

Progression from allergic sensitization to asthma

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Asthma is one of the atopic diseases strongly associated with allergy. High aeroallergen exposure in the immediate postnatal period has been associated with higher risk of sensitization and chronic asthma. It is proposed that following *in utero* allergen sensitization, postnatal high dose allergen exposure localizes inflammation to the airways. In association with adjuvantizing effects of some virus infections, eosinophils and neutrophils are recruited which contribute to epithelial damage and the initiation of the remodelling process. Eventually, the latter processes lead to sufficient airway narrowing to manifest as the first symptoms of asthma. Thus, the immunopathology of asthma is fully established by the time of first symptoms and future strategies will need to identify those at risk of developing the disease before irreversible changes in the airways are established.

**J. O. Warner, P. Pohunek,
C. Marguet, J. B. Clough
and W. R. Roche**

Child Health, University of Southampton/
Southampton General Hospital, Southampton,
UK

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J. O. Warner, Child Health, Level G(803),
Centre Block, Southampton General Hospital,
Tremona Road, Southampton SO16 6YD, UK.
Tel.: +44 2380 796160
e-mail: jow@soton.ac.uk

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Asthma is clearly identified as one of a number of atopic diseases and consequently is strongly associated with the presence of allergy to a range of factors. The risk of developing asthma is clearly increased in individuals from families with a history of atopic disease. Furthermore, it has become increasingly clear that the relative risk of developing asthma is increased in individuals with specific sensitivities. Thus Burr et al. showed that sensitivity to egg in the first year of life was strongly associated not only with eczema but also with asthma and subsequent sensitivity to the inhalant allergen, house dust mite (1). Similarly, house dust mite sensitivity and house dust mite exposure has been shown to be a strong risk factor for the development of asthma (2–4). The ETAC (Early Treatment of Atopic Child) has also established that the presence of sensitivity to cat and grass pollen, at least in infants who already have atopic dermatitis, is a very considerable risk factor for asthma. The question that needs to be asked is how does the sensitization to allergen evolve into airways inflammation?

Allergen and adjuvant exposure

Clearly, continuing exposure to allergen is likely to have an impact on the trafficking of sensitized

cells to target organs. Thus it is not surprising that high concentration exposure to allergen in infancy is associated with subsequent sensitivity to that allergen. In the case of aeroallergens, the focus is very much on airway allergic disease as indicated above. Thus there are a number of month of birth studies that have shown associations between high seasonal allergen exposure immediately postnatally and subsequent sensitization with disease. Similarly, early exposure to high concentrations of house mite and also, indeed, cat has shown similar associations (5).

To what extent any adjuvant factors might promote the development of airway inflammation is less clear. While some studies show that environmental tobacco smoke exposure increases the risk of wheezing illnesses, it is not clear whether this is non-atopic virus associated wheeze or whether it is truly associated with atopic asthma (6). There is even less information in relation to other air pollutants. Indeed, if anything, there is less atopy and asthma in the more highly polluted areas of Eastern Germany than in the less polluted Western Germany (7). Infections could have a significant impact on airway inflammation and, particularly when viruses are involved, may contribute to the initiation of the problem.

Prospective studies are, however, still required to establish whether this is the case.

Evolution of airway inflammation

The paradigm that exists for understanding the underlying airway inflammation of asthma, which is considered to be present even during remission, is very likely to apply to the onset of disease. Thus, it is inevitable that there will have been a gradual build-up of airway inflammation over some considerable time before the first symptoms appear. We have some evidence to support this assumption on the basis of bronchial biopsies taken from young children with respiratory symptoms not yet characterizable as asthma. Those children who went on to develop established asthma had far higher activated eosinophil numbers in the lamina propria and increased deposition of collagen below the basement membrane than those who did not develop asthma. There was no correlation with the severity of the two abnormalities and the duration of symptoms before the biopsy. These point to the almost inevitable conclusion that the immunopathology of asthma in the airways is present before symptoms (8). If these data can be substantiated, then the conclusion must be that early intervention after the onset of disease may already be too late to modify its natural history.

Unfortunately, there are precious few other studies that have investigated the development of airway inflammation in infancy. However, bronchoalveolar lavage studies, whether collected serendipitously during surgery or by bronchoscopy, have shown that asthma even early on is characterized by a eosinophilic infiltration (9, 10). We have, however, also noted that amongst infant wheezers there is a significant increase in neutrophil numbers. It is remarkable that the neutrophil count in the BAL in both infant wheezers and asthmatics correlated rather well with clinical severity of disease (9). As neutrophils are associated with more severe asthma in adults, one might ask the question whether they might not contribute significantly to the initiation of airway inflammation that leads to asthma. Virus infections, of which respiratory syncytial virus is the most classic, are clearly associated with airway neutrophilia (11).

Other studies have attempted to use circulating markers of airway inflammation to get some idea of the evolution of disease. Thus the Oslo birth cohort study has shown that there is a higher probability of Salbutamol responsiveness in infant wheezers than in matched controls that correlates well with the level of serum eosinophil cationic protein as a marker of eosinophil acti-

vation. One might predict that bronchodilator-responsive individuals with eosinophil activation would be asthmatics. However, we await the follow-up studies to see whether this will show that non-invasive monitoring of inflammation will provide a prediction of subsequent airway disease (12).

Conclusions

We, therefore, propose that following early allergen sensitization, which may well occur *in utero*, postnatal high dose allergen exposure results in trafficking of sensitized T-cells to the airway. There, subsequent allergen exposures with or without virus infection lead to recruitment of both eosinophils and neutrophils. At the same time, the airway remodelling process is also initiated. Further allergen exposures lead to established inflammation, tissue damage and further airway remodelling, all of which will eventually lead to sufficient narrowing of airways to manifest as the first symptoms of asthma. The great challenge for the future is to identify strategies which can interfere with this process before the disease is established and irreversible.

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