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The clinical differences of asthma in patients with molds allergy

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Abstract

Introduction: Bronchial asthma is an increasing problem worldwide. The course of bronchial asthma is dependent on the type of inducing allergens. The differences between the clinical features of asthma in patients with monovalent allergies to molds and with other allergies were explored.

Material and methods: Randomly selected 1910 patients (924 women and 986 men) between 18–86 years in age were analyzed according to type of allergy and asthma. The diagnosis of asthma was confirmed on the basis of GINA criteria, physical examination and spirometry. Allergy diagnosis was confirmed on the basis of medical history, a positive skin prick test and the measurement of serum-specific IgE to inhalant allergens, using an extended profile of mold allergens.

Results: Patients with monovalent allergies to molds (4% of analyzed group) had significantly more frequent diagnoses of asthma than patients in the other group (53% vs. 27.1–32.4%, $p < 0.05$). Patients with allergies to *Alternaria alternata* had an odds ratio of 2.11 (95%CI: 1.86–2.32) for receiving a diagnosis of bronchial asthma. They had less control over their asthma, which was more severe compared to patients with other allergies. Patients with asthma and allergies to mold had significantly more frequent exacerbation of asthma requiring systemic corticosteroids and/or hospitalization. They used a significantly greater mean daily dose of inhaled steroids compared to other patients.

Conclusion: Patients with monovalent IgE allergies to molds are at a higher risk for asthma than patients with other allergies. Their asthma is often more intense and less controlled compared to that of patients with other types of allergies.

Key words: asthma, molds, allergy

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Introduction

Bronchial asthma is an increasing problem in all age groups. According to the WHO, between 100 and 150 million people around the world suffer from asthma, and this number is rising. Worldwide, deaths from this condition have reached over 180,000 annually [1]. There are a number of documents relating to the diagnosis and treatment of bronchial asthma, but our knowledge is incomplete in some fields [2–4]. The natural course of asthma is dependent on many factors, such as the type of inducing allergens. The majority of the available literature is devoted to mites, pollen and professional allergens, while less attention has been paid to animal (except cats) or mold allergens. Molds are extensive source of allergens. Exposure and sensitization to fungal allergens can promote the development and worsening of allergic diseases. Although numerous species of fungi have been associated with allergic diseases in the literature, the significance of fungi from the genera *Alternaria*, *Cladosporium*, *Penicillium*, and *Aspergillus* has been well documented [5].

The clinical spectrum of hypersensitivity reactions elicited by molds is very broad; in addition to IgE-mediated type I allergies, it includes type II, III and IV reactions, which are defined according to the criteria proposed by Coombs and Gell [6]. Clinically, IgE-mediated sensitization to

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mold allergens can manifest as allergic rhinitis and rhinosinusitis, atopic dermatitis and allergic asthma [6].

Some information has been published regarding the differences in the nature of asthma in patients with allergies to molds [6, 7]. However, we still lack detailed information on this issue. Additionally, the precise prevalence of fungal sensitivities remains unclear.

The aim of this study was to attempt to assess the differences between the clinical features of asthma in patients with monovalent allergies to molds and those with other allergies. This could be the starting point to draw attention to the special needs of these patients.

Material and methods

Patients

32 654 patients from Outpatient Allergological Clinics were prescreened in data bases. 1910 subjects: 924 women and 986 men between 18–86 years were randomly selected. They were analyzed according to their types of allergy and asthma.

The diagnosis of asthma was based on GINA criteria [2], physical examination and spirometry with a positive result on the reversibility test (Lung test 1000). A positive test result was defined in accordance with the criteria of the ATS-ERS [8, 9]. Before testing, the patients did not use short-acting beta2 agonists for 8 hours, ipratropium derivatives or theophylline derivatives for 24 hours, long-acting beta2 agonists for 48 hours, and tiotropium derivatives for 72 hours. Smokers were asked to abstain from smoking for 1 hour before testing. The test was deferred for 4 weeks in cases of respiratory tract infections.

The allergy diagnosis was confirmed on the basis of history, positive skin prick tests (SPT) and measurements of concentrations of serum-specific IgE (sIgE) in response to inhalant allergens.

SPT (Allergopharma, Germany) was performed using the following allergens: *D. pteronyssinus, D. farinae,* mixed grass, mixed tree, birch, alder, hazel, mugwort, and the molds *Aspergillus fumigatus*, *Cladosporium herbarum*, *Botrytis cinerea*, *Alternaria alternata*, *Curvularia lunata*, *Penicillium notatum*, *Fusarium moniliforme*, *Helminthosporium solani*, *Mucor mucedo*, *Trichophyton mentagrophytes*, *Rhizopus nigricans*, *Pullularia pullulans*, *Neurospora sitophila*, *Candida albicans*, and *Serpula lacrymans*. Positive (histamine 10 mg/ml) and negative (a saline control) tests were included. Allergy was defined as having a positive skin test result for at least one allergen with a wheal max. diameter of at least 3 mm greater than that of the negative control. Patients with negative tests for histamine were excluded from further analyses.

The response of serum immunoglobulin levels (serum sIgE) to all mentioned allergens were measured using the Phadia Laboratory System (Phadia AB, Uppsala, Sweden), an immunoenzymatic test. The results were assessed as positive when the serum sIgE concentration was > 0.75 IU/ml (class II according to the manufacturer's brochure) [10]. After the initial analysis, 1475 patients with allergies and/or asthma were classified into four groups:

— Patients with monovalent allergies to molds, group M.
— Patients with monovalent allergies to house dust mites, group D.
— Patients with monovalent allergies to pollens (grass and/or trees and/or mugwort), group P.
— Patients with multivalent allergies (allergies to at least two groups of allergies, including house dust mites, molds, and pollens), group V.

The monovalent allergy was confirmed as followed: typical clinical symptoms (positive result of original questionnaire), positive skin prick test and/or allergen specific IgE to any allergen mold and negative results to other analyzed, inhalant allergens. Other monovalent allergies were diagnosed in a similar way.

The characteristics of the groups are shown in Table 1.

Study protocol

Each subject completed the Asthma Control Test (ATC) [11] and an original questionnaire about mold allergies (Table 2).

The study was approved by the local ethics committee (Medical University of Silesia, Katowice, Poland). All patients signed an informed consent form.

Statistical analysis

Data with a normal distribution, such as participant age, disease duration and spirometric test results were compared using Student's t-test for independent samples. Odds ratios were calculated to assess the likelihood of asthma in the presence of a particular trait in the subjects. Kruskal-Wallis test was used to compare non-parametric variables between the groups. $P < 0.05$ was considered statistically significant.

Table 1. Characteristics of the study groups

	Patients included in the analysis, n = 1475			
Features	**group M n = 64**	**group D n = 383**	**group P n = 388**	**group V n = 415**
Mean age	38.1 ± 19.1	43.2 ± 10.5	36.7 ± 11.9	34.8 ± 10.3
Female (%)	43.1	38.5	37.8	40.2
Duration of allergy in years (± SD)	8.2 ± 3.7	6.9 ± 1.4	6.8 ± 6.2	6.2 ± 4.9
Residence: village	22.1%	21.7%	22.5%	22.3%
Smoking (current or former)	27.4%	34.8%	39.7%	33.1%
Higher education	25.6%	22.1%	24.7%	18.7%
Allergy in the family	33.4%	35.1%	40.1%	38.9%
Allergy in childhood	35.9%	33.7%	29.7%	52.6%*

SD — standard deviation; group M — monovalent allergy to molds; group D — monovalent allergy to house dust mites; group P — monovalent allergy to pollens; group V — multivalent allergy; *significant differences for $p < 0.05$

Table 2. Original questionnaire about allergies to fungi

Do your disease symptoms, such as runny nose, cough, shortness of breath, and watery or itchy eyes, occur in the period from June to August and/or in the autumn and winter months?	YES or NO
Are your symptoms associated with being in humid areas, such as basements, old houses and other premises, where mold is visible on the wall?	YES or NO
Do similar symptoms as listed in paragraph 1 arise when you stay in a steamy bathroom?	YES or NO
Do similar symptoms occur during sleep in your bed?	YES or NO
Do you live in a home where there is visible mold on the walls?	YES or NO
Do you have allergic symptoms (at least one of the following symptoms: rash, cough, shortness of breath, runny nose, abdominal pain, or diarrhea) after eating any of these foods: yeast dough, moldy cheeses, red wine, or pickled preserves?	YES or NO
Have you ever had a confirmed allergic skin test or blood test IgE sensitization to mold fungi?	YES or NO
Do you have asthma-like symptoms (coughing or difficulty in breathing) that require treatment in the summer?	YES or NO
Do you suffer from bronchial asthma and are using drugs?	YES or NO
Does anyone in your family have a known allergy to molds?	YES or NO
Does the presence of a large number of potted plants have an effect on your disease symptoms?	YES or NO
Do you badly tolerate staying in air-conditioned rooms or in the car with the air conditioner?	YES or NO

Results

Patients with monovalent allergy to molds represented 4.3% of all respondents with inhalant allergy. The original questionnaire about mold allergies indicated the special importance of patient exposure to damp basements (89% of the patients with allergies to mold answered YES to the second question and the questions about steamy bathrooms; 86% of respondents answered YES to the third question) in describing the symptoms of allergies to mold fungi. The questionnaire results from the control groups without allergies to molds were significantly negative in relation to the study group for all of the targeted questions.

Patients with monovalent allergies to mold had significantly more diagnoses of asthma than the patients in the other analyzed groups: 53% (34 subjects) vs. 32.4% (124) in group D vs. 27.1% (105) in group P and vs. 29.2% (121) in group V ($p < 0.05$). There were no correlation between diagnosis of asthma and age or sex in all analyzed groups.

IgE-specific skin prick tests

In the group of patients monosensitized to molds, allergies to the following species dominated: *Alternaria alternata* in 57.2% of patients (based on a positive SPT and/or sIgE), *Cladosporium herbarum* in 40.9% of patients, *Aspergillus fumigatus* in 34.7% of patients, *Mucor mucedo* in 30.1% of patients, *Trichophyton mentagrophytes* in 21.2% of patients and *Fusarium moniliforme*

Table 3. Profile of mold allergies in group M (% of patients) according to asthma severity

Allergy to mold species	Episodic asthma	Mild or moderate asthma	Severe asthma	p
Alternaria alternata	17.1	20.8	22.1	NS
Cladosporium herbarum	10.1	14.2	11.5	NS
Aspergillus fumigatus	6.9	9.2	18.1	> 0.05
Mucor mucedo	8.8	11.9	10.2	NS
Trichophyton mentagrophytes	2.7	7.3	16.1	> 0.05
Fusarium moniliforme	5.6	4.9	5.5	NS
Other species	1.1	0.8	0.7	NS

NS — no significant differences

Table 4. Characteristics of bronchial asthma in patients with different types of allergies

Characteristics	Patients with asthma diagnoses				P^
	group M n = 32 (%)	group D n = 124 (%)	group P n = 105 (%)	group V n = 121 (%)	
Mean age	42.9 ± 10.4	44.1 ± 13.9	42.1 ± 10.2	39.5 ± 8.9	NS
Female (%)	16 (47.1)	60 (48.4)	45 (42.9)	53 (43.8)	NS
Duration of asthma	10.4 ± 5.2	9.2 ± 5.1	9.7 ± 3.6	9.3 ± 6.3	NS
Mean result of ACT	11.9 ± 3.1*	15.9 ± 4.8	19.7 ± 3.7	18.5 ± 7.4	< 0.05
Severe asthma (%)	8 (26.5)*	18 (14.5)	11 (10.5)	15 (12.4)	< 0.05
Moderate asthma (%)	9 (26.8)	35 (28.2)	30 (24.2)	32 (26.4)	NS
Mild asthma (%)	12 (35.3)	43 (34.7)	39 (37.2)	47 (38.8)	NS
Episodic asthma (%)	5 (14.7)*	28 (22.5)	25 (23.8)	27 (22.3)	< 0.05
Fully control asthma	11 (32.4)*	58 (46.8)	49 (46.7)	54 (44.6)	< 0.01
Partially controlled asthma	10 (29.4)	32 (25.8)	35 (33.3)	36 (29.8)	NS
Uncontrolled asthma	13 (29.4)*	34 (27.4)	21 (20)	31 (25.6)	< 0.01
Allergic rhinitis	30 (88.2)	108 (87.1)	97 (92.4)	107 (88.4)	NS

Degree of asthma control according to the GINA; ACT — asthma control test; *Significant difference for $p < 0.05$

in 19.1% of patients. Other allergens occurred in less than 20% of the patients.

In group M, patients with diagnoses of varying degrees of bronchial asthma had similar profiles to those with mold allergies. However, patients with allergies to *Aspergillus fumigatus* and *Trichophyton mentagrophytes* were significantly more likely to suffer from severe asthma. The detailed results are shown in Table 3.

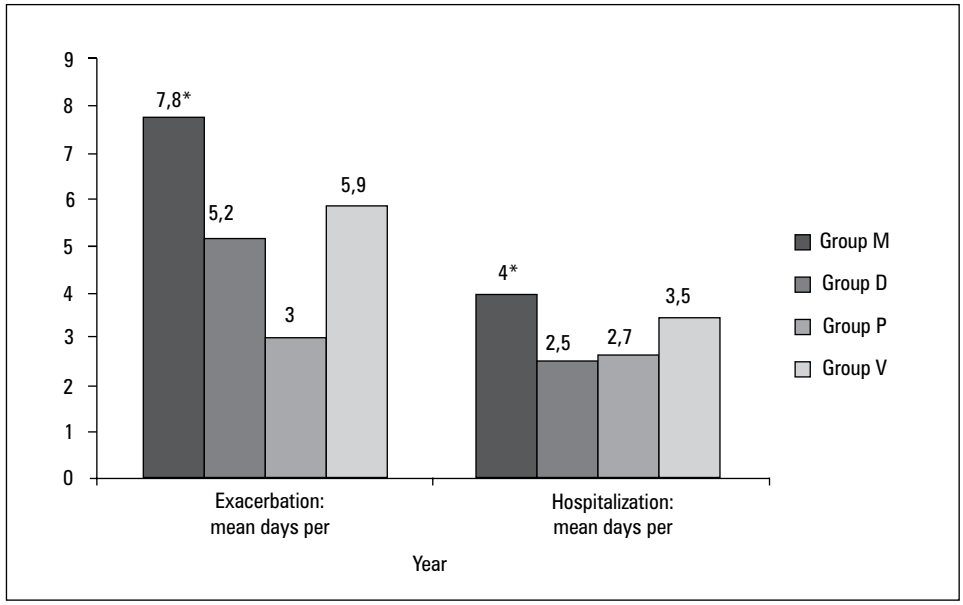
Additionally, patients with an allergy to *Alternaria alternata* had an odds ratio of 2.11 (95%CI: 1.86−2.32) of receiving a diagnosis of bronchial asthma.

Furthermore, they had less control over their asthma, which was more severe compared to that of patients with other allergies (Table 4). Patients with both asthma and allergies to mold had significantly more exacerbated asthma requiring systemic corticosteroids and/or hospitalization. The results are shown in Figure 1.

Patients with both asthma and allergies to mold used a significantly greater mean daily dose of inhaled steroids compared to patients with other types of allergies and asthma; the use of fluticasone propionate in the groups was 730 ± 425* mcg vs. 430 ± 225 mcg vs. 470 ± 165 mcg vs. 340 ± 140 mcg ($p < 0.05$).

Discussion

The obtained results indicate the important problem of bronchial asthma in patients with allergies to mold. Of the analyzed allergic patients, those with monovalent allergies to mold had



group M — monovalent allergy to molds; group D — monovalent allergy to house dust mites; group P — monovalent allergy to pollens; group V — multivalent allergy; *significant differences for $p < 0.05$

Figure 1. The number of asthma exacerbations per year and hospitalizations caused by asthma in the study groups

significantly more frequent diagnoses of asthma. In this group, patients with allergies to *Alternaria* were predominant. This finding is consistent with previous observations. *Alternaria* is a major environmental allergen associated with asthma and allergic rhinitis [12, 13]. *Alternaria* spp. are generally considered to be outdoor fungi, although they also exist in indoor environments [5, 14]. Airborne outdoor *Alternaria* spores are detectable from May to November, with the highest levels occurring in cultivated areas containing grasslands and grain [14]. The clinical significance of *A. alternata* as a respiratory allergen has been well documented. Studies have revealed a strong association between sensitization to *Alternaria spp*. and the presence of asthma or allergic rhinitis, as well as the severity of asthma [5, 15, 16]. In addition, sensitization and exposure to *Alternaria* has been associated with epidemics of severe asthma exacerbation, including respiratory arrest [17]. Thunderstorms appear to be a contributing factor to high levels of fungal spores and epidemics of asthma exacerbation [5].

We found that sensitivities to two molds, *Aspergillus fumigatus* and *Trichophyton mentagrophytes*, were more common in patients with severe asthma than in others. *Aspergillus*, *Penicillium, Alternaria* and *Cladosporium*, play important roles in the induction of asthma as well as in its intensity patterns [6, 7]. *Aspergillus fumigatus* can cause allergic bronchopulmonary aspergillosis, which is characterized by its exacerbation of asthma, recurrent transient infiltrates on radiographic images, coughing up of thick mucus plugs, peripheral and pulmonary eosinophilia, and increased total serum IgE and specific IgE levels, especially during exacerbation [18]. In this study, five patients with bronchial asthma, allergy to molds and episode of bronchopulmonary aspergillosis were observed. The importance of *Trichophyton mentagrophytes* had not been previously confirmed. Fungi in the genus Trichophyton are known to be the causal pathogens of dermatophytosis, a fungal infection of the skin, hair and nails. *Trichophyton rubrum* and *Trichophyton mentagrophytes* are the most common pathogens in the genus [5]. However, the route of exposure to *Trichophyton* allergens in such *Trichophyton*-infected patients has not been identified. A few reports have suggested the possible role of inhaled *Trichophyton* in the pathogenesis of asthma or rhinoconjunctivitis among subjects without *Trichophyton* infections [19, 20]. Occupational exposure to airborne *Trichophyton* in nail dust has been shown to induce nasal and eye symptoms in chiropodists [21]. There was no such data in our study. Sensitization to *Trichophyton* is also reported to be a risk factor for more severe disease among the general asthmatic population [22, 23]. However, there is no published information regarding whether a potential correlation exists between *Trichophyton* and asthma severity.

An important limitation of this study is our testing of IgE-dependent responses only. There is

evidence that these species of molds also induce type II, III and IV reactions [6]. Thus, the obtained results about the roles of different types of molds on asthma are not final.

Worse asthma control, a greater number of exacerbations and the need for larger doses of inhaled steroids are the results of the higher prevalence of severe asthma that was observed in this study. The important role of fungi in the exacerbation of asthma has been confirmed in previous literature. TNF-alpha as well as IFN-alpha are secreted by fungi-prestimulated leukocytes from the lower respiratory tract and may be involved in the processes of exacerbation of asthma complicated by fungal infections [24]. However, further details on this role have not been provided [2, 6, 12, 16].

Conclusion

The obtained data suggest that patients with monovalent IgE allergies to mold are more at risk for asthma than patients with other allergies. These patients require more attention because their asthma is often more severe and less controlled than that of patients with other types of allergies.

Conflict of interest

The authors declare no conflict of interest.

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