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Recognizing early asthma

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Asthma symptoms often develop during the first years of life. Longitudinal studies show that at least 40% of children with wheezing lower respiratory illnesses (LRIs) during the first 3 years of life still have wheezing episodes at 6 years of age. Thus, it is important to identify children at risk of developing asthma, and to distinguish these from those in whom early wheezing is likely to be transient. This is complicated, however, by the variable nature of asthma and the lack of specific and sensitive markers. Genetic markers and epidemiologic risk factors for asthma have been identified, but cannot be used to predict the development of asthma in an individual patient. Similarly, infants who subsequently develop asthma in childhood have higher serum immunoglobulin E (IgE) and peripheral eosinophil counts than those who do not develop asthma, but, again, these factors are not sufficiently sensitive and specific to allow identification of children at risk of developing asthma. An algorithm is presented that outlines possible criteria to determine the risk of developing asthma in infants.

Introduction

Many infants who develop wheezing lower respiratory illnesses (LRIs) associated with viral infections go on to develop recurrent episodes of airway obstruction and asthma later during childhood. Recent longitudinal data suggest that, although the majority of wheezing infants have a transitory condition probably related to lower levels of airway function (1), at least 40% of all children with wheezing LRIs during the first 3 years of life still have reported episodes of wheezing at the age of 6 (2). When the same data are analyzed prospectively, infants who have wheezing LRIs are 4–5 times more likely to have had more than three episodes of wheeze during the previous year until

the age of 13 (3). The risk of continued wheezing is even larger among infants hospitalized with proven bronchiolitis due to respiratory syncytial virus (RSV) (4).

Two main explanations have been proposed for these results. The first suggests that viral LRIs may themselves be a causative factor in the development of persistent wheezing and asthma. This hypothesis has had many backers during the last 25 years, and is particularly attractive from the point of view of public health. If RSV infection is indeed associated with some form of lung damage that permanently increases the risk of subsequent airway obstruction, prevention of RSV *infection* could not only decrease morbidity and the mortality rate in early life, but also could become a major tool in the primary prevention of asthma. When intravenous anti-RSV immunoglobulins were recently tested in "at-risk" children, prevention of asthma was explicitly proposed as a potential benefit of this treatment (5). Unfortunately, several lines of evidence suggest that RSV infection by itself cannot be considered a risk factor for asthma. Over 95% of children are infected with RSV before the age of 2 (6), but only 30% have lower respiratory involvement. This distinction between RSV *infection* and RSV-related *illness* is crucial because it points to individual susceptibility as decisive in determining not only who is prone to wheeze during RSV-LRIs, but also who will go on to develop persistent wheezing after RSV-LRIs.

This second explanation for the association of wheezing LRIs with asthma, i.e., that genetic and developmental conditions interact with RSV to determine wheezing during RSV, and that some (but not all) of these conditions may be associated with subsequent asthma, is the most widely accepted by the scientific community today. This certainly does not exclude the possibility that viral infections may contribute to the pathogenesis of asthma. It does, however, center our attention on the factors that determine susceptibility to damage associated with inflammatory reaction not only to virus, but also to other environmental stimuli.

Identification of children at risk of asthma

There are many potential benefits associated with a reliable method to identify infants at risk of asthma. The availability of potent anti-inflammatory treatments for asthma has raised the possibility that these drugs may also be used in the treatment of recurrent infant wheezing. The results of clinical trials with inhaled corticosteroids will be discussed elsewhere in this volume. However, what is relevant here is that retrospective studies suggest that treatment of asthma with controller medication that is started shortly after the initiation of asthma symptoms may be more effective in preventing long-term changes in lung function than treatment initiated years after disease onset (7). The realization that, in most cases of asthma, symptoms of airway obstruction are first manifested in infancy (8) has led some to conclude that asthma treatment should be started in infancy. Unfortunately, no prospective studies are available that have clearly shown that such a strategy is feasible and efficacious. One problem is that in certain localities at least 30% of all children aged 3 years or less have had one or more episodes of lower airway obstruction. In addition, as explained earlier, the majority of young children with wheezing LRIs have transient symptoms and a rather benign prognosis. There are serious ethical and financial limitations to a strategy that entails treating a large proportion of children who will obtain no benefit with medicines not certainly devoid of side-effects (albeit usually mild and self-limited), in order to prevent a noncommunicable disease such as asthma in a minority.

Unfortunately, the task of identifying subjects at risk of asthma in early life is hampered by the complex nature of asthma itself. Most experts now believe that the label of asthma is used to identify different conditions that are associated with different causes and pathogenetic mechanisms, but have in common a "final common pathway" characterized by recurrent airway obstruction. The fact that asthma is difficult to define is simply the consequence of its composite nature and of the absence of specific and sensitive markers of disease.

Genetic markers

The recent advances in studies of the genetics of asthma have raised new hope that genetic markers could be found in the future that will allow identification of subjects at risk. These hopes are based on the premise that the known family aggregation of asthma is due to a rather small number of genes in which infrequent alleles are responsible for the expression of the disease in the population. Unfortunately, this is not the case: both statistical assessments of the hereditary mechanisms of asthma in large samples of nuclear families (9) and initial results of linkage studies using molecular markers spread all along the genome (10) reveal a much more complex picture. Asthma seems indeed to have a strong genetic component, but this component is the result of the interactive expression of variants in many different genes. Moreover, variants (or "*alleles*") within each asthma-related gene seem to be frequent with low pene-

trance, rather than rare and highly penetrant. In other words, a large proportion of individuals within a population may have (in different combinations) one or more "asthma alleles". Who among these individuals may develop asthma will thus depend on what are called "epistatic" or "epigenetic" effects. These effects consist of complex interactions between different sets of genetic variants that will be expressed as a phenotype only if certain combinations of environmental influences are present at specific times during the process that leads to the development of the phenotype itself. It is certainly plausible to surmise that there will indeed be some rare alleles in specific genes that will be associated with a very high risk of developing asthma. But, by definition, the attributable risk proportion (e.g., the proportion of all cases of asthma attributable to that specific allele) will be very low. In other words, as has been elegantly argued by Singh et al. (11) for all complex diseases, most cases of asthma will be the result of the combined influence of many genes, each of which is only "responsible" for a small proportion of the risk of the development of the disease. We are thus back to square one: identification of asthma-related genetic variants will allow us to define risk for the disease in carriers of different combinations of these variants, but not to identify specifically a large number of individuals who are at high risk of developing the disease.

Epidemiologic tools to define risk

The above discussion stresses an aspect of the genetics of complex diseases that is not usually understood: in the study of conditions such as asthma, genetic markers have all the limitations of any other epidemiologic tool to define risk. The fact that there are sophisticated tests to identify variants in DNA structure does not confer on these markers some sort of immunity from the basic problem we face in identifying asthma risk: that asthma is "epigenetic", as described above. In these circumstances, knowledge of the natural history of asthma becomes decisive. There is no shortcut away from the difficult job of identifying those risk factors (familial, genetic, environmental, developmental) that entail increased likelihood of developing the disease. There will also be no simple formula to define such risk; as explained earlier, there will be a few conditions that by themselves, almost independently of any other, will be enough to entail a very high risk. Chronic lung disease of prematurity (CLDP), for example, is associated with a very high prevalence of asthma-like symptoms many years later (12). It may be debated whether CLDP-related "asthma" is the same type of asthma as that of subjects who have recurrent wheezing at the ages of 6–14 years and who were not premature and did not require mechanical ventilation. In fact, it is quite likely that these two forms of asthma are indeed different conditions: von Mutius et al. (13) found that, when studied during school years, former ventilated premature babies were more likely to be female and were not more likely to be allergic to certain local aeroallergens, both risk factors that are strongly correlated with asthma in schoolchildren who were born at term. These caveats, however, are not very relevant to our discussion. We have already accepted that there are different mechanisms through which wheezy infants become wheezy children, but, at the present state of our knowledge, we have no means to prevent or treat these different forms of asthma with different pharmacologic tools. In other words, if the objective is simply to define risk, then CLDP is a strong risk factor for subsequent "asthma". Whether CLDP will respond differently to any preventive measures that we may want to define as potentially useful for the more common forms of childhood asthma is at present unknown.

Acute IgE response to LRIs and subsequent asthma

The discussion regarding CLDP is relatively straightforward when compared to that of other risk factors for asthma such as wheezing LRIs. As discussed earlier, wheezing LRIs are an independent risk factor for the subsequent development of asthma, but most children who have wheezing LRIs will not develop the disease. At the present state of our knowledge, it is not possible to say what factors determine this association. Some authors now believe that the immune reaction to the usual viruses that induce wheezing LRIs in this age group (i.e., RSV and parainfluenza) may be different in children who will go on to develop asthma as compared to those who will not. This hypothesis is certainly not new and was first proposed more than 40 years ago by Wittig & Glaser (14). These authors found that, out of 100 children who were hospitalized for "bronchiolitis" in early life, 32 had developed asthma (as assessed through a check of medical records) by the school years. Although the study had no controls, the high prevalence of asthma in these children suggested to the authors that either bronchiolitis "might prime the tissue structures for the development of later asthmatic disease" or local edema in bronchiolitis "might be a form 'fruste'" of the pathology found in older children with asthma. They concluded that the latter hypothesis was more likely because of the high frequency of allergic diseases (44%) among first-degree relatives of patients hospitalized for bronchiolitis. Our knowledge of the association between

bronchiolitis and asthma has certainly progressed during the last decades, but the basic challenge described by Wittig & Glaser has not changed: we need to develop tools to identify those children with acute bronchiolitis who will go on to develop asthma.

The description by Welliver et al. (15) of virus-specific IgE as a marker of increased risk of subsequent wheezing raised hopes that immune parameters measured at the time of the first LRIs could be of great help. Unfortunately, the results by Welliver et al. have not been easy to reproduce, probably because the techniques to identify virus-specific IgE are not easily amenable to standardization. More recently, we observed that children with wheezing LRIs during the first 3 years of life who were still having recurrent wheezing episodes at the age of 6 had higher total serum IgE levels at a mean age of 9 months than children whose wheezing LRIs were not followed by persistent wheezing (2). Moreover, we observed that the acute responses to LRI were also different in these two groups: whereas persistent wheezers showed increased levels of total IgE during the acute LRI, transient wheezers did not. These observations suggest that the IgE-mediated mechanisms of disease that are presumed to be involved in asthma in older children may already be present at the time of the first episode of asthma-like symptoms during infancy. Unfortunately, these observations are valid for group comparisons, but are not particularly helpful in identifying individual children at risk.

Acute LRIs, eosinophils, and subsequent asthma

Eosinophils are known to be important mediators of disease in older children and adults with asthma (16). Thus, it is not surprising that the possible role of eosinophils in acute LRI in infancy as a marker of asthma risk has also been a matter of recent interest. The availability of specific circulating markers of eosinophil activation such as eosinophil cationic protein (ECP) has raised the hope that these markers could be used in assessing such risk. Indeed, serum levels of ECP at the time of an acute LRI in infancy were found to be correlated with the subsequent development of recurrent wheezing (17). We studied eosinophil counts at the time of the first acute LRI in transient wheezers and persistent wheezers. We found that, both in transient wheezers and in children with nonwheezing LRIs, eosinophil counts assessed at the time of an acute LRI were markedly decreased when compared with those obtained in the absence of an LRI (18). A similar observation had been made earlier by Garofalo et al. (19). However, subjects who did go on to develop persistent wheezing after a first episode of LRI did not show an eosinopenic response at the time of the LRI. Moreover, eosinophil counts at a mean age of 9 months were significantly higher in children who went on to develop asthma than in those who did not. Unfortunately, once again, the specificity and sensitivity of these tests were not high enough to allow us to use them as isolated tests for asthma risk.

An algorithm to define asthma risk

The main conclusion from the above discussion ought to be that, although we have been able to describe factors that at the population level should be considered useful tools to assess asthma risk during infancy, none of these tools has sufficient predictive power to be used as a single marker to identify the "asthmatic" infant. I have also argued that no such "miracle" should be expected from the future description of genetic markers of asthma risk at the molecular level. The clinician is thus left with the following dilemma: which infants should I treat as if they had asthma with the expectation that, given the potential prognosis, they will respond to my treatment? As importantly, the investigator who wants to determine whether early treatment with antiasthma therapy may change the natural course of the disease also needs tools to identify those infants who may truly respond to such therapy, and wants to avoid having to treat many infants whose symptoms will remit spontaneously.

I propose the algorithm shown in Table 1 to define asthma risk in early life. Much like the Jones criteria for rheumatic fever, this algorithm includes both major and minor criteria. These criteria are defined by their relative predictive power. I propose that both children who meet one of the first two major criteria and any other major criteria (including the remaining one among the first two) and those who meet one of the first two major criteria and two minor criteria should

Table 1. Algorithm to define asthma risk. Children who meet one of first two major criteria and any other major criteria (including remaining one among first two) and those who meet one of first two major criteria and two minor criteria should be considered at very high risk of persistent wheezing

Major criteria	Minor criteria
1. Hospitalization for bronchiolitis/ severe wheezing	1. Rhinorrhea apart from colds
2. At least three wheezing LRIs during previous 6 months	2. Wheezing apart from colds
3. Parental history of asthma	3. Eosinophilia (≥5%)
4. Atopic dermatitis	4. Male sex

be considered at very high risk of persistent wheezing. Over two-thirds of children who meet these combinations of risk factors during the first 3 years of life still have reports of persistent wheezing at the age of 3. I realize that there may certainly be other factors to be considered and different opinions regarding the relative importance of the criteria described above. It is also important to stress that other specific situations (e.g., post-CLDP wheezing, as described earlier) may need specific and separate consideration. My main goal has been to propose general guidelines for asthma risk to be used both in general practice and in prospective studies of early treatment of asthma. Naturally, decisions about length of treatment and type of treatment to be used go beyond the scope of this paper.

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