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Original Article

The Relationship between Decreased Lung Vital Capacity in Children with Respiratory Asthma Associated with *Aspergillus* and *Candida* in North of Iran

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Abstract

Background and Aim: Environmental factors play an important role in the development and progression of respiratory diseases. In this regard, the species *Aspergillus* and *Candida* fungi are very important environmental factors, which play a prominent role in the development, persistence, and severity of respiratory diseases, especially asthma. The study aimed to investigate the relationship between susceptibility to fungi and lung function in children referred to Deziani Allergy Clinic patients in 2010-2011.

Methods: Children with age less than 12 years (n=40) were volunteered to participate in this case-control research. Two groups of patients susceptible to fungal (20/40) and not susceptible to fungal allergens (20/40) were selected. The groups were age and sex-matched. Demographic data and Forced Vital Capacity (FVC), Forced Expiratory Volume in the first second (FEV1) and Tiffeneau-Pinelli index was obtained from patient records. Statistical analysis performed by SPSS 16.0 program.

Results: Examination of the lung function variables showed that the mean of FVC in the control group (76.075 liters/s) was higher than the patient group (71.5 liters/s). FEV1 was also higher in the control group than in the patient group ($p<0.05$). The Tiffeneau-Pinelli index was also higher in the control group than in the patient group ($p<0.05$).

Conclusion: Allergy to fungi, such as *Candida* and *Aspergillus*, decreases lung function in children with asthma, which is directly related to reduce vital capacity in these patients.

Keywords: Asthma; Lung vital capacity; *Aspergillus*; *Candida*; Fungal-associated asthma.

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Introduction

Asthma is a chronic inflammatory condition characterized by reversible obstruction of the airway (1). It is one of the most common chronic diseases in the world and it is estimated that there are currently 300 million asthma patients worldwide and it is expected that another 100 million asthma patients will be added to the world population by 2025 (2). The incidence of allergic diseases is growing both in the world and in Iran. In several studies, the prevalence of respiratory allergies in Iran was reported to be between 11% and 31% (3). Studies have shown that genetic and environmental factors play an important role in the development and progression of this disease (1). Susceptibility to fungi is a very important environmental factor in the development of respiratory diseases, which play a key role in the development, persistence, and severity of respiratory diseases, especially asthma (4).

In areas where the presence of fungi is more prevalent, susceptibility to fungal allergens is normal among atopic patients, as shown by skin tests or the presence of particular IgE antibodies in the serum of patients (5–7). Hypersensitivity to one or more respiratory allergens is also a major risk factor for airway hypersensitivity reactions (8–10)

among school-aged children. There appears to be a correlation between exposure to allergens, sensitivity to allergens, and development of asthma and sensitivity to airways (AHR). Measures to prevent allergens can play an important role in the treatment of patients with allergic asthma (11,12). It is therefore important to investigate the role of fungal allergens in respiratory diseases such as asthma.

The association between susceptibility to fungi, such as *Aspergillus* and *Candida*, and pulmonary function is still uncertain and may be obscured by drug treatment with inhaled steroids and by the effects of improved lung function. The presence of various allergens in 25 fungal species has been thoroughly established (13). So far, 30 allergens from 5 *Aspergillus* species have been clearly and precisely described. *Fumigatus*, *Niger*, *Oryzae*, *Flavus*, and *Terreus* are the most common allergy associated species of *Aspergillus* (14). These allergens include polysaccharides, glycoproteins, and enzymes such as chymotrypsin, proteases, elastases, ribonuclease, catalase, and superoxide dismutase (15,16). Some of these enzymes have been associated with the pathogenicity of disease-causing species. *Aspergillus*-induced asthma (AIA) is a general health condition affecting people of all ages around the world (17,18). This condition can cause significant limitations in a person's daily activities if it is not managed and can even lead to death (19). *Candida albicans* is a typical human mouth, vagina, respiratory tract, and digestive tract flora. This factor is present in humans and a wide variety of animals in the form of flora or pathogens (20,21).

Not only does the fungus cause opportunistic infections in immunocompromised patients, but it also induces allergic reactions in susceptible individuals (22,23). Hypersensitivity to this fungus has been documented in diseases such as asthma, allergic rhinitis, atopic dermatitis, and hives. In a report in 2019, Anoushirvani et al. Examined pulmonary fungal infection in immunocompromised patients (24). The most common isolated fungi were *Candida albicans*, *Aspergillus Fumigatus*, and *Mucor* (24). Considering the role of *Aspergillus* and *Candida* fungi in the high prevalence of asthma in the population and their significance in the development and stabilization of asthma in patients with this illness, we are looking at the relationship between susceptibility to fungi and decreased lung function in patients who attended the Deziani Allergy Clinic in 2010-2011.

Methods

Patients

In this case-control study, 20 children with asthma who were allergic to fungi (*Aspergillus* and *Candida*) and 20 children with asthma who were not allergic to fungi were included as patients and control groups, respectively. The study population consisted of children under 12 years of age who were referred to Deziani Allergy Clinic in Gorgan in 2009-2010. Children were evaluated by a specialist in asthma and susceptibility to respiratory fungal allergens. In the prick skin test, the IgE positivity for *Aspergillus* or *Candida* was considered susceptible to fungal allergens. Inclusion criteria included informed consent of parents to participate in the study, no pneumonia and chronic respiratory disorders, no chest anomalies and congenital lung diseases, no gastroesophageal reflux, and no history of antihistamine and beta-blocker use 48 hours and 24 hours prior to the experiment, respectively.

Further information such as skin test reports, forced vital capacity (FVC), the forced expiratory volume in one second (FEV1), and Tiffeneau-Pinelli index and demographic data were collected from patients' records. FVC was tested to determine the maximum amount of air that a person can expel after maximum inhalation from the lungs. In addition, FEV1 was measured in order to determine the maximum amount of air that the patients can expel forcibly during the first second following the maximum inhalation. Finally, The FEV1/FVC ratio or Tiffeneau-Pinelli index was calculated to diagnosis of obstructive and restrictive lung disease.

Ethical considerations

This research was approved by the Golestan University of Medical Sciences Ethics Committee

under IR.GOUMS.REC.1399.152. The researcher introduced himself to the officials of the Taleghani Educational and Medical Center and explained the purpose of the research to the patients ' families. Parents have given their informed consent and permission to access documents to comply. Patients were told that the information obtained would remain confidential until the end of the research.

Evaluation of pulmonary function

All children referred to asthma were included in the study following screening protocols such as history and physical examination based on clinical guidelines for asthma under the Global Initiative for Asthma (GINA) protocol. Fungal antigen skin tests have been performed on all patients. Patients have been classified into two groups with and without allergies to fungi allergens. Pulmonary function (PFT) and bronchial stimulation tests have been conducted in patients for 5 months by a pulmonologist, allergist, and clinical immunologist to confirm and determine the severity of asthma.

Statistical analysis

The data were analyzed by the software SPSS V.16. The Shapiro-Wilk test was used to determine the normality of the distribution of data. The T-test was used to compare quantitative data and the Mann-Whitney test was used if the distribution of data was not normal. A *P-value of* less than 0.05 was considered significant.

Results

The mean age of the patients was 8.55±1.86 years (minimum age 6 years and maximum age 12 years). Of the 40 children surveyed, 20 were boys and 20 were girls. Based on the results of the skin examination, patients were divided into two groups: sensitive to fungal allergens (patient group) and non-sensitive to fungal allergens (control group). Both groups were sex and age-matched. There was no substantial difference in the incidence of asthma between the two groups (Table 1). There was also no significant difference between the two groups based on their inhabitants (p>0.05).

Examination of lung function-related variables showed that the mean of FVC in the control group (76,075 liters/s) that were not susceptible to *Aspergillus* and *Candida* was higher than the patient group (71,5 liters/s).

Table 2 shows details on pulmonary vital capacity variables for patient and control groups. The mean amount of FEV1 was also higher in the control group than in the patient group. The Tiffeneau-Pinelli index was also higher in the control group than in the patient group (Table 2).

Table 1. The frequency of different types of asthma severity between patient and control groups

		Groups		p-value
		Patient	Controls	
Asthma severity	Minor	6 (30%)	4 (20%)	0.55
	Moderate	7 (35%)	11 (55%)	
	Severe	7 (35%)	5 (25%)	
Grand total		20 (100%)	20 (100%)	40

Based on age, in those less than 9 years of age, the FVC, FEV1, and Tiffeneau-Pinelli index did not vary significantly from the control group, but in those older than 9 years of age, these indices were significantly higher than in the control group (Table 3).

Table 1. Liver capacity status between patient and control groups

Liver Capacity Variables	Groups		p-value
	Patient (Mean±Std)	Control (Mean±Std)	
F.V.C (Liter/sec)	71.5±5.48	76.25±4.70	0.006
F.E.V1	71.05±5.56	76.05±4.21	0.004
Tiffeneau-Pinelli index	0.99±1.01	~1.00±0.89	0.005

F.V.C: Forced Vital Capacity. F.E.V1: Forced Expiratory Volume in the first second.
Tiffeneau-Pinelli index: FEV1/FVC ratio

Table 2. The status of liver capacity variables between patients and control groups based on age and gender.

Groups	Liver Capacity variables	Age (years)		Gender	
		≤ 9	≥ 9	Male	Female
Patients (Mean±Std)	F.V.C (Liter/sec)	73.60±5.89	69.40±4.35	72.40±6.05	70.60±4.99
	F.E.V1	73.50±5.68	68.60±4.52	71.60±5.48	70.50±5.89
	Tiffeneau-Pinelli index	~1.00±0.96	0.99±1.04	1.03±0.91	~1.00±1.18
Control (Mean±SD)	F.V.C (Liter/sec)	75.70±4.85	76.80±4.73	75.90±4.99	76.60±4.62
	F.E.V1	75.10±4.43	77.00±3.97	75.30±3.62	76.80±4.80
	Tiffeneau-Pinelli index	0.99±0.91	1.00±0.84	0.99±0.73	1.00±1.04

In addition, lung function variables between girls and boys have been examined. Table 3 shows that the FVC, FEV1, and Tiffeneau-Pinelli indexes were not substantially different in patient and control boys. However, the FEV1 and FVC indexes were higher in the control group of girls than in the patient group. The index of Tiffeneau-Pinelli was higher in the control group. The discrepancy, however, was not statistically significant.

Discussion

Because the respiratory function is influenced by different factors such as environmental factors, genetics, climatic conditions, physical activity, dietary factors, and unknown factors (25), sensitivity to fungal allergens is also of special importance. Allergy to respiratory fungi can have a major economic and social burden and adversely affect the quality of life of this community of people, particularly children (26). The effect of susceptibility to *Aspergillus* and *Candida* species in the respiratory function of children under 12 years of age was therefore evaluated in this research.

The findings of this study showed that lung function indices, including FVC, FEV1, and FEV1/FVC ratios were lower in children with sensitivity to fungi, such as *Candida* and *Aspergillus*. They had lower respiratory function than their counterparts did. In addition, the FVC, FEV1, and FEV1 / FVC amounts were higher in children who were not allergic to fungi than in children who were allergic, although this result was not expected. In this regard, Byeon et al showed that the mean FEV1 in children with asthma allergies to fungal respiratory allergens was significantly lower than in children with respiratory allergies other than fungi (27). Respiratory fungi can also reduce lung function in children. This may imply pathways of cytokine and receptors in the subtle response to the *Aspergillus*, suggesting that asthma and allergies to respiratory fungi are interrelated (28). The strength of this study was the assessment of fungal sensitivity in asthma patients, as it could be inferred that there could be a link between allergies to fungi and asthma in children. In other words, reactions to fungi can be considered a risk factor for pediatric asthma. To support this statement, future studies benefiting a control group with a large sample size are required.

Bogacka et al recorded that the incidence of asthma was 70.6% in susceptible fungal subjects and 43.6% in susceptible non-fungal patients. Fungal allergies have also been shown to facilitate asthma (29). In a study conducted by Zureik et al., exposure to *Aspergillus* and *Candida* fungi was a strong risk factor for severe asthma. According to the findings of their research, the incidence of allergies to respiratory fungi was directly related to the severity of asthma (30). Another significant finding in this study was a decline in lung function in children over 9 years of age with susceptibility to fungi. This result shows that allergies in children over 9 years of age with asthma have much worse effects on lung function than in children under 9 years of age. According to our findings, it could be possible to justify this finding by suggesting that as children age, they refuse their care and cause reduced lung function. Owing to modern technologies and the tendency of children to be present indoors for a

long time, as well as the prevalence of airborne fungal spores in indoor environments, the risk of developing respiratory diseases and fungal induced asthma is growing. It can also include both males and females.

Our further findings were decreased forced vital capacity and forced expiratory volume in the first second in girls with allergies compared to boys with respiratory fungi allergies. Of course, since similar studies in this field are small, it is not possible to compare the findings. This may be because girls spend more time at home than boys do. Fungal susceptibility is a very important factor in the development, persistence, and the severity of respiratory allergies, especially asthma, in patients with respiratory allergies.

Conclusion

Allergies to fungi such as *Candida* and *Aspergillus* decrease the lung function of children with asthma, which is directly related to the decreased vital capacity of these patients. In addition, staying indoors for a long time, particularly among girls, may increase their risk of developing respiratory diseases associated with fungal allergens.

Conflict of Interest

The authors declared that they have no conflict of interest.

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Ethics

The study protocol was approved by the Ethics Committee of the Golestan University of Medical Sciences with this code (IR.GOUMS.REC.1399.152).

Authors Contributions

Conceptualization, M.E.; methodology, M.E.; formal analysis, M.E., and S.A.A; investigation, S.Z.Z.; data curation, M.E., and S.A.A; writing—original draft preparation, S.Z.Z, and S.A.A.; writing—review and editing, M.E.; supervision, M.E.; project administration, M.E.

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