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Asthma and mould allergy – Does it matter?

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Impact of poorly controlled asthma

In the United Kingdom the prevalence of asthma has been rising. While some of this rise has been attributed to re-labelling of respiratory disease there is world wide evidence of an increase in atopy amongst particularly westernized populations.

It is estimated that between 25–35% of children have experienced wheeze in the last 12 months and in a study from Manchester up to 25% of 4–15 year olds merited a trial of asthma therapy after a questionnaire study validated by clinical examination and three paediatrician assessment [1].

Whilst for many asthma is a benign condition which acts as a nuisance and does not significantly interfere with quality of life, for others it can be life controlling or even life threatening.

Fortunately the death rate from asthma has now peaked and is beginning to fall; it still represents 1,500 predominantly avoidable deaths per year. Over 70,000 admissions to hospitals occurred last year in the UK due to exacerbations of asthma.

The cost of treating the condition is also considerable. It is estimated that the drug bill alone for asthma in the UK in 2000 was £500 million. In addition, 7 million working days were lost (estimated to cost the country up to £1 billion) and the costs of providing care might approximate £10 billion. Of those effected, the 5% of sufferers worst effected might represent up to 50% of the total cost of treatment.

espite the provision of highly effective medical treatment, over 40% of asthma sufferers experience symptoms everyday and report some limitation of activity on a daily basis. One third report interference with sleep due to their asthma at least once per week.

Severe asthma and fungal sensitization

The first report of fungal sensitization aggravating asthma dates back to 1698 and reports an attack induced during fermenting of wine [2].

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The earliest epidemiology on the subject relates to a study in 1928 when 15% of asthma patients attending a single physician were demonstrated to have skin test positivity to either aspergillus or penicillium [3].

While modern literature struggles to find examples of asthma prevention or improvement in asthma symptoms occurring due to allergen avoidance, there were abundant early reports of asthma control improving due to removal of mouldy housing materials, such as mattresses, pillows and furniture [4].

Studies from around the world have shown an association between mould sensitivity and patients requiring specialist referral for assessment, hospital admissions, intensive care admissions and death from asthma attacks.

In a recent international study of 1132 adults, skin sensitization to alternaria (OR 2.03) or Cladosporium (OR 3.2) were significantly associated with the risk of having severe asthma. Interestingly in this study, house dust mite was weakly associated with a risk of severe asthma, but other allergens such as animal atopy was not a significant predictor [5].

In a study from Manchester, UK [6], patients defined as having severe disease as determined by experiencing 2 or more hospital admissions within the preceding 12 months, 76% of those patients fulfilling this criteria were found to be allergic to one of the following moulds (*Aspergillus fumigatus*, *Penicillium notatum*, *Cladosporium herbarum*, *Alernaria alternata* or *Candida albicans*) on skin test, compared to only 16–19% of mild to moderate control asthma patients ($p < 0.0001$). In a separate study we demonstrated those with more severe disease based on stable state lung function, 31–35% were mould sensitized compared to those with mild asthma with normal lung function and controls (17–19% $p < 0.01$) [7].

Asthma and environmental mould allergens

In the UK, the peak time for asthma deaths is July–September which coincides with the peak period for the prevalence of mould spores particularly alternaria and hospital admissions have been frequently associated

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with rises in fungal spore concentrations USA, UK, Mexico and Canada [8].

The relationship between asthma and damp and mould in homes is more controversial. Studies using self reported home dampness as a surrogate for mould exposure have frequently demonstrated an association between asthma prevalence and dampness, but fewer studies using more rigorous assessments have been supportive of a causal role. Indeed where self reported home dampness and objective assessments of the prevalence of mould and damp have been studied in combination, there has appeared to be little association between disease and objective measures. In such a study in Manchester UK, home dampness almost negatively correlated with objective measures of damp suggesting demonstrated epidemiological associations between asthma and home dampness, may be false positives due to recall bias. Some studies have however found a relationship between asthma presence and home mould growth, predominantly in Scandinavia where associations with water damaged schools and other buildings are also present in the literature.

Fungi are present in high concentrations in pillows and may act as a food source for house dust mite, but to date there are no studies correlating fungi in pillows and asthma prevalence/severity.

Thunderstorm asthma is a phenomenon of acute outbreaks of asthma admissions occurring at the time of regional thunderstorms. While it is not fully known whether these epidemics are caused by fungal or grass or other pollen exposures, studies which have attempted to measure both, have found better statistical associations with fungal spore levels [9].

The prospect of treating mould allergy

Allergic broncho-pulmonary aspergillosis/mycosis is arguably an extreme manifestation of aspergillus/mould allergy, characterized by eosinophilic pulmonary infiltration in aspergillus allergic asthmatics. Two randomized placebo-controlled trials of the effectiveness of itraconazole have been reported in patients with ABPA [10,11] and have demonstrated positive benefit. While immunological benefits were demonstrated in these studies notably reduced sputum eosinophils, cationic protein and systemic immune activity, there are methodological problems and patients were treated with oral steroids as well as anti-fungal therapy.

It remains uncertain whether the antifungal therapy is reducing the biological load of colonized airways, or inadvertently through its interaction with corticosteroid metabolism. No systematic study of non-ABPA patients has been performed to date. One small study evaluated the effectiveness of Fluconazole in tricophyton sensitized asthma patients and demonstrated reduction in steroid therapy requirements.

Review of pilot study of pragmatic antifungal treatment

In our own severe asthma clinic we have treated 23 patients with itraconazole. Fourteen had severe asthma and fungal sensitization only (SAFS), while a further 9 fulfilled the definition of ABPA, specifically with a total IgE of $>1{,}000$ IU/l. Using the 12 month prior to treatment in this group of patients as a control period, hospital admissions in the group of patients fell from 1.2 admissions per patient per year to just 0.4 ($P<0.05$). Oral corticosteroids courses or bursts (in those on maintenance) fell from 2.4 per patient per year to 0.6 ($P<0.05$). Total IgE fell from mean 1046 to 664 IU/l ($P=0.005$). Interestingly specific IgE to aspergillus and eosinophilia in the blood did not reduce statistically.

Sub-analysis using those with severe asthma with fungal sensitization (SAFS) only $n=14$; showed bigger falls in hospital admission rates (1.63–0.4 $P<0.05$) and steroid courses 2.15–0.43 $P=0.07$) than in those with ABPA. The latter group demonstrated bigger immunological falls, with significant reductions in specific IgE and blood eosinophilia [12].

This is a small retrospective audit rather than scientific evidence, but it led us to propose a formal multi-centre regional trial. In the last 12 months we have recruited 60 severe asthma patients from 5 hospitals in the North West of the UK. All have SAFS, as defined as severe asthma (uncontrolled despite 1,000 Beclomethasone equivalent plus 2 or more A&E attendances or steroid courses in last 12 months) with fungal allergy (skin or RAST positive to one of 8 fungi/moulds), but with a total IgE of less than 1,000 IU/l and absence of significant central bronchiectasis. Recruitment finished on 16 February 2006. Treatment is blinded with Itraconazole up to 200 mg bd, controlled by blood level monitoring or placebo for 8 months with a 4 month post treatment follow-up period. Efficacy and Safety are controlled by measurement of liver function tests 4 weekly, urinary free cortisol and serum cortisol 8 weekly. Endpoints measured include lung function, quality of life, exacerbation rate and steroid burst requirement. Preliminary results are expected in 12 months time.

Conclusion

The evidence that fungal sensitization and exposure plays a role in asthma severity is substantial. We believe that in a sub-group of patients it may be central to the presentation of the disease as a severe and previously un-controllable phenotype. Anti-fungal therapy may have a role in carefully selected patients if the pattern of uncontrolled airway inflammation and mucous hyper-secretion is associated with airway colonisation by mould, prior to the development of full-blown Allergic Broncho-pulmonary Aspergillosis/Mycosis.

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