Post-viral Bronchiolitis Obliterans

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Chronic pulmonary disease in infancy is common in premature newborns with bronchopulmonary dysplasia secondary to mechanical ventilation or oxygen therapy and in children with cystic fibrosis. A less frequent cause is Bronchiolitis Obliterans (BO) that results from an insult to the lower respiratory tract\(^1\). BO has been reported more frequently in Argentina\(^2\), Chile\(^3\) and south of Brazil\(^4\); less frequent in Korea\(^5\), Turkey and Russia; and infrequent in developed countries. BO is characterized by fibrosis of the terminal and respiratory bronchioles. This leads to narrowing and/or complete obliteration of the small airways. The pathologic correlate of BO is a common endpoint for many disorders that insult the bronchial and/or bronchiolar mucosa. Aside from chronic rejection of lung or heart-lung transplantation\(^6,7\) and graft-versus-host disease associated with bone marrow transplantation, post-infectious BO is the most common form of BO in children worldwide. Adenovirus\(^8\) in young children and Mycoplasma\(^9\) Pneumoniae in older children are the more frequent causes associated with this entity. Respiratory syncytial virus\(^10\), parainfluenza\(^11\), influenza\(^12\) and measles\(^13\) also have been associated with BO. Chronic aspiration, toxic fume inhalation and drugs are other causes of BO. Children with BO have a highly and variable prognosis, with significant long-term morbidity reported in 78% to 92% of patients, depending on the etiology of the initial result.

Clinically, it is characterized by tachypnea, increased antero-posterior chest diameter, crackles, wheezing, and hypoxemia for at least 30 days after the initial injury. Pathologically, BO is characterized by bronchiectasis of the large airways and luminal obstruction with inflammation, granulation tissue, and/or fibrosis and obliteration of the small airways\(^14,15\).

During the past 30 years, there have been occasional reports of children who presented with severe adenoviral lower respiratory tract infection and experienced subsequent chronic respiratory insufficiency\(^16,17,18\). Since 1984, a new genome type of adenovirus (AV7h) has been associated with epidemic outbreaks of respiratory tract infection in Argentina and Chile\(^19,20\). The increased pathogenicity of this serotype, a potential host genetic susceptibility, or environmental factors might have predisposed certain children to develop BO. We performed a case-control study\(^8\) that included 109 cases (with bronchiolitis followed by bronchiolitis obliterans) and 99 controls (patients with bronchiolitis who did not develop bronchiolitis obliterans). The two main factors associated with the development of bronchiolitis obliterans were adenovirus bronchiolitis (odds ratio (OR) 49) and mechanical ventilation (OR 11). Although mechanical ventilation was a significant risk factor for post-infectious BO, the results do not indicate whether it causes injury to the lung that increases the risk for developing post-infectious BO or whether it merely serves as an indicator of severity of illness. The central role of AV in the development of post-infectious BO has been well documented and in our cohort is present in 70–80% of post-infectious BO patients.
The host immune response against AV infection was well described by Mistchenko et al. in Argentina. Patients with severe AV infection have been shown to have immune complexes containing AV antigen in the lung, as well as increased serum levels of interleukin-6, interleukin-8, and tumor necrosis factor-α. Kajon et al. studied the immune response to AV 3p and 7h in an animal model. A marked infiltration of neutrophils into the lung air spaces was observed at 1 and 2 days postinfection, with a concomitant increase in the levels of neutrophil chemokines MIP-2 and KC. Remodeling of the airway epithelia and mucous cell metaplasia were noted in the proximal airways of infected mice, indicating marked epithelial differentiation and/or injury. The proinflammatory cytokines interleukin-beta (IL-1beta), tumor necrosis factor-alpha (TNF-alpha), interferon-gamma (IFN-gamma), and interleukin-12 (IL-12) were induced by viral infection.

Chronic lung disease after adenoviral infection in native populations was described by Lang et al (New Zealand, 1969) and Wenman et al (Canada, 1982). Although both studies have not discussed the difference in the prevalence of this disease between natives (Maoris or Amerindians) and white population, is worth to note that the incidence of BO was significantly higher in natives. This findings and the observation that almost all of our BO patients have similar phenotypic characteristics, have encouraged us to study the possible association of BO with a genetic predisposition. We have studied the Amerindian lineages in 56 BO patients compared with 41 healthy controls. Maternal lineages were studied by the molecular analysis of the mitochondrial DNA and paternal lineages by the analysis of the Y chromosome. BO patients had significant more prevalence of Amerindian lineages in the mitochondrial DNA. In addition, we have investigated the association of BO with Human Leukocyte Antigens (HLA) comparing 58 patients with 342 Caucasian controls. Patients with BO showed a significant increase of HLA A31, HLA DRB08 and DR-QB10302. These particular HLA antigens are more frequent in Amerindian population. Both studies suggest that native Amerindian population have a probable genetic predisposition to develop post-infectious BO.

In our cohort of post-infectious BO patients, illness occurred in very young infants, younger than six months, but our findings did not show that age was a risk factor for developing post-infectious BO. Initially, these patients present with symptoms that do not differ from a typical RSV bronchiolitis. During the admission examination, most patients are found to have severe airway obstruction with hypoxemia and in many cases require mechanical ventilation. Physical findings are usually nonspecific. Expiratory wheezing and occasional crackles may be heard on chest auscultation. When an AV infection is detected and the patients do not get better after three weeks, BO should be suspected. After patients’ conditions have become stable they still show persistently high respiratory rates, rigid thorax, wheeze and productive cough. Oxygen saturation is often lower than normal.

Chest X-rays in BO patients are nonspecific but show air trapping, atelectasis, peri-bronchial thickening and honeycombing. Some patients show unilateral lung/lobe involvement, with hyperlucent and small lung, known as Swyer-James or MacLeod syndrome, due to loss of the pulmonary vascular structure and air trapping. Lung
perfusion scans show perfusion defects, with lobar, segmental, or subsegmental pattern. Comparing lung perfusion scans with chest radiographs, the defects on lung scans correspond to areas with more prominent abnormalities, such as bronchial wall thickening and bronchiectasis. Lung perfusion scans cannot describe the nature of bronchopulmonary abnormalities; however, this examination provides an objective evaluation regarding the extent, distribution and severity of bronchopulmonary lesions. The most characteristic signs of BO with High-resolution CT (HRCT) are areas of mosaic attenuation pattern due to shunting of blood away from the under-ventilated to the normally ventilated lung, where perfusion is reduced in areas of decreased parenchyma attenuation due to hypoxic pulmonary vasoconstriction. Other signs include air trapping, especially on expiratory CT, and bronchial abnormalities. Air trapping, as detected on expiratory HRCT, has been described as the most sensitive and accurate radiological indicator of BO in the lung transplant population. Infant pulmonary function in post-AV BO shows severe and fixed bronchial obstruction decreased pulmonary distensibility and increased airway resistance. These patients have more severely affected V'/maxFRC than in other diseases such as bronchopulmonary dysplasia or asthma which, even in their most severe forms, usually respond to bronchodilators. These findings might represent the functional expression of the histopathological damage of bronchiolitis obliterans. When other causes of chronic lung disease have been eliminated, the patient’s clinical history, chest radiographies and HRCT images are sufficient in most cases to confirm the diagnosis and to differentiate post-infectious BO from other pulmonary disorders. These clinical evaluations should be considered in tandem with the functional pattern in post-infectious BO. If doubt persists about the diagnosis, a lung biopsy may be needed. Recently, Colom et al developed a diagnostic score for BO. We compared a group of confirmed BO patients under 2 years old (clinical history, lung function tests and CT scan compatible) with infants and young children with other confirmed chronic lung diseases such as primary ciliary diskinesia (PCD), cystic fibrosis (CF) and bronchiectasis of different etiologies than BO, PCD and CF. BO diagnosis was considered the dependent variable. Predictive variables were: a) “clinical history”, defined as a previous healthy child, who suffered a severe viral infection and remained with chronic respiratory symptoms and hypoxemia (SaO₂ <92%) for more than 60 days; b) antecedent of “adenoviral infection”; c) “mechanical ventilation” requirement; and three HRCT patterns: d) “mosaic pattern”; e) “atelectasis” and f) “bronchiectasis”. This score was constructed assigning 4 points to “clinical history”, 3 points to “adenoviral infection” and 4 points to “mosaic pattern”. A score of ≥ 7 has 100% specificity (95% CI, 79-100) and a sensibility of 67% (95% CI, 47-80) with a positive predictive value of 100% (95% CI, 82-100) and a negative predictive value of 57% (95% CI, 37-75). The score was internally validated using the data-splitting.

Most patients with post-infectious BO require oxygen supplementation for nearly a year after discharge from the initial hospital admission. Readmission to hospital will probably be required for subsequent infections of the lower respiratory tract. The number of readmissions diminishes and hypoxemia improves slowly over several years. We performed a second pulmonary function test one year after the diagnosis, and results did not differ from the initial lung function test. In older children, only few patients require oxygen supplementation. Spirometry test results show evidence of airflow limitation, and plethysmography demonstrates gas trapping with normal or high total lung volumes.
Therefore, pulmonary function remains severely impaired, showing a moderate-severe obstructive pattern\(^3\). Children with post-infectious BO have moderate compromise of mechanics as measured by forced oscillation, with high resistance and low compliance\(^3\). Clinical improvement during the disease process may be due to the growth of the lungs in these children, and probably does not indicate regression of the pathology in the small airways. The overall prognosis of pulmonary function was poor in the majority of the cohort studies published. Mortality and morbidity rates associated with post-infectious BO remain uncertain.

The majority of evidence suggests that BO is immune mediated, so therapeutic interventions have focused on the suppression of the inflammatory response. Anti-inflammatory therapy such as corticosteroids, chloroquine and hydroxychloroquine has been tried in small clinical trials and case reports with minimal success. Because bronchiolitis obliterans is so rare, controlled and randomized therapeutic clinical trials have been impossible to perform. Although multiple cytokines and chemokines have been identified in the pathogenesis of BO, tumor necrosis factor-\(\alpha\) (TNF) seems to play a central role in the inflammatory reaction and enhances fibroblast proliferation. A case report describes successful treatment of BO in a bone marrow transplant patient with TNF-\(\alpha\) blockade\(^3\) (Infliximab). Other studies suggest a potential role for maintenance of Macrolide\(^7\) therapy in the treatment of bronchiolitis obliterans where the anti-inflammatory properties and ability to reduce inflammatory mediators of IL-8, TNF-\(\alpha\), and IL-1\(\beta\) may play a role. When the disease is well established, however, the principal treatment is supportive and includes bronchodilators, chest physical therapy, antibiotics for acute respiratory infections, and in some patients, diuretics. Gastroesophageal reflux has been increasingly recognized as a factor that may significantly contribute to BO, so when it is recognized, treatment is warranted.

Post-infectious BO has been reported in limited areas, where its impact is profound. Although research has identified the risk factors that can lead to post-infectious BO, knowledge about factors inherent to the population, such as a genetic predisposition to develop the disease is still scarce. Clinical trials of potential therapeutic agents should be multicenter studies in order to include a significant number of patients. Important factors to consider include the ideal timing, dosage and best choice of immunosuppressive agent to avoid the development of the disease.

References


