



EDITORIAL

Virus and wheezing in infants. Certainties or doubts? ☆



Virus y sibilancias en el lactante. ¿Certezas o dudas?

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In the current issue of *Anales de Pediatría*, Calvo et al.¹ present a study in a cohort of children that were followed up in the first year of life to assess for the presence of viruses in nasopharyngeal aspirate specimens and its association with symptomatic and asymptomatic respiratory tract infections. The findings of this study contribute significantly to our knowledge of the epidemiology of respiratory diseases in infants in Spain. They show that rhinoviruses (RVs) are the viruses isolated most frequently from respiratory specimens. In addition, the study analysed the contribution of respiratory infections to the future risk of recurrent respiratory problems (specifically wheezing). Only “severe” respiratory infections (those that required hospital admission) were associated with recurrent wheezing in the first year of life. The continued followup of these children will probably show that this association persists beyond this period.

Further research is still needed to elucidate important aspects. One is defining the actual impact of each virus in severe respiratory illnesses in infants. Calvo et al. found that RVs are the type of virus isolated most frequently from respiratory specimens, and that this is the case in infants that are asymptomatic or present with isolated rhinorrhoea (in which 82% of positive specimens were positive for RV) as well as infants with symptomatic infections, whether “mild” (RV detected in 55.8% of the total positive specimens) or

“severe” (RV detected in 52% of total positives). On the other hand, respiratory syncytial virus (RSV) was found in 1.6%, 12.5% and 42% of the total positive tests in these groups of children, respectively. In light of these findings, it appears that RVs are ubiquitous and can be isolated from the respiratory tract of many infants at any given time, yet are not found more frequently in ill infants compared to healthy ones. Conversely, isolation of RSV was 8 times more frequent in children with symptoms than children without, and up to 26 times more frequent in children with severe infection. This is consistent with the international literature, with studies showing that RV infections are often asymptomatic and that isolation of RSV is much more frequent in children with lower respiratory tract infections than healthy children, which is not the case with RV infections.² Thus, while it seems unquestionable that RSV is pathogenic in the general population, it is possible that RV only causes severe respiratory symptoms (characteristic of lower respiratory tract infections) in children that are predisposed to develop them.

Another important aspect to consider is the recurrence of wheezing after an initial episode (bronchiolitis), which was much more frequent when the first respiratory infection was severe (58.3% versus 8.6%). How should we interpret this finding? We could hypothesise that infection itself may leave sequelae that facilitate subsequent episodes of lower airway obstruction. This effect could be specific to certain viruses or a generalised effect of severe infections. However, it is also possible that some children have a congenital predisposition that makes respiratory infections more severe and symptomatic to begin with, which would make hospital admission in the first episode and recurrent episodes more

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likely. Either of these possibilities would result in a statistically significant association of severe infections (of the lower respiratory tract in most cases) and recurrent wheezing. Conducting research in this field is challenging, but there is a growing body of data that support the second hypothesis. Some of them are:

1. Impaired respiratory function in newborns prior to any respiratory infection is associated with both the severity of the initial bronchiolitis and the probability of future wheezing episodes.³ Furthermore, bronchiolitis does not cause further impairment of respiratory function.
2. Part of the risk of hospital admission in bronchiolitis can be attributed to genetic determinants, which can be inferred from the different probability of admission found in monozygotic and dizygotic twins.
3. Some immunologic factors may have an impact on the risk of recurrent wheezing, as suggested by the association of specific genetic variants of certain cytokines with respiratory morbidity after bronchiolitis.
4. Children that had asthma at age 6 years had a higher incidence of wheezing episodes from the first months of life, which suggests the presence of risk factors from birth.
5. There is evidence of an association between asthma and *ORMDL3* gene polymorphisms at locus 17q21. This gene is involved in the synthesis of sphingolipids and the contraction of bronchial smooth muscle in response to different stimuli. Its association with asthma is restricted to childhood-onset asthma, and more specifically to a phenotype with onset of symptoms in the first year of life and persistent wheezing episodes.⁴ The association of genotypic variants at the 17q21 locus with asthma is also exclusive to children infected by RV (it has not been found in children with infections by RSV), which reinforces the hypothesis that lower respiratory tract infections by RV could be a manifestation of an innate predisposition to respiratory illness.
6. The frequency of recurrent wheezing episodes can predict whether respiratory symptoms will persist more accurately than the identification of the virus that has caused the respiratory infection.⁵ This suggests that the reason for the recurrence is probably a congenital

predisposition to having these episodes, rather than the effect of infection by any given virus.

If RV is less likely to cause lower respiratory tract infections than RSV, the development of these infections in association with RV could indicate a predisposition to airway obstruction of which the infection is a manifestation. This would explain the reason why some studies have found an increased risk of wheezing or asthma following bronchiolitis due to RV, and why the difference is no longer observed if the analysis takes into account the frequency with which episodes recur.

However, we are still far from having a definitive answer. We expect that new data will shed more light on the subject in upcoming years, paving the way for an individualised approach to care capable of identifying specific risks in specific patients.

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