Adenovirus Pneumonia in Infants and Factors for Developing Bronchiolitis Obliterans: A 5-Year Follow-Up

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Summary. To describe clinical, pulmonary function, and chest tomography profiles in a 5-year follow-up of infants with adenovirus pneumonia and determine the factors that potentially contributed to the development of bronchiolitis obliterans (BO). We prospectively assessed 45 hospitalized infants with adenovirus pneumonia with additional follow-up for 5 years. At the end of the study, pulmonary function by impulse oscillometry technique (IOS) and chest tomography were performed in the 38 surviving patients (mean 5.7 years of age). We divided the population between those who developed chest tomography evidence of BO and those who did not. Most of the children developed adenovirus infection before 2 years of age. During the 5 years of follow-up, almost half (47.4%) developed BO. Children who developed BO had significantly more respiratory compromise (intensive care admission, need for mechanical ventilation and for oxygen therapy, and systemic corticosteroid and beta agonist use) during their adenovirus pneumonia episode than those who did not develop BO. Only 33.3% of children with BO had normal impedance compared with 85% in the no BO group. Children who developed BO had significantly higher levels of Zrs, R5, X5 and predicted Zrs, R5, and X5 and frequency. However, there were no differences in the beta 2 agonist response between the children with and without BO (94% vs. 80%, respectively). This study represents the spectra of adenovirus pneumonia ranging from relatively mild to severe and fatal cases. Children with severe pulmonary compromise are usually more prone to develop BO.

Key words: bronchiolitis obliterans; adenoviridae; pneumonia; children.

INTRODUCTION

Adenovirus infections occur primarily in infants and children less than 5 years of age, accounting for 2–5% of pediatric respiratory illnesses and 4–10% of childhood pneumonia.[1] The severity of adenovirus lower respiratory tract infections (LTRIs) varies according to serotype, age of onset, immunological status, and socioeconomic and environmental factors. Most patients recover from adenovirus LRTIs, but severe adenovirus infection can result in considerable morbidity and mortality.[2] Adenovirus pneumonia may occur in two phases: acute with extensive pulmonary consolidation mimicking a bacterial pneumonia and accompanying systemic compromise characterized by multi-organ involvement, causing considerable morbidity and mortality;[2,3] and in some cases followed by a chronic phase characterized by persistent wheezing and crackles, perhaps severe enough to require prolonged mechanical assistance or domiciliary oxygen therapy and development of cor pulmonale, culminating in bronchiolitis obliterans (BO) with hyperinflation, hyperlucency, athelectasis, and bronchiectasis.[4–7] It has been noted that 14–60% of children with documented LRTIs due to adenovirus have some degree of pulmonary sequelae.[3]

In childhood, BO has been described as a result of a number of infections, including measles, *Bordetella pertussis, Mycoplasma pneumoniae*, and *Influenza* A; however, adenovirus—type 3, 7, and 21 appear to be the

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agents most often associated with the disorder in children.[8,9] Post-infectious BO is clinically characterized by severe and persistent airway obstruction despite prolonged use of both bronchodilators and corticosteroids.[10] The most frequent variety found in histological studies is the constrictive BO form with a spectrum of changes ranging from minimal bronchiolar inflammation to peribronchiolar fibrosis and ultimately complete cicatrization of the bronchiole lumen.[11] In addition to clinical characteristics and biopsy studies, high resolution chest CT (HRCT) is a useful tool for BO diagnosis.[9]

The increased incidence of post-adenovirus BO in Polynesians in New Zealand,[12] Metis and Native North Americans in Canada[13] and some countries in Asia[3,14] is well-recognized. In Chile and the rest of the Southern coast of South America (Southern region of Brazil, Uruguay, and Argentina), adenovirus LRTIs in children is endemic with sporadic epidemic outbreak, primarily nosocomially transmitted.[2] And although there are no epidemiological data, post-infectious BO has generated a very high demand for medical resources as it is one of the main causes of chronic respiratory disease in children from developing countries.[10]

There are many reviews of long-term sequelae of adenovirus LRTIs, however, there are few describing post-adenovirus BO risk factors and evolution in children.[15–18] Further, little is known about respiratory health on a long-term basis in children who suffer adenovirus pneumonia and do not develop BO. The aim of our study was to describe clinical, pulmonary function, and chest-HRCT profiles in a 5-year follow-up of infants with adenovirus pneumonia and determine factors associated with subsequent development of BO.

METHODS

We prospectively followed all the children hospitalized with adenovirus pneumonia in an outbreak occurring between June and August 1998 at the E. Gonzales Cortes University Hospital, a 300 bed tertiary children's hospital located in Santiago, Chile with a service population of around 1 million people. Children were defined of having adenovirus pneumonia if they had a clinical diagnosis of pneumonia with radiological confirmation (presence of opacifications and/or a diagnosis of bronchopneumonia or pneumonitis made by a pediatric radiologist [CV]) and a positive immunofluorescence assay for adenovirus.[2] Due to financial problems in our hospital at that time, we did not perform adenovirus serotype analysis. Medical charts for the adenovirus pneumonia event (with demographics, clinical, laboratory, and chest X-ray findings) and for the 5 years of followed-up (at least three visits per year) were analyzed in a structured computerized questionnaire.

At the end of the 5 years, pulmonary function testing and chest HRCT were performed. The pulmonary function was evaluated using the impulse oscillometry technique (IOS) done by one chest therapist each time (RM) according to standardized techniques.[19,20] For all subjects, three replicate measurements of impedance respiratory (Zrs) were obtained using the system software (MasterScreen-IOS, Jaeger® Co, Germany). Impedance measurements were retained for analysis if reproducible, that is, if the coefficient of variation between replicates measurements was $<10\%$. Briefly, the sitting child was asked to breathe for 15–20 sec using a rigid oval mouthpiece with a tongue guard, with the head in a neutral position, nose clip in place, and while supporting both cheeks. For the respiratory system, resistance represents the effective resistance of lungs and chest wall, whereas reactance is the net effect of the two opposite (a compliant and an inertial) components. Each recording on the MasterScreen IOS assessment yielded both the expiratory resistance (R5 and R20) and reactance (X5) (kPa/l/s) at different oscillatory frequencies between 5 Hz and 35 Hz within the flow range of normal tidal breathing. R5 measure the total resistance, R20 the central resistance, and X5 the peripheral reactance. In addition, the resonant frequency (Fres) (i.e., the frequency at which the reactance was zero) was also computed. A bronchodilator response to 200 μg of albuterol administrated by MDI plus volume spacer device with a mouthpiece (Volumatic®, Allen and Hanburys, Middlesex, UK) was also evaluated. Compromise in IOS values was evaluated as described by Duiverman EJ et al.[21]

The chest HRCT, performed during quiet breathing, was interpreted by a blinded radiologist (KM) and BO was defined on the presence of bronchiectasis and/or a mosaic pattern.[10] Mosaic pattern was defined as segmental or lobular areas of hypoattenuation that are associated with narrowing of the caliber of the pulmonary vessels. Patients were thus divided into two groups: BO and no BO. Patient demographics and clinical characteristics of the adenovirus pneumonia episode, as well as the 5-year follow-up period and IOS characteristics were compared between these two groups and risk factors for subsequent develop of BO were evaluated.

In a subset of children ($n = 22$), peak flow rate was measured using the mini-Wright in accordance with published recommendations,[22] and a post-bronchodilator response to 200 μg of albuterol administrated by MDI plus spacer device with a face mask we also studied.

This study was approved by the Ethical Committee at the E. Gonzalez Cortes Children University Hospital and written consent for participation in the study was obtained from the parents.

Statistical Analysis

Chi-square test and student *t*-test were used for comparing categorical and continuous variables, respectively, between the two groups. All tests were calculated in a two-tailed manner and significance was defined by alfa

level of 0.05. STATA 7.0 (Stata Corp, College Station, TX) were used for data analyses.

RESULTS

During the adenovirus outbreak of 1998, 45 children were hospitalized with adenovirus pneumonia. Seven (18.4%) died during the initial hospitalization (mean age 15.8 months, five females, five with previous severe chronic condition: biliary atresia, Langerhans hystiocytosis, West syndrome, Down syndrome, and bronchopulmonary dysplasia). The remaining 38 children were prospectively enrolled in the study and followed for 5 years.

Among these 38 children, 18 (47.4%) developed BO. No significant differences were found in most of the demographic characteristics between children who developed BO and those who did not (Table 1). Interestingly, children who developed BO tended to have their first wheezing episode early in life ($\leq$3 months of age), more day care attendance and more rhinitis, though none of these findings reached statistical significance ($P = 0.09$).

Among the clinical characteristics of the adenovirus pneumonia episode, those children who developed BO were more likely to have contracted adenovirus nosocomially and have more severe respiratory compromise (accessory muscle use and crackles) than those who did not develop BO (Table 2). Also, those children who developed BO had significantly longer hospitalization, were more likely to require ICU admission (mean 4.1 days of duration), and mechanical ventilation (mean 3.4 days of duration), both need for oxygen and longer duration of need, use of antibiotics (mainly penicillin), use of systemic corticosteroids and longer duration of corticosteroid use, and systemic beta 2 agonist therapy (infusion of fenoterol) than children who did not develop BO (Table 2).

TABLE 1— Demographic Characteristics of Children who Developed BO Versus Those who do not

	Developed BO (n = 18)	No BO (n = 20)
Males (%)	66.6	70
Tobacco at home (%)	61.1	79
Maternal asthma (%)	11.1	5.6
Maternal rhinitis (%)	11.1	27.8
Maternal eczema (%)	16.7	16.7
Paternal asthma (%)	11.1	11.1
Paternal rhinitis (%)	16.7	16.7
Paternal eczema (%)	11.1	5.6
Maternal educational (years)	8.8 ± 3.0	9.1 ± 3.1
No wheezing episode (%)	11.1	20
Day care attendance (%)	0	15
Mild wheezing (%)	38.9	30
Moderate wheezing (%)	50	50
Onset of wheezing in the first 3 months of life (%)	83.3	57.9
Rhinitis (%)	27.8	55
Eczema (%)	11.1	30
Previous pneumonia (%)	72.2	50

TABLE 2— Clinical Characteristics During the Adenovirus Pneumonia Episode in Children who Developed BO Versus Those who did not Develop BO

	Developed BO (n = 18)	No BO (n = 20)
Age at onset (months)	12.5 ± 10.3	13.4 ± 15.5
Eutrophic (%)	88.9	78.9
Nosocomial infection[1] (%)	50**	10.5
Duration of symptoms (days)	8.4 ± 5.9	6.4 ± 3.9
Fever (days)	1.8 ± 2.2	1.5 ± 1.5
Cough (%)	100	95
Wheezing (%)	55.6	55.6
Tachypnea (%)	72.2	50
Stridor (%)	11.1	17.6
Accessory muscle use (%)	83.3**	45
Diminished lung sounds (%)	66.7	50
Crackles (%)	77.8**	30
Wheezing (%)	72.2	60
Duration of hospitalization (days)	15.7 ± 14.7**	6.1 ± 4.8
ICU admission (%)	50***	0
Mechanical ventilation (%)	44.4***	0
Oxygen use (%)	100**	60
Oxygen therapy (days)	14.2 ± 15.3**	4.1 ± 5.1
Antibiotic use (%)	88.9***	45
Systemic corticosteroid use (%)	82.4*	45
Systemic corticosteroids (days)	8.9 ± 8.5**	2.6 ± 3.3
Systemic beta 2 agonist use (%)	44.4***	0
Inhaled beta 2 agonist use (%)	100	100

*$P \leq 0.05$.
**$P \leq 0.01$.
***$P \leq 0.001$ comparing those who developed BO versus no BO.
[1]Adenovirus nosocomial pneumonia, is defined as a pneumonia develop after 7 days of admission to the hospital for non-respiratory diseases.

Furthermore, there were more children in the BO group with overall extrapulmonary complications than in the no BO group (27.8% vs. 5%, respectively, $P = 0.05$). When we analyzed separately each extrapulmonary complication the only significant difference between the groups was hepatomegaly (33.3% vs. 5%, respectively, $P \leq 0.05$). Though the remaining extrapulmonary complications did not reach significance they were more frequent in the BO vs. no BO group (diarrhea: 11.1% vs. 5%; cardiomyopathy: 11.1% vs. 0%; pulmonary hypertension: 5.6% vs. 0%; sensorial alteration: 11.1% vs. 5%; seizures: 5.6% vs. 5%; and renal failure: 5.6% vs. 0%, respectively). There was less conjunctivitis in the BO than no BO group (5.6% vs. 30%, $P \leq 0.05$, respectively).

Laboratory findings during the adenovirus pneumonia episode, revealed that children who developed BO had a lesser degree of lymphocytosis than those with no BO (26.7 ± 12% vs. 45.6 ± 17.5%, respectively, $P = 0.005$). There were no significant differences between those in the BO versus no BO group in total white count (14,205 ± 9,980 per mm^3 vs. 14,423 per mm^3 ± 6,447 per mm^3, respectively), percent bands (18.9 ± 10.7% vs. 15.2 ± 12.8%, respectively), platelet count (367,454 ±

216,563 per mm^3 vs. $303{,}142 \pm 92{,}081$ per mm^3, respectively), erythrocyte sedimentation rate (28.9 ± 16.2 mm/hr vs. 42.2 ± 21.2 mm/hr, respectively) or C-reactive protein (47.2 ± 35.3 mm/L vs. 43.1 ± 37.4 mm/L, respectively).

Two patients in the BO group and four in the no BO group had a concomitant respiratory infection during the adenovirus pneumonia (one RSV and one *B. pertussis* in the BO group; and two RSV, one influenza and one *M. pneumoniae* in the no BO group).

Chest X-ray during the adenovirus pneumonia demonstrated more atelectasis in the BO versus no BO group (61.1% vs. 25%, respectively, $P = 0.02$). However, there were no significant differences between the groups in interstitial infiltrates (47.1% vs. 70%, respectively), consolidation (64.5% vs. 45%, respectively), or hyperinflation (17.6% vs. 35%, respectively).

During the 5 years of follow-up (mean 63.2 ± 4.0 months), children who developed BO had higher incidence of domiciliary oxygen use than those without BO, higher number of new pneumonia episodes, higher wheezing exacerbations and hospitalizations and persistent disease (Table 3). Although the use of inhaled corticosteroids (ICS) was similar between the two groups, those children who later develop BO received higher doses of ICS than those without BO. Also, children who developed BO had significantly higher proportion of oral corticosteroid use (mainly prednisone bursts), more productive cough, digital clubbing, prevalence of malnutrition (weight/height <5 percentile), and longer persistence of atelectasis (>3 months) on chest X-ray than children who did not develop BO (Table 3). Also, children who developed BO tended to have more pulmonary hypertension (diagnosed by echocardiogram), though the difference did not reach statistical significance.

The results of IOS performed at the end of the follow-up period (mean 5.7 ± 1.2 years of age) were different between the groups. Only 33.3% of children who developed BO had normal IOS[23] compared with 85% in the no BO group ($P < 0.01$). More children in the BO group had moderate-severe compromise of IOS than in the no BO group (22.2% vs. 5%, respectively, $P < 0.01$). Children who developed BO had significantly higher levels of Zrs, predicted Z, R5, predicted R5, X5, and predicted X5 and frequency than those without BO (Table 4). However, there were no differences in the beta 2 agonist response between the children with and without BO (94.4% vs. 80%, respectively), (Table 4). The greatest improvement following beta 2 agonist was in X5 (66.7% vs. 35% for the BO vs. no BO group, respectively, $P = 0.05$). Peak flow (basal and post-bronchodilator) was significantly lower in those children with BO versus no BO, however the number of children tested was small (basal: 131.11 L/min vs. 183.85 L/min, $P = 0.032$,

TABLE 3— Five Years of Follow-Up of Children With Adenovirus Pneumonia in Those who Developed BO Versus Those who did not Develop BO

	Developed BO (n = 18)	No BO (n = 20)
Follow-up (months)	63 ± 4.1	63.5 ± 4.1
Oxygen therapy at home (%)	27.8**	0
% Recurrent pneumonia (≥3 episodes)	38.5*	5.6
# Episodes of pneumonia	3.4 ± 4.4**	0.6 ± 1.1
Persistent wheezing >3 months (%)	93.6*	66.7
Monthly wheezing exacerbations (%)	88.9**	40
Hospitalized wheezing episodes (%)	33.3*	5.6
Inhaled corticosteroid use (%)	100	94.73
Dose of inhaled corticosteroid (beclomethasone μg/day)	832 ± 160**	600 ± 250
Oral corticosteroids >3 months (%)	22.2*	0
Productive cough (%)	66.7***	5.6
Digital clubbing (%)	16.7*	0
Thoracic deformation (%)	22.2	10
Chronic atelectasis >3 months of duration, chest X-ray (%)	68.8***	5.9
Right ventricular dilatation by echo (%)	33.3	0
Pulmonary hypertension by echo (%)	25	0
Malnourished (weight/height <5 percentile) %	20*	0

*$P \leq 0.05$.
**$P \leq 0.01$.
***$P \leq 0.001$ comparing those who developed BO versus no BO.

TABLE 4— Pulmonary Function by Impulse Oscillometry Technique (IOS) at the end of the 5 Years Follow-Up in Children who Developed BO Versus Those who did not Develop BO

	Developed BO (n = 18)	No BO (n = 20)
Age (years)	5.61 ± 0.61	5.7 ± 1.5
Basal		
Zrs	1.41 ± 0.45**	1.06 ± 0.23
% Zrs	157.86 ± 58.68**	114.47 ± 23.39
R5	1.26 ± 0.37**	0.99 ± 0.23
% R5	150.78 ± 52.66**	115.11 ± 22.77
R20	0.67 ± 0.13	0.65 ± 0.15
%R20	86.41 ± 17.84	81.85 ± 13.70
X5	-0.61 ± 0.29***	-034 ± 0.11
%X5	193.81 ± 100.83**	109.21 ± 42.1
Fres	24.61 ± 3.66**	21.2 ± 3.02
Post-bronchodilator		
Z	0.93 ± 0.30*	0.75 ± 0.16
%Z	104.01 ± 37.39**	80.70 ± 13.70
R5	0.86 ± 0.27*	0.70 ± 0.15
%R5	102.44 ± 36.41*	80.94 ± 14.12
R20	0.53 ± 0.13	0.51 ± 0.11
%R20	68.21 ± 14.80	64.03 ± 11.05
X5	-036 ± 0.15**	-025 ± 0.09
%X5	111.71 ± 50.83**	77.17 ± 25.01
Fres	18.83 ± 4.08	16.6 ± 3.86

*$P \leq 0.05$.
**$P \leq 0.01$.
***$P \leq 0.001$ comparing those who developed BO versus no BO.

respectively; post-bronchodilator: 100 vs. 251.66 L/min, $P = 0.048$, respectively).

As we divided the population into two groups (BO and no BO) according to HRCT findings, it is obvious that HRCT was significantly different among the BO and no BO groups. Children in the BO group showed a higher percentage of air trapping (41.2% vs. 0%, $P = 0.008$), diminished vascularity (100% vs. 0%, $P < 0.0001$), density alteration (94.1% vs. 0%, $P < 0.0001$), atelectasis (76.5% vs. 19%, $P < 0.0001$), loss lung volume (82.4% vs. 4.8%, $P < 0.001$), bronchiectasis (47% vs. 4.8%, $P < 0.001$), bronchial enlargement (64.7% vs. 20%, $P < 0.001$), and alveolar filling (23.5% vs. 0%) than children without BO, but bronchial plugging—an opacity filling a defined bronchus—(0% vs. 4.8%, $P = 0.3$) and ground glass appearance (11.8% vs. 9.5%, $P > 0.05$) were similar.

DISCUSSION

To our knowledge this is the first long-term, prospective report of sequelae of adenovirus pneumonia in children. Most of the children studied suffered adenovirus infection before 2 years of age and had a history of antecedent pneumonia (60.5%) and wheezing (84.2%) episodes. During the 5 years of follow-up, almost half of the cohort (47.4%) developed BO. Children who developed BO had more respiratory compromise with more ICU admission, mechanical ventilation, oxygen use, and systemic corticosteroids and beta agonist administration during the episode of adenovirus pneumonia than those who did not develop BO. However, there were no cases with progressive deterioration of respiratory symptoms or decreased functional capacity during follow-up.

Also, this study represents the spectra of adenoviral pneumonia ranging from relatively mild to severe and fatal cases. Our fatality rate (18.4%) was higher compared with other series,[23–25] however five out of the seven deaths occurred in children with previous conditions. Some studies found a relation between the serotype of adenovirus (e.g., subgenus B genome type 7 h) and more severe clinical outcome in the Southern cone of America.[24,26,27] A limitation of our study is the lack of adenovirus serotype analysis, considering that BO was associated with some specific serotypes.[8,9] In our series significantly more nosocomial infection by adenovirus was found in children with BO than in the no BO group, it is plausible to suspect that a specific adenovirus serotype would be responsible for that outbreak and play a role in the severity of subsequent disease, as was previously described in our country by Palomino and coworkers.[2] However, it is also possible that host characteristics play a role in the development of post-adenovirus BO as has been described for the HLA haplotype DR8-DQB1*0302 in the Argentine Amerindians.[28]

Kim et al.[29] demonstrated that in both Korea, where the etiology of childhood BO is more frequently post-infectious, and in US, where it is more frequently idiopathic, HRCT and pulmonary function are similar regardless of the etiology of BO or the ethnic/geographic origin of the patient. In our study, 47.4% of the children developed post-adenovirus BO (defined by HRCT) and interestingly pulmonary function as measured by IOS was normal in one-third of proven BO cases. Another third had a mild reduction of expected values and only the remaining third exhibited moderate to severe impairment on IOS. These results, taken together with HRCT, demonstrate that BO varies from mild cases with normal pulmonary function and minimally altered HRCT to severe damage with an important loss of pulmonary function and extensive anomalies in the HRCT. Complete pulmonary fibrosis of the left lung was found in one case of BO, representing a rare consequence of adenovirus pneumonia and perhaps an extremely severe form of BO.

It is also remarkable that most of the children in our series demonstrated a significant response to bronchodilators, irrespective of the severity of BO developed. This finding has not previously been described and may have two potential explanations. First, the high prevalence of previous wheezing episodes (up to 82.4%) in our children may indicate a pre-disposition to BO in children with airway hyperreactivity. Second, IOS may be a more sensitive measure of the lung function abnormalities in these patients. IOS allows to distinguish between the elastic (Xrs, reactance or compliance) and (R5, R20) resistance components of pulmonary function. Additionally, IOS can measure directly the inspiratory and expiratory phases, in contrast to the indirect measurements by spirometry.[30] Finally IOS is more precise in measuring the mechanics of the peripherical airways than other methods.[31,32] In our study, those children who develop BO have more alteration in the peripherical airways (X5 and Fres), with higher beta agonist responses found in those parameters. We did not observe any paradoxical response to beta 2 agonists as was described previously.[33] There are some data suggesting that changes in VEF1 are due to air flow limitations instead of the R5 parameter, which is more closely related to airway caliber.[34,35] Moreover, in a short report on 19 children with post-adenovirus LRTIs a significantly higher bronchodilator response was found using IOS versus spirometry (76.4% vs. 29.4%, respectively).[36] Teper et al.[37] using tidal and partial forced expiratory flow/volume curves reported a severe and fixed bronchial obstruction in 13 infants with chronic pulmonary disease after severe adenovirus infection; however, we do not know what would be their pulmonary function when they reach pre-school age. Besides, those differences could be explained due to dissimilar population. Taking all of these facts into consideration, we conclude that our patients

have a peripheral airway compromise which improved with the use of beta 2 agonists, as has been recently described.[10]

In our study, the characteristics of the adenovirus pneumonia event were similar to previous reports.[23,25,26] It is well known that adenovirus, compared with other viruses responsible for LRTIs in childhood, causes more severe respiratory and extra pulmonary manifestations[38] and is more prone to be followed by the development of BO.[39] Indeed, in our series children who developed BO post-adenovirus pneumonia had significantly more severe respiratory compromise (accessory muscle use, crackles, ICU admission, mechanical ventilation, duration of oxygen therapy, systemic corticosteroids and beta 2 agonists use). Another interesting finding in our study was the higher prevalence of wheezing episodes—up to 84.2%—prior to adenovirus pneumonia in both groups. Reina et al.[40] very recently reported a high prevalence of antecedent wheezing disorders in 100 children with adenovirus LRTI in Spain. Although extrapulmonary complications did not reach significance they were more frequent in the BO versus no BO group; unfortunately, since we did not performed liver enzymes test or ultrasound, we can not prove that hepatomegaly was genuine or only due to hyperinflated chests displacing the liver downwards.

During the 5 years of follow-up children who developed BO were more likely to have used home oxygen therapy, to have had recurrent pneumonia episodes, to have been hospitalized with wheezing, to have severe wheezing disease, and chronic or changing atelectasis on chest X-ray than those who did not developed BO. By 1 year after the adenovirus pneumonia event, home oxygen therapy could be discontinued in all patients who received it, and towards the end of follow-up wheezing became less severe with symptom-free intervals lasting several weeks or longer. Therefore, as a group, they experienced an improvement in those aspects and in quality of life. The management our patients received through the entire follow-up was moderate to high-dose of inhaled steroids, oral steroids in the exacerbation periods, B2 agonists, chest physiotherapy, and promptly instituted antibiotics for bacterial infections. However, since this is an observational study, the therapeutic guidelines for this type of patients need to be confirmed by interventional studies.

In summary, this study represents the spectra of adenovirus pneumonia ranging from relatively mild to severe and fatal cases. Adenovirus pneumonia appearing very early in life and with severe pulmonary and extra pulmonary compromise factors associated with subsequent development of BO. Two-thirds of the children in the BO group had an alteration in pulmonary function (by IOS), however, most of them responded significantly to bronchodilators.

ACKNOWLEDGMENTS

We thank Dr. Karla Moenne (Radiology Department, Clinica Las Condes, Santiago) for reviewing the HRCT; Dr. Carlos Vildósola (Flemming Radiologic Center, Santiago) for reviewing the chest X-rays; and Dr. Mark A. Brown (Arizona Respiratory Center, University of Arizona, Tucson, AZ) for his advice and critical review.

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