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Mini Review

Asthma and Aspergillosis: Which one causes the other?

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Abstract

The respiratory system of the human body is always exposed to a great number of fungal spores. Asexual spores of Aspergillus are the most frequent type of spores that can be found in various environments. The inhalation of these spores can lead to various undesirable effects in the human body. Aspergillosis is a common type of these harmful effects of inhaled spores, while sensitization, which is resulted from a long-term exposure to Aspergillus spores, is a second type. In some cases, sensitization can develop into various types of allergic diseases such as asthma, which may play a role as a predisposing factor for aspergillosis in other cases. In conclusions, Asthma and Aspergillosis have shared responsibility to form each other in a reversible relationship.

Keywords: Aspergillosis, Asthma, Aspergillus, Allergic Bronchopulmonary Aspergillosis (ABPA).

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Introduction

Asthma is a chronic inflammatory disease of the airway caused by multifactor agents.[1] It characterizes by a variable resistance and obstruction in air flow hyper responsiveness, which can also mean a resistance to air flow and smooth muscle sensitivity to bronchoconstricting stimuli.[2] In the US, this disease is ranked eighth among diseases needing a physician's visit.[3] Its prevalence and mortality has sharply increased over the past decades. There are approximately 300 million people worldwide suffering from asthma with 180,000 deaths annually. This numbers increases by 50% every decade.[4] Based on the estimation of the Institute for Health Metrics and Evaluation (IHME), a gradual increasing in morbidity and mortality of asthma with a prevalence of 4% is specifically found in African adults.[5]

Sensitization to the fungal allergen is the most effective factor to trigger or worsen asthma.[2,6] Antigens of *Aspergillus* species are a common type of allergen responsible for developing or stimulating such allergic diseases.[5,6] Exposure of the respiratory epithelial tissues to the *Aspergillus* antigen may initiate from two sources; the entering spores or from colonization of fungi in the pulmonary system in the form of aspergillosis disease.[7-11] There are different types of pulmonary Aspergillosis with variable invasive ability into the pulmonary system.[12,13] Allergic Bronchopulmonary Aspergillosis (ABPA) is the most frequent type of aspergillosis recognized to associate with asthma, especially that caused by *A. fumigatus*. [10,11,14-16]

A strong correlation between asthma and aspergillosis makes it difficult to understand which one has more effect on the other. Many clinical evidence supports the fact that Aspergillosis plays a major role in asthma.[10,11] Others demonstrated that asthma is the main predisposing factor for the development of aspergillosis.[11,17,18] This review tries to clarify the actual relationship between asthma and aspergillosis based on many related factors associated with each of them.

Asthma

Asthma is considered to be a chronic inflammatory disease that may result from the interaction of environment and genetic factors.[19] Most clinical features of asthma are represented by airway obstruction, bronchial hyper responsiveness and greater airway wall thickening, with episodes of various symptoms, including chest tightness, wheeze, cough, and shortness of breath.[19,20] Epithelial destruction of the airways, especially ciliated cells, is also recognized in most asthmatic patients.[21]

Asthma is most commonly developed in females with more serious symptoms and with less comfortable lives compared to males.[22] Estrogen in females could be responsible for this situation through its anti-inflammatory activity by decreasing the production of TNF-α, expression of interferon-γ and the activity of NK cells.[23] Thus, in order to manage asthma in females, the relationship between variation in hormones and asthma symptoms should be focused on.[24] Race has no great effect on the severity of asthma,[25] while other factors may have a role in this severity such as obesity, changing in diet, depression, and gastroesophageal reflux disease.[24-26] Rhinitis can also have a

role in the development of asthma.[27]

The prevalence of asthma has increased all over the world, especially in Western countries, while it's less common in developing countries.[28] Severe types of asthma can increase the death rate as recorded in the UK when it causes death in about 1500 patients per year.[3] The prevalence of asthma in children is much higher compared to adults especially in the age range of 0-17 years.[25] The prevalence of uncontrolled asthma was estimated to be 35% of children with non-respiratory complaints, while it was at 54% in those with respiratory complaints.[29] Infants are also at risk of developing asthma, which may be a result of exposure to various factors when they are in utero.[28]

Control of asthma is usually an obligatory requirement for patient management.[30] Such a control should include management of rhinitis, smoking and low adherence to inhaled corticosteroid.[31] Therefore, controlling asthma leads to a better life with less time spent in emergency and hospital rooms.[32]

Asthma and Fungi

Fungi are one of the most common types of organisms that can be found all over the world. They contain diverse species with an ability to live on a variety of organic compounds. Some are used as food, some are decomposers and recyclers, and some have a potential capacity to cause diseases in animals and plants. Thus, continuous exposure to fungal elements is considered as a fact that humans should live with.[1] Such exposure can lead to three main adverse effects: infections, allergic diseases, and toxicity with irritable effects.[33] Asthma is one type of allergic disease that can develop or increase its severity in the presence of fungi. Although asthma is a multifactorial disease, fungi is not completely proved as a unique exogenous causative agent for asthma. This may be due to the fact that the exposure to fungi is highly variable in time and density or because it is hard to measure.[3] Diverse distribution of fungi both outdoors and indoors can also be considered as an important factor for the development of asthma. Most of asthmatic severity is associated with exposure to outdoor fungi,[33] this is while data about the contribution of indoor fungi are less strong.[3] However, damp conditions in an indoor environment may stimulate asthma to become worse in the presence of fungi.[34]

Currently, accumulated evidence support the association between mold exposure and asthma.[1,3] This type of association may be built on the fact that inhalation of fungal spores will lead to fungal allergy or sensitization or may cause allergic bronchopulmonary mycosis.[6] The prevalence of fungal sensitization is usually recorded at high percentage all over the world. It is found relatively higher (3-52%) among the asthmatic African population.[5] Moreover, the mortality risk among asthmatic people can increase by 2.16 times in case of exposure not less than 1000 spore/m^3. [35] Evidence of the role of fungi causing asthma is supported by an observation that asthma is elevated with high air contents of mold in summer and autumn, while it declines when fungi have a low count during the snow season.[3] The admission of asthmatic patients into the hospital, especially those at the age range of 16-40 years, was also found to be in greater number during the mold season of July and October.[36]

Fungi have the ability to induce asthma when they colonize the human body for a long time. This may cause damage in the airway tissue via production of toxins or Volatile Organic Compounds (VOC) or even stimulate an auto-reactive response by fungal proteins as they have similar antigens to that of the human body.[3,6] Although both fungal allergy and sensitization developed through immune-mediated response to fungi, inflammation with tissue damage may only result from fungal allergy, while fungal sensitization is characterized by the absence of such events and only indicated by elevated level of fungal-specific IgE or cutaneous hyperreaction to fungal antigen.[1-2,37] Thus, fungal sensitization can be diagnosed by performing the Skin Prick Tests (SPT) with fungal antigens or by measuring the level of specific-IgE in blood.[6, 37] Based on a skin test, about 63 cases from 645 asthmatic patients were found sensitive to various species of fungi.[38] However, perfect diagnosis of asthma with fungal exposure remains dependent on the results of clinical, radiological and immunological features all together.[2]

Fungal allergen, the antigen of fungi causing allergy, is the most effective factor to trigger or worsen asthma.[2,6] Five groups of allergen are diagnosed to have an effect on asthmatic individuals, including two enzymes (protease and glycosidases), which have a direct effect on the host, and three metabolized proteins association with spore germination.[3] Long-time exposure of the human body to these compounds either by directly entering as inhalation fungi or their release from colonization in tracheobronchial tracts will certainly stimulate asthma symptoms in the lower airway sections.[2,6,33] During the time of exposure to fungal allergen, mild asthma can firstly develop without any effect on lung functions, but over time, clinical symptoms such as airflow obstruction, bronchiectasis and chronic pulmonary aspergillosis will gradually increase to form severe asthma.[1] Sensitization in asthmatic patients to fungal exposure can develop one or more fungal allergens depending on the variety of fungi without denying the possibility of the occurrence of cross-reactivity between these various allergen sources.[3] Currently, a new term called Severe Asthma with Fungal Sensitization (SAFS) has become very common as an indicator for the association between fungal sensitization and this severe type of asthma.[1,3,39] The main characters of SAFS are suffering from severe asthma with less than 1000 IU/ml of total IgE.[1] The SAFS usually causes high rates of death and

hospital admissions of adults or bronchial allergy in children.[3,6] More than 6.5 million people suffering from SAFS with up to 50% of asthmatic adults need secondary care for fungal sensitization.[1]

There are many species of fungi that have the capacity to cause sensitization in the human body of the asthmatic individuals, without knowing the specific one for SAFS. Species of *Aspergillus* were recorded to be the most important agents for such sensitization in asthmatic people.[5,6] A positive sensitization of patients to *Aspergillus* spp. (45%), with severe asthma to fungal species was extremely high followed by six other fungal species.[37] This also was observed in an Egyptian asthmatic population when sensitization to *Aspergillus* spp. (41.8%) was higher than the other three species.[38] *Penicillium* spp. are also considered as a sensitizing agent in various ages of asthmatic patients starting with infants. [38,40] Among 121 patients with severe asthma, 29% of them had sensitivity to *P. notatum,*[37] while it represented 33.4% from 645 asthmatic patients with predominant allergic factors.[38] Several other fungi also have a sensitization effect associated with asthma such as *Alternaria* spp., *Candida albicans, Trichophyton* spp., *Cladosporium* spp. and *Helminthosporium* spp.[1,37,38,41] Thus, management of fungal allergy in patients with asthma should be done in almost five steps; avoiding fungal exposure; keeping inflammatory reaction under control; enhancing airway flow by reducing obstruction and the amount of mucus; and controlling bacterial infection.[1,2]

Aspergillus and Aspergillosis

Aspergillus is one of the large groups of saprophytic fungi containing more than 180 species; of which a fifth of them have the ability to cause human and animal diseases.[12, 42] Its wide distribution in outdoor environments as saprophytic fungi living on organic materials in the soil result from plant debris, and decaying plants and animals.[7,8] Indoor environments also contain *Aspergillus* as in factories of the food industry, hospitals and houses.[9,13] Asexually produced conidia are the most common shared features in all *Aspergillus* species.[43] Conidia, which are usually produced as interconnected chains on broadly clavate structure on the vesicle of fungal body, are usually hyaline color when presented singularly and on the other hand are presented with variable colours when collected in clusters.[12,13]

Aspergillosis is a fungal disease mainly caused by several members of *Aspergillus.* [9,12] Asexual conidia of *Aspergillus* are usually considered as the most causative agent for this disease due to their production in thousands, while sexual spores have a minor role in different diseases.[43] Separating conidia from producing fungi is accomplished under the effect of strong air currents or by animal activities, to facilitate dispersing such small conidia by air and distributing them in outdoor and indoor environment.[9,13] Thus, conidia can enter the respiratory tract of the human body by the inhalation of contaminated air, but without developing any disease in most people with a good immune system.[7,9,13] Alveolar macrophage and epithelial cells normally destroy inhaled conidia.[9] Thus, any weakness in the immune system or the presence of other underlying conditions can facilitate the development of aspergillosis after germination of conidia into hypha.[7-9,44] However, immunocompromised conditions may result from various factors such as cancers (leukemia, Aplastic anemia), treatment with immunosuppressive drugs (chemotherapy or corticosteroids for various disorders as with organ transplantation and allergic diseases), viral infections such as HIV and cytomegalovirus, and the occurrence of chronic lung diseases like asthma, TB, or cystic fibrosis.[8] Generally, the respiratory tract is the most common route of entering *Aspergillus* conidia, while other sites such as skin, gastrointestinal, kidney, eye, and peritoneum are less commonly described in association with infections.[13] The small size, thermotolerance, and hydrophobic nature of conidia are considered as important factors in causing aspergillosis.[12] *Aspergillus* species also have other virulence factors which play a role in the development of different types of aspergillosis, including production of proteases, antioxidants, pigments, adhesins, siderophores, and mycotoxins.[12,13] *A. fumigatus* is considered as the most virulent species with an ability to cause a wide range of aspergillosis (90%), especially in immunocompromised patients.[7,12,13] Many characters can facilitate *A. fumigatus* to be the most dangerous infectious species, including its production of small size green echinulate conidia (2.5 to 3 mm in diameter) with large numbers of spores, tolerance to the temperature of the human body, secretion of protease, its highly antigenic nature, and drug-resistance to common antifungal agents.[9,12,13] Other species of *Aspergillus* rather than *A. fumigatus* are also recorded to cause aspergillosis such as *A. flavus, A. niger, A. terreus, A. nidulans* and *A. ustus.*[12] Otherwise, fungal groups that differ from *Aspergillus* could play a role in the development of aspergillosis as with zygomycetes and *Fusarium,* especially in the form of aspergilloma or a fungal ball.[7]

Recently, aspergillosis has become a well-known type of fungal disease due to an increased use of immunosuppressive drugs.[13] Several types of infections and allergic diseases have been identified resulting from the direct pathogenic activity of *Aspergillus* spp. or from host sensitization to this type of fungi such as asthma, allergic sinusitis and alveolitis.[7,9,13,41] High morbidity and mortality rates are continuously recorded for aspergillosis.[45] Thus, aspergillosis which may involve any tissue in the human body mainly depends on the immune state of the host and pulmonary structure.[7, 46] It can, in general, be classified into invasive and noninvasive diseases.[46] Invasive Aspergillosis (IA) has been observed with

a fourfold increase in the last 12 years.[13] Actually, great numbers of aspergillosis types are difficult to classify because of their cross-interaction in clinical characters, pathological features, and diagnostic properties.[47] Aspergilloma, as an example, is characterized by non-inflammatory nature, while it becomes inflamed, even slightly, in the presence of some conditions.[48] However, aspergillosis can be classified based on the site of infection in the pulmonary tract and clinical features into: invasive aspergillosis such as Invasive Pulmonary Aspergillosis (IPA), chronic aspergillosis such as aspergilloma and Chronic Pulmonary Aspergillosis (CPA), and allergic aspergillosis such as Allergic Bronchopulmonary Aspergillosis (ABPA).[12,13]

Asthma and Aspergillosis

Hundreds of *Aspergillus* spores are inhaled into the respiratory tract every day without any effects on human health. Aspergillosis is one of the important types of fungal infections strongly associated with asthma.[10] The epithelial cells of the respiratory tract become sensitized after any contact with *Aspergillus* antigen leading to the development of Allergic Bronchopulmonary Aspergillosis (ABPA) or Severe Asthma with Fungal Sensitization (SAFS).[10,11,49] Thus, individuals with allergic asthma are always under the risk of developing pulmonary aspergillosis. Inflammation in the airway of patients with asthma increases after the inhalation of *Aspergillus* antigens.[10]

The ABPA is the most frequent type of aspergillosis recognized to associate with asthma.[10,11,14,15] It is clear when the presence of asthma becomes one of the important criteria to the diagnosis of ABPA, and because of that any patients with asthma should be expected to have such a type of aspergillosis disease, especially those with poor response to corticosteroid treatment.[11,17,18] An eosinophilic asthmatic patient under the treatment of mepolizumab was diagnosed to have ABPA.[50] A positive result for ABPA is also found in 40.4% of asthmatic patients.[51] The prevalence of ABPA in bronchial asthma is estimated to be about 12.9% based on worldwide estimations from 1965 to 2008.[52]

Antigenic structure of *A. fumigatus* is mostly responsible for the sensitization of asthmatic patients to *Aspergillus* exposure.[11,16,53,54] This fungus was diagnosed in 63% of IgE-sensitized patients with asthma.[16] Sensitization to fungal exposure can increase the risk value for the development of ABPA in 1-2% of patients with asthma and in 7-9% with cystic fibrosis.[11] The clinical features of the association between *A. fumigatus* and asthma are usually represented by clearly observable bronchiectasis with greater airflow obstruction.[53] In general, the characteristics of sensitization in asthmatic patients to *A. fumigatus* include lower lung function, neutrophilic airway inflammation, more bronchiectasis and high levels of *A. fumigatus*–IgE.[16]

The Skin Prick Test (SPT) is the most significant test for detecting sensitization to the *A. fumigatus* infection. It can divide asthmatic patients into reactors and nonreactors groups.[55] About 46% of asthmatic patients have a positive SPT for *Aspergillus* and some of them have ABPA based on the positive *Aspergillus*-precipitin test and radiological features.[14] In North India, 35.1% of 350 asthmatic patients showed positive SPT and 21.7% of them had ABPA.[15] Another study in India from 2012 to 2013 revealed that 59.5% of asthmatic patients have sensitization to *Aspergillus* according to the results of SPT and spirometry.[56] About 11.7% of the Asian population with severe asthma showed positive SPT to *Aspergillus* antigens which was used as an indicator for the development of SFSA.[57] On the other hand, intradermal test for diagnosis of hypersensitivity to *Aspergillus* exposure can be more sensitive than SPT.[52]

Avoiding exposure to *Aspergillus* antigens is a master key to limit the severity of asthma in most patients.[17] Antifungal treatment for at least 3 months, for example with voriconazole and systemic steroids, are important to moderate the severity of sensitization to *A. fumigatus*.[17,54]

In conclusion, many evidence currently support the association between mold exposure and asthma. Aspergillosis can develop asthma after long-term exposure to *Aspergillus* antigens. Asthma can also encourage infection with aspergillosis in many cases. Thus, asthma and aspergillosis have shared responsibility to form each other in a reversible relationship.

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