ORIGINAL ARTICLE

Postinfectious bronchiolitis obliterans: clinical aspects and complementary tests of 48 children*

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Background: The clinical evaluation of patients with postinfectious bronchiolitis obliterans (BO) is variable.

Objective: Substantiate the clinical characteristics, the evolution and the complementary tests of 48 patients with postinfectious bronchiolitis obliterans (BO).

Method: Observational and retrospective study. Diagnosis of BO was based upon clinical criteria, CT scan findings and exclusion of other diseases. History prior to diagnosis and complementary tests were evaluated as well as initial and final values of oxygen saturation.

Results: Mean age of patients at the acute stage of the infectious disease was of 9.6. Thirty-two of the patients were male. All were hospitalized during the acute stage, 14 (29%) in the ICU. Four patients died two years after onset of acute bronchiolitis. During evolution, all patients required emergency care due to exacerbation of the pulmonary condition and 24 (50%) were hospitalized, 2 of them in the ICU. In the majority of cases, cough, wheezing, crackles and hyperinflation persisted, albeit to a lesser degree. The mean baseline arterial saturation was 89% and the final mean was 92%. The most common infectious agents identified in sputum samples were *H. influenzae, S. pneumoniae* and *M. catarrhalis.* Increased serum levels of IgC and IgM were found in 7 and 9 patients, respectively. The most frequent findings at thorax CT scan were mosaic perfusion, bronchiectasis, atelectasis and bronchial wall thickening.

Conclusion: Postinfectious BO is a chronic and severe disease with persistent symptoms that usually affects infants. Positive serum cultures and increased serum immunoglobulins are suggestive of chronic infectious inflammation.

***Key words*: Bronchiolitis obliterans. Lung diseases, obstructive.**

* **Study carried out at the Hospital de Clínicas, Federal University of Paraná.**

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Abbreviations used in this paper:

BO – Bronchiolitis obliterans
ICU – Intensive care unit
CAT – Computed axial tomography
GERD – Gastroesophageal reflux disease
UFPR – Federal University of Paraná

INTRODUCTION

Postinfectious bronchiolitis obliterans (BO) is a chronic obstructive disease of the lower airways. This disease preferentially affects male infants after the onset of acute viral bronchiolitis, whose most common agent is adenovirus.[1] The virus infects the surface of endothelial cells and replicates intracellularly, forming squamous metaplasia in the bronchi and resulting in destruction of the ciliary epithelium. Peribronchiolar inflammatory infiltrates, edema of the submucosa and connective tissues and increased mucus production cause the obstruction of bronchioles, which results in air entrapment, atelectasis, and bronchiectasis.[2] Postinfectious BO is clinically characterized by cough for more than 2 weeks, crackles, dyspnea, and wheezing after the acute stage.[1] Chest deformities due to air

entrapment may be seen. Digital clubbing and cyanosis are common in severe patients.[3] High-resolution computed tomography of the chest typically reveals characteristics such as mosaic perfusion, peribronchial wall thickening, atelectasis, bronchiectasis, air entrapment, and sometimes lung volume reduction.[4] In order to confirm a diagnosis of postinfectious BO, other diseases with similar clinical manifestations must first be ruled out.[1] Gastroesophageal reflux disease (GERD) with aspiration and airway lesions, for example, may be observed concomitant with BO, both as a cause and as a consequence.[5]

The clinical course of postinfectious BO, as well as epidemiological factors, prognosis, and treatment are indefinite, and although the first cases were described in 1964, few studies of this disease have been conducted. The objective of this study was to determine clinical characteristics and analyze evolution, as well as evaluate results of complementary tests performed, in 48 patients diagnosed with postinfectious BO.

METHODS

An observational and retrospective study was conducted involving 48 patients diagnosed with BO and treated at the pediatric pulmonary center of the Federal University of Paraná (UFPR) Hospital de Clínicas from May 1990 to May 2001. Criteria for the diagnosis of BO included: absence of respiratory disease from the neonatal period to the beginning of the viral disease; severe bronchiolitis in a previously healthy infant who was hospitalized and submitted to oxygen therapy; persistence of signs and symptoms (dyspnea, obstruction, air entrapment and arterial oxygen saturation below 95%) for more than 3 months.[6] A diagnosis of GERD was based on clinical symptoms and on evidence seen in a series of contrast radiographs taken in rapid succession (a technique formerly known as seriography) of the esophagus, stomach and duodenum. The GERD was considered secondary since patients were asymptomatic before the onset of viral bronchiolitis. Computed axial tomography (CAT) scans were taken with a conventional scanner (high resolution scans, 2-mm thick every 5 mm). All patients were under general anesthesia and were intubated during the exam. Scans were taken at end expiration. Diseases such as asthma, cystic fibrosis, tuberculosis, bronchopulmonary dysplasia, hereditary or acquired immunodeficiency, and alpha-1 antitrypsin deficiency were excluded clinically and through laboratory tests. History prior to patient care and records of physical examinations conducted during each visit, as well as results of complementary examinations, were evaluated. Clinical evolution was evaluated through comparison of the first 6 to the final 6 months of follow-up. For patients whose follow-up was less than 12 months, the first 3 and the last 3 appointments were evaluated. Transcutaneous oxygen tension was measured with a pulse oximeter (model 9500, Nonin, Minneapolis, MN, USA). The first and the last hemoglobin-oxygen saturation results were evaluated. A non-parametric test (Wilcoxon test) with a significance level (alpha) of 0.05 was used to compare the results. The UFPR Research Ethics Committee approved the study.

RESULTS

Of the 48 patients, 32 were male and 16 were female (ratio, 2:1). Mean age during the acute stage of the disease was 9.6 months (range, 0.5 to 48 months). Age at the initiation of medical care ranged from 3 to 126 months (mean, 30.5 months) and the mean duration of treatment was 3.3 years. All patients were hospitalized due to the initial respiratory tract infection, and 14 were transferred to the ICU (Table 1). Upon admission, digital clubbing was observed in 12 patients, and 5 presented with cyanosis and oxygen dependence. Of the 48 patients studied, 34 (70%) presented with cough, wheezing, crackles, dyspnea and increased anteroposterior diameter. The remaining 14 (30%) presented no wheezing or tachypnea. In 31 (65%) of the patients studied, initial signs and symptoms persisted, but decreased in intensity over the course of the study. In the remaining 17 (35%), no clinically detectable changes were observed. However, we did determine that there was a reduction in the number of hospitalizations, since only 22 (45%) were readmitted during the follow-up period – and only 2 of those to the ICU. All patients had been previously hospitalized, some more than once. One had required hospitalization 16 times, another, 7 times, and 22 had been hospitalized 4 times. Table 2 correlates morbidity to BO. Five patients were oxygen dependent but recovered during

evolution. All patients presented worsening of their pulmonary condition and needed 1 or more emergency appointments. Significant dyspnea upon physical exertion was observed in 70% of the patients. During evolution, symptoms improved in 55% of patients and 16% showed no signs of dyspnea during examination.

Arterial saturation was evaluated in 20 (45%) of the patients, with a mean interval of 12 months between the first and last evaluation. At the beginning of treatment, arterial oxygen saturation ranged from 68% to 98% (median, 92%), and after 12 months it ranged from 80% to 98% (median, 94%). The difference between values was not significant. A diagnosis of GERD was made in 25 patients (Table 2). In all patients, the most common findings in chest radiographs were pulmonary hyperinflation, atelectasis and bronchial involvement. Chest tomography was performed in 42 patients (88%) of the patients (Table 3). Patient age at CAT scan ranged from 5 to 192 months (mean, 58 months). The most common findings in CAT scans were mosaic perfusion (in 64%), bronchiectasis (in 54%), air entrapment (in 64%), bronchial wall thickening (in 42%) and consolidation involving reduced lung volume (in 9%) (Figure 1). Spirometry was performed in 6 patients, and the results showed 2 patients to be normal, 2 patients to have airway obstruction, 1 patient to have airway restriction, and another patient to have airway obstruction and restriction. A total of 22 sputum cultures were obtained from 15 of the patients. Analysis of the cultures identified 20 (91%) as positive. The microorganisms most commonly found were *H. influenzae* (in 50%), *Moraxella catarrhalis* (in 23%), *S. pneumoniae* (in 18%) and *S. aureus* (in 9%). One patient tested positive (in 2 cultures) for *Pseudomonas sp*, another for *Aspergillus fumigatus* and another for *Candida sp*. Levels of the immunoglobulins IgM, IgA and IgG were elevated in 22 patients. Of these 22, 9 (41%) presented elevated levels of IgM, 7 (32%) presented elevated levels of IgG, and 4 (18%) presented elevated levels of IgA, all higher than the standard deviation corrected for age. None of the patients presented immunoglobulin levels below the second standard deviation.

Since there is no specific standard treatment for postinfectious BO, therapy was individualized. All patients were given orientation regarding respiratory physiotherapy and nutrition, as well as flu and antipneumococcal vaccines. Oxygen therapy was administered when necessary. The most commonly prescribed drugs were inhaled corticosteroids, systemic antibiotics, prednisone (via oral), inhaled beta-2 agonists, oral aminophylline and long-term courses of oral cisapride and oral erythromycin.

DISCUSSION

In infants, BO usually appears postinfection, and, although it can be caused by any infectious agent, it most commonly results from the introduction of a viral agent such as an adenovirus.[1] Incidence is higher in males, which is in accordance with studies in the literature that describe proportions up to 5 to 1.[5] Although lung biopsy is considered the diagnostic method of choice,[7] only 1 of our patients underwent this procedure, and the results obtained from the 3 samples collected were inconclusive. This justifies the current trend of dispensing with the biopsy in the diagnosis of BO. Therefore, before biopsy is indicated, certain aspects should be taken into consideration. Since the disease affects segments of the lung, false-negative biopsy results may be obtained. In addition, because there is no specific treatment regime, it is often difficult to obtain parental consent for a biopsy. Furthermore, biopsy results can be nonspecific.[3] Due to these limitations, current diagnostic methods are based on clinical findings, pulmonary function tests, scintigraphy, and chest CAT scans.[3,6,8] Perfusion scintigraphy demonstrates the redistribution of pulmonary circulation after the acute stage, and reveals patterns similarly to those seen in CAT scans.[3,8] Scintigraphy was not used In this study. This was due to technical problems and to its redundancy with the chest CAT scans. Necropsy was not performed in any case because consent was not given. In 6 patients, CAT scans were not taken, and a diagnosis of BO was made through clinical criteria combined with chest radiograph findings, as previously described by Hardy (disproportional findings in radiographs, hyperlucent lung and localized hyperaeration).[3]

The clinical course of BO is variable and can range from asymptomatic to severe to fatal.[5,9] In this study, all patients were hospitalized during the acute stage of the disease, 14 (29%) in the ICU. None of the patients were asymptomatic during evolution. These results are similar those of Zhang et al.,[9] who evaluated 31 patients diagnosed with postinfectious BO. The authors reported that 24 (77.4%)

were hospitalized during the acute stage of the disease, 8 (33%) in the ICU. In our study, the patients who were asymptomatic during evolution were the ones who were not hospitalized during the initial phase, which suggests that the severity of the disease is directly related to the severity of the acute stage and possibly to the nature of the infectious agent as well. The patients who died were younger than 2 years old, and persistence of signs and symptoms was more common during the first year after the acute stage. In most patients, signs and symptoms of the disease, as well as the number of hospitalizations, decreased over the study period. The most common radiographic and tomographic findings were similar to those from other studies (Table 3 and Figure 1).[4,10]

Twenty-five patients were diagnosed with GERD, which was considered secondary since these patients were asymptomatic until entering the acute stage of viral bronchiolitis. When symptoms are disproportionate to the chest radiograph findings, there is aspiration of stomach contents, and symptoms such as wheezing, crackles, and exercise intolerance are persistent, a diagnosis of BO should be considered.[3]

In the microbiological analysis of culture samples obtained during routine examinations, 91% tested positive. The most common agent identified was *H. influenzae*, followed by *M. catarrhalis,* and *S. pneumoniae*, which probably contributed for the persistence of symptoms. The microbial colonization and airway infection seen in our patients were secondary to changes in the immune system[11] and in mucociliary clearance.[12] *H. Influenzae*, a microorganism which is present in the commensal flora of the nasopharynx[13] and in macrophages in the adenoids of infants, and which may facilitate colonization,[14] was identified in 50% of the culture samples.

The higher serum immunoglobulin levels, combined with the positive sputum culture, confirms a chronic and persistent infectious and inflammatory process. Latent adenoviral infection is confirmed by the presence of adenovirus 5 E1A protein in the nuclei of epithelial cells in the lungs of infected animals.[15] Complications may be caused by external viral agents or by activation of the latent virus in epithelial cells.

Therapy is nonspecific and has been targeted at bacterial infections, the inflammatory process and the attendant gastroesophageal reflux. Patients diagnosed with chronic bronchitis clinically benefit from macrolide antibiotics. However, it is not clear whether this happens as a result of the anti-inflammatory effect or the anti-bacterial effect.[16] Despite regular, prolonged use (up to 90 days) of macrolides (for their anti-inflammatory effects)[17] and the fact that, when pulmonary complications arose during respiratory physiotherapy, the macrolides were replaced with other antibiotics, none of our patients became asymptomatic. This was probably due to the influence of one or more bacterial colonization mechanisms, in particular, *H. influenzae*, bacterial resistance to antibiotics, the delay in the restoration of mucociliary clearance, and adenovirus latency. These factors may be related to aggravation of the disease.[15] The response to therapy with inhalation therapy or pulse therapy with corticosteroids in patients with BO, in order to control inflammation, is variable.[1,5] The lack of response to corticoids may be partially related to the adenovirus 5 E1A protein, inhibits the steroid hormone through interaction with transcription coactivators.[18] Some patients may benefit from beta-2 agonists since there is spirometric evidence of a positive bronchodilating effect.

BO is a frequent, severe disease with persistent lesions. Therefore, treatment plans should target prevention of the acute stage of the disease and secondary infections, especially those caused by adenovirus and *H. influenzae.*

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TABLE 1
Clinical characteristics of patients with postinfectious bronchiolitis obliterans

Male	32 (66%)
Number of patients previously hospitalized	48 (100%)
Number previously hospitalized in the ICU	14 (29%)
Number of patients with history of pneumonia	29 (60%)
Age, in months, at the first appointment (range)	30.5 ± 29.6 (3 - 126)
Age, in months, at the acute stage (range)	9.6 ± 10.4 (0.5 - 48)

TABLE 2
Morbidity related to postinfectious bronchiolitis obliterans

Hospitalizations	20 (45%)
Pneumonia	18 (41%)
Oxygen dependence	5 (10%)
Gastroesophageal reflux	25 (52%)

TABLE 3
Tomographic findings in 42 patients with postinfectious bronchiolitis obliterans (%)

Mosaic perfusion	64
Bronchiectasis	54
Air entrapment	69
Atelectasis	47
Bronchial wall thickening	42
Consolidations	9
Lung volume reduction	9

Figure 1 – *Tomography findings in patients with postinfectious bronchiolitis obliterans*

1) Bronchiectasis

2) Diminished perfusion

3) Bronchial wall thickening