ORIGINAL ARTICLE

Prevalence of Cypress Pollen Sensitization and Its Clinical Importance in Izmir, Turkey, With Cypress Allergy Assessed by Nasal Provocation

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■ **Abstract**

Background and objective: Pollens from the Cupressaceae family are considered important allergens in the Mediterranean area, though reports of the prevalence of allergic symptoms have ranged from 1.04% to 35.4%. Our aim was to detect the prevalence of cypress pollen sensitization and determine its clinical importance in patients with seasonal respiratory allergy.
Methods: We used skin prick tests (SPT) and serum specific IgE assays to reveal sensitization to cypress pollen. In patients who showed positive results to cypress pollen, a nasal provocation test (NPT) with pollen extract was used to assess the target organ response.
Results: Sixty-five (14.3%) of 455 patients showed positive SPT responses to *Cupressus sempervirens* extract. Only 1 patient was monosensitized while 64 patients were polysensitized. Among those, 2 pollen cosensitizations were found to be significant (86% were cosensitized to grasses and 72% were cosensitized to olive ($P < .001$). Serum specific IgE to cypress pollen was measured in 50 of the 65 patients; findings were positive for 37. When these 37 patients underwent NPT with *C sempervirens* allergen extract, only the single monosensitized patient had a positive NPT.
Conclusion: A positive SPT to cypress pollen may not reflect the true prevalence of sensitization. We assume that in the absence of a positive NPT, positive SPT results might be related to the presence of cross-reactivity between pollen species.

Key Words: Allergy. Cypress pollen. Cross-reactivity. Nasal provocation.

■ **Resumen**

Antecedentes y objetivo: Los pólenes de los árboles de la familia de las Cupresáceas (Cupressaceae) se consideran alérgenos importantes en el área mediterránea, teniendo en cuenta que los informes de prevalencia de los síntomas alérgicos han oscilado de 1,04% a 35,4%. El objetivo fue detectar la prevalencia de la sensibilización al polen de ciprés y determinar su importancia médica, en pacientes con alergia respiratoria estacional.
Métodos: Se utilizaron la prueba cutánea y los análisis de IgE sérica específica para desvelar la sensibilización al polen de ciprés. A los pacientes que obtuvieron un resultado positivo al polen del ciprés, se les realizó una prueba de provocación nasal (PPN) con extracto de polen, para evaluar la respuesta del órgano diana.
Resultados: Sesenta y cinco (14,3%) de los 455 pacientes tuvieron respuestas positivas a la prueba cutánea para el extracto de *Cupressus sempervirens* (ciprés común). Sólo un paciente estaba monosensibilizado, mientras que 64 pacientes estaban polisensibilizados. Entre los últimos, se observó que 2 cosensibilizaciones al polen eran significativas (el 86% estaba cosensibilizado a las hierbas y el 72% a las olivas ($P < 0{,}001$). La IgE sérica específica al polen del ciprés se determinó en 50 de los 65 pacientes y 37 de ellos tuvieron un resultado positivo. Cuando se realizó la PPN con el extracto alergénico de *C sempervirens* a estos 37 pacientes, sólo el paciente monosensibilizado tuvo un resultado positivo.
Conclusión: Es posible que la prueba cutánea con resultado positivo para el polen de ciprés no refleje la verdadera prevalencia de la sensibilización. Por lo tanto, hay que admitir que ante la ausencia de una PPN, se pueden relacionar los resultados positivos de la prueba cutánea con la presencia de una reactividad cruzada entre especies de polen.

Palabras clave: Alergia. Polen de ciprés. Reactividad cruzada. Provocación nasal.

Introduction

Pollens from wind-pollinated seed plants are the most common cause of immunoglobulin (Ig) E mediated respiratory allergic diseases. The allergenic characteristics of pollens and their levels of expression may vary depending on the plant species, climate and environmental factors. Some tree pollen grains release small respiratory allergenic particles which, when wet from rain water, can penetrate the mucosa of deep airways and induce allergic asthma. These pollens come from trees belonging to certain orders such as Fagales (including birch, alder, hazel, and oak), Scrophulariales (the dominant pollen sources in the Mediterranean area, along with olive and ash trees). Pollens of other angiosperms (Juglandaceae, Plantanaceae, Ulmaceae, and Salicaceae) are less often implicated as allergen sources [1,2].

In recent years the Cupressaceae family has been accepted as an important cause of pollen allergy. Pollen producing trees are found in various geographic areas throughout the world, including North America (*Juniperus ashei*), Japan (*Cryptomeria japonica*), and the Mediterranean space (*Cupressus sempervirens*, *Cupressus arizonica*, and *Juniperus communis*). High rates of cross-reactivity within the family have been detected by means of in vivo and in vitro testing [3].

The amount of Cupressaceae pollen in the atmosphere has been monitored especially at the areas where the cypress tree is planted largely for ornamental purposes in gardens and parks. A tree spreads a large amount of pollen into the atmosphere, often in greater amounts than grass [4]. Pollination is generally in winter, starting in October and ending in February or starting in January and ending in April, although variations in the dates occur depending on species and country [5]. Our city, Izmir, is located just on the east coast of the Aegean Sea in the western part of Turkey in a region that has a typical Mediterranean climate.

Aeropalynologic records for the city reveal that the detection of cypress pollens begins at very low levels in January [6]. Although the pollen concentration depends on climatic conditions, it generally starts to increase in the last week of February and reaches peak levels in March, April, and May [6]. Pollens continue to be detected until July. In the peak months, the total cypress pollen concentration is high, displaying values close to the concentrations of grass and olive tree pollens [6].

Cypress pollinosis is characterized by allergic symptoms such as conjunctivitis, rhinitis and asthma. Many reports suggest that cypress pollen has become an increasing cause of respiratory allergic diseases, particularly in Mediterranean areas such as France, Italy, Israel, Spain, and Greece [7-12]. The climatic conditions of these countries are optimal for the growth and abundant pollen production of cypress trees [1]. In most of these studies, questionnaire and skin prick test results have been used to detect the prevalence of cypress pollen allergy and reports of sensitization to cypress pollen have revealed great variations, from 0.6% to 35.4% [5,7-12].

In this study we aimed to detect the frequency of sensitization to cypress pollen in our patients with seasonal respiratory allergy living in the area. We also evaluated whether this identified allergen sensitization is responsible for clinical symptoms.

Materials and Methods

Selection of Patients

The symptoms of patients coming to our outpatient allergy clinic between September 2003 and October 2004 with complaints of upper or lower respiratory tract disorders and conjunctivitis were considered as candidates. Patients were selected consecutively for the study if they had recurrent seasonal respiratory allergic symptoms. All underwent skin prick testing (SPT). The study group consisted of the 455 seasonally allergic patients who were diagnosed based on symptoms and positive SPT results. Patients receiving allergen-specific immunotherapy with any kind of allergen currently or previously were excluded.

Patients were notified about all the procedures and signed informed consent forms were obtained. The ethics committee of the Ege University Medical Faculty approved the study.

Skin Prick Tests

The 455 patients were tested with common aeroallergens (Stallergenes SA, Antony, France) according to standard procedure [13] using a panel containing the following 26 allergen extracts: grasses (cocksfoot, meadow fescue, rye-grass, meadow grass, timothy), weeds (mugwort, wall pellitory, plantain, dandelion), trees (olive, birch, oak, alder, poplar, plane), mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), molds (*Alternaria*, *Aspergillus*, and *Cladosporium* species) and animal danders (cat, dog, bird, horse, and cow). Additionally an nonstandardized commercialized extract of *C sempervirens* (index of concentration [IC] per mL of 100) was used (Stallergenes). Positive control (histamine phosphate 10 mg/mL) and negative control (glycerol) solutions were applied. Tests were read after 15 minutes. Both the largest and smallest diameters of the wheal and erythema were measured with a millimetric ruler and summed. Results were recorded in millimeters as the mean value of the wheal and flare reactions. In the presence of erythema of at least 10 mm, a wheal 3 mm greater than the negative control was considered a positive response.

Specific IgE in Serum

We also assayed the *C sempervirens* specific IgE in sera from patients who had positive SPT responses to cypress and who agreed to give blood for testing. Specific IgE levels were measured by using the CAP System (Pharmacia Upjohn, Uppsala, Sweden) according to the manufacturer's instructions.

Nasal Provocation Test

The nasal provocation test (NPT) has been used mainly for research on allergic rhinitis to evaluate the nasal response to allergens. Although it is not routinely used for diagnostic purposes, the NPT may be valuable for evaluating specific hyperreactivity when skin and radioallergosorbent tests are unhelpful. In the subjects who show skin reactivity to multiple allergens, the role of a specific allergen can be determined only by NPT with the allergen in question [14].

Cupressaceae family allergy has been associated with diagnostic difficulty [15,16]. For that reason, we carried out NPTs in patients to assess the clinical relevance of positive test results. NPT with *C sempervirens* allergen extract was applied to 37 nonasthmatic patients who had positive SPT and CAP assay results to cypress pollen. NPT was performed in the absence of nasal symptoms (nasal discharge, sneezing, itching, or blockage) after the season ended for all pollen species. Topical and systemic antiallergic treatments were stopped 6 weeks before NPT. None of the patients was using medications known to interfere with NPT [14]. A nonphenolic aqueous solution of *C sempervirens* allergen extract (Stallergenes) at a concentration of 100 IC/mL was used. Serial dilutions of the allergen extract (10 IC/mL, 1 IC/mL, and 0.1 IC/mL) were prepared immediately before NPT using a nonphenolic physiologic saline diluent (Stallergenes). NPT started with physiologic saline; then, the allergenic extracts were sprayed into a nostril at 15 minute intervals.

The response to the allergen challenge was assessed with nasal symptom scores. The severity of each nasal symptom was recorded with points between 0 and 3. Clinical symptoms of nasal blockage, sneezing, itching and rhinorrhea were evaluated at baseline. Then symptom scoring was repeated after applications of saline and different concentrations of the allergen [14]. Together with symptom recording, nasal flow rates were measured in each step by anterior rhinomanometry (Jager Rhinoscreen, Hochberg, Germany). When the patient had a symptom score of more than 3 and a reduction in nasal flow of more than 20%, it was considered a positive response [14].

Statistical Analysis

The statistical analyses were carried out with SPSS software (version 11.0). Data were presented as mean (SD). The frequency of the other pollens indicating cosensitization in cypress pollen sensitized and nonsensitized groups was compared with the ^{2} test. We calculated odd ratios (OR) with 95% confidence intervals (CI) using logistic regression analysis to estimate the relationship between cypress pollen sensitivity and cosensitization to other pollens.

Results

The 455 patients diagnosed with seasonal allergic rhinitis with or without asthma were included in the study. Three hundred seventy of the patients (81.3%) suffered from only allergic rhinitis, whereas 85 patients (18.7%) were diagnosed with allergic rhinitis with asthma. There were 324 females (71%) and 131 males (29%) with a mean age of 32.5 (11) years.

The characteristics of the 65 cypress-pollen–sensitized patients (14.3%) and the 390 patients (85.7%) who were not sensitized to this pollen are shown in Table 1. Only a single sensitized patient (0.22%) was monosensitized. All differences were nonsignificant.

Sixty-four of the 65 cypress-pollen–sensitized patients (98.5%) were polysensitized, *C sempervirens* specific IgE assay could be performed in 50 of these SPT-positive patients who agreed to give blood. The results of specific IgE assays in these patients are shown in Table 2. All of the 36 patients with elevated titers were also sensitized to other pollens according to SPT findings. NPTs performed in these 36 patients plus the single monosensitized patient were negative in all except the monosensitized patient (10 IC/mL) as shown in Table 2. Neither nasal symptoms nor a reduction in nasal flow was observed in any of the other patients, even at the strongest concentration (100 IC/mL).

Upon negative cypress pollen challenge results for these 36 patients, we decided on an ad-hoc basis to administer NPTs against the other pollens to which they had proven sensitized in SPTs. Nearly all were sensitized to grass pollen or/and olive pollen, sometimes together with other pollen species. Thus 27 of 36 patients showed cosensitization to grass pollens, and 22 were sensitized to olive pollens. Eight olive-pollen–sensitized and 11 grass-pollen–sensitized patients underwent NPT with grass pollen or olive pollen allergen extracts (Stallergenes).

Table 1. The Characteristics of Cypress-Pollen–Sensitized and Nonsensitized Patients[a]

	Cypress Pollen Sensitized (n=65)	Cypress Pollen Nonsensitized (n=390)
Frequency, %	14.3	85.7
Sex-ratio, F/M	1.9	2.5
Age, mean (SD), y	30.4 (10)	32.9 (11)
Age at onset of symptoms, mean (SD), y	22.6 (10)	26.5 (11)
Duration of allergic disease, mean (SD), y	7.9 (6.7)	6.3 (6.0)
Diagnoses, n (%)		
Allergic rhinitis	52 (80)	319 (81.8)
Allergic rhinitis + asthma	13 (20)	71 (18.2)

[a] All differences are nonsignificant.

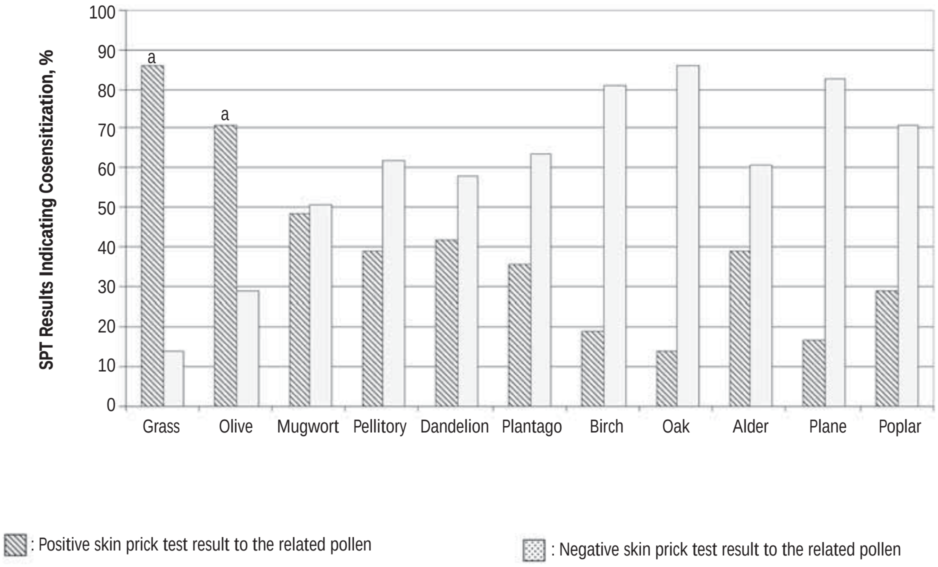

Figure. The distribution of other pollens showing cosensitization with cypress pollen in the 64 polysensitized patients. [a]Significant positive difference, $P<.001$, ^{2} test.

Table 2. Characteristics of the Cypress-Pollen–Sensit Patients.

Monosensitization, n (%)	1/65 (1.5)
Polysensitization, n (%)	64/65 (98.5)
Gender, n (%)	
Female	43/65 (66)
Male	22/65 (34)
Age, mean (SD), y[a]	
Female	31.3 (10)
Male	28.8 (9)
Cypress specific IgE (+), n (%)	37/50 (74)
Cypress specific IgE (-), n (%)	13/50 (26)
NPT (+) with cypress pollen, n (%)	1/37 (2.7)[b]
NPT (-) with cypress pollen	36/37 (97.3)[c]

Abbreviations: IgE, immunoglobulin E; NPT, nasal provocation test.
[a] The age difference was nonsignificant.
[b] The single monosensitized patient.
[c] All polysensitized patients

NPTs were performed following the same method as described above for *C sempervirens* extract. Positive NPTs were observed in all patients in response to allergen challenge with olive or grass pollen at concentrations ranging from 0.1 index of reactivity (IR) per milliliter to 1 IR/mL.

Cosensitization with *C sempervirens* according to SPT results are shown in the figure for the 64 polysensitized patients. The most frequently detected concurrent sensitizations were to grass pollen (56/64, 86%) or olive pollen (46/64, 72%). The frequencies of these associations were found statistically significant ($P<.001$). However, the close relationship demonstrated between *C sempervirens* sensitization and grass and olive pollen sensitization was not detected for the other pollen groups, as the presence and the absence of cosensitization to weed pollen species which most frequently cause respiratory allergy symptoms in our area did not show great differences (figure). Interestingly, in contrast to the high rate of olive pollen sensitization (72%), cosensitization to other tree pollens occurred at quite low rates This analysis revealed that grass pollen and olive pollen sensitizations predispose the patients (OR, 7.1; 95% CI, 3.45-14.9 for grass pollen and OR, 4.9; 95% CI, 2.78-8.80 for olive pollen) to positive SPT results against cypress pollen, even though those sensitizations are without clinical relevance.

Discussion

In recent years *C sempervirens* pollen has been reported as a major cause of sensitization and allergic symptoms in Mediterranean countries. Epidemiologic studies performed in the general population revealed that the prevalence of sensitization to *C sempervirens* varies greatly between countries, ranging between 2.4% and 9.8% in more exposed communities and from 0.6% to 2.7% in less exposed areas [7,17,18]. Such prevalence results were defined on the basis of positive SPTs.

Many studies from Mediterranean countries have documented the prevalence of sensitization to cypress pollen among allergic patients. A multicenter study from Italy demonstrated positive SPTs in 18% of the study group [19], although sensitization rates also varied greatly, 9.2% to 28.2%, in different parts of the country. In that study, 14.7% of the cypress-sensitized patients were found to be monosensitized. Much lower rates from Italy were reported by Passalacqua et al [20], however, even though cypress pollen counts were recorded at high levels in the atmosphere during the pollen seasons. Those authors demonstrated positive SPTs to cypress only in 18 (1.04%) of 1735 patients suffering from respiratory allergy. Five of those patients were monosensitized (0.29%), whereas the remaining 13 patients showed sensitization to other pollen allergens. In Israel, 24% to 32% of allergic patients have cypress allergy according to SPTs and a questionnaire survey and 13% of cypress allergic patients were monosensitized [10]. The rate of sensitivity to cypress pollen according to SPT results was 12.7% in Thessaloniki, Greece, although the most frequently recorded pollen grain in the atmosphere was cypress followed by oak, wall pellitory and olive [11]. Aerobiological data from another Mediterranean city, Tirana, in Albania, showed that 43% of the total airborne pollen per year comes from the Cupressaceae family; despite this high burden, of 110 patients with respiratory allergic diseases only 3 (2.7%) were found to be SPT-positive to cypress pollen and all 3 were polysensitized [21]. Another study was performed in Cordoba, Spain where high levels of Cupressaceae pollen are found in the air [9]. Positive SPTs to cypress were observed in 13% of 1532 allergic patients. Consistent with our results, cypress pollen-sensitized patients were also found to be sensitized to other pollens in the Spanish study ($P < .001$). A very interesting finding of that study was that all of the cypress-sensitized patients showed positive reactions to olive pollen. In our study, olive pollen sensitization was present in 72% of our cypress-sensitized patients, and the overall rate of cypress pollen sensitization determined by SPT, at 14.3%, was close to the Spanish and Greek results of 13% [9] and 12.7% [11], respectively. Monosensitization was very rare in our patients (0.22%) and low rates have also been documented in Albania (0%) [21] and western Liguria, Italy (0.29%) [20].

Even though standardized allergen extracts were used in all these studies, sensitization rates were not consistent with aerobiological data showing high concentration of cypress pollens. An interesting Italian study by Ariano et al [22] demonstrated that while the rate of sensitization to cypress was increasing in outpatients over a 10-year period, the pollen count was unchanged during same time period [22]. Although the influence of the environment is obviously accepted as a major factor in pollen allergy, additional factors other than airborne pollen concentrations might be playing a role in the occurrence of sensitization. In large case series, certain personal characteristics have been identified with cypress-sensitized patients. It has been found that these patients were older at the onset of allergic symptoms, the prevalence of a family history of atopic diseases was lower, and their total IgE levels were lower [23,24]. These observations have been explained by some authors as reflecting an allergic, but not necessarily atopic pattern, in cypress-sensitized patients [23]. This behavior might be related to the low molecular weight carbohydrate nature of cypress pollen allergen. Indeed pollen extracts from different species of the Cupressaceae family are characterized by low protein and high carbohydrate content [16]. Protein and carbohydrate epitopes are involved in both IgE recognition and also allergenic cross-reactivity. Molecular studies that tested the IgE-binding properties of cypress pollen indicated that IgE reactivity and histamine release from basophils is higher for the glycosylated recombinant protein and lost its reactivity when the protein was deglycosylated [15,25]. These carbohydrate structures were termed cross-reactive carbohydrate determinants (CCDs) and they play a major role in the cross-reactivity between allergens from both taxonomically related and unrelated pollen families [26,27]. CCDs have been determined in different allergenic materials from plant sources such as grasses [28] and olive [29], confirming this concept. Gonzales et al [30] used IgE binding and inhibition assays to analyze cross-reactivity among olive pollen and other unrelated pollen species, making the important observation that cypress pollen was the reactive one in sensitizations to grasses, birch, mugwort and pine pollens exhibiting cross reactivity. The authors suggested that these extracts share common epitopes recognized by olive-specific IgE. There were earlier observations of the cross-reactivity of Cupressaceae allergenic extracts with taxonomically distinct pollens [31,32], and Tinghino et al [33] reported IgE-binding epitopes shared by different cypress species and other pollen extracts, including *Parietaria judaica*, *Olea europea*, and *Lolium perenne* [33]. In recent years, advances in allergen extraction and purification, as well as recombinant allergen technology, have contributed to our understanding of multiple positive test results especially in patients who are allergic to pollens. Many studies have shown data on highly conserved common cross-reactive molecules, termed panallergens and found mostly in carbohydrate structures [34,35].

In our study, positive SPT and RAST results to cypress pollen in polysensitized patients in the absence of positive NPT could possibly be attributed to grass or olive pollen cosensitization which is commonly presented as a major factor in allergic diseases in our area. A positive reaction with cypress pollen might be attributed to the CCDs recognized by olive- or grass-specific IgE. This cross reactivity seems to be clinically irrelevant and does not induce a response in the target organ, even though it causes positive results in both in vivo and in vitro testing. We conclude that the presence of positive SPTs to cypress pollen may not reflect the true prevalence of sensitization.

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