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Editorials

A new look at the natural history of aspergillus hypersensitivity in asthmatics

Introduction

Aspergillus fumigatus had long been recognized as a pulmonary pathogen, forming mycetomas in pre-formed cavities and/or invading lung tissue in immunocompromised patients. The discovery of its capacity to induce IgE-mediated hypersensitivity and cause bronchial and lung damage through immunologically-mediated mechanisms is more recent. Allergic bronchopulmonary aspergillosis (ABPA) was first described in 1952 (1) and for a time was considered to be a British disease. In due course however it was recognized in other countries (2–4), and its discovery led to reappraisal of the significance of aspergillus hypersensitivity (AH), usually defined for clinical purposes as the presence of an immediate-type cutaneous reaction to commercial extracts of *A. fumigatus* or to an aspergillus mix. In particular, attention has focused on the prevalence of AH, pulmonary and environmental factors that predispose to its development, the relationship between AH and tissue-damaging events like ABPA and its longterm course and natural history. As it is more than 40 years since this phenomenon first attracted interest, it is relevant to review how knowledge and recommendations have changed.

Prevalence of Aspergillus Hypersensitivity in Adult Asthmatics

The incidence of positive skin reactions to *A. fumigatus* in unselected extrinsic asthmatics in the U.K. ranges from 10 to 25% (5). Similar figures have been reported from the U.S.A. (6), but regional differences might exist. In Cape Town, South Africa, which has a Mediterranean climate very similar to California, 44% of adult patients referred to a specialist respiratory clinic for assessment of suspected asthma react to *A. fumigatus* or an aspergillus mix (7). This proportion of reactive patients has remained constant over the past two decades, and aspergillus ranks fourth as a cause of positive reactions after the house dust mite, feathers and grass pollen (7). When performed by the intradermal rather than the skin prick method, a large proportion of patients also demonstrate a late-phase cutaneous response. A positive IgE–*A. fumigatus* RAST titre is found in approximately 50% of patients with positive skin reactions, particularly those with a late-phase response (8).

Factors Favouring the Development of Aspergillus Hypersensitivity

The aspergillus fungus is found world-wide in soil and decaying vegetable matter, with peak atmospheric concentrations of spores occurring during winter. Average atmospheric *A. fumigatus* spore concentrations in Cambridge (9) and Cardiff (10), St Louis (10) and Cape Town (7) are similar, but it is likely that in fungal-induced disease the micro-environment in the home and at work is more important than it is in pollen allergy. High counts have been reported in hospital wards in the U.K. (11) and in homes (4,12), and in individual cases ABPA has been linked to living near a municipal leaf compost site (13) and to occupational exposures (14).

High concentrations alone do not account for the high incidence of sensitization to this fungus, as in both outdoor and indoor air other fungi are found in greater numbers. Instead this tendency results from the size of their spores (2·5–3 μm) which favours inhalation and peripheral deposition in the lung, and their thermotolerance which enables them to grow at body temperature. Thus their numbers in sputum and in specimens from bronchi sampled at post-mortem are high relative to other atmospheric fungi (15).

A prerequisite for the development AH is sustained or repeated exposure to aspergillus antigen. Two distinct antigens Asp f I (a 18 kDa protein) and a 45 kDa protein have been identified as important causes of IgE antibody responses in patients with an immediate response to *A. fumigatus* (8). Exposure results from colonization of the respiratory tract within cavities of healed tuberculosis or sarcoidosis, abnormal bronchi found in cystic fibrosis (16) and other forms of bronchiectasis (17), and rarely in the middle ear and paranasal sinuses. Recently sensitization has been described after colonization of

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residual cavities caused by pneumocystis pneumonia in patients with AIDS (18). Growth of fungi in any of these locations permits sustained presentation of antigen to the host immunological system and the opportunity for stimulating IgE production and/or inducing predominantly IgG-related immunopathology. In atopic subjects features of AH precede the development of more complex tissue-damaging pathology whereas in non-atopic patients a larger antigenic load as in the case of an aspergilloma may provoke high concentrations of IgG antibodies without the development of hypersensitivity. As AH is rare in non-asthmatic atopic subjects, it is suggested that asthmatic airways provide favourable conditions for colonization with aspergillus, possibly through increased trapping of air-borne spores or impaired clearance. The incidence of *A. fumigatus* is highest in long-standing asthmatics with asthma dating to childhood, those sensitive to several additional aeroantigens, and in patients with severe asthma requiring multi-drug therapy (7). The role of local factors rather than genetically determined atopic predisposition is suggested in cystic fibrosis, where up to 12% develop features of ABPA (16).

What is the Significance of a Positive Skin Reaction to Aspergillus Antigen?

A distinction must be made between a positive reaction to *A. fumigatus* obtained in the commonly used skin prick test, and that occurring after intradermal testing. The wheal size is larger and incidence of late-phase reactions higher after intradermal testing. This method is advised for patients in whom ABPA is suspected, and initial skin prick testing is negative (19). Skin prick reactions to *A. fumigatus* are usually smaller than those to house dust mite and induration of as little as 3 mm greater than that obtained with the diluent indicates hypersensitivity. As cross-reactivity exists between commercially available preparations of different aspergillus species, individual differences should be interpreted with caution. Although 95% of cases of ABPA are caused by *A. fumigatus*, rare cases caused by *Aspergillus niger, terreus* (20) and *oryzae* (14) have been described. It is therefore recommended that *A. fumigatus* and an aspergillus mix be included in the allergy work-up of all asthmatics. Positive reactions may be expected in a quarter of subjects tested and ABPA diagnosed in approximately 5% of these (less than 2% of all asthmatics).

The relevance of AH to asthma symptoms is unclear. In ABPA, worsening of symptoms is frequently associated with immunological evidence of increased reactivity to aspergillus (8,19). No such relationship has been demonstrated in asthmatics with AH alone. Most have evidence of other sensitivities, usually to house dust mite and pollen. Thus, its relevance cannot be assumed except where it occurs as an isolated or dominant reaction. Bronchial allergen challenge is not recommended as it is costly, potentially hazardous, provides no additional clinically useful information, and treatment is not materially altered by a positive finding.

What is the Relationship Between Aspergillus Hypersensitivity and ABPA?

An exaggerated form of AH is a component of ABPA and is responsible for several of the features of this condition. Clinically, ABPA manifests as bronchial asthma with transient pulmonary infiltrates that may proceed to proximal bronchiectasis and lung fibrosis. Laboratory findings include sputum and blood eosinophilia, markedly elevated serum IgE level, positive IgE–*A. fumigatus*, and IgG–*A. fumigatus* and precipitating antibodies to *A. fumigatus*-allergens (19,20). Because of its relationship to ABPA, AH has been viewed as the first phase in the development of ABPA. Although this may be so, the progression is seen in a small minority of patients. In a longitudinal survey of patients in our clinic followed for a minimum of 10 years on conventional asthma treatment, skin reactivity to *A. fumigatus* and other features of sensitization including RAST, and in some, precipitating antibodies resolved in a significant proportion of subjects and none went on to develop ABPA. Identification of patients who might progress to ABPA is complicated by the fact that the features of ABPA vary according to the stage of disease and the effect of modifying treatment with systemic corticosteroids (19). Serological tests have been used to identify the stage of development in individual asthmatics. Specific serum immunological patterns have been recognized, which distinguish asthma with AH from the remission, intermediate and active phases of ABPA (21). In the former IgE–*A. fumigatus* RAST titres are low but they are invariably high in active ABPA. Titres of *A. fumigatus*-specific IgE measured by ELIZA show similar differences. Utilizing an immuno-blotting technique to detect serum IgE and IgG fractions directed at a variety of *A. fumigatus* antigens, patients with active ABPA exhibit reactions with up to 12 major *A. fumigatus* allergens, while patients in remission react weakly to fewer than five major *A. fumigations* allergens, but have strong IgG-mediated reactions to high molecular weight *A. fumigatus* antigens (21). Fewer than 20% of patients with asthma and AH showed reactions on immunoblots

and these are generally weak. Although this technique is not in general clinical use, the results illustrate the continuum of immunological reactivity from AH to ABPA and its greater complexity and intensity during the active phase of ABPA.

What is the Natural History of Aspergillus Hypersensitivity and the Influence of Treatment?

In view of its tendency to resolve specific measures intended to reduce AH are unnecessary. However, early diagnosis of ABPA is important as treatment has been shown to control exacerbations, prevent relapses and the development of bronchiectasis and pulmonary fibrosis. Although systemic corticosteroids are necessary for active ABPA and exacerbations, usual maintenance treatment of asthma of which inhaled corticosteroids form a central part are usually adequate and progression is rare. With time even patients with cystic fibrosis and ABPA may show improvement in respiratory status and reduced sensitization to *A. fumigatus* (16).

Prevention of AH is difficult to achieve since environmental measures are seldom effective except where a particular source is identified. Combined surgical and medical treatment of middle-ear and paranasal sinuses to eradicate aspergillus colonization in these locations is effective in rare instances. Treatment with itraconazole (22) and other azoles (23) has been proposed for patients with structural lung disease as a means of eradicating colonization and reducing the tendency to relapse. These initial studies suggest that they are of limited value, but further trials are necessary.

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