

ORIGINAL ARTICLE

Sensitization to *Alternaria* and *Cladosporium* in Patients with Respiratory Allergy and Outdoor Counts of Mold Spores in Ankara Atmosphere, Turkey

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Sensitization to *Alternaria* and *Cladosporium* has been reported to be 3% to 30% in European countries. However, in Turkey, there is limited data about the prevalence of sensitization to these molds and the intensity of the two mold spores in Ankara atmosphere. This study was designed to evaluate the sensitization to *Alternaria* and *Cladosporium* in patients with respiratory allergy in Ankara and also the concentration of the two molds in Ankara atmosphere.

Allergic rhinitis and asthma patients living in Ankara were included in the study. Demographic and diagnostic data of the patients were recorded. A skin prick test with extracts supplied by three different laboratories was used to evaluate the sensitization to *Alternaria* and *Cladosporium*. Mold spores were measured using a Burkard 7-day recording volumetric spore trap in Ankara atmosphere during a year.

Overall sensitization to the two molds was found to be 14.8%, and isolated *Alternaria* or *Cladosporium* sensitization was 3%. Considering the positive reaction to at least one of the three suppliers, the sensitization rate was 11.9% and 8.1% for *Alternaria* and *Cladosporium*, respectively. Cochran's Q homogenization test demonstrated that the positive and negative reaction were not homogeneous among three laboratories. The total number of mold spores in Ankara atmosphere was 429,264 spores/m³ of which 75.5% and 6% were constituted by *Cladosporium* and *Alternaria*, respectively.

The prevalence of *Cladosporium* and *Alternaria* sensitization in respiratory allergy patients is quite similar to European countries; however, our data indicate that commercial mold extracts should be standardized to establish the real sensitization rates. Additionally, considering the great numbers of these mold spores in Ankara atmosphere, long-term follow-up studies are needed to evaluate the relationship between the mold load and sensitization patterns.

Keywords *Alternaria*, *Cladosporium*, mold spores, respiratory allergy

INTRODUCTION

Molds are known to be one of the causative allergens inducing respiratory allergies as are house dust mites, pollen and animal dander. As microscopic organisms, molds are found in any environment. People are always exposed to varying concentrations of these mold particles everywhere such as home, school, working place or outdoors (1). This exposure results in sensitization of atopic individuals. Outdoor airborne fungi such as *Alternaria* and *Cladosporium* are especially important in inducing IgE antibody formation (2, 3). Contrary to their abundance in the atmosphere, sensitization to molds is not as prevalent as to those of pollen and house dust mites (4). A few previous epidemiologic studies demonstrated the prevalence of sensitization to inhaled allergens including molds in Turkey (5, 6). However, none of these studies particularly focused on mold sensitization and the actual prevalence of sensitization to molds is not fully known.

The aim of this study was to assess the prevalence of sensitization to *Alternaria* and *Cladosporium*, the most common

outdoor molds, in patients with allergic respiratory disease in a local region, Ankara, of Turkey. The reasons for selection of these two molds were both their documented clinical relevance in respiratory allergy and their abundance in Ankara atmosphere. The skin prick test (SPT) was used to evaluate the sensitization to molds since this method is considered as easy to perform, inexpensive, convenient to patients, and sufficiently specific and sensitive for the diagnosis of mold sensitization (7). However, considering the variable quality of commercial mold extracts, extracts were selected from three different commercial sources to allow for manufacturer bias (8, 9).

MATERIAL AND METHODS

Throughout one year, consecutive patients who applied to our tertiary allergy clinic located in Ankara, Turkey, with nasal and bronchial symptoms and diagnosed as allergic rhinitis and/or asthma were included in this study. Allergic rhinitis and asthma were diagnosed according to Allergic Rhinitis and its Impact on Asthma Workshop Report and Global Initiative for Asthma guidelines, respectively (10, 11). Subjects who met the following inclusion criteria were admitted to the study:

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1. living in various socioeconomic regions of Ankara for at least 3 years;
2. a valid SPT (subject responded to the histamine positive control with a wheal greater than 3 mm); and
3. not taking medications, such as antihistamines, which could interfere with the SPT.

A questionnaire composed of items on demographics, symptoms, duration, and season of symptoms was completed for every patient. All patients were informed in detail about study protocol and volunteers were enrolled the study.

Skin Prick Tests

SPTs were performed by a trained nurse with a panel of *Dermatophagoides pteronyssinus* and *D. farinae* and grass, tree, weed pollens, cat, dog antigens. (Stallergenes, France). Additionally, considering the variable quality of commercial mold extracts, extracts supplied by three laboratories including Stallergenes arbitrarily designated as "a," "b," and "c" were used for detection of *Alternaria* and *Cladosporium* sensitization to allow for manufacturer bias. Each patient was tested three times on the same day by the same technician. The volar surface of both forearms was used so that the space between each test solution was at least 3 cm. The drop of the extract was wiped off 1 minute after the prick. The skin reaction was recorded at 20 minutes. A mean wheal diameter 3 mm or greater than control solution was considered positive. Histamine dihydrochloride (10 mg/1 ml) and glycerol diluents were used each time as positive and negative control subjects, respectively.

Air Sampling

Fungus air spores were collected by means of a Burkard 7-day recording volumetric trap in Ankara atmosphere from January 2003 to December 2003. A Burkard 7-day recording trap was placed on the roof of the Geology Department, Ankara University, at a height of 15 m above the ground. The air was sucked at a flow rate of 10 L per minute, and spore grains impacted on to tapes that were coated with a thin film of Vaseline-paraffin wax in toluene. The tape was then mounted glycerin jelly (12), and 24 transverse travels were observed for a daily slide. Spores were identified visually with light microscope at a magnification of $\times 400$. Counts were done at one travel per hour, and total daily counts were converted to numbers per cubic meter of air (13).

Fungal spore counts are expressed as fungal spores per cubic meter of air. *Alternaria* spp. and *Cladosporium* spp. were the selected fungi for this study since they are considered to be the major mold aeroallergens (14).

Statistical Methods

All the analyses were performed using computer software (SPSS version 10.0; SPSS; Chicago, Illinois, USA). Descriptive statistics were expressed as mean $\pm$ SD, median and range. The Mann-Whitney U test was used for comparison of the continuous variables. Categorical data were tested using the chi-square statistics.

Positive and negative SPT results obtained with the different diagnostics were statistically analyzed by Cochran's Q homogenization test (15).

RESULTS

This study included 135 patients: 81 women, 54 men. The ages ranged from 14 to 63 years of age, and respiratory allergy symptoms were present from a minimum of 1 month to a maximum of 35 years. A total of 77, 19, and 39 patients were diagnosed as allergic rhinitis alone, allergic asthma alone, and allergic rhinitis with asthma, respectively; 92 patients had seasonal symptoms, and 43 patients had perennial symptoms. None of the patients received specific immunotherapy for any mold species tested in the study.

Of the 135 patients, 20 patients (14.8%) were found to be positive to at least one of the two mold allergens under investigation (*Alternaria* and *Cladosporium*). No differences were found in terms of age, gender, and clinical diagnosis between mold-positive and mold-negative groups ($p > 0.05$), but duration of illness was statistically higher in the mold-positive group ($p < 0.05$). The skin reactivity pattern observed in mold-positive and mold-negative groups was similar for other inhalant allergens. The majority of patients belonging to each group were sensitized to pollen allergens. Within the pollen allergens, the highest sensitization rates were observed in grass pollens followed by cereals and weed pollen sensitivity. Lower skin reactivity was detected in mite, cockroach, and pet allergens (Table 1).

Among 20 (14.8%) patients with mold sensitivity, considering the positive reaction to at least one of the three suppliers' extracts, the positivity rates were 11.9% (16/135) and 8.1% (11/135) for *Alternaria* and *Cladosporium*, respectively. Isolated *Alternaria* and *Cladosporium* sensitivity was 3% (4/135) (Figure 1). The patient monosensitized to *Alternaria* was a 44-year-old woman who presented with rhinitis and mild persistent asthma and had perennial symptoms for 7 years. The patient monosensitized to *Cladosporium* was a 37-year-old woman with mild to moderate asthma who had perennial symptoms for 6 years.

The sensitization rates for *Alternaria* were 8.1% (11/135), 8.9% (12/135), and 8.1% (11/135) when tested with a, b, c laboratories, respectively, and, 7.4% (10/135), 5.9% (8/135), and 4.4% (6/135) for *Cladosporium*. When positive and negative SPT results obtained with three different laboratories were analyzed by Cochran's Q homogenization test, results demonstrated that the reactions were not homogeneous among laboratories. Furthermore, in some of the positive reactions, great differences were observed between the diameters of the reactions (Table 2).

The total number of mold spores in Ankara atmosphere was 429 264 spores/m³ of which 75.5% and 6% were constituted by *Cladosporium* and *Alternaria*, respectively. The numbers of mold spores ranged between 1,284 to 84,126 spores/m³ and 58 to 6,443 spores/m³ for *Cladosporium* and *Alternaria*, respectively. The remaining of the mold spores in Ankara atmosphere were *Leptosphaeria*, 9,598 spores/m³ (2.23%), *Ustilago*, 9,586 spores/m³ (2.23%), *Askorspor*, 9,168 spores/m³ (2.13%), *Exosporium*, 8,616 spores/m³ (2.0%), *Pleospora* 6691 (1.55%), and *Drechslera*, 5411 (1.26%). The dispersion of concentrations of *Cladosporium* and *Alternaria*

TABLE 1.—Demographics and prevalence of sensitization to inhalant allergens of mold positive and negative groups.

	Mold positive (n:20)	Mold negative (n:115)
Age (years)		
Mean $\pm$ SD	30.65 $\pm$ 2.5	30.65 $\pm$ 1.035
Min-max	14–51	12–63
Median	27	29
Duration of symptoms (days)		
Mean $\pm$ SD	124.05 $\pm$ 25.65	67.75 $\pm$ 9.59
Min-max	3–420	1–264
Median	84	48
Gender		
Female	12 (60%)	69 (60%)
Male	8 (40%)	46 (40%)
Diagnosis		
Rhinitis	9 (45%)	68 (59.1%)
Asthma	4 (20%)	15 (13%)
Rhinitis Asthma	+7 (35%)	32 (27.8%)
Season of symptoms		
Seasonal	11 (55%)	81 (70.4%)
Perennial	9 (45%)	34 (29.6%)
House dust mite		
+	8 (40%)	29 (25.2%)
–	12 (60%)	86 (74.8%)
Grass pollen		
+	14 (70%)	85 (73.9%)
–	6 (30%)	30 (26.1%)
Cereals pollen		
+	10 (50%)	72 (62.6%)
–	10 (50%)	43 (37.4%)
Tree pollen		
+	6 (30%)	56 (48.7%)
–	14 (70%)	59 (51.3%)
Weed pollen		
+	9 (45%)	57 (49.6%)
–	11 (55%)	58 (50.4%)
Pollen total		
+	15 (75%)	96 (83.5%)
–	5 (25%)	19 (16.9%)
Cockroach		
+	5 (25%)	18 (15.7%)
–	15 (75%)	97 (84.3%)
Cat		
+	3 (15%)	13 (11.3%)
–	17 (85%)	102 (88.7%)
Dog		
+	3 (15%)	11 (9.6%)
–	17 (85%)	104 (90.40%)

spores according to months are presented in Figures 2 and 3.

DISCUSSION

In the present study, 15% of patients with respiratory allergies reacted to *Alternaria* and/or *Cladosporium* by means of SPT. Epidemiological studies indicate that sensitization to molds determined by SPT is common among patients with respiratory allergies. However, commercially available mold extracts used for SPT are far from standardization and therefore give variable results. In a general population study in the United States, 36% of the population was found to be sensitized to *Alternaria alternata* (16). Skin prick test positivity to *Alternaria* and *Cladosporium* was 0.5% and 2.9%, respectively, among children living on the Isle of Wight (17). A Finnish study reported 7.1% of asthmatic children had positive skin test reactions to *Cladosporium* (2). D'Amato et al. evaluated the prevalence of SPT positivity to *Alternaria* and *Cladosporium* in patients with respiratory allergies in nine European countries. Although the average percentage of mold sensitization was found to be 9.4%, the ratio of

positive skin reaction was changed from country to country (e.g., sensitization to *Alternaria* and *Cladosporium* was 3% in Portugal; in Spain 20% of patients turned out to be positive [9]). In our trial, the prevalence of mold sensitization detected by a quite similar method used by this group seems to be comparable to sensitization to molds in European countries.

Isolated mold sensitization is not common, and most reactions to molds are associated with reactions to common inhalant allergens (7, 9, 18). Isolated mold sensitization was 3% in our study group, and the prevalence of pollen and mite sensitizations were 70% and 40%, respectively, among mold-sensitive subjects. The lower prevalence of sensitization to molds may be related with their allergenicity or unreliability of diagnostic extracts (4, 7, 18).

Among outdoor molds, *Alternaria* and *Cladosporium* are considered as two most important outdoor allergenic molds worldwide (19–21). In keeping with that, these molds produce often positive skin test reactions in allergic subjects. Changing prevalence of sensitization *Alternaria* and *Cladosporium* from a minimum of less than 2% to a maximum of more than 30% has been reported in different studies (2, 7, 9, 18). In our study, SPT positivity rates for *Alternaria* (11.9%) and *Cladosporium* (8.1%) were similar to those already demonstrated in the international studies.

Although correlations between respiratory allergic symptoms and the presence of fungal spores in the atmosphere have been demonstrated, clinical relevance of mold sensitization is often not clear (22, 23). The clinical relevance of mold sensitivity was not the objective of our study; therefore, we did not record daily symptoms during mold counts in the Ankara atmosphere.

As far as disease pattern and severity correlated with sensitization to molds is concerned, rhinitis has been more frequently diagnosed as respiratory allergy than asthma and/or conjunctivitis (7, 9). Conversely, some epidemiologic studies suggested that sensitization to *Alternaria* is associated with asthma, particularly with severe asthma and life-threatening exacerbations (22, 24, 25). In the present study, clinical diagnosis of respiratory allergies were not different among patients with or without mold sensitization; however, we did not evaluate the severity of all patients with asthma except patients monosensitized to tested molds. The literature data pointed out that a small percentage of subjects show monosensitization to *Alternaria* or *Cladosporium* (7, 9, 24). Each subject turned out to be monosensitized to *Alternaria* and *Cladosporium* in our trial. The *Alternaria*-sensitive patient had mild asthma and rhinitis. Similarly, the patient with *Cladosporium* sensitivity had mild-moderate asthma except rhinitis. Very limited numbers of monosensitized patients prevent us to discuss the relationship between severity of asthma and sensitization to individual molds.

Patients with mold allergy are often sensitized to several mold species indicating a high degree of cross-reactivity (26, 27). Seven subjects of our study were found to be sensitive to both *Alternaria* and *Cladosporium*. However, since we did not perform RAST inhibition, it seems difficult to draw any conclusion on that issue.

A wide variety of fungal spores disperse in the atmosphere in a pattern that is characteristic for each region. In general, the ranking order is presented as 1-*Cladosporium*,

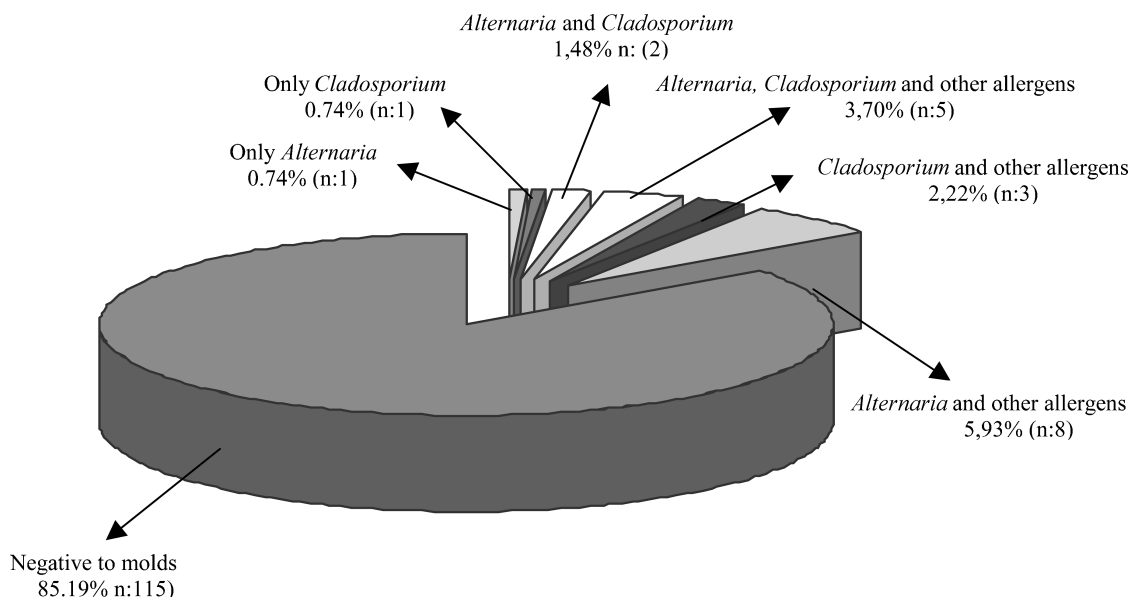


FIGURE 1.—Prevalence of skin prick test positivity to *Alternaria*, *Cladosporium*, and other inhalant allergens.

2-*Alternaria* (20, 21, 23, 25). In our 2003 survey, the total number of mold spores in the Ankara atmosphere was 429.264/m³ of which 75.5% and 6% were constituted by *Cladosporium* and *Alternaria*, respectively, with the same ranking order. Additionally, previous studies in which mold spores had been measured in Ankara since 1990 constantly

documented that these two mold spores were the first two most common molds (14, 28–33). Although, the total number of *Cladosporium* spores was significantly higher than those of *Alternaria* in the Ankara atmosphere, the prevalence of *Cladosporium* sensitization was not higher than that of *Alternaria*. This discordance has been repeatedly observed (24, 27). High spore numbers do not indicate high allergenicity, and sensitization to molds may be associated with other factors besides their load in the air. The accuracy of sampling techniques for quantifying the natural occurrence of molds is still doubtful (34). Additionally, the differences in environmental conditions, genetic predisposition, and variation in the amount of inhaled allergenic mold spores within individuals and quality of commercial extracts in the potency of extracts all may contribute to the prevalence of mold sensitization (35).

The variable quality of commercial mold extract is a well-known feature. Few studies documented the difference in SPTs with the use of different commercial sources (9, 17). Although great efforts have been spent to increase the quality of mold extracts; thus far, they are still far from being optimum

TABLE 2.—Comparison between results of skin prick test positivity for *Alternaria* and *Cladosporium* with three different allergenic extracts.

Patient number	a (mm)	b (mm)	c (mm)
<i>Alternaria</i>			
3	14 × 8	5 × 5	5 × 5
7	3 × 3	3 × 3	3 × 3
36	Negative	4 × 3	3 × 3
46	Negative	Negative	3 × 3
51	5 × 4	4 × 4	5 × 5
56	3 × 3	Negative	Negative
70	Negative	Negative	3 × 3
80	Negative	3 × 3	Negative
86	3 × 3	3 × 3	3 × 3
93	3 × 3	3 × 3	Negative
96	4 × 4	3 × 4	3 × 4
100	3 × 5	5 × 6	18 × 8
104	4 × 4	9 × 8	9 × 8
105	Negative	5 × 6	Negative
113	3 × 3	4 × 4	5 × 3
123	3 × 3	Negative	Negative
Prevalence of sensitization to <i>Alternaria</i>	11(8.1%)	12(8.9%)	11(8.1%)
<i>Cladosporium</i>			
2	3 × 3	3 × 3	Negative
36	15 × 15	4 × 3	3 × 3
45	3 × 3	Negative	Negative
46	Negative	Negative	4 × 3
51	7 × 8	3 × 4	4 × 4
86	3 × 3	3 × 3	3 × 3
87	3 × 3	Negative	Negative
96	3 × 3	3 × 3	3 × 3
100	7 × 5	12 × 8	13 × 9
101	3 × 3	6 × 5	Negative
105	3 × 3	4 × 4	Negative
Prevalence of sensitization to <i>Cladosporium</i>	10 (7.4%)	8 (5.9%)	6 (4.4%)

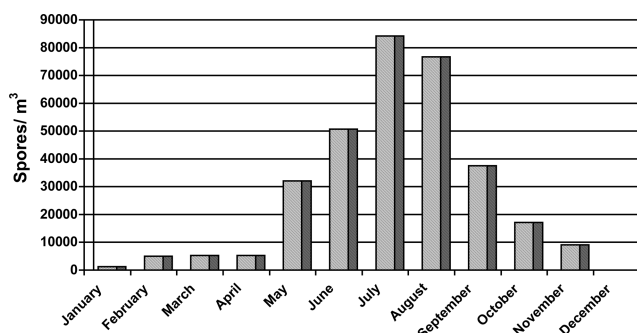


FIGURE 2.—Total monthly *Cladosporium* spores concentrations in 2003.

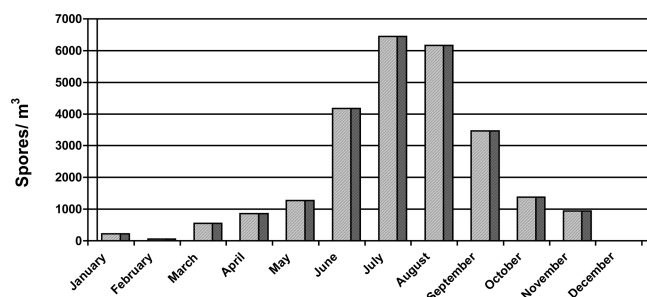


FIGURE 3.—Total monthly *Alternaria* spores concentrations in 2003.

(8, 9, 17, 36). Considering that issue, we performed SPT with extracts provided by three different laboratories. The average prevalence of sensitization to *Alternaria* and *Cladosporium* was not different, although sample “b” and “a” gave higher positive results for *Alternaria* and *Cladosporium* respectively. However, positive and negative reactions were not homogeneous among three manufacturers. Moreover, the diameters of reactions were even different among positive reactions. A limitation of our study was that ruler measurement was used in the evaluation of wheal size to mold extracts. Although a very experienced nurse obtained measurements, the use of caliper could be associated with more reproducible data. Nonetheless, the limited reliability of commercial mold extracts warrants further molecular-based studies for production of standardized extracts.

In conclusion, the prevalence of mold sensitization in respiratory allergy patients is quite similar to European countries; however, our data indicate that commercial mold extracts should be standardized to evaluate the real sensitization rate. The abundance of mold spores in the Ankara atmosphere as well as considerable prevalence of mold sensitization emphasizes the importance of molds in this local region. However, we need long-term follow-up studies to be able to comment on the relationship between the concentration of outdoor molds and sensitization patterns.

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