EDITORIAL

Childhood Asthma: Do the Answers Coincide With the Questions?

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Ramos-Barón[1] concluded an editorial on basic asthma research in this journal by affirming that, in science, asking the right questions is often harder and more important than finding the answers. It is hard to disagree with this statement but, if we reflect on childhood asthma in relation to the advances over the last couple of decades in terms of pathogenesis, pathophysiology, and diagnosis, and their therapeutic implications, we are in a somewhat similar situation to that of whoever wrote "when we found out the answers, they withdrew the questions." This suggests that new questions should be sought to find suitable answers,[2,3] in this case for better management of childhood asthma, the goal of which is complete control of the disease.[4]

The traditional approach was to equate (identify) asthma with atopy and eosinophilic inflammation, and to exclude from this definition other recurrent respiratory conditions that did not present such findings. However, the signs and symptoms seen in asthmatic children are common to other processes, a substantial component of which also respond to conventional asthma drugs, namely, inhaled corticosteroids. This has prompted us to extend the concept of asthma to include numerous obstructive diseases of the small airways, particularly in infants (infant asthma), although the subsequent disease course may be heterogenous.

Early transient wheezing, persistent nonatopic wheezing, and atopic wheezing in infants represent 3 different childhood asthma phenotypes,[5] both in epidemiological terms[6] and in terms of function[7] and disease course.[8] In this heterogenous group of infants with recurrent wheezing or risk of asthma, response to conventional treatment with inhaled corticosteroids is not clear-cut. In general terms, these infants respond satisfactorily to the intervention itself, but the natural course of the disease is not modified, as confirmed in 3 recent clinical trials (PAC,[9] PEAK,[10] and IFWIN[11] studies) with different inclusion criteria and therapeutic interventions.

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Manuscript received October 10, 2007. Accepted for publication October 11, 2007.

Asthma prevalence varies among countries[12] and even, as is the case in Spain, among different regions of the same country.[13] We might therefore be led to interpret childhood asthma as less likely to be a single pathological entity than a syndrome,[14] that is, a manifestation common to different diseases with a different genetic basis, different triggers, and no single inflammatory pattern.[15] Such a syndrome might require tailored management from disease prevention through to the active phase.

Unfortunately, firm conclusions about the pathogenesis of asthma can still not be drawn. Nevertheless, bronchial inflammation remains a central aspect of asthma and is directly or indirectly responsible for disease manifestations (symptoms, bronchoconstriction, and bronchial hyperresponsiveness), crises, and even remodeling of the bronchial wall.[16] There is no single pattern of inflammatory cells and response mediators. In fact, different inflammatory phenotypes—very similar to those reported in adults—have been described in childhood asthma. For example, inflammation may be predominantly eosinophilic (eosinophilic phenotype) or the inflammatory component may be limited (pauci-inflammatory phenotype) or even, on occasions, absent (noninflammatory phenotype).[17] However, these inflammatory patterns do show substantial overlap and the inflammatory phenomena may be so complex that it is often difficult to determine which inflammatory phenotype is present in children—a difficulty that is further accentuated in younger subjects.

Some studies published in recent years highlight this complexity. We know that most infants with recurrent wheezing will, in most cases, be free of respiratory symptoms by the time they are 4 years old, but we also know that a large number will continue with respiratory symptoms and some will subsequently develop asthma. Sanglani et al,[18] using endobronchial biopsy and bronchoalveolar lavage (BAL), reported a mainly neutrophilic inflammatory response without remodeling in infants with recurrent wheezing and reversible limitation of pulmonary airflow. In contrast, when the children are a little older—at the age of 3 years—severe wheezing is associated with predominantly eosinophilic inflammation and structural changes to the airway or, in other words, remodeling.[19]

The presence of different inflammatory patterns has doubtlessly introduced uncertainty in the pharmacological

management of these children. It seems there is now a tendency to link eosinophilic inflammation with inhaled corticosteroids and noneosinophilic inflammation with leukotriene-receptor antagonists and more recently with macrolides. The problem is that diagnosis is based on indirect data (presence or absence of atopy in the patient or in first-degree relatives, peripheral blood eosinophilia, elevated total immunoglobulin E, etc). The idea that traditional or eosinophilic asthma responds well to inhaled corticosteroids whereas noneosinophilic asthma does not is derived from findings in adult patients. The situation might be different in children. In fact, 2 recent studies have reached different conclusions. Lex et al[20] studied the cytology of induced sputum before and after oral or parenteral corticosteroids and observed that the initial cytology was not associated with the expected response, and that even patients with the pauci-inflammatory phenotype responded. Similar conclusions were reached by Panicker et al[21] in children with difficult asthma. In that study, intramuscular triamcinolone was effective in children with noneosinophilic asthma.

These findings beg new questions. It might be that the inflammatory phenotype of asthma is expressed differently in different compartments. The rationale for this hypothesis is as follows. The gold standard for studying the inflammatory phenotype of asthma has been endobronchial biopsy. Other methods include BAL and induced sputum, with increasingly lower degrees of invasiveness but of limited use in pediatric pulmonology settings; the identification of eosinophilic inflammatory biomarkers, such as exhaled nitric oxide (eNO), has opened up the study of inflammation to a wider range of investigators. When the degree of agreement between the first 2 methods (BAL and induced sputum) is studied, we see that the correlation is satisfactory. Correlation is also satisfactory when compared with eNO, which acts as a good surrogate marker of inflammation. The association is, however, often weak when studying the degree of agreement between these techniques (BAL, induced sputum, and eNO) and bronchial biopsy.[22] That is, endobronchial eosinophilia does not correlate with other techniques. Why might this be so?

Bush[23] suggested that eosinophils might perhaps need other factors to express the disease. He based this suggestion on studies in which anti-interleukin-5 monoclonal antibodies suppressed eosinophils in induced sputum but did not influence asthma control or the persistence of eosinophilic inflammation without symptoms. We should also point out that the pathological and structural findings in adults and children with asthma were obtained using endobronchial biopsies, BAL, or both, the significance of which is worth reflecting on. Endobronchial samples are taken from the proximal airway, whereas the findings from BAL cannot be said to be representative of a given part of the airway. Therefore, any interpretation of the inflammatory phenomenon is obviously limited by the study technique used, and it does not seem very consistent to extrapolate the inflammatory phenomena of the proximal airway to the peripheral airway and lung parenchyma. Indeed, more than 10 years ago, Kraft et al[24] reported that alveolar inflammation—involving eosinophils and macrophages—and not proximal inflammation is responsible for functional changes in adults.

We can now study bronchial and alveolar eNO production in children using mathematical models of pulmonary nitric oxide dynamics in conjunction with a conventional chemoluminescence analyzer to allow the fraction of eNO to be quantified by taking single-breath on-line measurements at different expiratory flow rates (50, 100, 200, and 260 mL/s). The evaluation of proximal and distal inflammation in the airways and the response to pharmacological interventions through noninvasive monitoring of an inflammatory biomarker opens up a line of investigation that might help understand inflammatory processes in childhood asthma. The answers will surely generate new questions.

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