The Role of the Respiratory Syncytial Virus in Airway Syndromes in Childhood

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The majority of infants admitted to hospital in infancy with lower respiratory tract infections (LRTIs) have been infected with the respiratory syncytial virus (RSV). Infants and young children experiencing RSV LRTIs experience increased respiratory morbidity in subsequent years, although the prevalence falls rapidly in early childhood. Recent data support the suggestion that in most subjects, this recurrent morbidity is not attributable to atopic asthma and that in most respects, the acute and long-term outcomes with RSV infections are similar in nature to those attributable to other viruses. The phenotype of the acute illness probably provides better prognostic information than the type of virus.

Introduction

The respiratory syncytial virus (RSV) is an extraordinarily successful virus that causes annual epidemics of respiratory disease [1,2]. In temperate climates, these epidemics start in late autumn, peaking in the winter and effectively disappearing by early spring. In tropical climates, the epidemics are more variable, often coinciding with the wet season [3,4]. The virus affects individuals of all ages but seems to cause particularly severe disease in the very young [1,5,6]. RSV lower respiratory tract infection (LRTI) is the single most common cause for hospitalization in the first year of life. In recent years, the importance of the virus in the causation of significant LRTIs in the elderly and those with chronic obstructive airway disease has been increasingly recognized [7,8]. In most children, outside the first few years of life, and in most adults, the virus generally causes upper airway symptoms with coryza and cough. During each winter epidemic, approximately a third of a population will be infected by the virus, although in infancy infection rates run at greater than two thirds of all infants [9]. The human form of the virus, which is closely related to but distinct from the paromyxoviruses, is related to a bovine RSV that causes LRTI in young claves kept in close proximity.

Soon after human RSV was first isolated nearly 50 years ago, it was realized that this virus played a very important role in the induction of LRTI in infancy and was the major pathogen responsible for "acute bronchiolitis." Around the same time, publications were starting to highlight the association between bronchiolitic illnesses in infancy and subsequent recurrent respiratory symptoms. Each winter, pediatric wards are inundated with young infants with RSV-induced lower airway obstruction, which can, superficially, appear to resemble attacks of asthma. This observation, linked with the realization that many went on to have recurrent symptoms, caused many to speculate that RSV LRTIs might in some way induce atopic asthma in susceptible individuals [10,11]. Data supporting this position have come from animal experiments and from some clinical studies [12–15]. However, most cohort studies have failed to identify any such link [16–22,23•,24•,25]. Recent studies appear to have shed light on these apparently contradictory findings in that they would appear to indicate that the outcome of cohort studies are more likely to be determined by the phenotype of the acute illness and, hence, the host response than by the organisms causing the LRTI. Moreover, differences in outcomes of studies addressing therapeutic interventions may again largely be determined by the phenotype of patients included in the study.

A number of important questions remain to be resolved in respect to the virus. In particular: Why is the virus so successful? What is the trigger for the annual epidemics? What is the relationship between the acute illness and subsequent symptoms?

Respiratory Viruses and Respiratory Illnesses in Childhood

The respiratory syncytial virus is one of a number of respiratory viruses that can infect infants and children.

It has probably been subject to more research than other viruses because of its ability to cause annual epidemics of disease and precipitate large numbers of admissions of patients to hospital with acute bronchiolitis, pneumonia, and viral-induced wheeze. As with other respiratory viruses, it can cause any of the common respiratory illnesses, including simple coryza, otitis media, pharyngitis, laryngotracheobronchitis (croup), bronchitis, bronchiolitis, viral-induced wheeze, and pneumonia. Additionally, it is an important cause of exacerbations of asthma in both children and adults, although it appears to be less important than rhinovirus in this regard [26]. Traditionally, RSV has been associated with "acute bronchiolitis," accounting for between 60% and 90% of cases, depending on definition, whereas paraflu has been typically associated with croup. However, many other viruses, such as rhinovirus and influenza [27], can cause a typical bronchiolitic illness. More recently, it has been recognized that many cases of the RSV-negative bronchiolitis are attributable to human metapneumovirus [28]. Consequently, it would appear that there is nothing unique about the virus in respect to its causing acute bronchiolitis. A possible explanation for the high numbers of young infants being admitted with RSV bronchiolitis is that the virus can cause annual epidemics of disease affecting such a high proportion of infants, many of whom are very young, and inevitably a small proportion of these will be hospitalized. The reason for the virus's success is unclear, but may be attributable to its ability to impair the development of effective immune response, resulting in poor herd immunity. It is certainly able to productively infect dendritic cells, and this may affect their ability to act effectively as antigen-presenting cells [29]. Although it is possible to demonstrate that isolates of RSV change over time [30], the role of antigenic variation in contributing to the virus's success remains to be resolved. Young infants will be at particular risk in an epidemic if they receive little in the way of neutralizing antibodies from their mother, either because of poor memory responses in the mother or exposure to a strain that the mother has not previously encountered. The synthetic monoclonal anti-RSV antibody palivizumab [31] appears to have retained its efficacy over time, suggesting that antigenic variation is not a major factor but the lack of documented strains that are resistant to the effects of the antibody and its partial efficacy might entertain the argument that the partial efficacy of the antibody is not sufficient to force evolutionary changes on the virus.

It is important to recognize that although the most visible and striking aspect of the annual epidemics are the hundreds of infants being admitted to individual hospitals each winter with airway obstruction, these infants represent only 0.5% to 2% of the infant population and 2% to 4% of those infected with the virus. Most infants infected with RSV, many of whom have mild LRT symptoms with bronchitis or mild bronchiolitis, do not get admitted. Therefore, hospital-based studies are only recruiting subjects who represent the most severe tip of the iceberg. Most infants admitted to hospital are young, typically 2 to 4 months of age, and it is clear that the two major risk factors for hospitalization are young postnatal age when infected and prematurity [6,32]. There are many older infants who develop acute bronchiolitis but who cope well and do not need admitting to hospital.

"Acute Bronchiolitis" and "Wheezy Bronchitis"

In addition to recognizing the importance of age as a risk factor for disease severity, it is also important to recognize that RSV may cause similar but distinct phenotypes of disease. Unfortunately, this has not always been recognized and, indeed, the same term is at times used for what are likely to be completely different phenotypes. Similar problems have been encountered when trying to define phenotypes of wheezing episodes. Studies in the 1960s have shown clearly that many children with wheezing associated with apparent viral infections ("wheezy bronchitis") in early childhood grew out of this tendency during the first decade of life and that they appeared to be a distinct group from those with asthma. However, in an attempt to address the underdiagnosis of asthma, a number of authorities in the 1980s advocated the abandonment of the term "wheezy bronchitis" and suggested that we should be labeling these children as having asthma. A number of studies then reinvented the wheel by rediscovering the fact that the majority of infants who wheezed with viruses in the first few years of life grew out of this tendency but that some went on to develop asthma [33].

In the United Kingdom, Australia, and some other countries, the term "acute bronchiolitis" is used to describe an infant with coryza, moist cough, airway obstruction, and widespread crepitations on auscultation. Such children may wheeze occasionally or intermittently, but many do not. In this context, it is important to recognize that doctors and parents frequently use the term "wheeze" imprecisely, using it for a variety of respiratory noises when it should be restricted to a continuous musical sound that is generally expiratory. In North America and other countries, the term "acute bronchiolitis" is widely used for the first episode of viral-induced wheeze. Because these children have a virus, a bronchitic cough, and wheeze, the term "wheezy bronchitis" would appear to be as appropriate as any. If the inflammatory and physiologic responses in these conditions are the same but the clinical picture is simply modified by the age of the child, such differences in terminology would not matter. However, if there are host-determined differences in the inflammatory and/or physiologic responses, these may not only affect the acute response but also have a bearing on the host's subsequent response to infections.

The concept that different host responses to the same virus may influence the outcome after an acute LRI in infancy is not new. In 1964, Reynolds and Cook [34] observed that "acute bronchiolitis" was the most common acute LRI in infancy and was due to more than one virus. Their observations led them to suggest that there were probably two groups of patients, those with edema and secretions and those with a predisposition to asthma. They also concluded that they cannot be easily distinguished, but most are in the former group. Forty years later, we are probably helping to confirm their observations. Part of the confusion in the interval is that, although there have been many fairly large cohort studies, they have varied in their inclusion criteria. The group under consideration has included RSV LRI irrespective of clinical presentation; RSV bronchiolitis (characterized by crepitation); RSV-induced wheezing illness; bronchiolitis irrespective of virus; and viral-induced wheeze irrespective of virus. Very few studies have recruited infants with RSV infection and then assigned them to bronchiolitic or wheezing phenotypes at recruitment to the study [35] (Elphick, Unpublished data). Many of the discrepancies in outcomes observed appear to be attributable to the differences in the initial cohort studied.

It should also be remembered that not only does the medical profession cause confusion by failing to agree on terminology for specific clinical conditions, they are also remarkably bad at using terms such as wheeze. Parents have been conditioned to refer to almost any form of noisy breathing and/or breathlessness as wheeze, whereas doctors frequently use the term for a variety of respiratory noises that are clearly not wheeze, based on the definition of a continuous, musical, added sound usually heard in expiration [36]. The lungs have a limited repertoire of responses to inflammation from whatever cause, be it infective, asthma, or aspiration. Consequently, subjects will cough, produce excess mucus, and frequently have noisy breathing. This all contributes to a situation in which different processes can generate very similar clinical symptoms. Agreement on labeling phenotypes of disease and improved precision in the use of terms such as wheeze would contribute greatly to our understanding of this field.

Post-RSV and Post-"Bronchiolitic" Symptoms

Although the morbidity associated with RSV infections in infancy is high, the mortality is fortunately low. Treatment has essentially remained unchanged for more than 40 years, with oxygen being vital in those with hypoxia. A small percentage require more aggressive supportive care, which might include ventilation and even extracorporeal membrane oxygenation (ECMO), but most infants admitted with RSV infections have a brief, self-limiting illness. In North America, the United Kingdom, and Northern Europe, the mean duration of hospitalization is 3 days, compared with approximately 9 days in continental Europe [37]. This may reflect the severity of illness in those admitted or may reflect treatment practices. It is clear that after discharge from hospitalization, infants experience persistent symptoms in the subsequent weeks, with cough being particularly troublesome. This is perhaps not surprising because, even with a viral upper respiratory tract infection (URTI), the residual cough may persist for several weeks in many subjects [38]. Previously, these immediate post-infective symptoms have received little attention, and although many clinicians would try inhaled therapy, there are no studies on which to base any recommendations. More recently, a study using a leukotriene receptor antagonist claimed to show some benefits [39] in terms of symptoms, but the outcomes of a larger study are awaited before any conclusions can be drawn. As with so many issues in this area, the entry criteria for the study may be critical. If wheeze is the main entry criteria, and children up to 2 or 3 years of age are recruited, then inevitably some children with asthma will be included. The role of leukotrienes in the acute illness and subsequent studies has been the subject of some debate. It is clear that leukotrienes can be detected in infants with RSV infections, but are also identifiable in infections with other viruses and in adults with URTIs due to a range of viruses [40], suggesting that production of leukotrienes during the acute illness is not unique to RSV. Of note, it is neutrophils, not eosinophils, that dominate the inflammatory infiltrate during the acute bronchiolitic illness [41]. Again, the host response and/or age [42] may influence the phenotype of disease and, therefore, the characteristic of recruited subjects needs to be carefully considered.

Studies in calves affected with bovine RSV have found that the inflammatory process appears to be very similar to the human form of the disease with intense neutrophil influx, and few, if any, eosinophils noted in lavage or post-mortem specimens. In contrast, some studies with rodents have been able to induce an intense eosinophilia, but this is only achieved after manipulating the model. Rodents do not naturally develop a bronchiolitic illness in response to RSV infection, and what inflammation occurs in response to primary exposure of the airways to RSV is again characterized by neutrophil influx [43].

Phenotype of Acute Illness and Long-term Morbidity

Although many studies have indicated an excess of respiratory symptoms in those admitted to hospital and amongst those managed in the community who experience RSV LRT symptoms, few have prospectively followed up the pattern of symptoms in detail. A recent study from the Netherlands has indicated that post-bronchiolitic symptoms beyond the first few weeks are clearly related to intercurrent viral infections, and that the prevalence falls rapidly over the first few years [44•]. This pattern

of viral-induced symptoms with relatively few interval symptoms could be consistent with mild asthma, but it has not been shown that there is an excess of asthma in the late primary school years. Indeed, it is clear that the natural history of post-bronchiolitic symptoms is quite different from that of atopic asthma with the prevalence of symptoms being maximal in infancy.

Those cohort studies recruiting patients with RSV-associated "acute bronchiolitis" (characterized by widespread crepitation) have found increased respiratory morbidity and in some cases increased bronchial hyper-responsiveness, although this is inconsistent. Importantly, these studies did not identify any increase in atopy [16–22,23•,24•]. Defining the nature of "post-bronchiolitic" symptoms is difficult. Many attribute these symptoms to "asthma" caused by recurrent cough and wheeze. However, with recent guidelines suggesting that asthma can only be diagnosed in those with an unequivocal response to asthma medication (bronchodilator or inhaled steroids) [45], it is difficult on the basis of previous studies to argue for a link between "bronchiolitis" and asthma, because none of the studies sought to determine whether symptoms were responsive to conventional asthma treatments.

Similar results were obtained in a community-based study reporting outcomes in children with any RSV LRTI in the first 3 years [21] of life, suggesting that disease severity alone does not predict future symptoms. In contrast, a number of recent studies have reported outcomes in infants admitted with viral-induced wheeze, a proportion of whom have RSV as the infecting organism. In these, there appears to be an excess of asthmatic patients, but this excess is not confined to those with RSV infection [46•,47•,48,49•]. Indeed, wheezing with rhinovirus in early childhood appears to carry a significantly greater risk for developing asthma than wheezing with RSV. This would suggest that among those who wheeze with viral infections, there are some manifesting early symptoms of asthma, and it is the host rather than the virus that determines outcome. It is possible that this may in part explain the results of a cohort study involving 50 infants with RSV LRTI, which reports increased levels of atopic asthma compared to controls [12,13]. The entry criteria for these subjects included the need to exhibit wheeze. Further support for this suggestion was obtained in a study from our group in which patients were assigned to phenotypic groups of RSV bronchiolitis (with crepitations) or RSV wheeze at admission to hospital (Elphick et al., Unpublished data). Subjects with RSV bronchiolitis had increased symptoms with colds compared with controls but no increase in atopy or inhaled corticosteroid use. In contrast, those with RSV wheeze had higher rates of atopy, inhaled corticosteroid use, and interval symptoms. As with other studies, those admitted with bronchiolitis outnumber the wheezing subjects by approximately 4:1, and, hence, the number of wheezing subjects was relatively small.

Further evidence that the host response rather than the particular virus is the major factor in determining the phenotype of the disease comes from another study that pre-assigned phenotypes [35] in the same way as did Elphick et al. This study recruited subjects irrespective of virus. RSV was the most common virus isolated, but they noted that differences in inflammatory profile reflected the type of illness rather than the type of virus isolated, and they suggested that the host rather than the virus was a major factor in disease expression. Again, they found that neutrophils were the overwhelming type of inflammatory cell isolated in those with bronchiolitis, wheeze, or URTI alone. Others have also highlighted the different inflammatory responses in infants with RSV bronchiolitis and those with viral-induced exacerbations of asthma [50].

Conclusions

Despite decades of research, we do not appear to have returned to the position suggested 40 years ago [34] that the airway obstruction in most infants with acute bronchiolitis is due to edema of airway walls and increased intraluminal secretions, and is not an early manifestation of asthma, as many have tried to demonstrate in the intervening years. Such infants do have increased symptoms in subsequent years, but these are mainly associated with viral infections. The acute illness can be caused by a number of viruses, but numerically RSV is the most important, probably due to poor herd and passive immunity, leading to a relatively large number of young infants being affected, and it is these young (< 6 months old) infants who cope least well, probably due to physiologic factors. There are relatively few follow-up data concerning non-RSV bronchiolitis, but there does appear to be a similar excess of symptoms in these subjects as well. A smaller number of infants and young children are admitted with wheezing episodes precipitated by viral infections. These subjects tend to be older than those with acute bronchiolitis, but, again, in the under 2s, RSV is probably the most important precipitating virus, probably due to the large numbers of infected infants. Amongst those with wheezing associated with viral respiratory tract infections, there is an increased risk for atopic asthma. However, atopic asthmatics still represent a minority of this group, and, as has been shown in many studies, the tendency to wheeze with viral infections will, in most subjects, tend to resolve during the first decade of life. The challenge at the outset is to anticipate who will develop asthma and benefit from treatment with inhaled corticosteroids and other treatments for asthma. Currently, there are no good discriminating tests. Clinical suspicion and an unequivocal response to a trial of therapy remain the only guides.

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