ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA) – CHARACTERISTIC OVERVIEW IN CYSTIC FIBROSIS

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Summary:
Recognizing allergic bronchopulmonary aspergillosis (ABPA) in the context of cystic fibrosis (because of overlapping clinical, radiographic, microbiologic, and immunologic features), is often difficult. Advances in understanding of the pathogenesis of allergic aspergillosis, new possibilities in therapy have been done recently. Unlike in asthma, pulmonary infiltrates, bronchiectasis and obstructive lung disease are common manifestations of Cystic Fibrosis (CF) lung diseases with or without ABPA resulting from recurrent and chronic bacterial infection. Atopy as well as an onmset of a variety of immune responses to *Aspergillus fumigatus* antigens early in life in patients with Cf complicates the interpretation of various serological parameters for the diagnosis of ABPA. Early diagnosis and treatment aiming to suppress the inflammation is, however, important to prevent irreversible lung tissue damage.

There is a short overview of main characteristics of ABPA in patients with CF.

Key words: allergic bronchopulmonary aspergillosis, cystic fibrosis

Aspergillus fumigatus, a widely distributed spore bearing fungus, causes multiple diseases in humans. The diseases produced by *A. fumigatus* include invasive pulmonary aspergillosis, aspergilloma and different forms of hypersensitivity diseases. Pneumonia due to *Aspergillus* and systemic aspergillosis occur primarily in patients who have immunosupresion or T cell or phagocytic impairment. Although no protective antibody response was detected in these patients (1), a CD4+ Th1 cytokine pattern was suggested to be important in rendering protection. Hypersensitivity lung disease includes allergic asthma, hypersensitivity pneumonitis, and ABPA; all result from the exposure to allergens of *A fumigatus*.

Pathogenic *Aspergillus* generally grows easily and relatively quickly on routine bacteriologic and mycological media in the clinical laboratory. Only pathogenic species are capable of growth at 35°C–37°C and *A. fumigatus* in particular is capable of growth at ≥ 50°C. *Pseudomonas aeruginosa* may inhibit the growth of *Aspergillus.*

Aspergillus spores or inhalation trigger an IgE-mediated allergic inflammatory response in the bronchial airways, leading to bronchial obstruction and asthma. The immune response to *Aspergillus* antigens in patients with ABPA, as well as in allergic asthmatic patients and patients with CF, is a Th2 $CD4^+$ cell response A central question, then, is how ABPA differs from *Aspergillus* sensitivity in atopic asthma and CF. It is proposed that ABPA develops in genetically susceptible asthmatic patients and patients with CF because of increased frequency and/or activity of *A. fumigatus*–specific Th2 $CD4^+$ cells.

The allergic inflammatory response in patients with ABPA appears to be quantitatively greater than that in *Aspergillus*-sensitive atopic asthma patients and patients with CF. In the proposed model of the immunopathogenesis of ABPA, as illustrated in *A. fumigatus* spores are inhaled into the bronchial airway, where they are trapped by the luminal mucus, germinate, and form mycelia. *A. fumigatus* mycelia release allergens that are processed by antigen-presenting cells bearing HLA-DR2 or -DR5 and presented to T cells within the bronchoalveolar lymphoid tissue (BALT). The T cell response to *Aspergillus* allergens becomes skewed toward a Th2 $CD4^+$ cell response, with synthesis and secretion of cytokines IL-4, IL-5, and IL-13.

One of the characteristic features in patients with ABPA is that *A. fumigatus* is found bound to the surface epithelium and is growing on and between the epithelial cells without being efficiently killed by mononuclear and eosinophilic infiltrates. It has also been shown that spores of *A. fumigatus* are attached to epithelial surfaces cultured in vitro (17). The physical presence of *A. fumigatus* on and between the epithelial cells is possibly of importance for the modulation of the immunologic response toward a Th2-type response (18). Over the past decades, virulence factors of *A. fumigatus* that interfere with or even block normal functions of the humoral and cellular defense of the airways have been detected (19).Virulence factors were discussed above. Some of these virulence factors are the proteolytic enzymes of *A. fumigatus.*

ABPA is found in highest incidence among atopic patients with CF. It has been hypothesized that in CF, the abnormal mucus promotes the trapping of *Af* spores within the bronchial airway, permitting and perhaps promoting growth of *Af* mycelia and probably, in genetically susceptible individuals, stimulate a Th2 cell response with subsequent ABPA.

Proteases of *Af* may play a role in facilitation of antigen transport across the epithelial cell layer by damaging the epithelial integrity and be a direct interaction with epithelial cell surface receptors. These mechanisms would result in production of proinflammatory cytokines and corresponding inflammatory responses.

The classic case of ABPA fulfills the following criteria:

1. asthma
2. chest roentgenogtaphic infiltrates – current or in the past – may be detectable on CT when roentgenographic is unremarkable
3. immediate cutaneous reactivity to *Aspergillus* species
4. elevated total serum IgE >417 IU/ml (>1000ng/ml)
5. serum precipitins antibodies to *AF*
6. central bronchiectasis on chest CT
7. peripheral blood eosinophylia
8. elevated serum IgE and/or IgG to *Af*

It has been suggested that the minimal essential criteria for diagnosis of ABPA include the following: (2)

1. asthma
2. immediate cutaneous reactivity to *Af* species
3. elevated total serum IgE concentration
4. elevated serum IgE to *Af* and IgG to *Af*
5. central bronchiectasis

Other diagnostic elements that may be supportive include a history of coughing up either mucus plugs or sputum flecked with brown, black or green elements, culture of sputum yielding *Af* or a sputum smear in which *Af* was identified microscopically, a sputum smear showing eosinophils, or a chest radiographic sign suggesting bronchial inflammation with or without plugs.

The diagnosis of ABPA in CF is often delayed because many of the diagnostic criteria overlap with common manifestations of CF.

The *Epidemiologic Study of Cystic Fibrosis (ESCF)* proposes two of the following 3 criteria:

1. immediate cutaneous reactivity to *Af*
2. precipitating antibodies to *Af*
3. total serum IgE>1000IU/ml

In addition at least 2 of the following are required:

1. bronchoconstriction
2. peripheral blood eosinophilia >1000 eosinophils
3. history of pulmonary infiltrates
4. elevated serum anti-*A. fumigatus* IgE or IgG
5. *A. fumigatus* in sputum found by culture or smear
6. Response to steroids

The literature reviews mention several predisposing factors for ABPA in CF:

- the increase in frequency and severity of bacterial lung infections that lead to an increased use of antibiotics that "may pave the way" for fungal infections
- the use of inhaled tobramycin
- HLA-DR molecules DR2, DR5 and possibly DR4 or DR7 that contribute to susceptibility; whereas HLA DQ2 contributes to resistance – their combination may determine the outcome of ABPA in CF
- atopy with different patterns of allergic response to *Af* compared to other allergens (3,4)
- association with delayed onset of *P.aeruginosa*

Factors that have been found to be associated with ABPA in CF are: males, adolescents, lower levels of lung function, presence of wheezing/asthma, positive cultures for *P.aeruginosa*, atopy, lower clinical and radiographic scores.. There was also a significant association found in patients colonized with *Staph. aureus* and with an increased decline in lung function (greater than expected/year).

Therapy for ABPA involves prophylaxis against and treatment of acute exacerbations as well as prevention of end-stage fibrotic disease. There are two aspects of treatment: first attenuation of the inflammation and immunological activity –for which corticosteroids are the mainstay of therapy (5,6); second – the attenuation of the antigen burden arising from fungal colonisation of the bronchial tree (5).

Therapy of ABPA in CF is problematic. This is because of several reasons: first – several of the diagnostic criteria of ABPA overlap with common manifestations of CF (therefor treatment must be rigurous); second – both cause many of the same clinical and physiological derangements; third- systemic corticosteroids (the cornerstone of treatment for ABPA) have toxicities that are concerning patients who are prone to develop diabetes, osteopenia, infections.

In this regard there are no specific indications for how long may corticosteroids be given in case of high IgE values; it has been accepted that efficacy of treatment may be judged when levels decrease more than 50%; different schemes were proposed: starting dose of 1-2 mg Prednisolone/kg/day (maximum 40 mg) for up to 2 weeks, followed by 1 mg/kg for the same period, before changing to alternate day therapy. Weaning should be guided by the clinical response over the following weeks (it may take months for a favourable response).

Although corticosteroids are the mainstay of therapy in ABPA because they attenuate inflammatory and immunological activity, they have no effect on the antigen burden arising from the fungal colonization of the bronchial tree. Reducing the fungal burden in the respiratory tract might decrease antigenic stimmulation, reduce inflammatory response, ameliorate symptoms and possibly reduce the long term risk of disease progression.

Itrakonazole which has been used in doses of 200-400 mg/day for 1-2 weeks with tappering over several months (minimum of 3 months for decreasing the antigen load in the bronchial tree) has the disadvantage of limited oral bioavailability, and this particularly for the capsule form, requiring an acidic environment for dissolution which is inhibited by antiacid therapies (20). The liquid formulation is better absorbed but not available in this country.

Vorikonazole is a recently introduced triazole antifungal with superior oral bioavailability which has been aproved for the treatment of invasive aspergillosis (7). It is however expensive, has a high potential for drug interactions and has been associated with a number of adverse effects. It appears to be generally well tolerated, but a transient disturbance in vision has been reported to occur in up to 30% of patients (8). Skin reactions (rash or photosensitivity) are the next common adverse effect (reported in up to 15% of patients), and elevations in hepatic enzymes have been reported in up to 10% of patients (8,9).

Although several small case series have suggested that inhaled corticosteroids are useful in treating patients

with ABPA without CF (11), a double-blind, multicenter study conducted in the United Kingdom in the 1970s of beclomethasone, at 400 μg/day without a spacer (a volume holding chamber used with steroid metered-dose inhalers), failed to demonstrate clinical benefit (12). Inhaled corticosteroids have been shown minimally to reduce bronchial hyperresponsiveness in patients with ABPA without CF (13). There are minimal data to formulate conclusive treatment recommendations for ABPA in CF

Every case has to be interpretated taking into consideration the clinical data, laboratory data and intensity of allergic response to *Af.*

Some authors have suggested that serum IgE levels be followed regularly in patients with ABPA (10) because IgE levels correlate with disease activity, and that corticosteroid therapy should be instituted even for asymptomatic patients if the serum IgE level doubles from the baseline value (10). The great majority of IgE is not directed against *Aspergillus* antigens but is nonspecific (14). Although the serum IgE level remains part of a constellation of clinical parameters used to decide when corticosteroids should be given, it cannot be used in isolation to make that decision (14, 15,16).

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