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CME review

Post Infectious Bronchiolitis Obliterans in Children

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EDUCATIONAL AIMS THE READER WILL BECOME FAMILIAR WITH:

- The risk factors and epidemiology of post-infectious bronchiolitis obliterans (PBO)
- The diagnostic criteria of PBO
- The importance of imaging and pulmonary function testing in the diagnosis and follow-up of PBO
- The multidisciplinary strategy for treating PBO
- What is known about outcomes and prognosis of PBO

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SUMMARY

Bronchiolitis Obliterans (BO) is an infrequent chronic and obstructive lung disease secondary to an insult to the terminal airway and its surroundings. In children, the most common presentation is the post-infectious variant, closely related to a severe viral infection in the first three years of life. However, the increase in the number of lung and bone-marrow transplants has also been followed by an increase in post-transplant BO. Post-transplant BO is progressive while post-infectious BO does not seem to be, but both forms share some common pathways that result in a characteristic histopathology of bronchiolar obliteration. This review covers up-to-date evidence on epidemiology, diagnosis, treatment and prognosis of post-infectious bronchiolitis obliterans, including areas of controversy that need to be addressed in future studies.

INTRODUCTION

Bronchiolitis Obliterans is a rare form of chronic obstructive lung disease secondary to a severe insult to the lower respiratory tract that leads to a variable degree of inflammation and scarring. The ultimate result of this process is the narrowing and/or complete obliteration of the small airways.[1] In children, the most common form is post-infectious bronchiolitis obliterans (PBO), except in locations with a considerable number of paediatric lung or bone marrow transplant recipients.

As a disease, PBO has been reported in North and South America, Western and South-Eastern Europe, India, South-Korea, Taiwan, Malaysia, New Zealand, and Australia. In the last two decades of the 20th century, South American countries accumulated an unexpected number of cases: more than seven hundred, according to the Bronchiolitis Obliterans in Latin America (BOLAT) initiative. This review covers important information on the epidemiology, risk factors, diagnosis, imaging, lung function, treatment and prognosis of PBO.

EPIDEMIOLOGY

There are reports of PBO secondary to influenza, parainfluenza, measles, respiratory syncytial virus, varicella, and Mycoplasma pneumoniae. However, adenovirus (Ad) is by far the most common agent linked to the development of PBO.[2–4] Thus, although the prevalence of PBO is not known, its epidemiology is directly related to the epidemiology of severe viral respiratory tract infections in

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young children, particularly of adenoviral aetiology. The serotypes mostly involved are Ad3, Ad7 and Ad11, according to a surveillance study in South America.[5]

One study from Chile analysed respiratory samples from over nine thousand children younger <2 years old hospitalized due to lower respiratory tract infection (LRTI), in an eight year period.[6] Three percent of children had adenovirus confirmation which represented 20% of all viruses identified. The predominant strain, Ad7 h, was associated with more severe cases in the region.[5] Another two studies from Argentina and Chile analysed inpatient children <2 years old hospitalized with adenoviral confirmed LRTI. Of these, 10-15% died and 30-40% progressed to develop PBO.[7,8] High viral prevalence and low socio-economic status, which is related to poor sanitation, lower hygienic practices, indoor smoking and overcrowding, contribute to facilitate the transmission of viral diseases, particularly from adenovirus, elevating the risk for developing PBO.[9] Race has also been suggested as a predisposing factor for PBO. In a preliminary study on genetic profiles, an Argentinean group found that their PBO patients had an increased frequency of an allele highly expressed in an Amerindian population.[10] In contrast, 70% of the PBO children followed-up in Porto Alegre (Southern Brazil) are Caucasian,[11] and a different distribution may be found in other centres with PBO patients, according to their local racial composition.

The number of new cases seems to be dropping since the beginning of the 21st century. More than improvement in socio-economic conditions, the epidemiology of viruses is a plausible explanation for this shift. A recent study demonstrates how the prevalence of human adenovirus serotypes affecting the respiratory system may change over time due to adaptive mechanisms of viruses or to changes in the host immune response to these agents or both. The most important serotypes related to respiratory disease in hospitals from two provinces of South Korea, from 1990-2007, were Ad3 and Ad7. However, although Ad7 outbreaks were more frequent in the first years of the period, the frequency of outbreaks and number of cases progressively diminished so as to not identify any cases in the last two years of surveillance. Conversely, Ad3 had less frequent outbreaks and number of cases at first but became prevalent thereafter with frequent outbreaks and a stable number of cases through the second half of the period.[12] Coincidently, their most severe cases of LRTI were due to Ad7.[13] In the southern cone of South America, Ad7 h was the predominant and most aggressive variant during a 10-year surveillance from 1985-1995,[5] but, after a progressive decline, it was last detected in 2005. This could explain part of the reduction in new PBO cases seen in the region.

Risk Factors and Diagnosis

In children, the most important risk factor related to the development of PBO is, by far, a LRTI caused by adenovirus. In a group of 109 children with PBO and 99 controls, Colom *et al.* [2006] found that those with adenoviral infection were more likely to develop PBO disease when compared to other viruses, including respiratory syncytial virus, influenza and parainfluenza (OR = 83; 95% CI = 22 – 44) [4]. In their multivariate logistic regression analysis, adenoviral infection (OR = 49; 95% CI = 12 – 99) and mechanical ventilation (OR = 11; 95% CI = 2.6 – 45) were two strong risk factors for developing PBO.[4] Castro-Rodriguez *et al.* [2006] studied prospectively the risk for developing PBO in a 5-year follow-up of 45 infants previously hospitalized with adenoviral pneumonia [8]. Compared to those who did not develop the disease, children who developed PBO had more respiratory treatment (intensive care admission, mechanical ventilation, need for supplemental oxygen, as well as use of systemic corticosteroids and beta-2 agonists).[8] Murtagh *et al.* [2009] studied risk factors for PBO in 415 children hospitalized with confirmed adenoviral LRTI.[7] Of those 150 that developed the disease, the risk factors for developing PBO were hospitalization >30 days (OR = 27.2; 95% CI = 14.6 – 50.9), multifocal pneumonia (OR = 26.6; 95% CI = 5.3 – 132), and hypercapnoea (OR = 5.6; 95% CI = 3.5 – 9).[7]

Table 1
Criteria used in Conjunction to reach the Diagnosis of PBO

1) History of an acute and severe bronchiolitis/viral pneumonia in previously healthy children during their first three years of life;
2) Evidence of persistent airway obstruction after the acute event, identified either by physical examination and/or by lung function tests. This airway obstruction is unresponsive to, at least, a two-week course of systemic corticosteroids associated to bronchodilators;
3) Chest radiograph findings of obstructive lung disease such as hyperinflation, atelectasis, airway wall thickening and bronchiectasis;
4) Mosaic pattern and air trapping in chest computed tomography;
5) Exclusion of other chronic lung diseases that progress with permanent respiratory symptoms, including tuberculosis, cystic fibrosis, bronchopulmonary dysplasia, immunodeficiencies, severe asthma, and alpha-1- antitrypsin deficiency.

In terms of diagnosis, there are no specific signs and symptoms of PBO. The ideal diagnosis requires histopathologic confirmation but the clinical instability of patients increases the risks of lung biopsy complications, and the patchy distribution of the lesions makes adequate sampling challenging.[2,14] Therefore, clinical and imaging criteria are combined along with laboratory testing for agent identification and ruling out other forms of chronic lung disease[15–17] (Table 1).

Clinical criteria from Table 1 are applied and test results are obtained, but a final diagnosis is reached only after the triggering event is over. The clinical presentation of this initial infection depends on the interaction between the host's immunological status and response, and the immuno-challenging characteristics of the infecting microorganism. Different to respiratory syncytial virus, adenovirus elicits an intense Th1 response during the infecting period that is maintained while the virus is still present, leading to an intense inflammatory response.[18]

A clinical prediction rule to diagnose PBO was recently published,[19] although the authors acknowledge that its development was based only on severe forms of the disease. It is composed of the following four variables: typical clinical history, history of adenovirus infection, high-resolution computerized tomography (HRCT) with mosaic pattern, and history of mechanical ventilation. It will be interesting to assess its external validity in other centres as well as considering its applicability in less severe forms of the disease. Recently also, the first national guidelines for the diagnosis and care of children with PBO were developed by an expert panel and published in Chile with a multidisciplinary approach.[20]

Histopathology

At lung biopsy an inflammatory process surrounding the lumen of bronchioli resulting in concentric narrowing and obliteration of the small airways is observed. The variability of chronic inflammation among patients was shown by Mauad *et al.* [2002] in a Brazilian study.[1]

Imaging in PBO

Imaging techniques, particularly HRCT, play an important role in the diagnosis of PBO.[2,21] There is no individual method or image that is specific for PBO. However, imaging assists in reaching the diagnosis when considered in conjunction with clinical and laboratory information and provides an indication of the extent of pulmonary involvement. The three commonly used imaging methods are: conventional chest radiograph (CXR), lung ventilation/perfusion scans (V/Q scan) and high resolution chest