EDITORIAL

Infection: friend or foe to the development of asthma?

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Of the most common diseases among humans, respiratory infections are important causes of disease and disability in high-income countries [1] and some of the most common causes of death in low-income countries, especially among children [2].

Since the late forties and the early fifties, severe bacterial infections have decreased in frequency and severity in industrialized countries. At the same time, allergy and asthma have increased, starting at the same time but especially from the late seventies and eighties. In Norway, an epidemiological study from 85 health districts showed a lifetime prevalence of asthma of 0.4% among schoolchildren [3], whereas in the mid-nineties it was 10–12% [4]. In 1966–1971, the risk of acquiring asthma increased by 2.33% compared to 1946–1950 in 15 industrialized countries in Europe [5]. Strachan [6] formulated the hygiene hypothesis based upon the finding that children with siblings had fewer allergies than children without, and based this upon the finding that children with siblings had more respiratory infections early in life. Later findings, both epidemiological as well as basic scientific research [6], have supported this hypothesis. However, there are more complex relationships between infections and asthma (and allergy).

In this issue of European Respiratory Journal (ERJ), a new series of articles highlighting this topic from different points of view and based upon different types of scientific studies, starts with an article by Von Mutius [7], taking up the epidemiological part of this problem. Von Mutius [7] gives an impressive review of the existing epidemiological evidence.

Respiratory syncytial virus (RSV) is the most frequent cause of acute bronchiolitis and lower respiratory tract disease during infancy [8, 9]. It is still not known why some infants acquire severe lower respiratory tract infection with symptoms of bronchial obstruction, while most young children only have symptoms of upper respiratory tract infection with RSV. It has been speculated that acute bronchiolitis is the cause of later obstructive airways disease during infancy, or that acute bronchiolitis occurs in infants with a pre-existing predisposition. It is accepted that certain pre-existing illnesses predispose to severe manifestations, such as congenital heart disease [10], immune deficiency [11] or prematurity [12]. Interestingly, a recent study reported that there was an association between the severity of RSV infection during infancy and the genetic locus of the IL8-251A allele, which tended to be associated with increased interleukin (IL)-8 production by lipopolysaccharide [13]. In order to respond with cytokine production, the response to RSV protein F in mice was dependent upon the presence of CD14 and Toll-like receptors type 4 [14]. Thus, there seems to be, at least in part, a genetic basis for the severity of acute bronchiolitis.

Acute bronchiolitis and RSV infections have been known for many years to be closely related to recurrent obstructive episodes after acute bronchiolitis [15–21]. The risk of recurrent obstructive episodes is most pronounced among hospitalized infants [22, 23], but it is also present in infants not admitted to hospital. Bont et al. [24] recently reported that RSV infections provoked increased IL-10 production, especially in children who later suffered from recurrent wheezing. However, it has been found that with increasing age, the impact of acute bronchiolitis upon recurrent obstructive episodes gradually diminishes [25, 26], although bronchial responsiveness may remain [27, 28]. A meta-analysis based upon follow-up studies taking up this problem was published, although strict inclusion criteria led to the inclusion of only six studies in the analysis [29].

Another aspect of disease occurring after acute RSV bronchiolitis has been highlighted by Sigurs et al. [30], who performed a carefully designed case-control follow-up study of patients admitted to hospital with RSV bronchiolitis compared to healthy children without allergic or obstructive airways disease. They followed the children until they were 3 [30] and 7 yrs of age [31]. At both 3 and 7 yrs of age they found acute bronchiolitis to be the most important factor predisposing for asthma, but they also found increased occurrence of allergic sensitization to both food and inhalant allergens [30, 31]. This latter finding has not been confirmed by many other studies. The features of recurrent obstructive episodes and asthma, as well as the possible effect of RSV infections upon allergic sensitization in infants and young children, will be addressed by Wennergren and Kristjansson [32] in a comprehensive article in the present series.

It is a continuing debate what the mechanisms are

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underlying the relationship of acute RSV bronchiolitis with later occurring obstructive airways disease and the possible relationship with later allergic sensitization. Several study groups have performed experimental studies in mice and other animals to try to solve this problem. Some studies indicate that the timing of RSV infection, in relationship to possible allergen exposition, may determine whether the “patient” will react in a T-helper (Th2)-type way, with production of IL-4 and IL-5, or in a Th1-type way, with predominant interferon-γ production [33]. During those circumstances and in these animal models, treatment with antibodies to IL-5 inhibits airway inflammation and hyperresponsiveness [32]. However, it is as yet unknown whether this can also be supported in humans. Other groups have focused on the role of RSV lower respiratory tract infection in potentiating neurogenic-mediated inflammation with increased microvascular permeability caused by stimulation of sensory nerves during RSV infection, and an upregulation of the high affinity receptor for IL-5 by sensory nerves. IL-5 induces the release of cytokines supporting in humans. Other groups have focused on the role of RSV lower respiratory tract infection in potentiating neurogenic-mediated inflammation with increased microvascular permeability caused by stimulation of sensory nerves during RSV infection, and an upregulation of the high affinity receptor for substance P [34]. The animal experiments may provide important information about the mechanisms involved in human children with RSV infection. This is highlighted in a very interesting article in the present series by Schwarze and Gelband [35].

Do infections represent a friend or foe in the development of asthma and allergy in the young child? During recent years, important immunological knowledge on the development of allergy has been acquired. Holt and coworkers [36, 37] have focused upon the development of the immune system in the very young and the maturing child, from a Th2-dominating immune system at birth to increasing Th1 function through stimulation by infectious agents. Renz and Herz [38], in their excellent review in the present series, provide insight into both immunological mechanisms and the recent developments in the research within this particular field, thus making it easier for the reader to understand.

Another aspect of the relationship of respiratory virus infections with obstructive airways disease is the role of respiratory virus infections, and especially rhinovirus infections, in causing acute exacerbations of asthma. This was described many years ago [39, 40] and found to be the most important cause of acute asthma in children [41–43]. It is of particular interest that the intracellular adhesion molecule-1 has been found to be the major human receptor for rhinovirus [44].

Reports in recent years have focused on the relationship of persisting intracellular pathogens with obstructive airways disease. Chlamydia may play a role in the initiation of obstructive airways disease and asthma [45–47], as well as in the aggravation and exacerbation of asthma and obstructive airways disease [48–51]. Von Hertzen [52] highlights both epidemiological, clinical and experimental data in an impressive review of the role of Chlamydia in relation to this topic [52].

Accordingly, viral and bacterial infections have important implications for asthma and other forms of obstructive airways disease, as well as for the development of allergy. The present series of articles starting in this issue of ERJ will highlight recent scientific development within this area.

In the present series, the authors have been asked to evaluate the evidence of the various studies included in their review articles. This is, of course, much more difficult to perform in epidemiological follow-up studies and experimental studies than in therapeutic trials, but it is felt to be important that the experts in the field should also assess the evidence in relation to the different hypotheses in this very complicated and intriguing field. It is hoped that this will be useful to the reader and possibly provide input for later reviews that take into account the evidence in topics other than therapeutic research.

References
5. Sunyer J, Anto JM, Tobias A, Burney P. Generational epidemiological, clinical and experimental data in an intriguing field. It is hoped that this will be useful to the reader and possibly provide input for later reviews that take into account the evidence in topics other than therapeutic research.

References


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