The wheezy legacy of infant bronchiolitis

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The association between bronchiolitis, recurrent wheeze (RW) and asthma is well known. Numerous studies have elucidated that respiratory syncytial virus (RSV) bronchiolitis is associated with RW, whereas disagreement remains regarding its association with asthma. RSV infection and RW may both be consequences of small airways dimensions,[1] dysregulation of the innate immune response or they may be the results of post-RSV infection intense inflammation and airways remodelling.[2]

The Tucson group demonstrated the association between RSV infection and the development of different RW's phenotypes, but not with asthma.[1] On the contrary, Sigur *et al* demonstrated that RSV bronchiolitis was associated with the development atopy and asthma.[3] Regarding the genetic characteristics of infants who developed asthma after bronchiolitis, two Danish studies performed on twins with RSV bronchiolitis, demonstrated that RSV is not responsible for the development of asthma, but that a strong genetic predisposition is crucial for the development of both bronchiolitis and asthma.[4 5]

The article in this issue of *Thorax* by Marlow *et al*,[6] presented an English birth cohort study on the association between bronchiolitis and wheezing at the age of 8 years. They used hospital discharge codes to create two cohorts: one with bronchiolitis cases and one with urinary tract infection controls. Infants with bronchiolitis were further divided into three groups: RSV bronchiolitis, non-RSV and unspecified. They identified 17 946 cases and 3326 controls; the risk of later hospitalisation with wheeze was 19% and 7%, respectively, with a relative risk (RR) of admission of 2.4 (95% CI 2.2 to 2.8) for the bronchiolitis group. They also reported an association between non-RSV bronchiolitis and wheeze (RR 3.1, 95% CI 2.4 to 3.9) with no differences among wheeze phenotypes.

Marlow *et al*[6] confirmed the association between infants with bronchiolitis and wheeze, but his study lacks some information that is missed when using discharge codes. The authors reported that a group of infants had bronchiolitis caused by RSV, but they did not describe the aetiological agents in the other two groups.

Through the use of new molecular technology, it has been demonstrated that other viruses such as rhinovirus (RV), human metapneumovirus and human bocavirus can be identified from infants with bronchiolitis.[7] In infants with bronchiolitis in which we tested for 14 respiratory viruses, we demonstrated that infants with RV bronchiolitis were older, had higher asthma familiarity, a less severe bronchiolitis and higher blood eosinophils compared with infants with RSV bronchiolitis.[7] There is growing evidence on the association between RV infection and asthma. Jackson *et al* have showed that wheeze from RV in early childhood is the most significant predicting factor for the development of asthma at the age of 6 years.[8] We demonstrated that the risk of wheeze at 3 years after bronchiolitis was greater for those infants with RV bronchiolitis compared with those infected by RSV.[9]

In the study by Marlow *et al*,[6] the definition used to diagnose bronchiolitis is not clear, as well as the clinical, demographic and biological characteristics of the infants included in the study. Bronchiolitis' clinical definition remains controversial. The need for a standardised definition becomes more significant as the evidence supporting the heterogeneity of bronchiolitis increase, as it may include infants with different clinical features, demographic characteristics and different biological mechanisms.

Dumas *et al*[10] identified three profiles in 1016 infants with bronchiolitis defined according to the American Academy of Pediatrics. Profile A: older infants with a history of eczema and of RW, elevated blood eosinophil, *Haemophilus* or *Moraxella* dominant microbiota and, most of them infected by RV Profile B: mainly infants with RSV bronchiolitis, with a less predominant history of RW or eczema. Profile C: younger infants with the most severe bronchiolitis, most of whom were infected by RSV. The RR to develop RW after 3 years of follow-up was high in infants from profile A, moderate in infants from profile B and low in infants from profile C. Asthma was associated only to profile A.

Marlow *et al*[6] confirmed the association between bronchiolitis and wheeze, but the question is still open. Is it RSV that causes bronchial hypersensitivity and the development of asthma or rather, does the virus identify those infants that have a genetic predisposition for the development of RW and asthma? Future studies with clear clinical, demographic and biological characterisation will give us the possibility to better understand the different phenotypes of infants with bronchiolitis and the relationship with RW and asthma.

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