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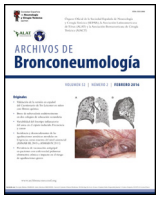

Review

Pediatric Asthma and Viral Infection☆

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ABSTRACT

Respiratory viral infections, particularly respiratory syncytial virus (RSV) and rhinovirus, are the most importance risk factors for the onset of wheezing in infants and small children. Bronchiolitis is the most common acute respiratory infection in children under 1 year of age, and the most common cause of hospitalization in this age group. RSV accounts for approximately 70% of all these cases, followed by rhinovirus, adenovirus, metapneumovirus and bocavirus. The association between bronchiolitis caused by RSV and the development of recurrent wheezing and/or asthma was first described more than 40 years ago, but it is still unclear whether bronchiolitis causes chronic respiratory symptoms, or if it is a marker for children with a genetic predisposition for developing asthma in the medium or long term. In any case, sufficient evidence is available to corroborate the existence of this association, which is particularly strong when the causative agent of bronchiolitis is rhinovirus.

The pathogenic role of respiratory viruses as triggers for exacerbations in asthmatic patients has not been fully characterized. However, it is clear that respiratory viruses, and in particular rhinovirus, are the most common causes of exacerbation in children, and some type of respiratory virus has been identified in over 90% of children hospitalized for an episode of wheezing. Changes in the immune response to viral infections in genetically predisposed individuals are very likely to be the main factors involved in the association between viral infection and asthma.

Asma y virus en el niño

Palabras clave:
Bronquiolitis
Asma
Virus respiratorios
Virus respiratorio sincitial
Rinovirus
Bocavirus humano
Metapneumovirus humano

RESUMEN

Las infecciones por virus respiratorios, especialmente virus respiratorio sincitial (VRS) y rinovirus, suponen el mayor factor de riesgo para la aparición de episodios de sibilancias en lactantes y niños pequeños. La bronquiolitis es la infección respiratoria aguda de vías respiratorias inferiores más común en menores de un año y constituye la causa más frecuente de hospitalización en este grupo de edad. El VRS causa aproximadamente el 70% de todas ellas, seguido por rinovirus, adenovirus, metapneumovirus o bocavirus. La asociación entre bronquiolitis por VRS y desarrollo de sibilancias recurrentes y/o asma ha sido descrita hace más de 4 décadas, aunque en la actualidad se desconoce con exactitud si la bronquiolitis es la causa de los síntomas respiratorios crónicos o si, más bien, es un marcador que señala a los niños con predisposición genética a desarrollar asma a medio o largo plazo. En cualquier caso, existe evidencia suficiente como para afirmar que esta asociación existe y que es especialmente intensa si el agente asociado a la bronquiolitis es el rinovirus.

El papel patogénico de los virus respiratorios como desencadenantes de exacerbaciones en el paciente asmático no está totalmente aclarado, pero sin duda los virus respiratorios, y en especial el rinovirus, son el desencadenante más frecuente de exacerbaciones asmáticas en los niños, llegando a identificarse algún virus respiratorio hasta en el 90% de los niños hospitalizados por un episodio de sibilancias. Muy probablemente, las alteraciones en la respuesta inmune frente a las infecciones virales en sujetos genéticamente predispuestos sean los principales implicados en la asociación virus-asma.

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Introduction

Asthma is a chronic inflammatory disease of the airways characterized by bronchial hyperresponsiveness to a wide variety of stimuli, recurrent episodes of wheezing, respiratory distress, and cough, associated with reversible airway obstruction. Asthma is one of the most prevalent chronic diseases worldwide, affecting more than 155 million individuals, so the impact of asthma is severe, and incidence is growing, particularly in developed countries.[1,2]

Respiratory viruses are one of the most common causes of asthma exacerbations in both adults and children.[3–6] Furthermore, increasing evidence is emerging to suggest that viral respiratory infections in early life are related with the medium and long-term development of asthma.[7,8]

This article aims first to review the role of viruses as precipitating factors for asthma, and then to summarize the current state of knowledge on their role in asthma exacerbations.

Respiratory Viruses as Precipitating Factors for Asthma

Viral bronchiolitis is a common feature in the clinical histories of children who go on to develop wheezing and asthma during childhood. The term bronchiolitis has been in use since 1940, but it has several different interpretations, and there is no general agreement on its definition. In this review, we will use the standard criteria of McConnochie, who describes bronchiolitis as the first acute episode of wheezing, preceded by a respiratory syndrome of rhinorrhea, cough, and tachypnea, occurring with or without fever, in children younger than 2 years of age.[9]

Bronchiolitis is the most common acute lower respiratory tract infection in children younger than 1 year, and accounts for 18% of all pediatric admissions.[10] Respiratory syncytial virus (RSV) is the causative agent in approximately 70%–80% of cases, followed by rhinovirus, adenovirus, human metapneumovirus (HMPV), and human bocavirus (HBoV).[11,12] The most common respiratory viruses are listed in Table 1.

Studies reporting global analyses of all patients with a history of bronchiolitis, irrespective of the causative agent, reveal a prevalence of recurrent wheezing that ranges from 75% in the first 2 years of life, 47%–59% between the ages of 2 and 4, and 25%–43% between 4 and 6 years,[13–16] showing a clear trend to diminish with age. Only 2 prospective studies included a long-term follow-up of children hospitalized for bronchiolitis, irrespective of the causative virus. They found a prevalence of asthma at the age of 17–20 years of 41%–43% in patients with a history of bronchiolitis, compared to a rate of 11%–15% in controls; between 25 and 30 years of age, prevalence was 35%, with significant impact on health-related quality of life.[17,18] These data suggest that recurrent wheezing occurs frequently in children after an episode of bronchiolitis, and also that respiratory symptoms frequently recur in young adults after a long symptom-free period during childhood and adolescence. This changes the previously held notion of a relatively good prognosis for early childhood wheezing, and indicates that the risk of asthma and lung function changes can persist until adulthood.[19,20]

RSV was the first virus to be associated with the development of asthma in children, although in recent years, other viruses, such as rhinovirus or the more recently described HMPB and HBoV, have also been studied in this context.

Respiratory Syncytial Virus

RSV is an RNA virus from the *Paramyxoviridae* family that often causes lower respiratory tract infections in infants and small children.[21]

In 1959, Wittig and Glaser[22] first described the epidemiological association between viral bronchiolitis in childhood and the subsequent development of recurrent wheezing and/or asthma. Since then, numerous studies have evaluated this relationship, although the different methodologies employed made it difficult to draw conclusions that definitively proved this association. However, more recently, several prospective studies, now considered seminal,[23–27] showed that a history of bronchiolitis caused by RSV is an independent risk factor for the development of recurrent wheezing and medically-diagnosed asthma. Of these authors, Sigurs et al.[27] performed the longest follow-up to date, with subjects reaching the age of 18 years in the last follow-up time point. The initial cohort consisted of 47 infants aged <1 year hospitalized with severe RSV bronchiolitis and 93 age- and gender-matched controls. Children who had been admitted for bronchiolitis had a higher prevalence of asthma/recurrent wheezing and allergic sensitizations at the ages of 3, 7 and 13 years, compared to the control group. At the age of 18, the bronchiolitis group maintained a significantly higher prevalence of asthma (39% vs 9%), allergic rhinoconjunctivitis (43% vs 17%), and perennial allergen sensitization (41% vs 14%). Moreover, at the age of 18, the bronchiolitis group had poorer lung function (FEV_1, FEV_1/FVC) than the control group, irrespective of whether they had concomitant asthma or not. They also had more prevalent bronchial hyperresponsiveness and bronchodilator response. Finally, the authors reported that the only 2 risk factors independently related with the diagnosis of asthma at 18 years of age were a history of severe RSV bronchiolitis and presence of allergic rhinoconjunctivitis. These results show that severe RSV bronchiolitis in the early months of life is associated with the development of asthma, bronchial hyperresponsiveness and allergic sensitization, and suggest that this association continues until adulthood.

The results of another reference follow-up study, Tucson Children's Respiratory Study, show that RSV bronchiolitis is an independent risk factor for the development of asthma up to the age of 11 years, but the association disappears after the age of 13.[24] This difference in the long-term prognosis may be related with varying severity of the acute episode, since in the Sigurs study, all patients needed to be hospitalized, while the Tucson cohort included mostly outpatients. The authors also observed a greater risk of asthma

Table 1
Classification of Respiratory Viruses.

Species	Family	Genus	Type	Subgroups
Syncytial respiratory virus	*Paramyxoviridae*	*Pneumovirus*	RNA	A, B
Parainfluenza 1, 3	*Paramyxoviridae*	*Respirovirus*	RNA	1, 3
Parainfluenza 2, 4	*Paramyxoviridae*	*Rubulavirus*	RNA	2, 4
Metapneumovirus	*Paramyxoviridae*	*Metapneumovirus*	RNA	1–4
Influenza	*Orthomyxoviridae*	*Ortomixovirus*	RNA	A, B, C
Rhinovirus	*Picornaviridae*	*Rhinovirus*	RNA	A, B, C
Adenovirus	*Adenoviridae*	*Mastadenovirus*	DNA	A to F
Human bocavirus	*Parvoviridae*	*Bocavirus*	DNA	1, 2, 3
Coronavirus	*Coronaviridae*	*Coronavirus*	RNA	I, II

among children who used more healthcare resources during the acute bronchiolitis episode.[28]

The RSV Bronchiolitis in Early Life (RBEL) study also supports the association between severe RSV bronchiolitis and subsequent development of asthma[29]: of the 206 infants admitted for RSV bronchiolitis, approximately 50% had been diagnosed with asthma by the age of 7 years.

Rhinovirus

Although RSV is without doubt the most common virus in the etiology of acute infantile bronchiolitis, the use of molecular diagnostic techniques – primarily polymerase chain reaction (PCR) – has established that other respiratory viruses, such as rhinovirus, are also associated with bronchiolitis, and probably with the development of asthma.[30,31] Indeed, several recent studies have shown that the risk of children hospitalized for bronchiolitis presenting asthma at 6 and 11 years is higher among those who were RSV-negative than those who were RSV-positive.[32,33]

Rhinovirus is an RNA virus from the *Picornaviridae* family, first isolated in 1950. It comprises a large RNA family of more than 100 serotypes, originally divided into 2 species, A and B, and now with the recent addition of the C type.[34]

Studies published in recent years suggest that rhinovirus infections involve a greater risk for the development of asthma than RSV-associated infections. In the Childhood Origins of Asthma (COAST) study, which followed a cohort of 289 newborns with high risk of developing asthma, lower respiratory tract infection associated with rhinovirus was the main risk factor for presenting recurrent wheezing at 3 and 6 years of life, with an odds ratio of 10 for rhinovirus bronchiolitis compared to 2.6 for RSV bronchiolitis.[35,36] Moreover, children with rhinovirus-associated wheezing in the first 3 years of life had worse lung function values (FEV_1, $FEV_{0.5}$, FEF_{25-75}) than those with other viruses or those who never presented wheezing.[37] Midulla et al.[38] confirmed the role of rhinovirus bronchiolitis as one of the main risk factors for the development of asthma at the age of 6 years.

The COAST study also showed that, in the case of rhinovirus, the risk of developing asthma is not limited to severe infection. In fact, only 1% of children with rhinovirus bronchiolitis included in the study needed to be hospitalized, demonstrating that even mild rhinovirus infections are associated with a greater long-term risk of asthma.

Finally, another cohort study with a follow-up of 15–18 years showed that the risk of asthma in adolescence is greater in children hospitalized due to rhinovirus bronchiolitis, compared to RSV bronchiolitis. This study also found that the risk of asthma is greater in children whose initial episode of bronchiolitis occurred in seasons other than winter, when the predominant virus is not RSV.[39]

Human Metapneumovirus

HMPV is a paramyxovirus, discovered in 2001 and identified throughout the world as a common cause of acute respiratory infection, particularly in infants and small children.[40] The clinical features of acute HMPV infection are similar to those caused by RSV, and can manifest as mild upper respiratory tract infections, pneumonia or severe bronchiolitis requiring hospital admission. The similarity of the clinical symptoms with those of RSV has led to speculation that HMPV infections may also be associated with the development of asthma in the long term. To date, the medium-term progress of children admitted for HMPV bronchiolitis has been examined in only 1 study that reported a similar rate of recurrent wheezing to that seen in children admitted for RSV bronchiolitis: 5-fold the rate of the control group in both cases.[41]

Human Bocavirus

HBoV is a DNA virus belonging to the *Parvoviridae* family. It was first identified in 2005 in respiratory samples from children with lower respiratory tract infections.[42] Since then, numerous studies have investigated its prevalence and its role in respiratory infections, but to date, only 1 has examined its possible role in the development of asthma: the study in question reported that 50% of children admitted for HBoV bronchiolitis had asthma by the age of 5–7 years.[43]

The high rate of HBoV co-infection with other respiratory viruses, and its tendency to infect older children confounds the study of the real role of early HBoV infections in the development of asthma.

The Bronchiolitis–Asthma Relationship: Cause or Coincidence?

As discussed above, a wide body of evidence relates viral respiratory infections with the subsequent development of asthma, but it remains unclear if severe bronchiolitis is the real cause of asthma, or if it is a marker of susceptibility, identifying children with a predisposition for developing asthma.

A prospective, multicenter study recently conducted in Europe, the United States, and Canada,[44] appears to support the causative role of RSV, after an 80% reduction was observed in recurrent wheezing in the medium term among premature babies with a family history of asthma and/or atopy who received prophylaxis with palivizumab, a monoclonal antibody used for preventing RSV infection. Curiously, the protective effect was only observed in children with a history of atopy, suggesting that RSV may have a causative role in the pathogenesis of recurrent wheezing, but only in patients with no genetic predisposition for atopy.

The possible causative role of viral bronchiolitis was questioned by an epidemiological study performed in monozygotic twins, discordant for severe RSV bronchiolitis in infancy. The authors found no difference in the frequency of asthma, lung function or nitric oxide levels at the age of 7 years between twin siblings with a history or no history of hospitalization due to bronchiolitis.[45]

Finally, another 2 recent studies support the hypothesis that early viral infections are markers of atopic predisposition, rather than the cause of asthma. One of these was the Danish Copenhagen Prospective Study of Asthma in Childhood, which followed a cohort of newborns with asthmatic mothers. Investigators measured lung function and response to methacholine of infants at 1 month of life, before any respiratory symptom had been observed. They found at this time point that children who subsequently developed severe bronchiolitis already had bronchial hyperresponsiveness as a precursor to bronchiolitis.[46] These results are supported by the recent COAST study, which identified allergic sensitization in the first year of life as a significant risk factor for virus-associated wheezing, while wheezing associated with respiratory infection does not increase the risk of developing allergic sensitization.[47]

It seems likely that the 2 hypotheses – bronchiolitis as a cause or as a marker of asthma – are not mutually exclusive, and that the pathogenic mechanisms of rhinovirus and RSV infections differ. RSV characteristically produces a cytopathic effect in the airway, affecting children younger than 3 months, frequently requires hospitalization and occurs in epidemic outbreaks during the winter months.[48] In contrast, rhinovirus outbreaks occur throughout the year and affect older children who are generally treated as outpatients, and who often have a family history of asthma or atopy.[7,49] These differences have led to the hypothesis of 2 different mechanisms: rhinovirus bronchiolitis may be more a marker of predisposition to asthma and atopy, while RSV bronchiolitis may

have a greater causative role, particularly in severe cases requiring hospitalization.[50,51]

Respiratory Viruses Triggering Asthmatic Exacerbations

The role of respiratory viruses as precipitants of asthma attacks in adults and children was identified over 30 years ago. In the early studies, in which viral diagnosis was not based on molecular methods, some viral activity was detected in between 10% and 25% of asthma attacks.[52] In contrast, in recent years, the use of PCR techniques has revealed that the proportion of asthma exacerbations associated with viruses is much higher, up to 63%, according to Khetsuriani et al.,[53] up to 80%, according to Johnston et al.,[3] or even up to 95%, according to Allander et al.[54] At least 1 respiratory virus was identified in 71% of patients included in a Spanish study of children hospitalized for an asthma exacerbation.[5]

Although practically all respiratory viruses, including the newly identified HMPV and HBoV, have been associated with asthma exacerbations, the agents most commonly detected in infants and schoolchildren are rhinovirus and RSV.[5,55] In fact, a recent cohort study in 263 infants suggests that rhinovirus is the most common pathogen in the first year of life and the most important precipitant of wheezing in infants.[56]

In children of school age, Johnston et al.[3] found that 80% of asthma exacerbations in asthmatic children aged 9–11 years were associated with viral respiratory infection, of which two thirds were caused by rhinovirus. Asthma exacerbations among pre-school- and school-age children tend to follow a seasonal pattern, and in temperate climates, the maximum incidence occurs in the month of September, coinciding with the beginning of the school year, and in Spring.[57] This pattern coincides almost exactly with the peaks of maximum circulation of rhinovirus in the community, suggesting a causal relationship between this virus and asthma exacerbations.

The frequency of detecting respiratory viruses in adults with asthma exacerbations ranges between 41% and 78%, according to the results of a recent meta-analysis.[58] Although rhinovirus is also most common in this age group,[59] other viruses, such as RSV, HMPV, or influenza virus appear to play an important role in asthma exacerbations in adults in clinical practice.[60]

Moreover, viral infections can act in synergy with other stimuli, such as exposure to allergens in allergic individuals[61,62] or exposure to high levels of environmental contaminants,[63] increasing the risk of asthma exacerbations.

Pathogenic Mechanism of the Viral Respiratory Infection–Asthma Exacerbation Association

Viral respiratory infections affect the lung in many ways, acting on epithelial cells and antigen-presenting cells. After it recognizes the viral infection, the immune system stimulates the production of cytokines, such as interleukins (IL) IL-25 and IL-33 and thymic stromal lymphopoietin (TSLP), in the epithelial cells of the airway. These cytokines induce the TH2 immune response to airborne allergens in the lungs. The production of certain cytokines, such as IL4, IL5, and IL13, by the TH2 cells subsequently increases eosinophil and mast cell recruitment, causing inflammation of the airway, cell metaplasia, and bronchoconstriction.[64]

However, not all individuals who contract a respiratory virus infection suffer an asthma exacerbation, so the possibility that certain risk factors increase susceptibility to present wheezing after viral infection has been explored. Studies conducted by Wark et al.[65] and Contoli et al.[66] suggest that the absence of an efficient innate immune response, manifested by low interferon levels in the epithelial cells of asthma patients, may assist viral replication, leading to an exaggerated asthmatic response.

It seems highly likely that an altered immune response to viral infections in genetically predisposed subjects are the major factors involved in the virus–asthma relationship.

Conflict of Interests

The authors declare that they have no conflict of interests.

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