What Is New In The Understanding Of Acute Asthma?
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Over the last few years, some of the most exciting developments in understanding asthma have come from studies that have investigated children at the time of an acute asthma attack. The most striking finding is the likelihood that respiratory viral infections are the cause of almost all acute asthma attacks in children.

For many years, asthma has been considered an allergic disease. This has been based on the close association between allergy and asthma. This association is relatively weak in infants and in the pre-school years, but is well established by around five or six years of age and remains so for the rest of childhood. The close relationship between allergy and asthma has been responsible for a strong focus on allergy or atopy in studies attempting to find out why some children develop asthma and others do not. It may also have been responsible for the majority of studies that aim to investigate asthma being carried out in children who are well at the time they are studied. These studies have provided a great deal of important information on the underlying status of the immune system in asthmatics. In particular, the bias in asthmatics towards producing T helper 2 (Th2) responses to allergens has been well established. In addition, the factors associated with asthma have been defined in hundreds of epidemiological studies performed in dozens of countries. In recent years, a great number of epidemiological studies have added an investigation into genetic factors predisposing to asthma to their methodologies. Despite this, a clear understanding of why some individuals are predisposed to asthma and others are not has not been obtained.

The relative failure of these studies to provide a better understanding of the mechanisms predisposing to asthma may be due to subjects being assessed at a time they do not have any clinical evidence of asthma. In a sense, studying asthmatics when they are well is illogical as the most important abnormalities may only be detectable when significant symptoms are present. None-the-less, very few comprehensive studies into childhood asthma have been carried out during an attack of asthma. The potential advantages of studying children at this time are many, but include:

- Children who develop acute exacerbations of asthma may demonstrate evidence of impaired or inappropriate immunological or inflammatory responses at the time of the acute attack that are not apparent when they are well.
- The effects of genetic polymorphisms important in asthma may be more readily detected during an acute asthmatic attack than in stable asthmatics due to enhanced differences in gene expression.
- During acute asthma, genes involved in protection from respiratory viral infection may have different expression levels in circulating effector cells in atopics compared with non-atopics, and this could contribute to acute airway inflammation.
- Previously uncharacterized genes may be selectively upregulated or uniquely expressed in vivo in response to viruses that precipitate acute asthma.
- Using the latest techniques for detection of predisposing agents, particularly viruses, should provide new insight into aetiological factors.

In a study on acute asthma, the Perth Children’s Acute Asthma Study (PCAAS), designed to address the above issues, we have recruited over 250 children aged 2 to 16 years from a hospital emergency department on presentation with acute asthma. Assessments include a comprehensive series of evaluations of known pathways (by studying in detail infective agents, genetic variations, immunological cellular function and protein expression), as well as parallel investigations to seek novel pathways (by using gene expression and protein data from microarray and proteomics to determine functional pathways). Each child is also studied approximately six weeks after they have recovered from the acute episode and again six months later.

Initial studies on the PCAAS cohort have shown that genetic studies can play a key role in elucidating allele specific factors involved in producing the excessive inflammation. For example, subjects with 38A allele in the key anti-inflammatory gene CC16 failed to increase CC16 levels during acute asthma and the lack of CC16 was associated with more severe asthma (1). A similar situation was seen with CD14 (1). Hence, asthmatics can be seen as individuals who are unable to adequately prevent excessive airway inflammation from acute viral...
respiratory infections. We have also reported that PCAAS children with the β2 adrenoeceptor polymorphisms Gly16 and Gln27, responded less effectively to β2-agonists (2). For Gln27Glu (n=148), individuals with Gln27Gln took longest to respond to β2-agonists, followed by heterozygotes who were intermediate and Glu27Glu who responded most rapidly. Identifying children who respond less effectively to β2-agonists may allow the generation of genotype-specific treatment pathways. Clearly, this research approach can clarify mechanisms involved in acute asthma in a novel and powerful way.

Over the last decade, the role of respiratory viral infections in acute asthma exacerbations has been studied in increasing detail. Specific respiratory viral infections have been identified in the majority of subjects with acute asthma and rhinovirus (RV) has been by far the most frequent isolate (3). Induced infection with RV16 has been used extensively to study mechanisms of acute airway inflammation in both animals and humans and these studies have established that both Th1 and Th2 immunity are involved (4). A key dilemma is the relationship between immune function and viral infection. Since respiratory viral infection is the most common cause of exacerbations leading to hospital admission, the essential elements of this dilemma are that: (1) protection from viral infections is largely mediated via Th1 mechanisms; (2) viral infections are the most important precipitator of acute asthma exacerbations and yet; (3) the principal immunological characteristic in asthma is deviation towards Th2 responses.

Therefore, the critical question is whether Th1 immunity in asthmatics is impaired, normal or enhanced. If it is impaired, viral proliferation may be enhanced and precipitate excessive acute inflammation by increased cell damage and destruction. If it is enhanced, the increased airway inflammation in acute asthma might be from “collateral damage” from overactive immunological processes directed primarily at destroying viruses. Recent studies have suggested that impaired Th1 responses are likely to play a major role in contributing to susceptibility to asthma. We have shown that pro-Th2 alleles in genes associated with Th2 responses are also associated with impaired Th1 immunity (5-7). The impairment is in reduced specific IgG levels in response to an allergen (in these studies, vaccine antigens were used), and also reduced cytokine responses in peripheral blood mononuclear cells stimulated with the same antigens (5-7). The significance of these findings is still unclear, but they do point to a potential problem with the asthmatics’ immune system’s ability to combat viruses.

The role of acute respiratory viral infection in acute wheezing in children

Given the strong evidence of problems in Th1 mediated anti-viral defenses from birth, the finding over the last few years that there is evidence of an acute viral respiratory infection in the majority of those presenting with a wheezing illness is not unexpected. Indeed, this appears to be true throughout life. In the first year of life, a community study has shown that viruses were detected in 69% of acute respiratory infections and the most common infective agents were rhinoviruses (48.5%) and respiratory syncytial virus (10.9%) (8). In children presenting to an emergency department with wheezing, rhinovirus is by far the most common virus detected, being found in 60% of children in our study (1). The same is true in adult asthmatics, rhinovirus again being the most common virus isolated during acute episodes of wheezing being present in 60% of adults with acute asthma in a study from the UK (9). In adults with chronic obstructive pulmonary disease, rhinovirus was again the most common infective agent detected, being present in 58.2% of those in whom an infective agent was found (9).

The above results need to be interpreted in light of new evidence related to rhinovirus detection from the Wisconsin group (10, 11). The first is that rhinovirus does not remain in the airway after more than a three or four weeks even in asthmatic children who have delayed clearance of this virus compared with non-asthmatics. This observation is important for two major reasons. First, it means that detection of rhinovirus in the airway in asymptomatic individuals is not evidence of a commensal infection, but rather evidence of an acute current asymptomatic infection (10). Typically, in studies comparing patients with acute asthma versus controls, the control population has a relatively high frequency of rhinovirus detection. For example, in a study of asthmatic children presenting with acute asthma, rhinovirus was found in over 60% of the acute asthma group compared with 18.2% in asthmatic control subjects who were well at the time of testing (12). Second, it suggests a mechanism for chronic asthma, since an infection that does not produced symptoms of a “cold” may still have the potential to produce an airway response that could contribute to chronic airway inflammation (13) and, in addition, rhinovirus has been shown to have a prolonged effect on increasing airway responsiveness.

A further important aspect of the work of the Wisconsin group is that their improved wholly PCR-based detection technique detects many RV infections that previous techniques miss (10, 11). A preliminary analysis
performed by the Madison group on nasal specimens from our PCAAS cohort has detected RV in 86 of 104 (82.7%) of specimens with acute asthma, whereas our previous detection approach found RV in only 60% of PCAAS children. In a cohort of infants with frequent respiratory illnesses, over 50% of RVs detected by the improved technique were of new serotypes (10) and again, a much higher percentage of specimens were positive for RV compared with a conventional technique for RV detection (71.8 vs 23.3%, respectively) (11). The implications of these data are most important, as they strongly suggest that the percentage of children with acute asthma associated with an RV infection is much higher than previously thought and that previous studies will have underestimated the extent of RV infection.

REFERENCES