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Review Article

Clinical aspects of Japanese cedar pollinosis

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Abstract

Japanese cedar pollinosis (JCPsis) is a major national health problem in Japan. The present review provides an update on information on JCPsis based on clinical data from our research group, through the support of the Department of Health and Welfare (Japanese Government), during the period from 1988 to 1997, because this disease is infrequently documented internationally despite a large number of publications from Japan. The information on JCPsis presented here may be of use in the management of various kinds of pollinosis prevalent in other countries. The prevalence rates of JCPsis vary from district to district and also depend on the age of the subjects, the method of analysis and the year of examination in population. Yet, on an average, the incidence of JCPsis is presumed to be 10–20% in adults and 5–10% in children. The risk factors for sensitization and the onset of symptoms seem to be dependent on the amount of air-borne pollen, the age of school children, hereditary disposition, including human leukocyte antigen type and the high levels of specific IgE in childhood. Because pollen counts also vary depending on many factors, such as the type of pollen samplers used, yearly variations, the number of pollen count stations, the atmospheric temperature and solar radiation in the previous year of the season, accurate predictions of daily and seasonal pollen counts are rather difficult. Commercial crude extracts and purified allergenic substances Cry j I and II correlate well with the skin test and the radioallergosorbent test. Japanese cedar pollen has an allergenic component that is cross-reactive with Japanese cypress. In many patients, the onset of symptoms occurs on the day when the air-borne pollen count is 10 /cm^2 (the Durham method) and, if severe symptoms occur due to intense exposure to pollen, the symptoms will last for a long time despite variations in the pollen count (priming effect). Eye glasses, face masks and keeping windows and doors of the house closed are useful measures for pollen avoidance. Symptom control during the season is not difficult by the continuous use of new anti-allergic drugs during the season. If medication is started 1–2 weeks prior to the onset of the season, more satisfactory results can be obtained. Specific immunotherapy can not only control symptoms, but can reduce the amount of medication and, after completion of the regimen, long-term remission without medication can be expected.

Key words: Japanese cedar pollinosis, management, pollen survey, prevalence, risk factor.

Introduction

In plant taxonomy, cedar trees belong to *Cryptomeria* D. Don, Toxadiaceae, Gymnospermae. Based on the analysis of fossil pollens, it is supposed that Toxadiaceae appeared 70 million years ago and were almost completely destroyed 10–20 million years ago during the glacial period; only the cedar trees survived the severe conditions and were distributed in the warm regions around the world.

Natural Japanese cedar trees (*Cryptomeria japonica* (JC); native tree in Japan) are distributed all over Japan, except in Hokkaido and the Okinawa Islands. However, many trees were destroyed during the Second World War. In 1957, the Japanese Government adopted a policy to plant JC trees on all the barren mountains in Japan in order to be able to use the timber for building houses and for preventing flooding due to overflow of rivers. This has resulted in 349 × 10^6 m^2 of JC forest in the Kanto bloc,

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680×10^6 m^2 in the Chubu bloc and 523×10^6 m^2 in the Kinki bloc and so on in 1982 (Japan is divided into eight blocs from north to south: Hokkaido, Tohoku, Kanto, Chubu–Tokai and Hokuriku, Kinki, Chugoku, Shikoku and Kyushu). When these trees reach the age of 16–35 years, they produce and disperse a large amount of pollen. Accordingly, air-borne JC pollen (JCP) has increased since 1965.

In 1964, Horiguchi and Saito *et al.* reported, for the first time, the existence of patients suffering from Japanese cedar pollinosis (JCPsis) in Tochigi, Kanto bloc.[1] Air-borne JCP has been further increasing with yearly variations and has finally resulted in a total of 8000 /cm^2 (pollen count by Durham's sampler) in 1979 and 1982, leading to a marked increase in the number of patients with JCPsis. These facts caused a big sensation in Japan. At present, the pollen counting system has been established at over 400 points in Japan and pollen forecasts are available in 41 of 47 prefectures in Japan. Since 1988, research groups for the management of JCPsis have been founded in Japan through the support of the Department of Health and Welfare (Japanese Government); Chairmen of these research groups: S Nishima (1988–90), M Okuda (1991–95) and T Shida (1996–97).

The purpose of the present review is to produce an update on the clinical information on JCPsis based on the work of our research group,[2–9] as this disease is infrequently documented internationally, despite a large number of publications from Japan. This information on JCPsis may also be useful for the management of various kinds of pollinosis prevalent in other countries.

Epidemiology

Japanese cedar pollen has been shown to be the most important cause of pollinosis in Japan. Of 353 patients with pollinosis at the out-patient clinic in Hamamatsu between 1992 and 1994, the predominant causative pollen was JCP (68%), followed by Japanese cypress (38%), orchard grass (23%), ragweed (12%) and mugwort (10%).[6] Air-borne JCP was counted all over Japan, except for Hokkaido and Okinawa, during the JCP season (February to April).

Pollen counts varied considerably, depending upon the districts and the year. Japanese cedar pollen counts were calculated as the number of pollens deposited on a glass slide in the Durham's sampler and are expressed as the number per cm^2 of slide. The average total number of JCP from 1989 to 1991 was different from district to district: 3150 /cm^2 in the Kanto bloc, 1730 /cm^2 in the Kinki bloc, 1580 /cm^2 in the Tohoku bloc and 1490 /cm^2 in the Chubu block.[4] The sensitization rates of JCP in the population coincided with the pollen counts in different districts. Japanese cedar pollen-specific IgE antibody levels were determined by radioallergosorbent test (RAST) in randomly selected pooled serum from 1983 to 1984 and the rates of elevated levels of specific IgE antibody in the sera were 40% in the Kanto bloc, 30% in Tokai, 25% in Shikoku and 15% in Tohaku and Kyushu blocs.[4] Another similar study was conducted in 1992 using pooled serum from a young population of approximately 20 years of age and the rates of positive RAST score (2 or more) was 21% in Osaka, Kinki bloc, 16% in Tokyo, Kanto bloc and Wakayama, Kobe and Nara, Kinki blocs and 13% in Oita, Kyushu bloc.[6]

The prevalence of pollinosis is on the rise worldwide and JCPsis is not exceptional. In population studies of adults in Tochigi, Kanto bloc from 1974 to 1986, the prevalence rates markedly increased year by year: 3.8% of 1183 subjects in 1974; 5.8% of 1332 subjects in 1977; 9.8% of 3133 subjects in 1984; and 16.2% of 1862 subjects in 1986.[5]

Because the prevalence rates of JCPsis are influenced by many factors, such as other allergic diseases, it is not easy to present an accurate prevalence rate of JCPsis in Japan. In 1993, the prevalence rates of JCPsis were examined by screening, using a telephone enquiry, and were confirmed by questionnaire or interview in randomly selected adult subjects. As a result, the prevalence rate of JCPsis was presumed to be 12.3% of 5530 subjects examined in the Tokyo district and 10.4% of 3260 subjects in the Osaka district.[4]

The prevalence of JCPsis in school children and in students was investigated in Shizuoka, Tokai bloc, in 1990 and was presumed to be 7.0% in a total of 50 000 children and students of primary, middle and high schools.[4] Another similar study was conducted in a total of 2000 school children and students by questionnaire and RAST in Tochigi, Kanto bloc, in 1988. As a result, there was a marked difference in the prevalence rates between children aged 6 years and less and those who were older. The prevalence of symptomatic JCPsis was 10% and the prevalence of asymptomatic JCPsis was 21% in the former group, while in the latter group these figures were 20 and 40–50, respectively.[4]

There are many reports that pollinosis is prevalent in urban areas rather than in rural districts.[10] By comparing the prevalence rate between rural and urban areas in the

Tokyo district between 1985 and 1989, the rates of positive RAST to JCP were 27.4% of 873 subjects in the rural population and 36.5% of 840 subjects in the urban population; the rates of symptomatic patients were 12.9 and 19.2%, respectively, although the pollen counts on an average were higher in rural (6000 /cm^2) than in urban (1250/cm^2) districts.[4] Contrary to this result, in an examination of 159 office workers in an urban district of Tokyo and 109 in the rural districts of Tokyo in 1990, the prevalence rates of symptomatic and asymptomatic subjects were higher in rural than in urban districts (23.9 *vs* 10.7% in the symptomatic group; 11.9 *vs* 6.3% in the asymptomatic group).[4]

Despite these differences in the age of subjects, districts, the method and year of examination, it was presumed that the prevalence of JCPsis was 10–20% in adults and 5–10% in children in Japan.

Risk factors for sensitization and the onset of symptoms

We studied, as risk factors, the age of subjects, allergen exposure, hereditary disposition and environmental conditions.

The age distribution of 1267 patients with JCPsis at our out-patient clinic was, in order of predominance, 20s, 30s, teens, below teens, 40s and > 50s.[4] In group examinations of school children by questionnaire and RAST, drastic increases in the sensitization and/or onset of symptoms occurred during the primary school period.[4,5,7] To determine the predominant factor for the onset of symptoms, 34 patients with house dust mite rhinitis, without any symptoms of JCPsis, were followed for a period of 5 years. Of these, 10 patients whose RAST scores ranged from 2 to 3 at the onset of the follow-up period and whose age was in the teens, became symptomatic to JCP.[4,6,7]

Intensive exposure to JCP may promote sensitization and may accelerate the onset of symptoms. The rates of sensitization increased from 39% of 405 subjects in 1994 (180 /cm^2 pollen count) to 53% of 380 subjects in 1995 (1780 /cm^2 pollen count) and symptomatic subjects increased from 18 to 27%.[9]

Hereditary disposition is well known as an important factor for atopic diseases. The analysis of the HLA typing may be a useful tool for searching atopic disposition. In both patients with allergy (n = 176) and in controls without allergy (n = 107), the frequency of the HLA class II allele was examined using the polymerase chain reaction–sequence-specific oligonucleotides method, which revealed that allergic manifestations were significantly correlated with DQB1*0303 and DPB1*401. Furthermore, the high levels of anti-Cry j 1 IgE antibody also correlated well with DRB1*1101, DRB1*1201, DPB1*501 and DPB1*901 and levels of anti-Cry j II antibody significantly correlated with DPB1*401.[4–7] In a separate study, there were significant differences in the frequency of DQB1*0303 (DQw9) haplotype between JCPsis (52%) and the control group (20%), but no differences were noted between JCPsis and mite allergy (69%) or orchard grass allergy (62%).[4–7]

Family studies of JCPsis, conducted in 9752 subjects in Tochigi, Kanto bloc, in 1990 revealed that the prevalence of JCPsis in children was different, based on the incidence of atopy in their parents. The incidence of atopy in children whose parents (both mother and father) were atopic was 46.7%, significantly greater than that when the father alone was atopic (25.9%), when the mother alone was atopic (30.0%) or when neither parent was atopic (13.7%; control).[5]

There was no evidence to support the theory that air pollution, the month of birth, occupation, the keeping of pets, nutrition and favourite food, or lifestyle cause an increase in the incidence of JCPsis.[2–4]

In conclusion, important risk factors are summarized as follows: exposure to a large number of JCP over a long period of time, hereditary disposition, high levels of IgE antibody to JCP in childhood and a rapid increase in the level of specific IgE antibody in primary school days.[6,8]

Pollen survey

The pollen sampler of Durham's type is commonly used in Japan to count air-borne pollen for economic reasons. The relationship between the three types of samplers (Durham's, rotary and Burkard samplers) in pollen collection were examined in the same place and on the same day between 1992 and 1996. There was a significant correlation in the average pollen counts between the Durham's and Rotary type samplers (correlation coefficient, r = 0.71), between the Durham's and Burkard samplers (r = 0.58) and between the Rotary and Burkard type samplers (r = 0.43). However, the Rotary and Burkard type samplers are more sensitive than the Durham's sampler.[7,9]

Usually, pollen samplers are set up on roof tops at levels that are quite high from the ground in order to avoid disturbance in the sampling from neighboring buildings. The question arises as to whether or not the pollen numbers counted on a high roof can truly indicate

the pollen count inhaled by patients at ground level. However, there was no difference found in the pollen count on a roof at a height of 30 m (676 /cm^2 count) in comparison with that on the ground (654 /cm^2).[9]

Total pollen counts vary greatly, year by year. In an examination in Toyama, Chubu bloc, from 1983 to 1996, pollen counts of less than 1000 /cm^2 per year were observed in 1983, 1987, 1989, 1992, 1994 and 1996; counts between 1000 and 4000 were observed in 1984, 1985, 1986, 1988, 1990 and 1997; and counts of over 4000 were observed in 1991, 1993 and 1995. The years with high pollen counts occurred at an interval of 1 or 2 years.[7]

Total pollen counts in the season also vary greatly, even in a limited district. At 10 pollen counting points in Shizuoka, Chubu bloc, in 1991, the total count in the mountainous areas was 5000 /cm^2 in Tenryu and 1100 /cm^2 in Fujinomiya; in the western sea side area it was 2800 /cm^2 in Hamamatsu, 2200 /cm^2 in Iwata, 3000 /cm^2 in Fujieda and, in the eastern sea side areas, it was 1000 /cm^2 in Shizuoka, 1800 /cm^2 in Shimizu, 2000 /cm^2 in Numazu, 2200 /cm^2 in Atami and 1900 /cm^2 in Shimoda.[6]

Accurate prediction of yearly pollen counts is required for proper avoidance of pollen by patients and for appropriate treatment by medical practitioners, as well as for the proper business management of pharmaceutical companies. For this purpose, many trials have been proposed with unsatisfactory results using parameters such as maximum air temperature or solar radiation in the previous summer season or the size of male germ in the autumn of the previous year. From statistical analysis of total pollen counts over the past 5 years, the following equation was proposed:[6]

$$y = 435.6SL + 592.2FL - 8021.6$$

where y is the predictive pollen in the next year, SL is the total solar radiation in the previous year's summer and FL is the size of the male germ in the previous year's November.

However, there is no evidence to support that this formula is applicable to any place in Japan, in any year and in any weather in the JCP season.

Allergen of JCP

Japanese cedar pollen is globe shaped with a short papilla, 30 μm in diameter, that ruptures easily in water, resulting in the escape of the intragrain plasma to the outside of the pollen particle.

Two allergenic substances, Cry j I and II, have been extracted and purified from JCP and their amino acid sequences have recently been clarified.[11,12] These substances are mainly contained in the exine.[13] The amount of Cry j I in two kinds of commercial crude extracts for prick test (Torrii, Tokyo, Japan and the Hollister-Stier, Washington, USA) were determined by ELISA and were compared with each other. In extracts of 1:20 dilution, the Cry j I content was 11 600 ng/mL (USA product) and 305.0 ng/mL (Japanese product).

Relationships between the allergenic potency of crude extract (1:1000 w/v; Hollister-Stier) and the purified allergenic substances Cry j I and II (100 ng/mL each) were examined and were compared by skin test and RAST in patients with JCPsis. The degree of skin reaction to the three agents correlated well between the three samples. The RAST correlation coefficients were 0.962, 0.733 and 0.694 between Cry j I and the crude extract, between Cry j II and the crude extract and between Cry j I and II, respectively.[4-6]

Clinically, it is known that patients with JCPsis react with Japanese cypress (Hinoki). Then, to examine a cross-reactivity between JCP and Hinoki, anti-Hinoki IgE antibody was determined in the serum of patients with JCPsis by RAST. It was revealed that 60% of patients were also positive to the Hinoki allergen.[6]

Furthermore, an IgE ELISA inhibition test was applied to detect IgE antibody in the sera of patients with JCPsis commonly reactive to JCP and Hinoki. As a result, patients were divided into two groups on the basis of their reaction to allergens. In one group, the antibody of JCP was strongly inhibited with the JCP extract only, but not with the Hinoki extract, and the antibody to Hinoki was strongly inhibited with the Hinoki extract only, suggesting that the sera contained two kinds of antibodies specific to each JCP and Hinoki. In the other group, the antibody to JCP was strongly inhibited with JCP and Hinoki extracts and the antibody to Hinoki was also inhibited with both extracts, indicating that the sera contained a common antibody to JCP and Hinoki. These results indicate that JCP and Hinoki have a common allergenic substance.[5,6]

Symptomatology

Major symptoms of JCPsis are similar to those of other pollinosis (i.e. nasal symptoms, such as itching, sneezing, a watery runny nose and a stuffy nose, and eye symptoms, such as itching and watery eye). However, asthmatic symptoms and itching of the skin are infrequent in

comparison with their prevalence in patients with grass or weed pollinosis.[8,9]

In statistical studies from past pollen counts in 1990–94 in the Tokyo district, Kanto bloc, the symptoms of many patients started on the day when the pollen count was 10 /cm^2 or on the day when accumulated pollen counts from 1 January of the same year reached 100 /cm^2.[7] A similar study was conducted in Kyoto, Kinki bloc, from an analysis of the past 6 years data and revealed that pollen counts of 30 /cm^2 as the square root of accumulated pollen counts from 1 January are an indicator for the first manifestation of symptoms in many patients.[7,8]

The severity of symptoms during the season is well correlated with the pollen count; namely, severe in the year of large dispersion and mild in the year of small dispersion. However, the degree of symptoms does not always correlate with the pollen count on individual days and in individual patients. When severe symptoms occur by exposure to a large amount of pollen, these symptoms persist for a longer time, without any close correlation with the variation in pollen count.[4] This may be explained by the fact that if the nasal reactivity is once increased after exposure to pollen, the resultant pathological changes may be precipitated, lasting for a longer time and causing a stronger reaction even when exposed to considerably lesser amounts of pollen.

In contrast, it is necessary to know the relationship between daily symptoms and pollen counts for pollen forecasts. Based on statistical analysis of the past data, the following equation was proposed:[6]

$$y = 1.688 + 0.484x$$

where y is the daily symptom score and x is the square root of the pollen count accumulated from the first day of pollen dispersion. The correlation coefficent between y and x was 0.95.

An equation was also proposed for the relationship between the rate of accumulation of patients visiting hospitals per total patients during the season (y) and the above-mentioned pollen count (x):[6]

$$y = 23.69 + 12.98x;\ r = 0.902$$

POLLEN AVOIDANCE

Pollen forecast

A daily pollen forecast is now available almost all over Japan during the JCPsis season. Based on the statistical analysis of the past year's data, the following equation was proposed:[4]

$$y = Wx[Fm + Nx(Ftx + Fwi + Frh + Z)]$$

where W is the factor for weather, Fm is the factor for the pattern of pollen dispersion during the season, N is the interval from the first pollen dispersing day, Ftx is the factor for maximum air temperature, Fwi is the factor for wind speed, Frh is the factor for relative humidity and Z is the mean solar radiation.

However, pollen forecasts are not always reliable (i.e. the rate of correct daily prediction was only 50% in the Tokyo district in 1997) because of unreliable weather forecasts and a limited number of pollen count stations. In addition, the degree of patient symptoms is not always well correlated with pollen counts, as has been stated elsewhere in this article.[4] Thus, further study is necessary to correctly predict the severity of symptoms in patients on the basis of the pollen forecast.

Eye glasses

It is believed, without any evidence, that eye glasses are useful in the inhibition of penetration of pollen into the eyes. To provide factual evidence of this, a model experiment was made using a phantom model of the head. Vaseline-coated small glass slides were placed on the spaces between the upper and lower eye lids of the phantom. Three phantoms, having usual eye glasses, eye glasses with side protectors or no glasses were left on the roof top of the hospital for 24 h on 6, 12 and 13 March 1991 and the pollen deposited on the glass slides was counted and averaged for 3 days. As a result, there were significant differences in the amount of pollen attached to the glass slides between the phantoms having glasses (63 /cm^2) or glasses with protectors (62 /cm^2) and those without glasses (175 /cm^2), but no difference was detected between the two types of glasses. Because this may be a model simulating subjects standing outside, further experiments were conducted simulating subjects walking around outside.

Three people were asked to walk around the streets for 3 h on 3 and 4 April 1991 with a bicycle. Each bicycle carried a phantom, with either eye glasses, eye glasses with protectors or no glasses, on its handlebar. The pollen deposited on the glass slides between the upper and lower lid spaces was counted and averaged. There were differences in the amount of pollen between the phantoms with eye glasses (9.8 /cm^2), eye glasses with

protectors (1.8 /cm^2) and those without glasses (29 /cm^2).[4,6] These results strongly suggest that eye glasses are useful for protection against the penetration of pollen into the eyes. However, it is necessary to determine the precise amount of pollen that can be prevented from entering the eyes in patients using these glasses. The conjunctival sacs of 18 non-allergic subjects were washed with 10 mL saline and the pollen count in the washings was compared between subjects having eye glasses and those with no glasses in March 1997. Contrary to results from the experimental model, there were no differences between subjects with glasses (3.4 ± 6.4 pollen count/10 mL saline) and those without glasses (2.0 ± 2.1 pollen count/10 mL saline).[4]

Face masks

Face masks are also believed to be of use for the prevention of the inhalation of pollen, without any factual evidence to support this. Therefore, the protective effect of the three types of face masks against pollen inhalation was examined in an experimental model. A box for dispersing pollen, in which the pollen number could be controlled, was connected to face mask A (for general anesthesia) and subjects were required to use either one of the three types of mask (cotton gauze (mask B), wet gauze (mask C) and a mask for workers in a dusty factory (mask D)) and inhale pollen grains in the box through mask A. The amount of pollen in the space of mask A and in the nostril behind masks B, C or D was counted. Inhibition rates (pollen count ratio: nostril/mask A) were calculated. The rates were 58.8, 83.3 and 87.0% for masks B, C and D, respectively. It was revealed that mask C was most preferable for inhibition due to its low inspiratory resistance and its cheaper price.[4]

In addition, 16 kinds of commercially available face masks were tested for inhibition rates and inspiratory resistance in an experimental model similar to the aforementioned experiment. The inhibition rates ranged from 75 to 99% and the resistances ranged from 3.2 to 7.6 mmH_2O. It was then concluded that the cheaper simple cotton gauze mask is satisfactory for use in the prevention of pollen inhalation.[7,9]

Keeping windows and doors closed

It is reasonable to think that keeping the windows and doors of a house closed is a means to avoid pollen. However, accurate evidence to support this has rarely been presented. To confirm this effect, vaseline-coated glass slides were left on the floor of the bedroom, living room and just outside the house for 1 week in March 1991 and 1996. During the period of the experiment, the doors and windows of the house were kept closed for as long as possible. The pollen deposited on the glass slides was counted. The pollen counts in eight houses were less than 5 /cm^2 in both 1991 and 1996, while pollen counts outside the house were 200–300 /cm^2 in 1991 and 100–600 /cm^2 in 1996.[4] This result indicates that keeping the doors and windows closed can prevent the entry of pollen into houses.

MEDICAMENT TREATMENT

Because many different anti-allergic drugs are now available in Japan, it is not difficult to control JCPsis symptoms during the season. The treatment method of preseasonal medication, proposed for the first time in 1986,[14] brought satisfactory results for JCPsis. Namely, medications were started 1–2 weeks before the onset of the season and continued until the end of the season. The reason why this method is effective is presumed to be that after patients have been exposed once to a large amount of pollen in the season, the sensitivity of their nasal mucosa to pollen increases due to an increase in the numbers of effector cells, such as mast cells, lymphocytes and eosinophils, the sensitivity of the nervous reflex system and histopathological changes. This increased sensitivity (primary effect) lasts for a long time and induces resistance to medication.

This treatment method was investigated using different kinds of drugs by assessing the change in clinical symptoms and nasal cytology in a total of 113 patients (the preseasonal group) and in a total of 116 patients (the mid-seasonal group used as a control). The drugs used were tranilast (a per oral mast cell stabilizer in 1992), azelastine (a new anti-histamine in 1992) and oxatomide (a new anti-histamine in 1993). The preseasonal group was better controlled than the mid-seasonal group, postponing the day of onset of symptoms in the season and by decreasing the number of monoclonal antibody to eosinophil cationic protein (EG2)-positive eosinophils, neutrophils and eosinophil cationic protein (ECP) levels in the nasal secretion.[5,6] However, the single use of each of these drugs was not satisfactory in controlling the symptoms in the season of a large number of air-borne pollens (more than 500 /cm^2 per day) and the combination of topical steroids or topical steroid alone instead of single use of the new

anti-histamines promised more satisfactory results in controlling the symptoms.[5] Topical steroids are known to be safe and potent for the treatment of allergic rhinitis, but their modes of action c re not yet completely understood. To clarify this, nasal scrapings were collected from nine patients with JCPsis twice before and after the season in 1993, after the continuous use of fluticasone nasal spray, a topical steroid, and the numbers of eosinophils, mast cells in scrapings and total histamine and ECP after crushing and extracting from scrapings were measured. In this experiment, the total amount of histamine and ECP indicated the number of mast cells and eosinophils, respectively. In contrast to the control group, without any medication, the increase in the number of cells as well as in the amount of chemical substances was strongly inhibited in the fluticasone group.[5]

The effect of fluticasone on cytokine release from nasal epithelial cells was also examined. Epithelial cells were collected from the nasal surface of patients with JCPsis and were cultured in collagen-coated wells of culture plates together with 10^{-7}, 10^{-6} or 10^{-5} mol/L fluticasone. The release of cytokines, such as interleukin (IL)-6, IL-8, tumor necrosis factor-α and granulocyte–macrophage colony stimulating factor, in culture supernatants was inhibited in a dose-dependent manner in the fluticasone group compared with the control group without fluticasone.[5]

Based on these experiments, the major mode of action of topical steroids in pollinosis is presumed to be the inhibition of the migration of effector cells locally and the inhibition of cytokine release from these cells.

IMMUNOTHERAPY

Immunotherapy (IT) is believed to be beneficial for atopic diseases, especially pollinosis. However, the clinical efficacy of IT in the treatment of JCPsis is not yet satisfactory in Japan compared with mite allergy. This may be due to a larger amount of air-borne pollen in the season and a lower potency of the extract used for IT, as has already been stated elsewhere in this article. Therefore, IT was conducted in patients with JCPsis using a more potent extract (Hollister-Stier) and the results were compared in the season of low and high pollen counts during the period from 1993 to 1997. Because many effective anti-allergic drugs are available for the treatment of JCPsis at present, the effect, specific for IT, should be evaluated from the point of view of its long-term remission after completion of the IT regimen. Patients with JCPsis who had completed an IT regimen of 2 to 3 years duration and were free from treatment at our clinic were followed up in 1997. Although we did not have a placebo control group, we used as a control a group of JCPsis patients who were treated with the drug alone. The parameter for evaluation was total days of symptoms and uptake of the drug during the season. The criteria for satisfactory results were defined as follows: the severity of symptom was classified into three grades (mild, moderate and severe) according to Okuda's classification[15] and the satisfactory symptom conditions were defined as no or mild symptoms in the entire season; otherwise, moderate or severe symptoms within a total 1 week period during the season. They were also defined from total days of medication during the season as no medication or medication within a total 1 week. Drugs often prescribed were combinations of topical steroids and novel non-sedative anti-histamines or per oral mast cell stabilizers; eye drops (a preparation of new anti-histamines or topical steroids) were also frequently used.

In 1993 (the year of a large pollen count), satisfactory symptom conditions were achieved in 100% of 14 patients in the IT group; although medications were combined, and in 87% of 79 patients in the drug treatment (DT) group.

In 1994 (the year of a small pollen count), satisfactory symptom conditions were achieved in 94.7% of 132 patients in the IT group with combined medication and in 93.5% of 46 patients in the DT group.

In 1995 (the year of a large pollen count), satisfactory symptom conditions were achieved in 87% of 116 patients in the IT group and 97% of 134 patients in the DT group.

Although the percentage of satisfactory symptom conditions were comparable with each other in both groups, the rate of medication for more than 1 month was lower in the IT group (17%) than in the DT group (67%).

In 1996 (the year of a small pollen count), satisfactory symptom conditions were achieved in 92% of 177 patients in the IT group and in 94% of 94 patients in the DT group and the rate of medication for 1 month more was 37% in the IT group and 72% in the DT group.

In 1997 (the year of a large pollen count), satisfactory symptom conditions were achieved in 83.5% of 187 patients in the IT group and in 96.5% of 57 patients in the DT group and the rate of medication of 1 month more was 49.7 and 100%, respectively.

These results strongly indicate the symptoms are satisfactorily controlled in 90% of patients with JCPsis in

both groups in seasons of large pollen counts as well as in seasons of low pollen counts. However, there is a significant difference in the rate of medication for over 1 month between the two groups (i.e. 20–40% in the IT group and 70–80% in the DT group).[7–9] One to 3 years after completing the IT regimen, the prognosis of 78 patients was examined in 1997 (the year of a large pollen count) by questionnaire. The response rate to the questionnaire was 80%. Fifty percent of patients had no or very mild symptoms and 60.9% did not need to take drugs in the IT group, compared with 21.3 and 30.7%, respectively, in the control DT group. In conclusion, IT, using a potent extract, has a long-lasting beneficial effect in decreasing symptoms and medication after cessation of IT treatment.[7–9]

After IT with JCP extract (Hollister-Stier) in 17 patients, serum IgE and IgG_4 antibody levels to Cry j I and Cry j II were increased, contrary to IT with the Japanese product.[7]

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