytes and mast cells. On the other hand, the Th1 cytokines interferon (IFN)-γ and IL-2 assist in the activation of monocytes and cellular immunity. Many allergic patients exhibit dysregulated production of Th1 and Th2 cytokines, exhibiting predominant Th2 cytokines imbalance. Tuberculosis is a typical infectious disease that induces Th1 cytokine production; among representative diseases capable of activating the Th2 system, parasitic infections such as helminth infection are examples. Relating to this, there have been a number of reports suggesting that modern decreases in helminthiasis may have had a direct causative role in the rise of allergic diseases [21–23].

Parasite infection

To clarify the relationship between intestinal parasite infection and allergic rhinitis, we examined high-school students in Ecuador where parasitic infections are common. Clinical history, nasal inspection, eosinophilia in nasal discharge, skin scratch testing and measurement of antihouse dust (HD)-specific IgE and total IgE levels in serum were recorded. Parasitological evaluation included examination of stool samples and quantification of specific anti-ascaris IgE levels in serum. Figure 3 shows the incidence of nasal allergy and detection rate of parasite infection. Students with helminths in stool samples demonstrated significantly lower incidence rates of HD allergic rhinitis than those with protozoan infections. Although this would seem to indicate that helminthic infection may protect against the development of allergic rhinitis and that protozoan infection may promote this allergy, there was a significant correlation between anti-HD IgE and anti-ascaris IgE ($r = 0.615$, $P < 0.01$) (Fig. 4). Antihelminthiasis IgE is thought to participate in elimination of helminths. Allergic patients had Th1/Th2 cytokines imbalance resulting in Th2 predominance; hence, when infected, patients with allergic rhinitis produced substantially higher levels of antihelminth IgE compared with those without rhinitis. This IgE production may persist for some period to prevent chronic infection or reinfection. The rate of positive skin scratch tests for HD in students with serum anti-HD

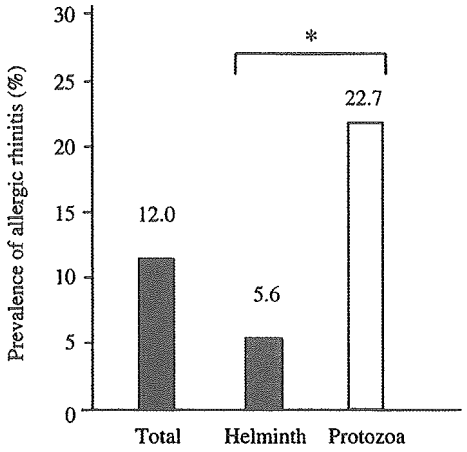

Fig. 3. Prevalence of allergic rhinitis in children with parasitic infection. Children exhibiting parasites in stool demonstrate significantly lower incidence rates of house dust allergic rhinitis than those with protozoan infections. *$P < 0.05$.

IgE antibody showed no significant difference when comparing skin test results stratified by total IgE levels (data not shown), suggesting that even with high concentration of total serum IgE, the allergen-specific antibody is able to bind to its specific Fc receptor on mast cells, indicating a nonsaturated state. In our study, evidence for helminthic infection affecting the development of HD allergic rhinitis was inconclusive.

Tuberculin reaction and BCG vaccination

Shirakawa et al. [24] studied the relationship between tuberculin reactions and allergic reactions by comparing the same cohort of Japanese junior high-school students at ages 6 and 12 years. Students who had negative response to tuberculin test at both 6 and 12 years of age showed significantly high prevalence rates of nasal allergy and asthma as well as high IgE values in blood as compared to those who were positive. This leads to the possibility that the recent decrease in tuberculosis infection may have

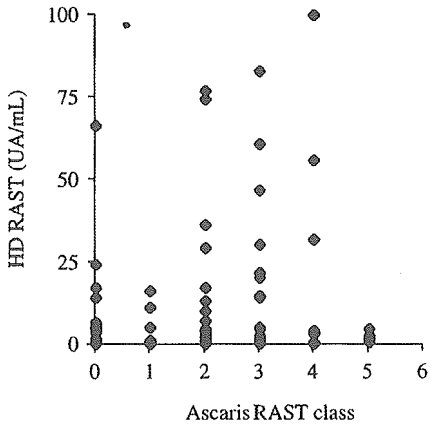

Fig. 4. Relationship between antihouse dust IgE and anti-ascaris IgE. A significant correlation ($r = 0.615$, $P < 0.01$) between anti-HD IgE RAST and anti-ascaris IgE scores is seen.

caused the high prevalence of allergic disease. However, the relationship between the tuberculin reaction and prevalence of allergic rhinitis remains controversial [25–28]. BCG vaccine is known to strongly induce Th1 cytokines and some studies have suggested that administration of BCG vaccine might reduce IgE levels of patients, including those with allergic rhinitis [29, 30]. However, it is not clear whether BCG vaccine-induced strong Th1 response in patients in whom Th2-dominant immune deviation has been established is able to improve their allergy symptoms.

Viral infection

The nasal cavity, the most frontal part of respiratory tract, is often the target of viral infection, although no relationship between such infections and allergic rhinitis has been defined [31, 32]. The common cold is the most widespread viral infection, usually induced by rhinovirus, parainfluenza virus, adenovirus and respiratory syncytial virus (RSV) [33]. We examined histamine sensitivity, defined as the lowest intranasally administered histamine concentration needed to induce sneezing attack in nonatopic patients with the common cold. During the early 3–4 days of common cold, increased nasal sensitivity to histamine was observed; however, this hypersensitivity was transient and returned to baseline values several days later. Histamine concentration of nasal wash in both the acute phase and covalescent phase of these patients showed no significant difference. Thus common cold induces transient nasal hypersensitivity that is not correlated with histamine concentration.

The mechanism of hypersensitivity to viral infection includes impairment and shedding of epithelial cells and concomitant exposure of sensory nerve endings [34]. In addition, viral infection may directly affect the nasal mucosal immunity. After RSV inoculation of isolated human nasal epithelial cells *in vitro*, both enhanced production of IL-6 and GM-CSF and increased ICAM-1 mRNA expression were observed [35]. Furthermore, tonsillar cells adherent to RSV-infected nasal epithelial cells produced more IL-4 than nonadherent cells (Fig. 5). However, no significant difference was observed for IFN-γ production in these tonsillar cells.

In another study, BALB/c mice were infected intranasally with RSV then treated with ovalbumin (OVA) by nebulizer, and the antibody response to OVA determined [36]. IgG anti-OVA antibody was significantly higher in RSV-infected than control mice, and furthermore IgE anti-OVA antibody, although in low concentrations, was detected only in the infected animals (Fig. 6). Thus RSV infection may augment the antibody responses including IgE to inhaled antigens. To examine further the influence of RSV infection in OVA-sensitized mice, B6 mice were sensitized with OVA administered intraperitoneally followed by intranasal infection with RSV (manuscript in preparation). Three days later, nasal sensitivity to OVA and to histamine was examined. Nasal rubbing attacks in response to both OVA and histamine challenge were

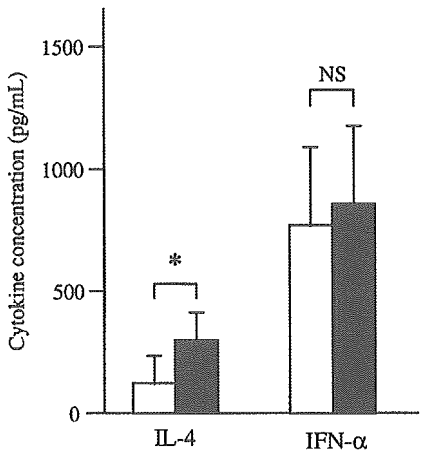

Fig. 5. Cytokine levels in tonsillar lymphocyte culture not bound (□) and bound (■) to RSV-infected nasal epithelial cells. Tonsillar cells adherent to RSV-infected nasal epithelial cells produced more IL-4 but not IFN-γ compared with nonadherent cells. $^*P<0.05$. Reprinted with kind permission of Blackwell Publishing from Matsuzaki et al. [35].

enhanced dramatically in RSV-infected mice compared with noninfected mice (Fig. 7). The eosinophil number in the nasal mucosa was also highly increased in RSV-infected animals. Thus acute viral infections enhance the responses to subsequent OVA sensitization as well as strongly enhancing the sensitivity of prior-sensitized mice.

The hygiene theory

The hygiene theory propounds that decreases in infections acquired during early childhood may be responsible for the increasing prevalence of allergic diseases in the population [37]. In support of the theory, the frequency of several allergic diseases including allergic rhinitis has been shown to be inversely associated not only with childhood infections [38, 39] but also with the number of siblings [40, 41]. The presence of older siblings naturally exposes children to more infections during early childhood and protects

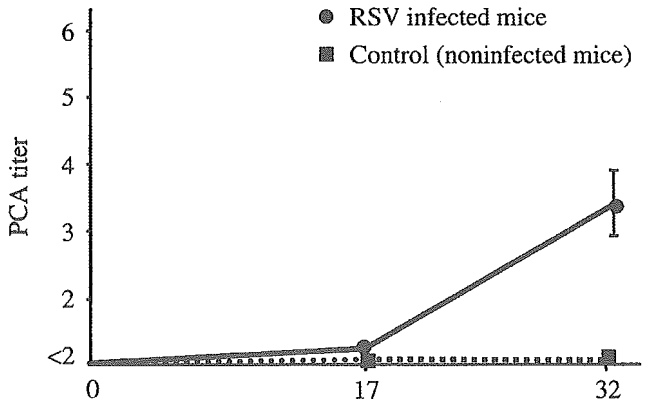

Fig. 6. Detection of IgE anti-OVA antibody in BALB/c mice intranasally infected or sham-infected with RSV then treated with OVA. Reprinted with kind permission of the Society for Experimental Biology and Medicine from Freihorst et al. [36].

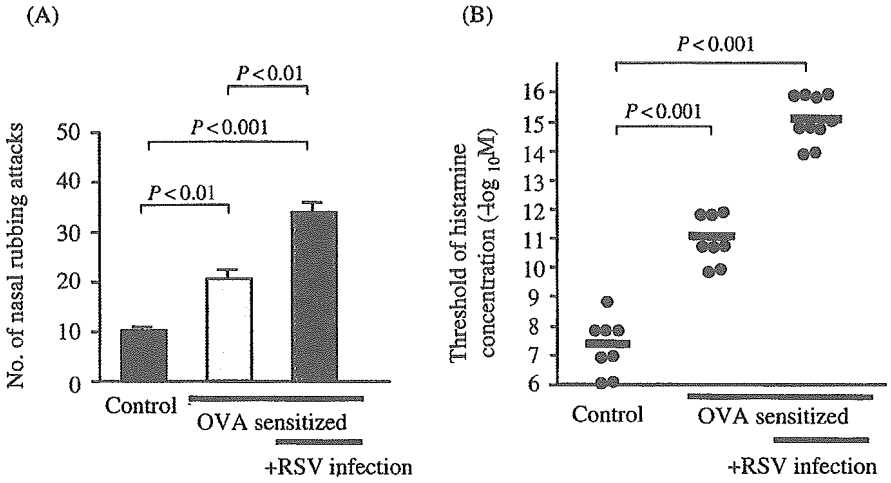

Fig. 7. Nasal rubbing attacks on provocation test with OVA (A) and sensitivity against nasally administered histamine (B) in B6 mice. Control: non-OVA sensitized, non-RSV infected mice; OVA sensitized: OVA sensitized but not RSV infected mice. OVA sensitized + RSV infection: OVA sensitized followed by RSV infected mice.

against the subsequent development of allergic diseases. Children who attend daycare are also known to have more frequent infections than those who remain at home. In a Japanese study [42], the presence of more older siblings at home had a protective effect against the development of allergic rhinitis (Table 2). However, studies examining the relationship between lower infection rates and the development of allergic rhinitis have produced either conflicting results or failed to establish any association [43]. Viral infection may induce Th2 cytokines and airway hypersensitivity and promote IgE synthesis; G glycoprotein of RSV is known to be a strong inducer of Th2 cytokines [44]. The nasal immune response to viral infection may depend on the type of virus as well as the age and immune condition of the patient [45, 46].

The role of bacterial infection in allergic rhinitis is also not clear. Although transient nasal hypersensitivity has been observed during the acute phase of common cold, the threshold for sneezing was rather higher if the patients had purulent rhinorrhoea of secondary bacterial infection [47]. However, no theory has been put forward to explain this effect.

Conclusions

To maintain pregnancy, the womb has evolved a Th2-dominant environment [48]. Following delivery, the Th2-dominant state prevails in the newborn infant into early life, when it is speculated that environmental factors such as viral infections, air pollution and diet greatly influence the development of well-balanced Th1/Th2 milieu [49].

In Japan, 50–80% of university students are estimated to be sensitized to Japanese cedar pollen [3]. Nowadays, people who are thus sensitized and carrying IgE antibody can be seen everywhere. Forecasts of cedar pollen scattering and predictions of the number of patients with Japanese cedar pollinosis are common. However, while the patient numbers keep rising, no solution has been given to the underlying problems and no end to the epidemic is in sight. The situation must be handled as a social matter. To fully understand nasal allergy, it is necessary for physicians to conduct accurate, large-scale epidemiological investigations to clarify the causes of the increased prevalence of allergic rhinitis. Subsequently, society as a whole will have to face and tackle the grave health problems presented by this epidemic.

Table 2. Difference in prevalence of allergic rhinitis in Japanese siblings

Child	Allergic rhinitis (%)
Oldest	8.2
Second	6.3
Third	4.9
Fourth	3.1

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Treatment options for children with allergic rhinitis

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Summary
Allergen avoidance, pharmacotherapy, immunotherapy and surgical procedures are indicated for the treatment of allergic rhinitis (AR) in children. Antihistamines are the usual pharmacotherapeutic option; however, second-generation antihistamines are of limited availability in Japan. Immunotherapy is the only strategy that can offer remission or cure of paediatric AR.

Keywords Allergen avoidance, immunotherapy, laser surgery, pharmacotherapy, second-generation antihistamines, topical corticosteroids

Introduction

The principles of treatment of allergic rhinitis (AR) in children are similar to those applied in adult patients. Current practical guidelines for the treatment of AR in Japan [1] recommend allergen avoidance measures, pharmacotherapy, immunotherapy and surgical procedures. The goals of therapy, dependent on the patient's disease profile, include elimination or reduction of symptoms so as not to disturb the patient's daily life, with little need for rescue medication; control of symptoms with low frequency or short duration of exacerbations; and absence of triggering of symptoms by nasal allergen provocation.

Children with AR usually present with the following characteristics: males are more affected than females, and paediatric AR patients probably have symptoms throughout the year due to house dust mite allergen. In addition, the child's nose is often anatomically narrow and easily obstructed with congestion, leading to nasal blockage.

Treatment

A range of treatments has been developed for AR in children. Good doctor communication with patients and their guardians is essential. Elimination and avoidance of allergen, pharmacotherapy, allergen-specific immunotherapy and surgical procedures are recommended management strategies. Treatment options for allergic rhinitis are summarized below [1]:

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1 Communication with patients;
2 Elimination and avoidance of allergens:
   - mites: cleaning, dehumidification, impermeable covers, etc.
   - pollen: wearing masks, glasses, etc.
3 Pharmacotherapy:
   - antihistamines: first-generation, second-generation (topical, oral)
   - antileukotrienes, antithromboxane A_2 (oral)
   - mast cell stabilizers (topical, oral)
   - corticosteroids (topical, oral)
   - autonomotropic agents (alpha-adrenergic, anticholinergic)
4 Specific immunotherapy (conventional, rush)
5 Surgical procedures:
   - cautery: electrical, laser, chemical (trichloroacetate);
   - resection: deviatomy, conchotomy, submucosal turbinectomy; and
   - lateral posterior inferior nerve neurectomy, vidian neurectomy, etc.

Allergen avoidance

The first step towards controlling AR is to reduce or avoid exposure to allergen. The Japanese practical guidelines [1] include useful tips on how to take measures to reduce house dust mite and pet allergens in the home.

Pharmacotherapy

Medical therapy is recommended according to the severity and type of AR in Japanese patients. Table 1 shows some treatment choices for AR in adults. In moderate cases with symptoms of sneezing and runny nose, second-generation antihistamines, mast cell stabilizers and intranasal corticosteroids are recommended. Concomitant topical corticosteroids may be used with antihistamines or mast cell

Table 1. *Treatment of allergic rhinitis in adults. Medicines are stepped down when nasal symptoms are well controlled after several months of treatment (adapted with permission from Baba et al. [1])*

	Severity				
	Mild	Moderate		Severe	
		Symptoms: sneezing and rhinorrhea	Symptoms: nasal obstruction	Symptoms: Sneezing and rhinorrhea	Symptoms: nasal obstruction
Treatment	1. Second-generation antihistamines	1. Second-generation antihistamines	1. Antileukotrienes	Topical steroids + second-generation antihistamines	Topical steroids + antileukotrienes or anti-TXA_2
	2. Mast cell stablilizers	2. Mast cell stabilizers	2. Anti-TXA_2		
		3. Topical steroids	3. Topical steroids		Topical decongestants for < 5–7 consecutive days as necessary
	Either 1 or 2	Either 1, 2 or 3 Combine 3 with either 1 or 2 if necessary	Either 1, 2 or 3 Combine 3 with either 1 or 2 if necessary		
			Surgical procedures		
		Specific immunotherapy			
	Elimination and avoidance of allergen				

stabilizers if necessary. In contrast, in moderate cases with nasal blockage antileukotriene or antithromboxane A_2 is recommended. Intranasal corticosteroids are the first-choice recommendation in severe cases. In addition, second-generation antihistamines are prescribed in patients with sneezing and runny nose, while antileukotriene or antithromboxane A_2 are indications for those with nasal blockage.

The anti-allergic medicines, including Th2 cytokine blocker, available in Japan are listed in Table 2. However, not all the medications available for the management of AR in adults are indicated for use in children. Among second-generation antihistamines only ketotifen and mequitazine are currently available for use in paediatric patients in Japan.

Mast cell stabilizers such as cromoglycate disodium, tranilast and pemirolast are approved for use in children in Japan. Cromolyn sodium is applied topically; tranilast and pemirolast are administered orally.

Intranasal corticosteroids are highly effective in relieving AR symptoms such as sneezing, rhinorrhoea and nasal

Table 2. Anti-allergic medicines for allergic rhinitis in Japan

	Generic name (Brand name)	Administration
Antihistamines (second-generation)	Ketotifen (Zaditen)*	Oral, topical
	Oxatomide (Celtect)	Oral
	Azelastine (Azeptin)	Oral
	Mequitazine (Zesulan, Nipolazine)*	Oral
	Emedastine difumarate (Daren, Remicut)	Oral
	Epinastine hydrochloride (Alesion)	Oral
	Ebastine (Ebastel)	Oral
	Cetirizine hydrochloride (Zyrtec)	Oral
	Levocabastine hydrochloride (Livostin)	Topical
	Bepotastine besilate (Talion)	Oral
	Fexofenadine (Allegra)	Oral
	Olopatadine (Allelock)	Oral
	Loratadine (Claritin)	Oral
Antileukotrienes	Pranlukast hydrate (Onon)	Oral
Antithromboxane A_2	Ramatroban (Baynas)	Oral
Mast cell stablilizers	Sodium cromoglycate (Intal)*	Topical
	Tranilast (Rizaben)*	Oral
	Amlexanox (Solfa)	Oral, topical
	Pemirolast potassium (Alegysal, Pemilaston)*	Oral
	Suplatast tosilate (IPD)	Oral

*Available for children.

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blockage. In Japan, beclomethasone dipropionate (for children aged ≥ 6 years) and fluticasone propionate (≥ 5 years) are currently available.

In children with AR complicated with asthma and in moderate or severe cases of adult AR of nasal blockage type, antileukotriene or antithromboxane A_2 are recommended.

Immunotherapy

Double-blind placebo-controlled studies have suggested that immunotherapy may be efficacious against allergies towards bee venom, pollens, mites, cat dander, and molds [2]. Ohashi et al. [3] reported that 5–10 years' immunotherapy in children may lead to suppression of interleukin (IL)-4 and specific IgE antibodies. Conventional immunotherapy requires frequent injections up to maintenance doses, with some minor reported risk of anaphylactic reactions. However, this therapy is currently the only means offering long-term remission or cure of AR.

Surgery

Surgical procedures in the AR setting are recommended only in certain patients such as those with severe nasal obstruction due to inferior turbinate hypertrophy and/or nasal septum deviation. However, such procedures are very limited in children for anatomical reasons. Of the available methods, laser surgery is easily conducted in children. Kubo has shown good relative effectiveness of laser surgery in children aged < 12 years compared with adults in terms of better improvement of nasal symptoms after 2 years of surgery (N. Kubo, personal communication 2003). However, the precise mechanism for this is not clear.

Conclusions

The first step in controlling nasal symptoms is to eliminate or avoid environmental allergens. Pharmacotherapy should be based on the severity and type of AR. Antihistamines control sneezing and rhinorrhoea effectively but are less effective against nasal blockage. However, these medications currently are of only limited availability for children in Japan. Topical corticosteroids are highly effective in controlling most nasal symptoms and are available for use in children aged ≥ 5 years. Immunotherapy is the only measure that currently might offer remission or cure of AR and thus should be considered in appropriate cases. Further research aimed at minimizing the risk of systemic adverse reactions to conventional immunotherapy will help popularize the use of this option.

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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

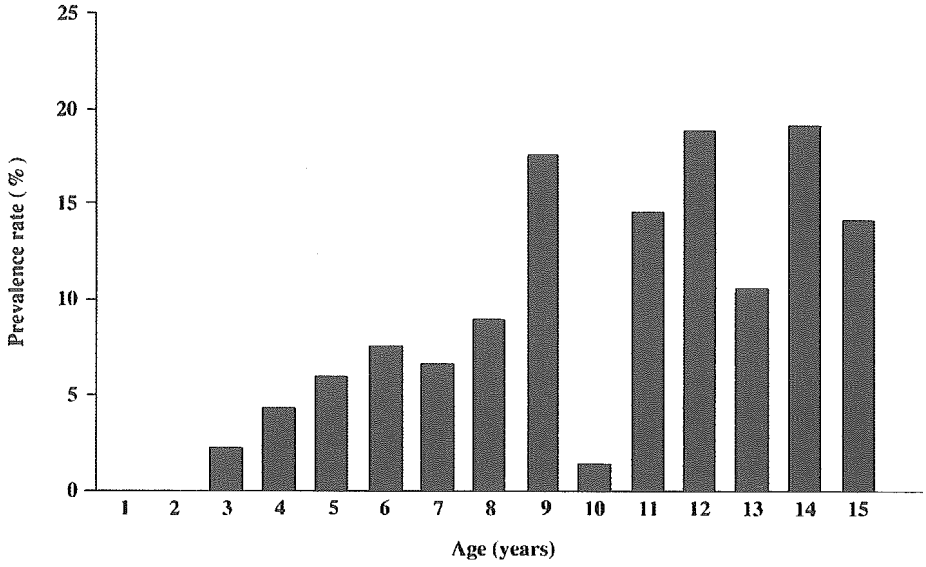

Fig. 1. Prevalence rate of JCP in children.

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.

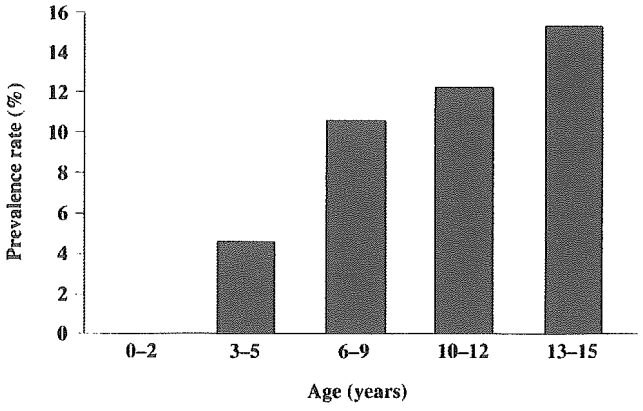

Fig. 2. Prevalence rate of JCP in children stratified by age.

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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Original Article

Effect of fexofenadine on the quality of life of Japanese cedar pollinosis patients

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Abstract

Background: The aim of the present survey was to investigate the changes associated with fexofenadine administration in the quality of life (QOL) of Japanese cedar pollinosis patients.

Methods: After obtaining informed consent, volunteers suffering from Japanese cedar pollinosis were divided into two groups: (i) the fexofenadine group (2 × 60 mg/day); and (ii) the placebo group. Changes in QOL were examined after administration for 14 days (randomized, double-blind comparison study). The study period was from 27 February to 13 March 2003. Subjects were recruited from the Tokyo metropolitan area; 104 were randomized to the fexofenadine group and 103 were randomized to the placebo group. The QOL was evaluated using the Japanese Allergic Rhinitis Standard QOL Questionnaire (JRQLQ no. 1). The JRQLQ is structured to evaluate six domains of usual daily activities, outdoor activities, social functioning, sleep problems, general physical problems and emotional function, as well as the overall QOL.

Results: On the 14th day after the start of fexofenadine or placebo administration, the QOL was improved in all domains of the JRQLQ in the fexofenadine group, whereas it had worsened in all domains, except outdoor activities, in the placebo group. The overall evaluation of QOL was significantly more favorable in the fexofenadine group on the 14th day after the start of administration.

Conclusions: The present study showed that fexofenadine administration suppressed the deterioration of overall QOL and alleviated the interference with daily life in patients suffering from Japanese cedar pollinosis.

Key words: allergic rhinitis, cedar pollinosis, daily life, fexofenadine, quality of life.

Introduction

Allergic rhinitis does not threaten life directly, but it has a significant impact on the quality of life (QOL) and sometimes restricts the daily activity of patients. Furthermore, allergic rhinitis symptoms influence study and work conditions, inflicting a significant burden socially and economically. In Japan, approximately 15% of the population nationwide suffers from cedar pollinosis.[1]

Many types of therapy are used for the treatment of allergies, including pollinosis. Among the most frequently used pharmacotherapies, antihistamines are often the drugs of choice. Antihistamines relieve symptoms, but they do not cure the disease. With antihistamines, patients can spend their daily life more comfortably and productively.

Fexofenadine HCl was approved as an antihistamine against allergies in September 2000 in Japan and it is currently used widely. Abroad, it has been approved in 102 countries, including the US, UK, France and Germany, and, as of March 2000, fexofenadine HCl was marketed in 57 countries.

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