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Risk Factors for Development of Bronchiolitis Obliterans in Children with Bronchiolitis

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ABSTRACT

Background: bronchiolitis obliterans (BO) is an uncommon and severe form of chronic obstructive lung disease in children that results from an insult to the lower respiratory tract.

Methods: we performed a case-control study with 109 cases and 99 controls in children under the age of 3 years to determine risk factors for the development of bronchiolitis obliterans. Participants were evaluated with immunoflourescence viral testing, pulmonary function, and questions to assess tobacco and other exposures.

Results: bronchiolitis due to adenovirus (odds ratio = 49, 95% confidence interval = 12-199) and the need for mechanical ventilation (odds ratio = 11, 95% confidence interval = 2.6-45) were strongly and independently associated with increased risk for bronchiolitis obliterans. Factors not associated with post-infectious BO included child age, gender, and environmental tobacco exposure (either in uterus or during infancy).

Conclusions: we found that adenovirus infection and need for mechanical ventilation are significant risk factors for developing bronchiolitis obliterans in children. Further research is indicated to why these risk factors are so strong and how they may contribute to development of the disease.

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INTRODUCTION

Bronchiolitis obliterans (BO) is an uncommon and severe form of chronic obstructive lung disease in children that results from an insult to the lower respiratory tract, which occurs in a number of forms. Among clinical scenarios reported in the literature are after Stevens-Johnson syndrome, as a complication of graft versus host disease in bone marrow transplant recipients and as a manifestation of chronic graft rejection in lung transplant recipients. However, in many parts of the world, BO is most commonly seen in children after severe viral lower respiratory tract infections. [1] Clinically, it is characterized by tachypnea, increased antero-posterior chest diameter, crackles, wheezing, and hypoxemia for at least 30 days after the initial injury. [2] Pathologically, BO is characterized by luminal obstruction with inflammation, granulation tissue, and/or fibrosis and obliteration of the small airways and bronchiectasis. [3]

Post-infectious BO has been reported mainly in the southern hemisphere (Argentina, Chile, southern Brazil, Australia, and New Zealand), where its impact can be profound. In the respiratory center of Ricardo Gutiérrez Children's Hospital in Buenos Aires, for example, post-infectious BO accounted for 14% of all bed-days during the 10-year period from 1993-2002.

A number of respiratory viruses, including respiratory syncytial virus (RSV), [4] parainfluenza, [5] influenza, [6] and especially adenovirus (AV), [7] were associated with severe lung injury leading to BO. Although BO has been observed commonly after viral infections, research has not yet quantified the importance of specific viruses as risk factors for BO. Instead, our current knowledge of post-infectious BO is based largely on a few case series in which the antecedent risk factors have not been clearly identified. [8][9][10]

In order to address this knowledge gap, we performed a case-control study of children in Buenos Aires, Argentina, in order to determine risk factors for the development of post-infectious BO.

METHODS

Potential cases included all children treated for post-infectious BO from 1991 to 2002 at the Children's Hospital in Buenos Aires, Argentina (identified from retrospective chart review). Children included were aged 3 years or younger, with chronic respiratory insufficiency (defined as tachypnea, increased antero-posterior chest diameter, crackles, wheezing, and hypoxemia (SaO_2<93%) lasting for at least 30 days after initial injury) after severe bronchiolitis in a previously healthy infant.[2] Children with co-existing cystic fibrosis, congenital heart disease, or primary ciliary dyskinesia, were excluded. One hundred nine children met these criteria.

Control subjects were identified from the population of new cases of bronchiolitis (first episode of wheeze) who were admitted to our hospital during 2002 and who did not subsequently develop BO. A 12-month period was chosen to encompass the full spectrum of bronchiolitis cases that are seen during a year and thus avoid biases associated with seasonality. Similar exclusion criteria were applied to controls as to cases. A total of 161 potential controls were identified in this manner, and 99 who meet the inclusion/exclusion criteria were included.

Our study identified results of indirect inmunofluorescence viral testing (IFI) in nasopharyngeal secretions performed for adenovirus, respiratory syncytial virus, influenza, and parainfluenza virus. These tests are routinely done on patients admitted for bronchiolitis and so were available

in the medical records of most cases (64%) and controls (93%). Several post-infectious BO patients were initially treated in other hospitals and thus did not have viral testing results available.

Chest X-rays and HRCT scans were reviewed and interpreted by two pediatric radiologists experienced in the interpretation of HRCT.

Infant pulmonary function tests (PFTs) were routinely performed only in BO patients. PFTs were done when the patient's condition was stable (absence of an acute respiratory tract infection for 30 days, lack of upper airway secretions, and normal hemodynamic parameters). Partial-forced flow/volume curves and compliance and resistance measurements were done according to the ATS/ERS guidelines. [11] Values of maximal flow at functional residual capacity (V`max FRC) were expressed as z-scores. [12][13]

Data about current environmental tobacco smoke (ETS) exposure and ETS exposures during pregnancy were obtained from the medical records or from interviews with the parents.

Statistical Analysis

Assuming that 10% of control subjects would have adenovirus exposure, the study had 80% power to detect a 16% difference in AV exposure probabilities between cases and controls. Risk factors were assessed using logistic regression analysis, and results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Interaction terms were used to test for lack of additivity of effects on the ln(odds) scale. The following variables were considered as potential risk factors for post-infectious BO: gender, pre- and post-natal ETS exposure, age younger than 6 months at the time of admission for bronchiolitis, evidence of specific viral etiologies for the

bronchiolitis, and the need for mechanical ventilation (MV) during the target admission. The 6-month age cut-off was used because 67% of the patients were younger than 6 months of age.

Analyses were performed using the STATA (College Station, TX) [14] and EPI-INFO [15] statistical software packages. A p-value ≤ 0.05 was selected for statistical significance.

RESULTS

Participants ranged in age from 1-26 months at the time of their initial admission for bronchiolitis, with mean age 7 months among cases and 5 months among controls (Table 1). Sixty percent of cases and 58% of controls were boys. The number of new cases of post-infectious BO during the period of the study showed substantial variation from year to year (Figure 1). Almost all (98%) of the controls were admitted in the fall or winter, compared with 75% of post-infectious BO patients. In those post-infectious BO patients tested, AV was detected in 72% , RSV in 10%, parainfluenza in 4%, and influenza in 1%. In control patients, RSV was the virus most frequently identified (58%), and only 3% were positive for AV. Thirty-four percent of post-infectious BO patients required mechanical ventilation, versus only 3% of patients in the control group. The median stay in the hospital was 30 days (range 11-120) in post-infectious BO patients and 6 days in controls (range 1-40 days).

In bivariate analyses, adenovirus infection (OR = 83, CI = 22-441) and the need for mechanical ventilation (OR = 12, CI = 5-34) stand out as exceptionally strong risk factors (see Table 1).

In multivariate logistic regression models, AV infection and the need for mechanical ventilation persisted as significant predictors of risk for post-infectious BO (see Table 2). A formal test for interaction in the logistic model was not significant.

Table 1. Study population and risk factors for developing post-infectious BO. Bivariate analysis.

	Progressed to Bronchiolitis obliterans				
	YES	**NO**	**Odds Ratio**	**95% CI**	**p value**
N	109	99			
Age (months)	6 (1-26)*	5 (1-20)*			
< 6 months	67%	72%	0.5	0.3-0.9	0.02
Male	60%	58%	1.1	0.6-2	0.8
Admitted in fall or winter	75%	98%	1	0.8-1.2	0.9
ETS exposure in uterus	24%	12%	1.6	0.7-4	0.3
Current ETS exposure	59%	38%	2.2	1.2-4	0.01
Adenovirus infection	72%	3%	83	22-441	<0.001
Mechanical Ventilation	34%	7%	12	5-34	<0.001

*data are expressed as median and range.

Table 2. Multivariate logistic regression analysis of risk factors for the bronchiolitis obliterans.

Variable	Odds Ratio	95% CI	p value
Age < 6 mos (vs >=6 mos)	1.4	(0.4, 5.4)	0.6
Gender: male (vs. Female)	0.8	(0.2, 2.6)	0.7
ETS at present	1.4	(0.4, 4.5)	0.5
ETS during pregnancy	0.4	(0.1, 3.2)	0.4
Adenovirus infection	*49*	*(12, 199)*	*<0.001*
Mechanical Ventilation	*11*	*(2.6, 45)*	*0.001*

Age: younger than 6 months; ETS: environmental tobacco exposure; ETS-P environmental tobacco exposure during pregnancy; AV: Adenovirus infection; MV: Mechanical ventilation.

Clinical Findings

At the time of our clinical evaluation of the post-infectious BO cases, which occurred an average of 4 months after the onset of illness (range 5-30 months), chest X-rays and PFTs were performed. Patients with BO had high respiratory rates (mean 37 breaths per minute, range 35-40). Seventy percent (56/80) had a rigid thorax, 74% (69/93) had wheeze, and 89% (81/91) had persistent productive cough. Oxygen saturation was lower than normal (mean SaO_2 = 92%, SD = 5). Most children were not malnourished (Z-score (mean ± SD) length for age –1.6±1, weight for length –0.45±1).

Chest X-rays (reported in 98 of the cases) in post-infectious BO patients showed air trapping (96%), atelectasis (75%), areas with an increased interstitial pattern (55%), and honeycombing (34%). The most frequent findings of the high-resolution computed tomography (HRCT) (reported in 62 of the cases) were mosaic perfusion (60%), bronchiectasis (58%), and atelectasis (44%).

Pulmonary function tests were performed in 68% of post-infectious BO patients (75/109) and showed (Figure 2) severe fixed airflow obstruction (mean V`max FRC z-score = -3.1 ± SD = 0.8), decreased compliance (1.21 ± 0.5 ml/cmH_2O/kg), and increased resistance (0.05 ± 0.02 cmH_2O/ml/seg). The mean bronchodilator response was 7%. Some patients did not perform the test because they were older than 2 years old or because of the severity of the illness.

Most post-infectious BO patients (57%) required oxygen supplementation after discharge from the initial hospitalization, for a median period of 17 months (range 1 to 62 months).and the vast mayority (95%) required hospitalization due to subsequent low respiratory tract infections. Hypoxemia improved slowly over several years and only 3% (1/37) remained on supplemental

oxygen requirements at the age of 6 years.

DISCUSSION

This study is notable as it reports the largest sample of pediatric post-infectious BO patients in the medical literature to date. This study demonstrates that adenovirus infection and the need for mechanical ventilation are strong, independent risk factors for developing post-infectious BO in children under 3 years. During the last two decades there have been a growing number of reports of patients with post-infectious BO. Although, there are no worldwide studies of the prevalence of post-infectious BO, it has been reported mainly in certain areas. These areas include Argentina, Brazil, Chile, New Zealand, Canada, and South Korea. For unknown reasons large areas such as the US and Europe have not had frequent reports. [2][8][9][10] The reason of the difference in the prevalence of the disease may be due to the severity of the adenovirus infections according to the serotype and to a genetic predisposition to develop the disease, particularly among unique populations derived from populations native to those regions [16][17][18][19]. The central role of adenovirus in the development of post-infectious BO has been well documented [16]. In our study, adenovirus was identified in 71% of the post-infectious BO patients in whom diagnostic testing was performed. Although since 1984 a new genotype of adenovirus, AV7h, has stood out as the most virulent serotype, other AV (e.g., 3, 5, and 21) also cause BO. [17] Epidemiological studies indicate that the global prevalence patterns of adenovirus genome types do shift over time and geographical region, which may make it technically difficult to develop a new vaccine with broad applicability. [20]”

Patients with severe adenovirus infection have been shown to have immune complexes containing adenovirus antigen in the lung, as well as increased serum levels of interleukin-6, interleukin-8, and tumor necrosis factor-α. [21][22] These previous studies suggest that a specific immunologic response may be important in the development of BO following adenovirus infection. [23] In the present study, illness occurred in very young infants--67% were younger than 6 months, and 93% were younger than 12 months--but our findings did not show that age was a risk factor to develop post-infectious BO. In previous studies, patients admitted with bronchiolitis and malnutrition had a more severe course [24]; however, malnutrition was not an important factor in the present study, as most of the children were not malnourished. Although AV was identified in most of the post-infectious BO patients at the onset of the illness, other viruses also were found. RSV is the most frequent casual agent of bronchiolitis, and occurs mainly during winter months. An association between BO and RSV has only rarely been reported, [25] [4] and the pathogenesis of BO is not clear in these patients. Simultaneous infections of RSV and AV also have been reported. [25] [26] In these cases, it would seem most likely that the AV infection is the cause of BO. About a quarter of the total diagnosed cases infected with influenza develop complications, mostly in younger children (0-4 years of age). [27] Bronchiolitis obliterans, however, is a rare complication of influenza, with only a few cases reported in infancy and early childhood. [6]

The use of mechanical ventilation, an important treatment for children in intensive care units, has apparently allowed severely ill children to survive who previously would have died before BO could be recognized. Mechanical ventilation is indispensable for support of critically ill patients with respiratory insufficiency. Although our study found MV to be a significant risk factor for post-infectious BO, our results do not indicate whether MV causes injury to the lung that increases the risk for developing post-infectious BO or whether MV merely serves as an indicator

of severity of illness. Mechanisms by which MV could cause lung injury could include untoward effects from volutrauma, oxygen toxic effects, and barotrauma. [28] Further research is indicated to clarify the relationship between MV and post-infectious BO, and to study whether lung protective strategies are needed for this vulnerable population. Cidofovir, a new antiviral agent is under investigation and may be an alternative for adenovirus treatment in the future. [29]

The ethnic background of patients is another factor that has been linked with risk for development of post-infectious BO. Two ethnic indigenous populations of children, in New Zealand and central Canada, [18][19] have been reported to be particularly susceptible to develop post-infectious BO, suggesting that genetic factors may be important. [30] Our study evaluated children of different geographic origins but did not assess ethnicity. The relationship of post-infectious BO to race/ethnicity is an interesting and important topic for future research.

All tested patients with post-infectious BO showed a V´max FRC that was severely affected even more affected than in other diseases, such as bronchopulmonary dysplasia or asthma, which even in their most severe forms usually respond to bronchodilators. This finding confirms our previous report about PFTs in post-infectious BO patients. [2] Evaluating pulmonary function allowed us to improve the diagnostic approach to pst-infectious BO. We believe that the patient's clinical history and the radiological and HRCT images allow us in most cases to confirm the diagnosis and to differentiate post-infectious BO from other pulmonary disorders. [2] These clinical evaluations should of course be considered in tandem with functional pattern, which in post-infectious BO is characterized by severe and fixed obstruction, with an increase in resistance and a decrease in lung compliance. In the few cases in which doubt persists about the diagnosis, a lung biopsy may be needed.

We conclude that both adenoviral infection and mechanical ventilation are strongly associated with the development of post-infectious BO. The immunological response of the host and genetically determined factors could be additional factors that modify or increase susceptibility to post-infectious BO. Strategies to prevent infection with AV, such as development of a vaccine, should be encouraged to prevent this devastating illness. For now, early recognition is key so that children can be isolated to prevent the spread of infection to others. When AV is suspected or isolated, early aggressive treatment is warranted, and future clinical studies are required to determine the best treatment strategies.

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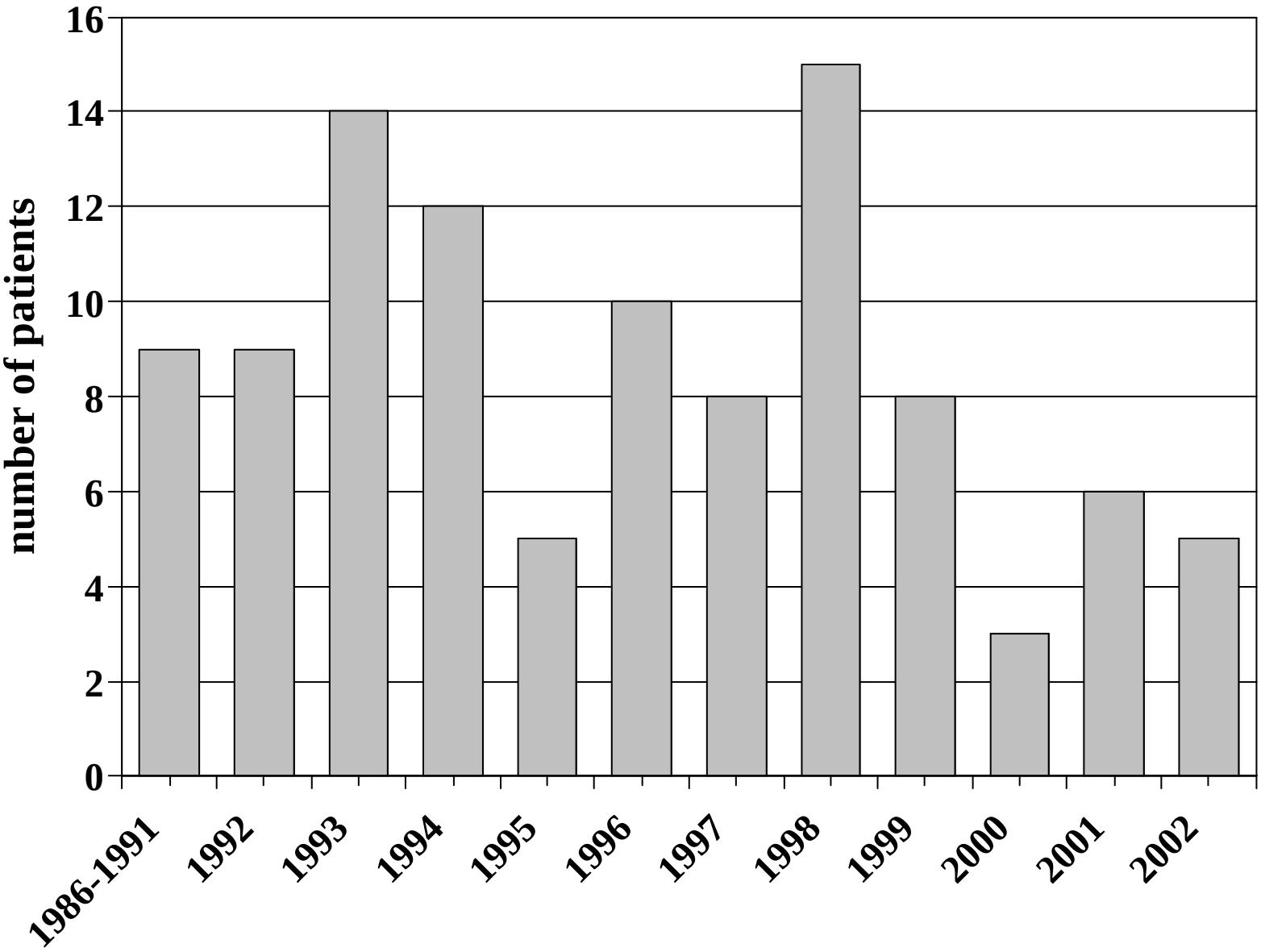
LEGENDS FIGURES

Figure 1. Cases of post-infectious BO by calendar year

Figure 2. Pulmonary function of patients with post-infectious BO

Figure 1. Cases of BO by calendar year.



Z-score V´maxFRC