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Narrative Review

Aspergillus Species and House Dust Mites: Their Allergenicity and Contribution: A Review Article

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Abstract

Allergies are pathological manifestations originating from a trigger-sensitized immune system. *Aspergillus* species have been reported to be one of the important inhalant allergens in different geographical regions of the world. House dust mite (HDM) allergens play a major role in causing allergic diseases. The emerging literature indicates the allergenicity and contribution of *Aspergillus* species and HDMs. Allergies erupt when innocuous foreign components are confused as foes by the immune surveillance. The incidence of fungal sensitization in patients with allergic respiratory diseases has been reported from 2.3% to even 80% in various studies worldwide. Human skin scales provide food for both mites and fungi. Fungi may either constitute a food supplement for mites or may have an indirect effect by decomposing human dander, thus making it more accessible for HDMs. There is a mutual relationship between fungi and HDMs. In addition to avoid exposure to an allergen as a secondary or tertiary preventive strategy, which is often not sufficiently effective against domestic mites, the treatment of mite allergy is mainly based on allergen-specific immunotherapy (AIT). Treatment with azole antifungal drugs in patients with severe asthma is effective and improves patient quality of life.

Keywords: Allergy, *Aspergillus*, House Dust Mite, Allergenicity, Dermatophagoides

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Introduction

Allergies are pathological manifestations originating from a trigger-sensitized immune system. Allergies erupt when innocuous foreign components are confused as foes by the immune surveillance. The immune system is a network consisting of lymphoid organs, lymphocytes, and cytokines meant to cordon off against all physical invaders and restore homeostasis. The immune system defends the host against the onslaught of pathogens by its two arms, innate and adaptive immunity.[1,2] Genetics and the environment are two potent factors that could trigger allergic reactions due to deviations in the immune system.[3]

Allergic diseases of the respiratory system are rapidly becoming global health problems.[4-6] Thirty percent of the world population suffers from allergies.[7] The prevalence of respiratory allergy that is clinically expressed by asthma or rhinitis is high and still increasing. The prevalence of asthma in 13-14 year-old children is 14.1%.[8] Lifestyle and dietary changes are factors that increase the prevalence of allergic diseases.[9]

Airborne fungi are involved in the etiology of allergic respiratory diseases.[10,11] Fungal exposure has been recognized as a factor in asthma and other respiratory conditions such as thunderstorm asthma and seasonal epidemic asthma.[12,13] The incidence of fungal sensitization in patients of allergic respiratory diseases has been reported from 2.3% to even 80% in various studies worldwide.[14-17] Exposure to house dust mite (HDM) allergens in early childhood is a significant factor in determining the subsequent development of asthma.[18,19] These allergens are not endemic or climate-controlled, but are present in geographically segregated countries like Vietnam, Thailand, Brazil, Italy, and China, to name a few.[20-25]

Allergenicity and the Immune System

The general pathway of allergic responses is based on the role of immunoglobulin E (IgE) and are either immediate or delayed. Allergenicity starts with the recognition of allergens by antigen-presenting cells (APC) like dendritic cells which polarizes Th differentiation towards Th2, causing excess IgE production. The allergens bind to IgE which adheres to the surface of basophils and mast cells and activates them, thus causing cytokine and chemokine secretion, cell degranulation, and the subsequent release of histamines. Released cytokines stimulate other immune cells and mediate inflammation phenomenon. In delayed hypersensitivity, T lymphocytes, eosinophils, and basophils are recruited to

the site of inflammation.[26-30] Allergies to HDMs can trigger immune responses and induce IgE-mediated hypersensitivity in predisposed individuals.[31,32] The higher the severity of the allergic respiratory disease is, the higher the levels of both total IgE and specific sIgE will be.[33-35]

The role of molecular diagnosis in HDM allergy has received little attention in previous studies. The availability of recombinant and natural allergens of Dermatophagoides species makes it possible to investigate the association of the specific molecular profile with clinical manifestations in HDM-allergic individuals. ISAC microarray–based determination of IgE against various Dermatophagoides components may be of value in defining the risk of asthma developing in children. The risk of asthma was twice as high in children with sIgE than in those with Der p2.[36,37]

In 2016, Vidal et al surveyed the association between asthma and sensitization to allergens of *Dermatophagoides pteronyssinus*. Their study revealed that the concentrations of sIgE to Der-p1 and sIgE to Der-p2 are higher in patients with asthma than in those without it. Reactivity to both Der-p1 and Der-p2 allergens was associated with asthma.[38] In 2012, Strong et al conducted a study on the application of chitin microparticles on symptoms of allergic hypersensitivity to *D. pteronyssinus* and *Aspergillus fumigatus*. Intranasal application of chitin microparticles could reduce serum IgE levels and eosinophilia, airway hyper-responsiveness, and lung inflammation, resulting in the increased release of IL-12, IFN-γ, and TNF-α cytokines and a reduction in IL-4 cytokine production. Lymphoid tissue stimulation due to the application of chitin microparticles could offer a novel approach for treating allergic diseases in humans.[39]

Aspergillus Species

Fungi are present everywhere due to an abundant asexual reproduction cycle, through which billions of spores are produced and survive in different environmental conditions. Aspergillosis fumigatus is an important cause of opportunistic infections in humans. Aspergillosis was a much-feared complication of immunosuppressive treatments associated with high mortality and morbidity.[40-42]

Among the different types of fungi, the *Aspergillus* species have been reported as important inhalant allergens in different geographical regions of the world.[14-16,43-52] *Aspergillus* species are the most common causes of invasive mold infections worldwide, especially in immunocompromised patients. *A. fumigatus* is the main etiologic agent of allergic, chronic, and invasive bronchopulmonary fungoides among the infections caused by *Aspergillus* species. These infections can cause high mortality and morbidity in both immunosuppressed and immunocompetent individuals.[53] *A. fumigatus* can causes allergic, acute, and chronic invasive diseases in both humans and animals.[54]

In 1999, Laurent Van Asselt investigated the interactions between domestic mites and fungi. Their study revealed that fungi and mites are two important causes of allergic manifestations such as asthma and rhinitis. Fungi may be a source of food and nutrients for HDMs which provide sterols and vitamins for one of the most important HDMs, *D. pteronyssinus*. In addition, 2 other mite species also found in the indoor environment, *Acarussiro* and *Tyrophagus putrescentiae*, are attracted by fungi and feed on some species of them.[55]

The azole antifungal drugs target lanosterol 14a-demethylase, which is involved in ergosterol biosynthesis. The resulting depletion of ergosterol leads to altered permeability of the fungal membrane and defective fungal cell wall synthesis.[56,57] Azoles differ from polyenes and echinocandins. Oral treatment with either itraconazole or voriconazole is commonly used in patients with chronic pulmonary aspergillosis.[58] The survival rates of immunocompromised individuals with invasive aspergillosis have increased significantly due to the availability of azole anti-fungal drugs. This class includes itraconazole, voriconazole, posaconazole (available for clinical use since 1997, 2002, and 2006, respectively), and, most recently, isavuconazole.[59] These agents have proved beneficial for the treatment of acute and chronic invasive pulmonary aspergillosis, for the prevention of invasive aspergillosis, and for difficult-to-treat diseases such as CNS Aspergillus disease.[60,61] Triazole antifungal drugs are the basis of treatment for aspergillosis. Azole antifungal agents are recommended for prophylaxis, treatment of acute disease, and long-term maintenance therapy for allergic and chronic aspergillosis. Azole resistance in *A. fumigatus* has been reported, especially in Europe and Asia, and has resulted in increased treatment failure.[62-67]

In 2013, Mastsuse et al investigated the differential effects of dexamethasone and itraconazole on *A. fumigatus*-exacerbated allergic airway inflammation. Their results showed that *A. fumigatus* infection significantly increased the level of neutrophils and eosinophils in the airway of *Dermatophagoides farinae*-sensitized mice. Dexamethasone significantly decreased eosinophils; itraconazole significantly decreased both neutrophils and eosinophils in Df-Af mice. Dexamethasone significantly decreased interleukin 5 (IL5), whereas itraconazole significantly reduced MIP-2. Alveolar significantly reduced phagocytotic activity of *A. fumigatus*. Thus, a combination of dexamethasone and itraconazole might be effective for the management of fungus-exacerbated asthma.[68]

House Dust Mites

HDMs are indoor allergens. It is difficult to get rid of these pesky allergens which occur in nooks and crannies of houses and heighten the risk of asthma, dermatitis, sinusitis, rhinitis, otitis and other allergic or inflammatory diseases.[69] Seventy-five percent of the mites' body weight is composed of water. They are not able to drink water; they absorb water through their legs from the humidity in the environment. They absorb water at a relative humidity of at least 65% and lose water through evaporation at approximately 55°C. Their survival rate decreases at humidity below 50%. HDMs are poikilothermic. They have optimal proliferation at 75%-80% humidity and 25-30°C. On the other hand, they are able to survive large fluctuations in humidity and temperature by

burrowing themselves into areas where moisture can be better retained, such as in mattresses, carpets, or sofas. Hence, it may take months of low humidity for HDMs to die and longer for their allergens to dissipate.[70-72] Approximately all body parts of mites are allergens which can trigger allergy in 85% of asthmatic individuals.[73]

More than twenty types of HDM allergens have been identified.[74] One of the most common groups of indoor allergens causing allergic rhinitis or allergic asthma is found in the bodies and feces of HDMs, with the two main species being *D. pteronyssinus* and *D. farina*.[75-77] Recently, α-actinin was recognized as a new type of HDM allergen.[78] These allergens have been identified not only in houses but also in schools, which can jeopardize the children's health and make them susceptible to health-related consequences.[79]

In 1987, de Saint Georges-Gridelet conducted a study on the vitamin requirements of *D. pteronyssinus* with its fungal association. Their investigation showed that additional B vitamins greatly enhanced the growth of *D. pteronyssinus* in the floor-dust habitat. Mite growth in the presence of added vitamin D was also greater in floor dust than in mattress dust. The differential effects of additional vitamins, depending on the substrate, confirmed the importance of fungal intervention in the diet of the mite.

In conclusion, the importance of certain factors such as diet on the ecology of the house-dust mite in relation to endemic fungi has been shown. Fungal activity in the natural substrate of *D. pteronyssinus* should furnish the needed vitamins B and D for the growth and development of this mite. Related to the sufficiency of these growth factors for mites in mattress dust as well as the greater growth of the endemic fungi on that substrate, this knowledge clearly defines the true biotope of *D. pteronyssinus*.[80]

In addition to avoiding exposure to allergens as a secondary or tertiary preventive strategy, which is often not sufficiently effective against domestic mites, the treatment of mite allergy is based mainly on anti-allergic pharmacotherapy as well as on allergen-specific immunotherapy (AIT).[77,81-83]

The World Health Organization (WHO) highlighted the clinical efficacy of AIT in patients with HDM-induced allergic rhinitis and allergic asthma.[84] A large number of meta-analyses have stated the clinical efficacy of both subcutaneous and sublingual AIT (SCIT and SLIT) in HDM allergy.[77,85-87] There are challenges on the efficacy of allergen avoidance as a therapeutic approach. Acaricide chemicals are effective in eliminating mites, but unfortunately, they have short-duration effectiveness, and there is concern about the safety of their use in homes. Physical interventions such as beds impermeable to domestic mites, regular use of vacuum cleaners, heating, freezing, and drying the equipment are suggested. However, no study has found any significant clinical benefit with these interventions.[70,88-90]

Conclusions

Frequent exposure to allergens can lead to allergic manifestations including asthma, rhinitis, atopic dermatitis, sinusitis, urticaria, and conjunctivitis in susceptible individuals.[74] HDM allergens are not limited to low-income and rural areas in developing countries; they are present in urban areas as well.[20,21] Avoidance of allergens is widely recommended to diminish the severity of allergic rhinitis or allergic asthma symptoms in susceptible individuals. Moreover, a comprehensive approach such as avoiding smoking, improving training and education, and regular assessments may be effective.[91,92]

Authors' Contributions

AM study conception and design, acquisition of data, drafting of the manuscript and revision of the article; MG conception and design of the study, critical revision of the article and final approval of the version to be published; RM substantial contributions to study design, acquisition of data and co-wrote the paper.

Conflict of Interest Disclosures

The authors declare they have no conflicts of interest.

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