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Mini-Symposium: Fungi and The Paediatric Lung

Aspergillus and the paediatric lung

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SUMMARY

Aspergillus spp produce a wide range of saprophytic and invasive syndromes in the lungs, including allergic bronchopulmonary aspergillosis (ABPA), aspergilloma and invasive pulmonary aspergillosis (IPA). ABPA results from hypersensitivity to the fungus, and mainly affects patients with asthma or cystic fibrosis (CF). The treatment of choice consists of systemic corticosteroids and itraconazole. Aspergilloma is managed by observation or surgery. IPA is predominantly seen in patients with haematological malignancies, chronic granulomatous disease or immunosuppressive treatment. With the use of aggressive therapies for end-stage CF, such as heart-lung transplantation, the potential for a patient to convert from colonization or ABPA to IPA has increased. Suggestive clinical and radiological findings, supplemented with mycological data using serology and molecular biology, have enhanced the capacity to diagnose IPA in paediatric patients. While voriconazole is considered the first-line therapy in IPA, several other antifungal agents may be appropriate alternatives.

INTRODUCTION

Aspergillus spp are ubiquitous fungi in nature and are commonly found as saprophytes in soil, plants and decomposing organic matter.[1] *Aspergillus* spp are typical opportunistic organisms producing a wide range of saprophytic and invasive syndromes in the lungs. Pulmonary infections due to *Aspergillus* spp are usually acquired through inhalation of conidia.[2] These forms measure 2–3.5 μm and are therefore able to reach the terminal airways and alveoli where they can grow to hyphae at human body temperature.

The innate host defence system against *Aspergillus* includes dedicated phagocytic cells [peripheral blood monocytes, monocyte-derived macrophages, pulmonary alveolar macrophages, neutrophils, myeloid dendritic cells (DC) and natural killer (NK) cells], cytokines, chemokines, Toll-like receptors and antimicrobial peptides.[3] These arms of the innate host response are part of a precisely regulated and complex network. Factors contributing to development of invasive aspergillosis (IA) include neutropenia, disorders in phagocytosis, deficiencies in T-cell number or function, immunosuppressive therapy and use of invasive devices, together with fixation methods like arm boards and adhesive tape, especially in children.[4]

Inhalation of *Aspergillus* conidia or hyphal fragments may result in colonization of the airways. Colonization may result in innocuous non-pathogenic saprophytic growth in healthy individuals or in disease. Aspergillomas, which may be quiescent or cause symptoms, especially recurrent haemoptysis, may develop in pre-existing cavities. In contrast, invasive disease in the lungs and elsewhere may develop in patients with compromised local or systemic antifungal defence mechanisms. In addition to its ability to colonize and invade the human respiratory tract, *Aspergillus* has a significant potential to act as a powerful allergen, resulting in asthma and allergic bronchopulmonary aspergillosis (ABPA).[2] In individuals with a predilection for allergic reactions, as in patients with ABPA, *Aspergillus* conidia and hyphal fragments in the bronchial tree induce an allergic state.

The most common species causing invasive pulmonary aspergillosis (IPA) is *Aspergillus fumigatus* (up to 90% in some series) followed by *A. flavus, A. niger, A. terreus* and *A. nidulans*. On the other hand, the most common allergens are *A. fumigatus* and *A. clavatus*. *Aspergillus* spp are the most frequent opportunistic organisms. Depending on the host's reaction, *Aspergillus* spp produce both invasive and allergic disease in humans.[2] The various presentations of pulmonary aspergillosis in children caused by *Aspergillus* spp, allergic disease, aspergilloma or invasive disease are reviewed here, focusing on the clinical aspects rather than the basic science.

COLONIZATION AND SACROPHYTIC INVOLVMENT OF THE LOWER RESPIRATORY TRACT

Aspergillus spp may colonize the human respiratory tract without causing tissue damage. Saprophytic involvement also is a

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common finding in otherwise healthy individuals with damaged airways. If asymptomatic, patients are seldom treated. However, in patients with increased susceptibility to invasive fungal infections, such as recipients of stem cell or organ transplants and those receiving antineoplastic chemotherapy for cancer, antifungal prophylaxis is often warranted.

Saprophytic involvement of the lower respiratory tract is found with increased incidence in patients with underlying pulmonary diseases, such as advanced stages of chronic obstructive pulmonary disease (COPD), asthma requiring corticosteroid therapy and primary ciliary dyskinesia syndrome. In patients with cystic fibrosis (CF), colonization of the airways is a common finding.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Epidemiology (underlying lung disease)

ABPA is a recognized complication of asthma and CF. It most often affects teenagers with CF and young to middle-aged adults with asthma; however, it has also been diagnosed in infants with CF and is extremely rare in paediatric asthma. While *A. fumigatus* is usually the causative organism, *A. niger* and occasionally other fungi are less commonly implicated.

ABPA is reported in 1–25% of adult asthmatic patients and in 6–25% of patients with CF.[5,6] North American statistics indicate its presence in 7–14% of corticosteroid-dependent asthmatics and in about 7% of patients with CF.[7] Data from European multicentre studies involving patients with CF showed an ABPA prevalence of 7.8% (2.1–13.6%).[8] The variation in ABPA prevalence is probably related to the lack of uniform criteria for the diagnosis of the disease, variation in laboratory techniques, as well as lack of clinical recognition. The prevalence of ABPA increases with patient age.[9]

Isolation of *Aspergillus* spp from respiratory secretions in patients with CF is relatively frequent (9–57%). The wide variability in the prevalence of bronchial colonization by the fungus is related to the degree of exposure to spores. Patients living in rural areas show relatively high rates of colonization, as do those living in inadequately ventilated houses or houses containing moulds.[9] However, the simple presence of the fungus is not associated with a worsening of lung function.

Pathophysiology

The factors underlying the development of ABPA remain unclear. The roles of genetic factors, mucus quality, pre-activation of epithelial cells and the extent to which this activation facilitates the germination of *Aspergillus* conidia into hyphae, the bronchial penetration of fungi, the immune response, and bronchial/bronchiolar inflammation and destruction are not yet fully understood. Hence, the mechanisms involved in ABPA development are complex[10] (Fig. 1).

Certain HLA antigens, especially HLA-DR2/DR5 and possibly DR4/DR7, predispose some individuals to ABPA, while HLA-DQ2 seems to have a protective role. Genetic variability may therefore protect or enhance susceptibility to ABPA.[11] It is hypothesized that a key role is played by antigen-presenting (dendritic) cells that express HLA-DR2/DR5 and have increased IL-10 synthesis along with increased sensitivity to IL-4. In addition to genetic factors, patients with CF and asthma may be more susceptible to ABPA due to the presence of excessive mucus in their airways. This mucus makes the efficient clearance of conidia from the airways difficult. The conidia subsequently germinate and release antigenic proteins. This provokes a host response that is predominantly mediated by Th2 lymphocytes. The Th2 cells attracted to the airways may be especially susceptible to cytokines such as IL-4 and IL-10, and respond by enhancing both the synthesis of IgE by B cells and the attraction of eosinophils into the tissue.[12] The Th2 response also results in increased mucus secretion into the airway, episodic eosinophil-rich pulmonary infiltrations and remodeling of the airway.

Patients with ABPA have markedly elevated total serum IgE levels as well as increased IgE antibodies to *A. fumigatus*. Furthermore, specific IgG and IgA levels may also be upregulated. In patients with CF, prolonged colonization with *Pseudomonas aeruginosa* or *Stenotrophomonas maltophilia* may increase the risk of developing ABPA.[13]

Diagnosis

ABPA can lead to extensive bronchiectasis and fibrosis if not diagnosed and treated early. This makes a timely diagnosis critical. The classical clinical and laboratory manifestations include episodes of wheezing, transient pulmonary infiltrates, a positive

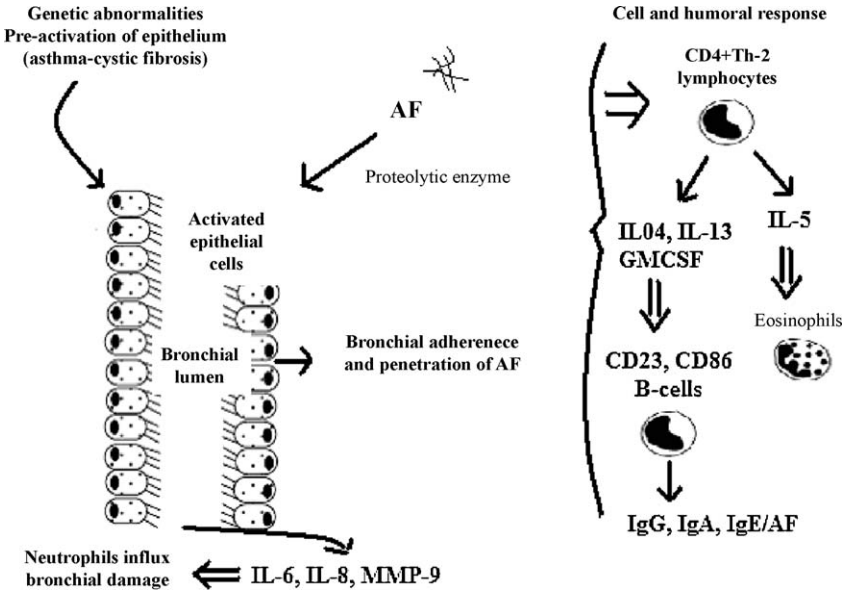

Fig. 1. Pathophysiology of allergic bronchopulmonary aspergillosis: from *Aspergillus* adherence and penetration of the bronchial mucosa to the B- and T-cell response.