

Editorial

Does RSV bronchiolitis cause asthma and atopy?

This challenging question has vexed investigators for almost 40 yr. Since Rooney and Williams' original description of ongoing wheeze following RSV bronchiolitis (1), there have been a substantial number of studies examining this relationship with varied and often contradictory findings. In the last issue of the journal, Henderson and colleagues add further fuel to the debate with a large, population based, prospective study aimed at determining the influence of hospitalization for RSV on the development of subsequent asthma, atopy and wheeze. They should be commended on the comprehensive study design which has enabled statistical correction for a large number of potential confounding variables in the final analyses. One possible weakness of the study is the potential bias introduced by the probable higher attrition rate to follow-up of those hospitalized with RSV compared to controls and this has been acknowledged by the authors. Notwithstanding, their results make interesting reading and confirm the findings of a number of recent studies. At 7½ yr of age the cumulative prevalence of asthma was 2½ times more likely in the RSV hospitalized group than controls, whilst atopy at 7 yr was no different between the two groups.

Does RSV bronchiolitis cause asthma?

An increased incidence of recurrent wheeze following RSV bronchiolitis has been consistently observed by the many studies in this research field. This observation has raised two important questions which appear to have been at least partly answered in recent years. Given that there is increased wheezing following bronchiolitis what is the natural history of this wheeze and does this, in itself, indicate an increased incidence of asthma in these individuals?

A number of studies have now demonstrated that the incidence of wheeze following RSV bronchiolitis diminishes with time to a point where there is no difference from control subjects. There has been some variation between studies in the age at which this point is reached, almost certainly reflecting differences between

recruited index cases, though a diminishing incidence has been a consistent finding. The link between this wheezing tendency and asthma, however, remains somewhat contentious but appears to be largely a matter of semantics. The characterization of a number of 'asthma phenotypes' has certainly helped to clarify the situation somewhat (2). These phenotypes enable the recognition of patterns of asthma progression based largely on family history and early medical history. Those children with lower respiratory tract infections with RSV in early life (including those who develop bronchiolitis) appear to typically fall into the 'non-atopic wheezing' phenotype characterized by resolving symptoms over the first decade of life (3). Thus current evidence suggests that RSV bronchiolitis is indeed associated with a subsequent form of asthma typified by a favorable long-term prognosis.

However, many vital questions remain. For example, are those infants who suffer from bronchiolitis severe enough to require hospitalization more likely to develop an atopic phenotype of asthma (4) and is there potential for those individuals whose wheezing symptoms resolve following bronchiolitis to become symptomatic again as adults (5)?

Does RSV bronchiolitis cause atopy?

The relationship between RSV infection and atopy remains uncertain despite a significant number of well-designed investigations. In keeping with the findings of Henderson et al. (6), several studies have found no association between RSV infection in early childhood and subsequent atopy for both hospitalized (7–10) and community infections (11). Conversely, an increased incidence of atopy has been demonstrated in a number of cohorts following hospitalization with RSV bronchiolitis (4, 12–14). Perhaps the most persuasive evidence for a positive association is the data from the ongoing longitudinal study by Sigurs et al. Each index case of hospitalized RSV bronchiolitis has been carefully matched with two controls and the prospective follow-up has had an impressively low dropout rate. At each review point to date,

RSV bronchiolitis has been a significant risk factor for subsequent atopy (4, 15, 16). Equally contradictory data have emerged from studies regarding the contribution of RSV infection to allergic sensitization in the well-characterized BALB/c mouse model (17, 18).

How can these apparent discrepancies be reconciled? First, it is important to realize that the reported studies to date have considerable differences of study design, particularly relating to inclusion criteria and illness definition. For example, Sigurs' cohort were all hospitalized with RSV bronchiolitis in the first year of life (15) whereas index cases in the Tucson respiratory study were community cases of RSV infection with signs and symptoms of lower respiratory tract illness (11). Secondly, and perhaps most importantly, both genetic and environmental population differences must be taken into account. For example, the Swedish children studied by Sigurs et al. had a relatively low rate of atopy (control subjects 28% at age 13–14) compared with the American children studied in Tucson (59% at age 11).

Pathogenic mechanisms

The potential association between RSV bronchiolitis, asthma, and atopy has led to a number of theories as to the role of RSV infection in disease pathogenesis. The early postnatal development of the immune system has been an area of intense research and it seems likely that RSV infection during this period of rapid maturation will have significant effects. The role of type 2 cytokine responses in RSV immunopathology remains a central question. Both asthma and atopy are associated with type 2 immune responses (19) presenting an attractive potential link between RSV infection and subsequent disease. Disappointingly, studies in this area have provided inconsistent results. In a carefully designed prospective study of infants with a family history of atopy (at least one parent with atopic asthma), we found that infants who develop signs and symptoms of bronchiolitis following RSV infection demonstrate a relative type 2 local and systemic cytokine response compared to infants with an upper respiratory tract infection alone (20). Other investigators have identified similar type 2 responses (21, 22), although balanced (23) or even type 1 responses (24–26) have also been identified in RSV bronchiolitis. Intriguingly, there is some evidence to suggest persistence of a type 2 milieu several years following RSV bronchiolitis (27). However, it is not yet clear whether RSV bronchiolitis stimulates type 2 responses in the course of

natural infection or whether type 2 differentiation only occurs in certain subgroups of infants such as those with an atopic predisposition.

Other possible mechanisms of disease pathogenesis following RSV bronchiolitis have also been proposed. Direct effects of RSV infection on the rapidly developing lung include disruption or destruction of the epithelial layer and loss of ciliated epithelium. In severe cases there is widespread necrosis of the bronchiolar epithelium together with peribronchiolar mononuclear cell infiltrates, submucosal edema and bronchorrhea. Such changes will potentially result in subsequent lung remodeling and altered lung growth perhaps accompanied by epithelial scarring due to severe viral or immune damage. In addition, the mouse model has demonstrated significant disruption and subsequent remodeling of the submucosal neural network, aberrant activation of which can predispose to airway inflammation and hyperreactivity (28). Animal studies have also suggested viral persistence (29) and bystander antigen sensitization (30) as further potential contributors to the delayed effects of RSV.

Future research

Despite significant recent advances in our understanding of the relationship between RSV bronchiolitis, asthma, and atopy, it is clear that many vital questions remain unanswered. At the core of this complex relationship lies the fundamental question of causation. Does RSV bronchiolitis *per se* affect the immature respiratory and immune systems to produce subsequent disease or does infection merely uncover susceptible infants with pre-existing diminished lung function and/or genetic susceptibility to lung disease (31). Large prospective interventional studies are required to adequately address these issues and results of preliminary work using the anti-RSV monoclonal antibody, palivizumab, are eagerly awaited (32). Ultimately, whilst studies such as those of Henderson et al. (6) provide valuable insights, it is only when interventional studies have been completed will we truly understand the extent to which RSV bronchiolitis effects long-term disease.

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