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EDITORIAL

Wheezing and pneumonia: A complex relationship

Acute episodes of wheeze are a common problem in children, particularly in preschool children (5 years of age or younger). Infections caused by respiratory viruses are the most common early triggers in this population, especially in those with intermittent wheezing.[1,2] Between 2 and 3 years of age, a significant proportion of these children will outgrow symptoms. Nonetheless, some of the children with persisting symptoms (known as "multitrigger") will continue wheezing after exposure to different triggers including various allergens, exposure to smoke, and infections.[2] School-age children with a history of wheezing or asthma, acute exacerbations can be precipitated by an underlying viral illness or pneumonia.

Pneumonia is a highly prevalent disease in childhood worldwide. It is a major cause of death in children younger than 5 years, especially in developing countries.[3,4] In developed countries, pneumonia is also a serious health care problem, as it represents a major cause of hospitalisation and morbidity.[5] The definition of pneumonia varies significantly. The World Health Organization has defined pneumonia solely on the basis of clinical findings and examination (specifically respiratory rate).[6] Others require only the presence of infiltrates on a chest radiograph.[7] Definitions are a particular problem in the young age group in which pneumonia and bronchiolitis are both common conditions. Therefore, many children who present to the emergency department with wheezing and tachypnoea are evaluated for the presence of pneumonia with a chest radiograph, particularly in children where the clinical history and examination are not different from those children without pneumonia.[8,9]

The interaction between respiratory infections and asthma is very complex. It is well known that in established asthma, respiratory infections (especially viral infections) are the principle cause of acute asthma exacerbations and visits to emergency departments.[10] Several studies have shown that between 50–80% of children with increased respiratory symptoms (asthma exacerbation) had a respiratory virus detected by PCR.[11,12] Clinical studies have demonstrated that rhinoviruses are the most common viruses detected after an asthma exacerbation.[13] Furthermore, there is evidence to suggest a direct relationship between viral infections (e.g. RSV) and increased risk of subsequent wheezing, development of asthma in later life and also deficits in lung function.[14] Nevertheless, whether this relationship is causal or due to a common risk (e.g. genetics, nutrition, or environmental pollution) is still unknown.

Epidemiological studies have shown that infants and children who developed pneumonia have an increased risk of developing chronic respiratory symptoms later in life (e.g. wheezing), but will also have a significant deficit in lung function.[15,16] Castro-Rodriguez et al.[15] studied the prevalence of respiratory symptoms, asthma diagnosis, and lung function, in a group of children with and without a radiologic diagnosis of pneumonia during the first 3 years of life. A total of 1246 children were included in this birth cohort, however only 888 were followed for lower respiratory tract infections. Sixty-six (7.4%) children had radiologically confirmed pneumonia. Also, this group were more likely to have physician-diagnosed asthma and wheezing at ages 6 and 11 years than those with no lower respiratory infections. In addition, children with a history of pneumonia had a significant reduction in FEV1 and FEF 25–75 at age 11. This same group of children who developed pneumonia had lower levels of maximal flows at FRC at mean age of 2 months. These findings shows how complex this relationship is and how it is not completely understood. Some authors have suggested that during early life, exposure to different environmental stimuli such as acute viral infections can lead to persistent alterations in immune responses and airway function in susceptible individuals.[14] Acute lung injury secondary to viral infections leads to remodelling at any age with further deficits in lung function. Damage to the epithelium, increased mucus production, inflammatory and antiviral responses such as the release of nitric oxide (NO), cytokines and chemokines are some of the effects of the viral infection and immune response to this infection. In addition, viral infections will generate factors that regulate lung development and airway remodelling, including vascular endothelial growth factor, NO, transforming growth factor (TGF-α and β), and fibroblast growth factor.[17]

Several cross-sectional studies have shown that wheezing along with malnutrition; overcrowding; immunisation; poor

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socioeconomic status; environmental pollution; and age are among the risk factors that can lead to a higher incidence of pneumonia in early childhood.[18–20] Castro-Rodriguez and colleagues studied the risk factors for radiologically confirmed pneumonia during the first year of life in a cohort of infants from a low-income community in Latin America. They found a significant association between wheezing in the first three months of life and pneumonia in the first six months, with OR 7.69 (95% CI 1.32–44.92 p=0.024). To the best of our knowledge, no epidemiological data is available specifically investigating the relationship between asthma/wheezing and pneumonia in children older than six years of age. In this edition of Allergologia et Immunopathologia, Moustaki et al. describe that there is a relationship between pneumonia and asthma in school-aged children, as there was an increase in the prevalence of wheeze prior, during and after an episode of pneumonia in this age group. In this study, the authors recruited all children over 6 years of age with radiologically confirmed pneumonia admitted to hospital during a two-year period. A control group of patients was selected from children hospitalised during the same period of time. A total of 103 patients were recruited in the pneumonia group and 55 controls. Wheezing and the use of bronchodilators were more prevalent in the pneumonia group than in the control group, however this is to be expected as the control group consisted of patients with no respiratory conditions (urinary tract infections and gastroenteritis). Twelve children (11.6%) in the pneumonia group had wheezing episodes during the two years following hospitalisation compared to one child (1.8%) in the control group (p=0.034). Past medical history of asthma or wheezing was not a risk factor for pneumonia. Although interesting, the results of this study should be interpreted carefully. The main limitations of the study, as mentioned by the authors, are the retrospective nature of the study, and also the lack of microbiologic data (e.g., identification of an infectious pathogen).

Streptococcus pneumoniae remains the leading bacterial aetiology of community-acquired pneumonia (CAP) in childhood, especially in young children.[21,22] However, bacterial infections are frequently preceded by viral respiratory infections (e.g. RSV or RV infection), which are associated with impairment in cough reflex and mucociliary clearance secondary to viral-induced damage to epithelium. Several authors have reported a high prevalence of atypical bacterial infections and mixed bacterial/viral infections in children with lower respiratory tract infections.[21] Recent epidemiologic and clinical data suggest that atypical bacteria such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* maybe implicated in the initiation and exacerbation of asthma.[13,23] Viral infections such as RSV and RV infect the lower airways triggering the initiation of both innate and adaptive immune responses such as activating inflammatory pathways and increasing proinflammatory cytokine and chemokine production, resulting in tissue damage and inflammation.[13,24] In addition, damage to epithelial cell ciliary function and increased mucus production is associated with viral induced airway obstruction. Moreover, there is evidence to suggest that bacterial infections reduce mucociliary clearance and increase mucus production in the upper airways, hence, increasing the risk of chronic inflammation of the lower airways. Choi et al.[25] compared cytokine secretion in a group of children with mycoplasma pneumonia (with and without wheeze) to a group with non-mycoplasma pneumonia. They found significantly higher serum levels of IL-5 and vascular endothelial growth factor (VEGF) in the group of children with mycoplasma pneumonia and wheeze than those without wheeze, suggesting a pathophysiological mechanism by which the *M. pneumoniae* contribute to the development of wheeze. This study is in agreement with other studies showing an increased immune response to *M. pneumoniae* possibly playing a role in the development of allergic airway inflammation. Esposito et al.[26] showed that children with acute *M. pneumoniae* and/or *C. pneumoniae* showed a significantly higher recurrence of wheeze during the follow up period compared to the control group suggesting a role in the development of persistent wheeze/asthma. The other bacterium to consider is *Chlamydia pneumoniae*, as it has an innate ability to persist inside host cells causing chronic infection. It has been shown that *C. pneumoniae* induces tissue damage through the release of a stress protein (HSP60), thus increasing proinflammatory cytokine production (TNF-α, IL-1, IL-6 and IFN-γ) and subsequent cell and tissue damage.

Although a clear association exists between viral and atypical bacterial infections with asthma, the precise mechanisms are not fully understood. What is still uncertain is the relationship between asthma and typical bacterial infections such as *Streptococcus pneumoniae*. It has been reported that individuals with asthma will have an increased risk of invasive pneumococcal disease. Juhn et al.[27] reported an association (although not significant) between prior history of asthma and the increase risk of pneumococcal disease with an adjusted OR for asthma status of 2.4 (95% CI, 0.9–6.6). This same group of investigators studied the association between asthma and the risk of developing *Streptococcus pyogenes* infection of the upper respiratory track in children. They found that patients with asthma have an increased incidence of *S. pyogenes* upper respiratory infections compared to non-asthmatic patients (risk ratio 1.40 95% CI 1.12–1.74 p=0.0092).[28] The aforementioned studies show an epidemiological association between certain infections and asthma, however a causal relationship has not been demonstrated in large longitudinal studies.

In conclusion, the demonstrated relationships between infection and asthma are difficult to understand due to their complexity and also because of the limitation in clinical studies in children. It appears that there is a strong association between viral infections and atypical infections in the development of asthma or chronic respiratory symptoms. It is likely that infections which occur early in life in association with other factors (e.g. genetics, environmental pollution) may impair lung development with risk of disease later in life. Longitudinal studies are needed to determine if there is a link between genetic, environmental and infective factors, and the development, persistence and prevention of asthma.

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