Original Article

Fungal Sensitization Is Associated with Increased Risk of Life-Threatening Asthma

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What is already known about this topic? Fungal sensitization in patients with asthma has been associated with severe asthma and worse asthma outcomes.

What does this article add to our knowledge? Fungal sensitization is common in patients with asthma referred to an urban pulmonary subspecialty clinic and is associated with sensitization to more nonfungal allergens and increased risk of life-threatening asthma compared with patients with nonfungal sensitization or no sensitization.

How does this study impact current management guidelines? The results of this study suggest that patients with persistent asthma should be tested for fungal sensitization, and those patients with asthma found to have fungal sensitization should have close follow-up and optimization of treatment to reduce their risk of life-threatening asthma episodes.

BACKGROUND: Fungal sensitization in patients with asthma has been associated with severe asthma and worse asthma outcomes.
OBJECTIVE: The purpose of this study was to determine the relationship between fungal and nonfungal sensitization, asthma severity, and clinical outcomes.
METHODS: A retrospective review of patients with asthma evaluated in an urban pulmonary subspecialty clinic in the United States was performed. Patients with fungal and nonfungal allergen sensitization were identified based on serum-specific immunoglobulin E (sIgE) testing. Demographic, clinical, laboratory, and spirometric data were obtained. The relationship between fungal sensitization and asthma outcomes was examined.
RESULTS: Of 390 patients with asthma identified, 307 had sIgE testing, of whom 53 (17.3%) had fungal sensitization, 117 (38.1%) had nonfungal sensitization, and 137 (44.6%) had no sensitization. Patients with fungal sensitization were more likely to be sensitized to ≥5 allergens than patients with nonfungal sensitization (66% for fungal vs 29% for nonfungal, $P < .001$). Serum IgE concentrations were highest in patients with fungal sensitization compared with patients with no sensitization or nonfungal sensitization (median, 825, 42, and 203 IU/mL, respectively, $P < .001$). Fungal sensitized patients were more likely to require intensive care unit (ICU) admission and mechanical ventilation than those with no sensitization or nonfungal sensitization (13.2%, 3.7%, and 3.4%, respectively, for ICU admission, $P = .02$; 11.3%, 1.5%, and 0.9%, respectively, for ventilation, $P < .001$).
CONCLUSIONS: Fungal sensitization is common in patients with asthma in an urban setting and is associated with greater sensitization to nonfungal allergens and increased risk of life-threatening asthma. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

Key words: *Allergens; Atopy; Serum-specific immunoglobulin E; Severe asthma*

Asthma is a common respiratory disease that affects approximately 7.7% of the population of the United States.[1] Up to 10% of patients with asthma suffer from severe disease,[2] which is defined as asthma requiring treatment with high doses of inhaled corticosteroids (ICS) plus a second controller medicine and/or systemic corticosteroids.[3] Severe asthma is associated with increased morbidity, mortality, and health care cost.[4] However, asthma is a heterogeneous syndrome with variable clinical presentations and outcomes[5] that can be classified into different phenotypes. One proposed phenotype includes patients who show evidence of sensitization to fungal allergens.[6]

Sensitization to allergens, particularly inhaled ones, has been linked to the development of asthma[7] as well as asthma severity.[8,9] Fungal sensitization in patients with asthma has been associated with increased asthma severity[10-12] as well as worse clinical outcomes, including worse asthma control,[12] decreased lung function,[13] increased hospital and intensive care unit (ICU) admissions,[14,15] respiratory arrest,[16] and asthma-related deaths.[17] The relationship between sensitization to nonfungal allergens and asthma severity and

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Abbreviations used
EMR- Electronic medical record
FEV_1- Forced expiratory volume in 1 second
FVC- Forced vital capacity
GINA- Global Initiative for Asthma
ICD- International Classification of Diseases
ICS- Inhaled corticosteroid
ICU- Intensive care unit
LABA- Long-acting β-agonist
NHANES- National Health and Nutrition Examination Survey
SAFS- Severe asthma with fungal sensitization
sIgE- Serum-specific immunoglobulin E
SPT- Skin prick test

outcomes is less clear, with some studies finding an association[15,18] and others finding no association.[11,14] The mechanisms underlying the link between fungal sensitization and asthma severity are not completely elucidated. Some proposed mechanisms include fungal-derived proteins acting as allergens or directly leading to airway damage and allergic response, chronic colonization of atopic patients by fungi, and mold exposure in the environment.[6] Because of the link between severe asthma and fungal sensitization, Denning et al[6] proposed the term "severe asthma with fungal sensitization" (SAFS) to describe patients with severe asthma who demonstrate evidence of fungal sensitization. Clinical trials investigating the use of antifungal agents in patients with SAFS have had conflicting results.

A wide range of prevalence of fungal sensitization in asthma has previously been reported.[11,14,16,19] Factors contributing to the differences in prevalence include variation in the specific fungal allergens tested as well as the method of diagnosis. Although the diagnosis can be made by the skin prick test (SPT) or measurement of serum-specific immunoglobulin E (sIgE), there may be poor concordance between SPTs and sIgE in severe asthma.[19] In addition, many studies examining the prevalence of fungal sensitization were performed in highly select and small groups of patients, including patients with severe asthma,[19] patients admitted to the ICU,[14] and patients with a history of respiratory arrest.[16] Two large studies based on the European Community Respiratory Health Survey found that the prevalence of fungal sensitization in patients with asthma increased with asthma severity.[11] More information is needed about the rates of fungal and nonfungal sensitization and its impact on asthma severity in outpatients with asthma. The aim of this study was to determine the relationship between fungal and nonfungal sensitization, asthma severity, and clinical outcomes in an urban subspecialty clinic in the United States. We hypothesized that fungal sensitization increases with asthma severity and is associated with worse clinical outcomes.

METHODS

This research was approved by the Institutional Review Board of Baylor College of Medicine and Affiliated Hospitals. A waiver of written consent was obtained.

Participants

Patients with asthma were identified by search of the electronic medical record (EMR) of Ben Taub General Hospital in Houston, Texas. The hospital primarily serves the uninsured population of Harris County. Patients who had outpatient visits to the hospital or its associated outpatient clinic between January 1, 2010, and December 31, 2015, and carried an International Classification of Diseases (ICD)-9 or ICD-10 code for asthma were identified. Patients not seen in the pulmonary subspecialty clinic were then excluded. For the remaining patients, the EMR was then reviewed to confirm a clinical diagnosis of asthma and to determine if patients had undergone sIgE testing. Patients were excluded if they did not have a clinical diagnosis of asthma (if an alternate diagnosis was made to explain the patient's symptoms/presentation or if the treating physician did not agree with a clinical diagnosis of asthma) or if there was a greater than 2-year time difference between the time of sIgE testing and the pulmonary clinic visit.

Clinical data

Data including sex, height, weight, asthma history, and existence of concomitant pulmonary diseases were obtained from a chart review. For patients with sIgE testing, the pulmonary clinic appointment closest to the date of testing was identified. For patients without sIgE testing, the most recent pulmonary clinic appointment was identified. Clinical data were extracted from this visit. Asthma medications and health care utilization in the year preceding the identified clinic appointments were recorded. Asthma control was assessed using the Global Initiative for Asthma (GINA) 2015 guidelines.[20] Laboratory data including sIgE testing results, serum IgE concentration, and blood eosinophil counts were collected. Spirometric parameters, based on the worst recorded forced expiratory volume in 1 second (FEV_1) when the patient was not in an exacerbation, were recorded.

Allergy testing

Decision to order sIgE testing was made by the treating physician. The testing was performed by LabCorp (Houston, Tex) and included the quantitative measurement of sIgE for 29 common regional allergens (zone 6) via the ImmunoCAP method. Fungal allergens in this panel include *Penicillium chrysogenum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Mucor racemosus*, *Stemphylium herbarum*, and *Alternaria alternata*. The full panel of tested allergens can be found in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org). An sIgE $\geq$0.35 kU/L was considered positive. Patients were considered to have fungal sensitization if they had a positive sIgE to one or more of the fungal allergens. Patients were considered to have nonfungal sensitization if they did not have a positive sIgE to any fungal allergens but had a positive sIgE to one or more nonfungal allergens.

Data analysis

Summary statistics are presented for continuous variables as mean $\pm$ standard deviation if they were parametric and median (interquartile range) if they were nonparametric. Two-way comparisons were performed using the unpaired *t*-test for parametric variables and the Wilcoxon rank-sum test for nonparametric variables. Categorical variables were compared using the χ^2 test or Fisher's exact test. Three-way comparisons were performed using ANOVA with post hoc Tukey's test for parametric variables and the Kruskal-Wallis test with post hoc Dunn's test for nonparametric variables. Poisson regression was performed for the number of episodes of clinical outcomes in patients with asthma and fungal sensitization compared with patients with asthma and no fungal sensitization (patients with no sensitization and nonfungal sensitization) in a model adjusted for race. All analyses were performed using Stata 11.0 software (StataCorp, College Station, Tex). All P values are 2-sided with $P < .05$ considered statistically significant.