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Impact of *Aspergillus fumigatus* allergen sensitivity on allergic rhinitis and asthma: a single center retrospective study

Wpływ czułości alergenu *Aspergillus fumigatus* na alergiczny nieżyt nosa i astmę: retrospektywe jednoośrodkowe badanie

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ABSTRACT

Introduction: *Aspergillus fumigatus* (A.f) is a common aeroallergen that can cause diseases such as allergic asthma, allergic rhinitis, and allergic bronchopulmonary aspergillosis (ABPA).

Aim: To investigate the clinical characteristics of patients with A.f sensitivity and allergic respiratory diseases in the Istanbul region of Turkey.

Material and methods: Patients with allergic rhinitis and A.f sensitivity, and patients with allergic rhinitis and sensitivities other than A.f were included in the study. Comparisons were conducted between A.f sensitive and A.f non-sensitive patients in terms of severity of allergic asthma, severity of allergic rhinitis, rhinitis visual analogue symptom (VAS) symptom scores, asthma and allergic rhinitis treatment steps, asthma frequency and asthma control.

Results: A total of 157 patients with allergic rhinitis were included in the study. The median (IQR) age of the patients was 33 (25–45), and 106 of them were female (67.5%). Severe asthma was more frequent in patients with A.f sensitivity than in patients with other allergen sensitivities ($p < 0.001$). Presence of A.f sensitivity was related to a lower asthma control score and higher asthma treatment step than presence of other allergen sensitivities ($p = 0.029$, $p < 0.001$, respectively). Additionally, VAS symptom scores for allergic rhinitis before and after treatment and allergic rhinitis medication scores were higher in patients with A.f sensitivity than in patients without A.f sensitivity ($p < 0.001$, $p = 0.015$, $p > 0.001$, respectively).

Conclusions: A.f sensitivity is associated with severe respiratory allergies. Clinicians should closely monitor these patients and remain vigilant for treatment unresponsiveness, exacerbations, and the potential progression of the disease to more complex clinical conditions such as ABPA.

KEY WORDS

allergic bronchopulmonary aspergillosis, allergic rhinitis, *Aspergillus fumigatus*, asthma.

ADDRESS FOR CORRESPONDENCE

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INTRODUCTION

Aspergillus fumigatus (A.f) is a common aeroallergen that can cause diseases such as allergic asthma, allergic rhinitis, and allergic bronchopulmonary aspergillosis (ABPA) [1]. A.f sensitivity is frequently observed among allergic individuals. In a study conducted in Turkey, the prevalence of A.f sensitivity in individuals aged 60 and above was reported as 8% [2].

ABPA is one of the most important clinical conditions caused by A.f. It is a chronic inflammation triggered by repeated exposure to A.f which is colonized in the airway for a long time. Clinical manifestations of ABPA include chronic asthma or bronchiectasis and recurrent pulmonary shadows or mucus blockage in lung images [3–6]. A study revealed that the estimated prevalence of ABPA in adults with asthma was 2.5% and could rise up to 45% in patients with A.f-sensitized asthma [3, 7, 8].

Although A.f sensitivity is often associated with ABPA, it also frequently causes common respiratory allergies such as allergic asthma and allergic rhinitis. Furthermore, studies have shown that A.f sensitivity can have a negative impact on the severity and control of allergic airway diseases [1, 9–12]. Considering its high prevalence as a respiratory allergen and its potential negative effects on patient outcomes, A.f sensitivity is a clinical condition that should receive more attention from clinicians and researchers.

AIM

The aim of this study is to compare the clinical characteristics of patients with A.f allergen sensitivity to those with non-A.f allergen sensitivity diagnosed with allergic rhinitis and/or allergic asthma in the Istanbul region. Being able to predict the effects of A.f allergen sensitivity on the severity and control of respiratory allergies in these patients beforehand would provide guidance to clinicians in managing their patients more accurately, especially in this region.

TABLE 1. Classification of treatments used in patients with allergic rhinitis [13]

1	Nonsedating H1-antihistamine (oral, intranasal, and ocular), leukotriene receptor antagonists, or cromones (intranasal and ocular)
2	INCSs
3	INCSs + intranasal azelastine
4	Oral corticosteroid as a short course and an add-on treatment
5	Consider referral to a specialist and allergen immunotherapy

INCSs – intranasal corticosteroids.

MATERIAL AND METHODS

PATIENT RECRUITMENT

The medical records of the patients with allergic rhinitis between January 2022 and March 2023 in the adult immunology and allergy clinic of Başakşehir Çam ve Sakura City Hospital were researched. The patients with A.f sensitivity were included in the study. Additionally, patients with allergic rhinitis and sensitivities other than A.f were randomly included in the study as a control group, ensuring that there was no significant difference in terms of asthma frequency or age and gender distribution. The patients who did not give informed consent were not included in the study.

STUDY DESIGN

All laboratory and clinical evaluation results used in the study were routinely obtained during patient examinations and retrospectively scanned from medical records. Skin prick and serum specific immunoglobulin E (IgE) test results, blood eosinophil counts, serum total IgE levels, respiratory function test results, asthma control test (ACT) scores and rhinitis visual analogue scale (VAS) symptom scores were all recorded in the patient follow-up forms. Patients with a VAS symptom score less than 5 were considered mild rhinitis, and those with at least 5 were considered moderate to severe rhinitis [13]. The Allergic Rhinitis and Its Impact on Asthma (ARIA) guideline was used to assess the severity of rhinitis and to determine the rhinitis treatment step [13]. The Global Initiative for Asthma (GINA) guideline was used to determine the severity of asthma and treatment step [14, 15]. The treatment step of allergic rhinitis was shown in Table 1.

Comparisons were conducted between A.f sensitive and A.f non-sensitive patients in terms of severity of allergic asthma, severity of allergic rhinitis, rhinitis VAS scores, asthma and allergic rhinitis treatment steps, asthma frequency and asthma control.

STATISTICAL ANALYSIS

All analyses were performed with the IBM Statistical Package for the Social Sciences version 25.0 (SPSS Inc., Chicago, IL, USA) for MacOS. Figures were developed in GraphPad Prism 9 (GraphPad Software, La Jolla, CA, USA) for MacOS. Descriptive data were given as percentages and as median (IQR 25–75). The comparisons

TABLE 2. Demographic and clinical characteristics of patients

Paramater	Presence of A.f sensitivity	Allergen sensitivities without A.f	*P*-value
Patients, *n* (%)	66 (42.0)	91 (58.0)	
Gender, *n* (%):			
Female	43 (27.4)	63 (40.1)	NS
Male	23 (14.6)	28 (17.8)	
Age (IQR)	33.5 (26.0–45.8)	33.0 (25.0–45.0)	NS
Concomitant asthma, *n* (%):			
Yes	32 (20.4)	45 (28.7)	NS
No	34 (21.7)	46 (29.3)	
Blood eosinophil count [cell/µl] median (IQR)	195.0 (90.0–407.5)	170.0 (90.0–380.0)	NS
Serum total IgE [kU/l] median (IQR)	305.5 (137.8–504.5)	234.0 (39.5–643.0)	NS

A.f – *Aspergillus fumigatus*, IgE – immunoglobulin E, IQR – interquartile range for 25th and 75th percentiles, NS – non-significant.

of VAS symptom scores, ACT scores, respiratory function test results, blood eosinophil counts, serum total IgE, rhinitis medication scores and asthma treatment step levels between the A.f sensitive and A.f non-sensitive patients were all performed with the Mann-Whitney *U* test. Categorical variables were analyzed with the χ^2 test. The results were assessed at a significant level of $p < 0.05$.

ETHICS STATEMENT

The study was started after obtaining approval from the ethics committee of the Turkish Republic Ministry of Health, Başakşehir Çam ve Sakura City Hospital (2023.05.204). The study was conducted in accordance with the principles of the Declaration of Helsinki. All participants were informed about the nature of the study and written informed consent was obtained.

RESULTS

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF THE PATIENTS

A total of 157 patients with allergic rhinitis were included in the study. The median (IQR) age of the patients was 33 (25–45), and 106 of them were female (67.5%) (Table 2). While 66 patients had A.f sensitivity, 91 patients had sensitivity other than A.f. Among patients with A.f sensitivity, 32 (48.5%) patients had concomitant allergic asthma and 2 (6.3%) patients with asthma had additional diagnosis of ABPA. In the patients with sensitivity other than A.f, the concomitant allergic asthma rate was 49.5% ($n = 45$) (Figure 1).

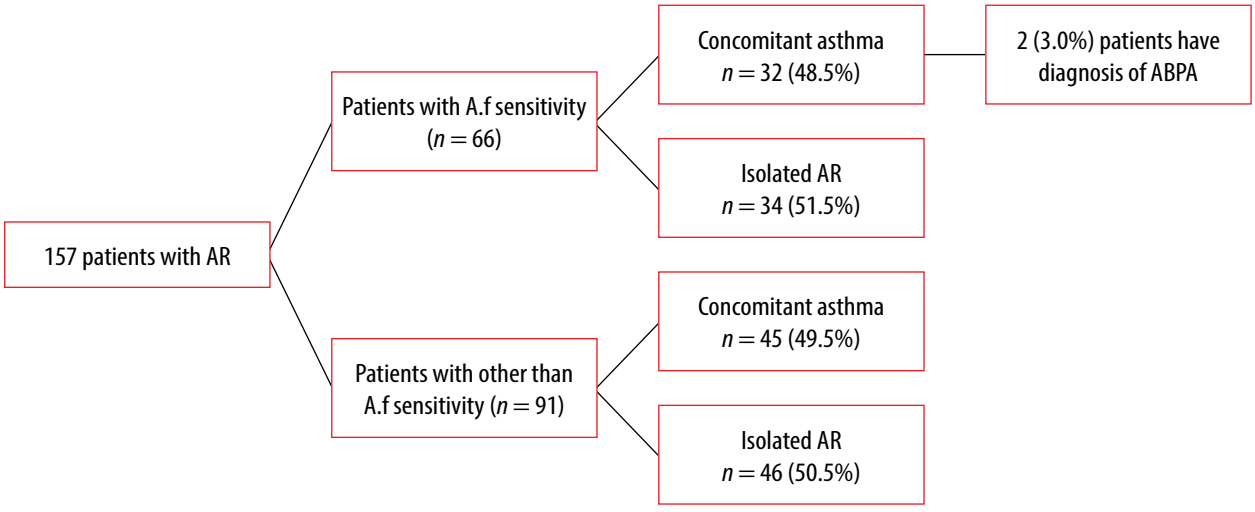

FIGURE 1. Patient groups

A.f – *Aspergillus fumigatus*, AR – allergic rhinitis.

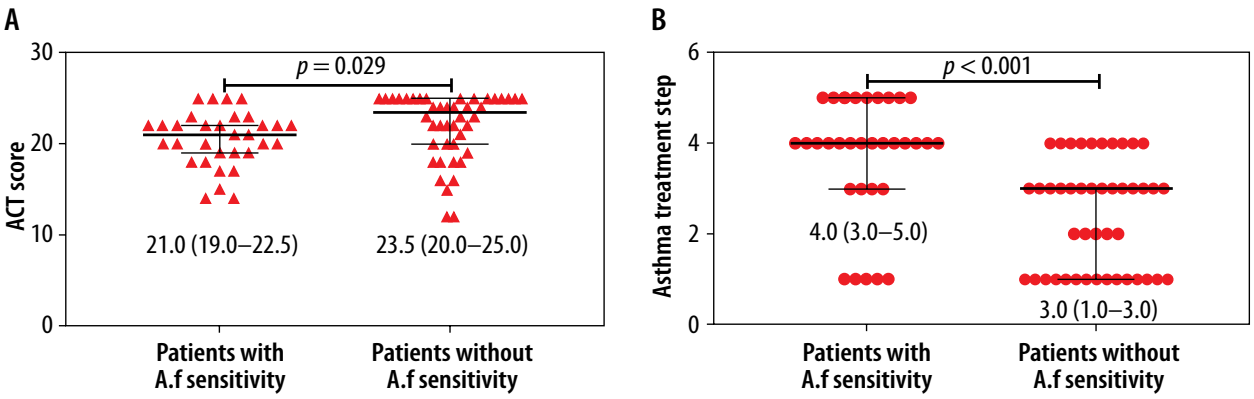

FIGURE 2. Impact of A.f sensitivity on asthma control test scores (**A**) and asthma treatment steps (**B**)

ACT – asthma control test, A.f – *Aspergillus fumigatus*.

IMPACT OF A.F SENSITIVITY ON ALLERGIC ASTHMA

Severe allergic asthma was more frequent in patients with A.f sensitivity than in patients with other allergen sensitivities ($p < 0.001$). Additionally, presence of A.f sensitivity was related to a lower asthma control score and higher asthma treatment step than presence of other allergen sensitivities ($p = 0.029$, $p < 0.001$, respectively) (Figure 2, Table 3). Forced expiratory volume in 1 s (FEV1) % and FEV1/forced vital capacity (FVC) were similar between the groups ($p > 0.05$ for each comparison) (Table 3).

IMPACT OF A.F SENSITIVITY ON ALLERGIC RHINITIS

VAS symptom scores for allergic rhinitis before and after medication and allergic rhinitis medication scores were higher in patients with A.f sensitivity than in patients without A.f sensitivity ($p < 0.001$, $p = 0.015$, $p > 0.001$, respectively) (Figures 3, 4, Table 3). In addition, frequency of moderate to severe allergic rhinitis was higher in patients with A.f sensitivity than in patients without A.f sensitivity ($p < 0.001$) (Table 3).

TABLE 3. Impact of A.f sensitivity on allergic rhinitis and asthma clinics

Variable	Presence of A.f sensitivity	Allergen sensitivities without A.f	*P*-value
Severe asthma among patients with asthma, *n* (%):			
Yes	23 (29.9)	10 (13.0)	< 0.001
No	10 (13.0)	34 (44.2)	
ACT score (IQR)	21.0 (19.0–22.5)	23.5 (20.0 – 25.0)	0.029
FEV1% predicted (IQR)	92.0 (85.8–101.3)	104.0 (100.0–121.0)	NS
FEV1/FVC (IQR)	79.5 (65.3–84.5)	85.0 (80.0–86.0)	NS
Asthma treatment step (IQR)	4.0 (3.0–5.0)	3.0 (1.0–3.0)	< 0.001
Moderate to severe AR before treatment, *n* (%):			
Yes	66 (42.0)	72 (45.9)	< 0.001
No	0 (0.0)	19 (12.1)	
Moderate to severe AR after treatment, *n* (%):			
Yes	56 (35.7)	77 (49.0)	NS
No	10 (6.4)	14 (8.9)	
Initial AR VAS symptom score (IQR)	7.5 (7.0–9.0)	6.0 (5.0–7.0)	< 0.001
AR VAS symptom score after medication (IQR)	2.0 (2.0–4.0)	2.0 (1.0–4.0)	0.015
AR medication score (IQR)	3.0 (2.0–3.0)	2.0 (1.0–2.0)	< 0.001

ACT – asthma control test, A.f – *Aspergillus fumigatus,* AR – allergic rhinitis, FEV1 – forced expiratory volume in 1 s, FVC – forced vital capacity, IQR – interquartile range for 25th and 75th percentiles, NS – non-significant, VAS – visual analogue score.

CLINICAL CHARACTERISTICS OF PATIENTS WITH ABPA

Among patients with allergic asthma and A.f sensitivity, 2 female patients had diagnosis of ABPA. Their IgE levels were 1403 kU/l, 2341 kU/l and eosinophil counts 460 cell/µl, 610 cell/µl, respectively. Both patients had bronchiectasis. They were taking step 5 treatment for allergic asthma and step 3 treatment for allergic rhinitis. Additionally, they were under itraconazole and systemic steroid treatment.

DISCUSSION

Our study, reflecting the clinical experience of a major center in Istanbul/Turkey, compared the clinical characteristics of A.f-sensitized and non-A.f-sensitized patients with allergic rhinitis and allergic asthma. We found that A.f-sensitized patients had higher rates of severe allergic asthma, higher asthma treatment steps, and a higher prevalence of moderate to severe rhinitis compared to non-A.f-sensitized patients. Additionally, the A.f-sensitized group exhibited higher VAS symptom scores for allergic rhinitis and required higher treatment steps for allergic rhinitis management.

Several studies have clearly established a link between A.f sensitization and exacerbations of allergic asthma, which subsequently result in increased morbidity and mortality rates [1, 9–12]. Additionally, a recent study showed that having A.f sensitivity causes a poor asthma control [3]. Consistent with previous studies, our patient population demonstrated that A.f-sensitized individuals had poorer asthma control, higher asthma severity, and were using higher treatment steps.

The current study included both patients diagnosed with allergic asthma and allergic rhinitis, providing an opportunity to observe the effects of A.f sensitivity on both groups. We found similar results to previous studies regarding the impact of A.f sensitivity on allergic asthma [3, 9, 11, 12, 16]. However, our study yielded different results regarding the effects on allergic rhinitis. In a previous study conducted in Poland, mold sensitivity was associated with milder rhinitis symptoms [16]. However, in our study, we observed that A.f sensitivity was linked to more severe rhinitis symptoms and higher medication scores. It is important to note that while our study focused exclusively on A.f sensitivity, the previous study included other mold species as well [16]. This difference in findings may be attributed to the inclusion of other mold types in the previous study. On the other hand, considering the similar immunological mechanisms underlying allergic rhinitis and allergic asthma, it is expected that A.f, which leads to severe asthma, could also contribute to the development of severe allergic rhinitis in the affected patient population.

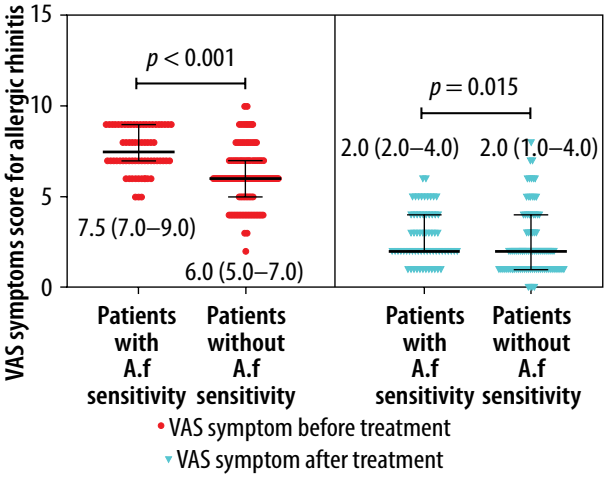

FIGURE 3. VAS symptom score differences between the groups

A.f – *Aspergillus fumigatus*, VAS – visual analogue scale.

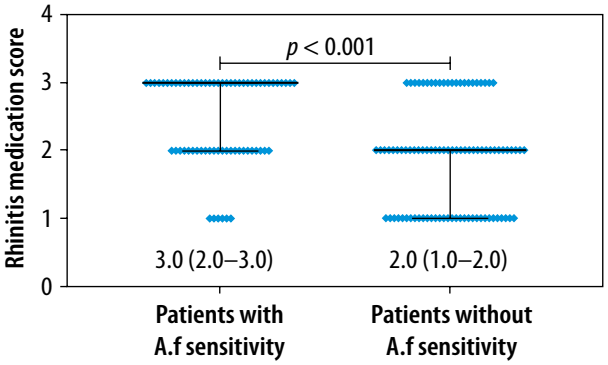

FIGURE 4. Medication score differences between the groups

A.f – *Aspergillus fumigatus*.

ABPA is the most complex allergic manifestation caused by A.f. Improved diagnostic methods and increased awareness have led to recent reports indicating a higher prevalence of ABPA in patients with chronic asthma (1–40%) and acute severe asthma (~38%) [17–20]. Additionally, a previous study has demonstrated that patients diagnosed with ABPA have higher asthma severity compared to both A.f-sensitized and A.f-non-sensitized patients with allergic asthma [3]. In our study, which included 32 asthmatic patients sensitized to A. fumigatus, 2 of them (6.3%) were diagnosed with ABPA and all of these patients had severe allergic asthma. Since the prevalence of fungal sensitization displays a wide geographical variation, the relatively low prevalence rate in our study may be attributed to the specific characteristics of the Istanbul region [21–23].

A potential limitation of our study is its retrospective design. However, the study's strength lies in its large sample size and the absence of similar studies conducted in this region previously. Despite its retrospective nature, our study is valuable as it provides guidance to clinicians

specializing in allergic rhinitis and allergic asthma in this region.

CONCLUSIONS

A.f-sensitized patients can have more severe respiratory allergies, necessitating treatment with medications at higher steps. Clinicians should closely monitor these patients and remain vigilant for treatment unresponsiveness, exacerbations, and the potential progression of the disease to more complex clinical conditions such as ABPA.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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