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Clinical significance of *Alternaria alternata* sensitization in patients with allergic rhinitis☆,☆☆

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Abstract

Purpose: The aim of the study was to determine the epidemiologic profile of *Alternaria alternata* (AA)–sensitized patients with allergic rhinitis including coexistence of other atopic diseases, seasonal distribution of AA aeroallergens, age of onset of AA sensitization, and prevalence of sensitization to other allergens.

Materials and methods: History, clinical examination, and skin prick tests were performed in 623 patients with allergic rhinitis from central Greece. Patients' age, cosensitization, place of living, seasonal distribution, and concomitant symptoms were the variables used to discriminate between AA-sensitized and non–AA–sensitized patients. Significant predictor variables for AA sensitization were determined.

Results: *A alternata* sensitization was associated with male sex, age younger than 18 years, living in new-built apartments in urban and semiurban areas by the sea, perennial distribution, and nonsmoking. *A alternata*–sensitized patients were affected more frequently by asthma than non–AA-sensitized patients. No significant differences were found in frequency of bronchitis, cough, conjunctivitis, urticaria, or eczema between patients sensitized or not to AA. Most (66.7%) of AA-sensitized patients were oligosensitized, 18.5% of patients were polysensitized, and 14.8% were monosensitized. Patients' age, cosensitization, place of living, and seasonal distribution were the significant predictor variables discriminating AA-sensitized from non–AA-sensitized patients. These variables correctly classified 79.7% of the patients. *A alternata*–sensitized patients were more frequently sensitized to grasses, cat epithelia, and flours-rye and less frequently sensitized to artemisia, *Dermatophagoides pteronyssinus*, *D farinae*, and chenopodium.

Conclusions: Patients meeting the aforementioned epidemiologic criteria should be preferentially offered skin prick tests for AA sensitization.

1. Introduction

Allergic rhinitis (AR) affects 25% of the European population [1]. Atopic sensitization to the mould *Alternaria alternata* (AA) has been associated with rhinitis and asthma [2-4]. Treating rhinitis might prevent asthma development [2]. However, AA sensitization still remains underdiagnosed in many countries [4]. It is therefore crucial to identify early individuals at risk, especially children, for AA sensitivity [5].

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Little is known about the significance of AA as a risk factor for asthma [6] because established factors for AA sensitivity have changed, including air pollution, lifestyle, food habits, air-conditioning and air heating, construction of new buildings with new materials, and ventilation systems. In addition, there is variability in epidemiologic data regarding geographical, climatic, and seasonal changes [2,3] even within the same broader region [7]. The actual prevalence of sensitization to AA mold is difficult to determine because of differences in diagnostic criteria in study design and unreliability of diagnostic extracts. In addition, to our knowledge, there is a lack of such epidemiological data in the Greek population.

The aims of our study were (1) to determine the prevalence of AA sensitization in respiratory allergic patients, (2) to explore the association of AA sensitization to other atopic diseases, (3) to examine the seasonal distribution of AA aeroallergens, (4) to estimate the age of onset of AA sensitization, and (5) to determine the prevalence of mono-, oligo- and multiple sensitization to other allergens in patients with AA sensitization.

2. Materials and methods

In this prospective study, 623 patients from central Greece (Thessaly) were included [3]. Patients from all 4 distinct prefectures of Thessaly (Larissa, Magnisia, Karditsa, and Trikala) were examined. Thessaly was chosen because there were no studies on the allergic profile of the respective population, and its climate conditions and geography are representative for the Mediterranean area. On the humid coastal strip of Magnisia, mean temperatures range from 3°C to 12°C in the winter to 20°C to 32°C in summer. The drier inner provinces of Trikala and Karditsa exhibit larger temperature variation between seasons, whereas Larissa is notorious for wet climate and high annual temperatures. The land is 45% mountainous or semimountanous and 55% lowland.

Patients complaining for rhinitis symptoms were recruited by general practitioners, otorhinolaryngologists, pediatricians, and pneumonologists from all 4 prefectures. A detailed history, clinical examination, and skin prick tests (SPTs) were performed. The study protocol was approved by the local institutional review board. All subjects were volunteers, and they have been informed about the study's aim, design, and clinical implications. The investigations were performed in accordance with the Declaration of Helsinki/Hong Kong.

Patients with AA sensitivity were 48 men (59.3%) and 33 women (40.7%) with a mean age of 15.94 ± 8.79 years (range, 7-67 years). Patient demographics are presented on Table 1.

All patients underwent SPTs with a panel of 20 commercial allergenic extracts (Allergopharma, Reinbeck, Germany) selected upon known local presence (Table 2). There was no current use of any antihistamine drugs within the preceding 30 days or systemic corticosteroids, leukotriene inhibitors, and immunotherapy within the last 28 days. All allergens were standardized, and most were single extracts; only 2 solutions were mixes: "grasses' mix" and "feathers' mix." More than twice the recommended number of tested allergens [8] were included to achieve a more thorough investigation. Histamine dihydrochloride (10 mg/mL) was the positive control, and the extracts' solvent (glycerin) was the negative control.

Wheal and flare sizes were measured in millimeters in 2 perpendicular directions at 20 minutes after the initial skin prick and considered positive only when wheals of at least 3 mm and flares of at least 10 mm in diameter larger than the negative control were found. Subjects with negative responses to all 20 aeroallergens were considered nonallergic. Subjects sensitized to only 1 allergen were referred as "monosensitized," to 2 or 3 allergens as "oligosensitized," and to 4 or more allergens as "polysensitized."

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 14.0 (SPSS Inc, Chicago, IL). Age was expressed as the mean ± SD. All other variables were categorical; they were expressed as frequencies and percentages (%) and analyzed using the χ^2 test. Odds ratios (ORs) and their 95% confidence intervals (95% CIs) were calculated using simple logistic regression analysis as the measure of association between AA sensitization and (1) patients' demographic characteristics, (2) concomitant symptoms/conditions, and (3) sensitization to other aeroallergens. Discriminant forward stepwise analysis was used to determine the significant predictor variables that provide the best discrimination between sensitization or not to AA. All tests were 2 tailed, and statistical significance was considered for $P < .05$.

3. Results

The demographic features of the patients are presented on Table 1. *A alternata* sensitization was statistically significantly associated with male sex (15.7% vs 10.4% in women; $P = .050$; OR, 1.6; 95% CI, 1.0–2.6), age younger than 18 years (30.0% vs 5.5% in >18 years; $P < .001$; OR, 7.3; 95% CI, 4.4–12.2), living in urban and semiurban areas (15.5% in urban, 14.3% in semiurban, and 5.1% in agricultural areas; $P = .008$; OR, 3.4; 95% CI, 1.5–7.7 and OR, 3.1; 95% CI, 1.2–7.8 for urban and semiurban areas compared with agricultural areas, respectively), in sea coast or valley regions (13.9% vs 0.0% in mountain regions, $P = .010$), in apartments (16.5% vs 5.5% in houses or farms; $P = .046$; OR, 1.6; 95% CI, 1.0–2.6), in new buildings (16.0% vs 9.5% in old buildings; $P = .011$; OR, 1.9; 95% CI, 1.2–3.2), and in nonsmokers (15.2% vs 6.5% in smokers; $P = .005$; OR, 2.6; 95% CI, 1.3–5.2).

Concomitant symptoms, such as asthma, bronchitis, conjunctivitis, urticaria, eczema, and cough, were more

Table 1
Patients' epidemiological and demographic data

	AA		Other aeroallergens		*P*
	No. of patients	(%)	No. of patients	(%)	
Sex					.050
Female	33	40.7	284	52.4	
Male	48	59.3	258	47.6	
Age, y					<.001
≤18	57	70.4	133	70.4	
>18	24	29.6	409	29.6	
Mean age ± SD	15.94 ± 8.79		31.72 ± 15.83		
Median (IQR)	13 (10–20.5)		30 (19–43)		
Contact to animals					.822
No	48	59.3	314	57.9	
Yes	33	40.7	228	42.1	
Residence					.008
Urban areas	58	71.6	316	58.3	
Semiurban areas	16	19.8	130	24.0	
Agricultural areas	7	8.6	130	17.7	
Geographic area					.021
Mainland	77	95.1	487	89.9	
Coastal	4	4.9	14	2.6	
Mountainous	–	–	41	7.6	
Type of house					.125
Flat	38	46.9	192	35.4	
Detached house	37	45.7	292	53.9	
Farm	6	7.4	58	10.7	
Age of house					.011
Old	24	29.6	242	44.6	
New	57	70.4	300	55.4	
Smoking					.005
No	71	87.7	397	73.2	
Yes	10	12.3	145	26.8	
Concomitant symptoms					
Asthma	47	58.0	233	43.0	.011
Bronchitis	42	51.9	231	42.6	.118
Conjuctivitis	28	34.6	183	33.8	.887
Urticaria	15	18.5	86	15.9	.546
Eczema	10	12.3	62	11.4	.812
Cough	26	32.1	133	24.5	.145
Seasonal distribution					<.001
Persistent	66	81.5	323	59.6	
Intermittent	15	18.5	219	40.4	
No. of allergens					<.001
Monosensitivity	12	14.8	226	41.7	
Oligosensitivity	54	66.7	275	50.7	
Polysensitivity	15	18.5	41	7.6	

IQR indicates interquartile range.

frequent in AA-sensitized patients compared with other (non-AA) allergic patients (87.7% vs 78.6%; $P = .058$; OR, 1.9; 95% CI, 1.0–3.9). In particular, AA-sensitized patients were affected more frequently by asthma than patients not sensitized to AA (58.0% vs 43.0%; $P = .011$; OR, 1.8; 95% CI, 1.1–2.9). No statistically significant differences were found in the frequencies of bronchitis and cough among AA- and non–AA-sensitized patients (bronchitis: 51.9% vs 42.6%; $P = .118$; OR, 1.5; 95% CI, 0.9–2.3; cough: 32.1% vs 24.5%; $P = .145$; OR, 1.5; 95% CI, 0.9–2.4). The presence of conjunctivitis, urticaria, or eczema was similar between patients sensitized or not to AA ($P = .887$, .546, and .812, respectively). Regarding seasonal variation, AA-associated AR presented a persistent pattern (66 patients, or 81.5%) rather than an intermittent one (15 patients, or 18.5%). Persistent disease was significantly more frequent among AA-sensitized patients compared with non–AA-sensitized patients (81.5% vs 59.6%; $P < .001$; OR, 3.0; 95% CI, 1.6–5.4).

Among the 623 patients, 56 (9.0%) had monosensitization, and only 12 (2.4%) had AA monosensitization; most AA-sensitized patients were oligosensitive (54 patients, or 66.7%), whereas 15 patients (18.5%) were polysensitive, and the remaining 12 patients (14.8%) were monosensitive.

Table 2
Sensitivity to other aeroallergens used in SPTs

	AA-sensitive patients		Patients sensitive to other aeroallergens		*P*
	n	(%)	n	(%)	
Type of aeroallergen					
Grasses mix	47	58.0	295	54.4	.544
Feathers—duck, goose, hen	0	0.0	3	0.6	.502
Artemisia vulgaris	1	1.2	43	7.9	.028
Plantain	3	3.7	32	5.9	.422
Epithelia of animals, dog	3	3.7	24	4.4	.765
Epithelia of animals, cat	22	27.2	82	15.1	.007
Epithelia of animals, goat	1	1.2	4	0.7	.640
Cladosporium	9	11.1	15	2.8	<.001
Aspergillus	6	7.4	13	2.4	.014
D pteronyssinus	16	19.8	222	41.0	<.001
D farinae	22	27.2	232	42.8	.008
Flours, wheat	1	1.2	4	0.7	.640
Flours-rye	2	2.5	3	0.6	.072
Olive	25	30.9	157	29.0	.726
Parietaria	6	7.4	58	10.7	.362
Chenopodium	2	2.5	44	8.1	.070
Hornbeam, *Caprinus detulus*	1	1.2	15	2.8	.416
Cypress	10	12.3	65	12.0	.927
Bermuda grass	35	43.2	225	41.5	.773

Monosensitivity was significantly more frequent in non–AA-sensitized patients than in AA-sensitized patients (41.7% vs 14.8%; $P < .001$; OR, 4.1; 95% CI, 2.2–7.8). Among the AA-sensitized patients, the frequency of mono-, oligo-, and polysensitization was 17.5%, 66.7%, and 15.8%, respectively, in patients 18 years or younger and 8.3%, 66.7%, and 25.0%, respectively, in patients older than 18 years. More than half of the patients with AR due to AA aeroallergen was sensitive to grasses (58%) (Table 2). Compared with patients not sensitized to AA, patients with AA sensitivity were more frequently sensitized to epithelia of cats (27.2% vs 15.1%; $P = .007$; OR, 2.1; 95% CI, 1.2–3.6), *Cladosporium* (11.1% vs 2.8%; $P < .001$; OR, 4.4; 95% CI, 1.9–10.4), *Aspergillus* (7.4% vs 2.4%; $P = .014$; OR, 3.3; 95% CI, 1.2–8.8), and flours-rye (2.5% vs 0.6%; $P = .072$; OR, 4.6; 95% CI, 0.8–27.6) and less sensitive to artemisia (1.2% vs 7.9%; $P = .028$; OR, 0.2; 95% CI, 0.1–1.0), *Dermatophagoides pteronyssinus* (19.8% vs 41.0%; $P < .001$; OR, 0.4; 95% CI, 0.2–0.6), *D farinae* (27.2% vs 42.8%; $P = .008$; OR, 0.5; 95% CI, 0.3–0.8), and chenopodium (2.5% vs 8.1%; $P = .070$; OR, 0.3; 95% CI, 0.1–1.2) (Table 2).

Discriminant forward stepwise analysis indicated that patients' age (≤18 vs >18 years, Wilks $\lambda = 0.931$, $P < .001$), cosensitization (mono- vs oligo- or polysensitivity, Wilks $\lambda = 0.858$, $P < .001$), place of living (sea coast or valley vs mountain, Wilks $\lambda = 0.848$, $P < .001$), and seasonal distribution (perennial vs intermittent, Wilks $\lambda = 0.846$, $P < .001$) were the significant predictor variables that provide the best discrimination between AA-sensitized and non–AA-sensitized patients. These variables correctly classified 79.7% (497/623) of the patients.

4. Discussion

A alternata is an outdoor allergen and one of the main allergens in the pediatric population. Its distribution is related to the geographic area, season, atmospheric conditions, and time of the day [9]. It is highly resistant to adverse climate conditions. On windy days, *Alternaria* diffuses easily in the air because of its small size [9].

In this study, AA sensitization was found in 13% of AR patients in Thessaly, in 30% of individuals younger than 18 years, and in 5.5% of individuals older than 18 years. Among children and adolescents (<18 years old), AA is the third most frequent aeroallergen after grass mix (59.5%) and *Dermatophagoides* (37.9%), a finding important for the management of a children having AR with or without asthma. In patients older than 18 years, other aeroallergens are more often responsible for allergy, such as grass mix, *Dermatophagoides*, olive, and epithelia of cats.

Our findings present similarities and differences to other epidemiological studies. Sensitization to AA allergen ranges between 3% and 30% in European countries. *A alternata* sensitization in Italian patients with respiratory symptoms ranges from 2% to 29% [10]. In Portugal, 11.2% of patients had a positive skin test, whereas in Spain, 20% demonstrated positive skin tests to these fungi [11]. In Turkey, the incidence of AA sensitization was 11.9% [12]. In a Scandinavian study [13], 4% showed positive skin test to AA. In the United States [14], the percentage of sensitization to AA varied from 3% in children aged 12 to 17 years to 7.5% in older children and young adults (age, 18–24 years). These differences in results may be due to differences in the standardization of mold allergen extracts or skin testing

techniques, differences in study design and diagnostic criteria, and differences in environmental factors and conditions [15]. This is the main reason for the need for epidemiological studies in every country or even in different regions of the same country.

We found a male preponderance of AA sensitivity in the pediatric population. In addition, an earlier onset and a more frequent persistent AR pattern were found in men compared with women. The present study confirmed previous reports of a higher prevalence of atopic sensitization in boys than in girls [16]. In our study population, the age at diagnosis was between 6 and 18 years, especially 8 to 10 and 12 to 15 years old (Fig. 1). Several studies have shown that, at 4 years old, AA is the third most common cause of sensitization after *Dermatophagoides* and grass pollens [17]. In these studies, the mean onset of AA sensitivity was at age 4 years for men and at age 5 years for women. The later diagnosis of AA sensitivity in our study population may be because AR, especially in children, is underestimated and that parents delay to visit a physician. This happens because asthma (a more severe condition) usually follows AR symptoms [2,18]. Moreover, AA sensitization was found in many children with no clinical disease [17]. The allergic response, as previous studies have shown, cannot be accurately correlated with symptoms because of immature immune system in children younger than 8 years old [18]. Our findings underline the need for children with AR symptoms to visit a physician early and for allergy tests (including AA) to be done. In people older than 23 years, the percentage of AA sensitization was almost nulled.

People living in new buildings were more frequently AA sensitized than people living in old ones (16% vs 9%). People living in apartments had more frequent AA sensitization than those who live in cottages and farms (16.5% vs 11.2% vs 9.4%, respectively). People in cities have more frequent AA sensitization than people living in villages (15.5% vs 5.1%), especially in mountain areas where AA sensitization is rare. Dampness and fungal problems occur in 20% to 50% of modern homes [19]. This may be because of the materials present in new buildings [19] that more often than not decrease the circulation of clean air and increase the indoor allergens' concentration. Peat et al [20] and Verhoeff and Burge [21] came to the same conclusions concerning a positive association between damp homes and respiratory morbidity of the occupants. Homes in a single- or multilevel apartment buildings were found with higher endotoxin levels [22]. On the other hand, in a study from India, sensitization to fungi was found to be higher in younger subjects from the rural area [23]. In any case, the disparity in allergen sensitization in different countries might primarily be caused by environmental factors rather than genetic differences, and that is why the importance of epidemiological studies in various climate conditions.

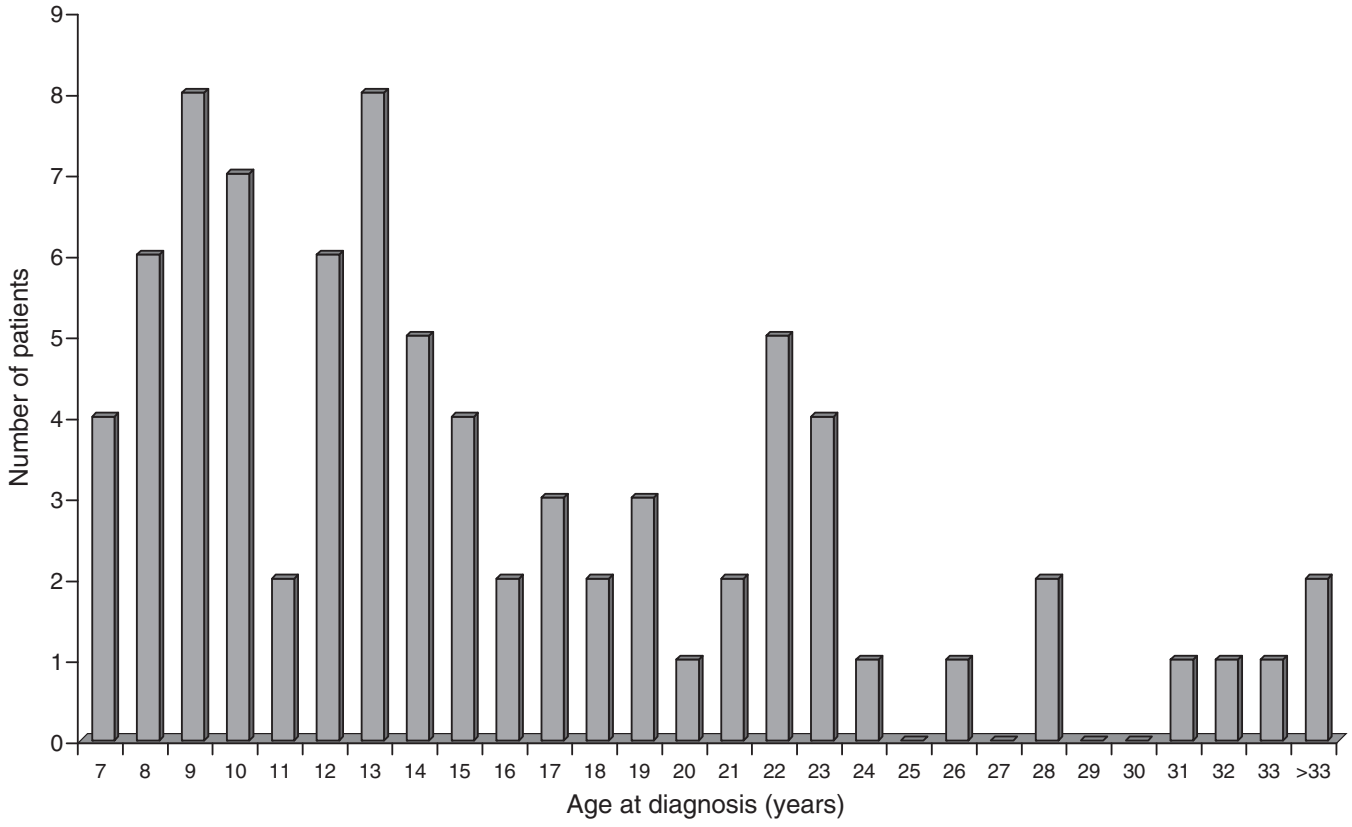

Fig. 1. Age at diagnosis of AA sensitivity.

We found that smokers are less frequently sensitized to AA than nonsmokers (6.5% vs 15.2%). Allergic rhinitis is less frequent in smokers, and AR symptoms in smokers are less severe than in nonsmokers [24].

Multiple comorbidities are associated with AR [2-4]. There is a strong association between AR and asthma, but the reason for this common comorbidity is still a matter of debate [25]. Asthma and AR might be 2 different manifestations of the same atopic disease [26] or they may interact with each other [2]. A key question is whether severe asthma is actually caused by sensitivity to molds or is simply associated with it. Several studies suggested that AA is an important risk factor for development and persistence of asthma [27]. *A alternata* is able to trigger asthma attacks and even anaphylactic shock especially in children and young adults [28].

In our study, patients with AR due to AA aeroallergen present more often concomitant conditions of the lower respiratory than to other systems, namely, asthma in 58%, bronchitis in 51.9%, and cough in 32.1%. This finding stresses the importance of ears, nose, and throat examination in children having lower respiratory symptoms problems for the early detection of a possible AA sensitivity and early treatment. Asthma as a concomitant symptom of AR due to AA aeroallergen is meaningful in children younger than 18 years and more particularly in those between 13 and 18 years old. It is not clear why mold allergens should produce more severe airway disease than other common allergens such as house dust mites, cat dander, or grass pollen. It may relate to the nature—quicker release—or intensity—they are very common in the environment—of exposure to mold allergens or to their ability to become airborne and to gain entry to human airways because of their small size. The recent observations on the relationships between atopy, rhinitis, and asthma support the hypothesis of a unique systemic condition with variable manifestations, supporting the concept of *united airways* [29].

Allergic rhinitis has been consistently associated with a higher risk of asthma in all countries [2,18]. The prevalence of asthma among AR patients may range between 7.6% and 26% [30]. Nonetheless, in other studies, these figures are closer to ours, namely, between 40% and 50% [31]. Unfortunately, these results are difficult to compare because of differences in the genetic background, the environmental exposure, the study setting, and definitions of rhinitis and asthma used [26]. Furthermore, the relative risk of asthma associated with specific allergens is difficult to assess because these patients are often polysensitized [2]. In children, rhinitis is usually diagnosed later than asthma. This may be a reason for the late diagnosis of AA sensitization as a cause for asthma and rhinitis. In adults, AR often precedes the development of asthma, and it has been suggested that AR might be a risk factor for asthma [30].

Another important finding is that AR due to AA aeroallergen is persistent rather than intermittent (81.5% vs 18.5%). This aggravates the problem because patients have symptoms continuously and because treatment is very important. However, seasonal (summer-fall) peak of asthma admissions occurs when ambient air counts of molds are high. These asthma admissions also coincide with the peak months for outdoor levels of fungal spores. It may because AA allergens come indoors in sufficient quantities so as to behave as an indoor perennial allergen [28]. Studies in young adults in England and Wales show that asthma deaths are commonest in July, August, and September, which coincides with peak levels of mold spores in outdoor air in the UK [32].

Notably, AA-sensitized individuals are polysensitive, and polysensitivity is increasing with age in this particular group. More specifically, 82.5% of these people who are younger than 18 years are polysensitive (the same age group in the atopic population are polysensitive in 62.4%). Later in life (>18 years old), this difference is enhanced (91.7% vs 57% in the general population). This polysensitivity among patients with AA sensitivity has been also reported by other authors [6,11]. A reason for this may be that AA sensitizations could play a “triggering” role in the development of polysensitization because a high proportion of children originally monosensitized to house dust mites or to pollens became polysensitized.

In addition, we found that 58% of AA-sensitized patients are also sensitized to grass mix allergen, although this figure is similar to the appearance of grass mix polysensitivity to the total atopic population. The same happens with Bermuda grass (43.2% vs 41.5%), cypress (12.3% vs 12.0%), and olive (30.9% vs 29.0%). Nonetheless, patients sensitive to AA present quite frequent sensitivity to *Aspergillus* (7.4% vs 2.4%), *Cladosporium* (11.1% vs 2.8%), and epithelia of cats (27.2% vs 15.1%). This has implications for clinical practice. It means that when we diagnose AA sensitization in a patient, it would be prudent to search for sensitization to other allergens that are present simultaneously in high frequencies, such as grass mix, olive, epithelia of cats, *Dermatophagoides* mix, cypress, and molds (*Aspergillus*, *Cladosporium*).

5. Conclusions

Allergic rhinitis is a risk factor for asthma (particularly for difficult-to-control asthma), and it often precedes asthma development. Treating comorbid AR may result in better asthma outcomes during long-term combined treatment. It is therefore crucial to early identify people—especially children—at risk for AR with SPTs and initiate treatment. Patients meeting the aforementioned epidemiologic criteria should be preferentially offered SPTs for AA. This mold should be included in the standard panel for diagnosis of respiratory allergy.

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