Bronchiolitis obliterans: clinical and radiological profile of children followed-up in a reference outpatient clinic

Bronquiolite obliterante: perfil clínico e radiológico de crianças acompanhadas em ambulatório de referência

Bronquiolitis obliterante: perfil clínico y radiológico de 35 niños acompañados en ambulatorio de referencia

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ABSTRACT

Objectives: To describe the clinical and radiological characteristics of patients with bronchiolitis obliterans.

Methods: This is a retrospective and descriptive study. Data were collected from patients diagnosed with bronchiolitis obliterans between 2004 and 2008 in the Pediatric Pulmonology Clinic of Hospital Infantil Albert Sabin, in Ceará, Northeast Brazil. Such diagnosis was based on clinical and tomographic criteria. Previous history, clinical findings at the diagnosis, complementary exams, and follow-up data were evaluated.

Results: 35 children diagnosed with bronchiolitis obliterans were identified. There was a predominance of male patients (3:1). The mean age at the onset of symptoms was 7.5 months, and bronchiolitis obliterans was diagnosed at a mean age of 21.8 months. The most common clinical findings were crackles/wheezing, tachypnea, dyspnea, and chest deformity. Post-infectious etiology was the main cause of bronchiolitis obliterans. Predominant findings at chest X-ray and high resolution computed tomography were peribronchial thickening and mosaic pattern, respectively. The treatment was variable and individualized. The majority of patients improved during follow-up, despite the persistence of respiratory symptoms.

Conclusions: In this study, the predominance of male patients and post-infectious etiology was noted, corroborating scientific literature. The most common tomographic findings were similar to those described in previous studies (mosaic pattern, peri-bronchial thickening, and bronchiectasis). Evidence about the treatment of this disease is still lacking. The diagnosis was delayed, which indicates that clinical suspicion of bronchiolitis obliterans is necessary in children with persistent and severe wheezing.

Key-words: bronchiolitis obliterans; child; tomography, spiral computed; lung diseases, obstructive.

RESUMO

Objetivo: Descrever as características clínico-radiológicas dos pacientes com bronquiolite obliterante.

Métodos: Estudo descritivo e retrospectivo. Foram coletados dados de pacientes diagnosticados com bronquiolite obliterante entre 2004 e 2008 no Ambulatório de Pneumologia Pediátrica do Hospital Infantil Albert Sabin, no Ceará. O diagnóstico foi baseado em critérios clínicos e tomográficos. Foram avaliados história prévia, quadro clínico por ocasião do diagnóstico, exames complementares e evolução.

Resultados: Foram identificados 35 pacientes com bronquiolite obliterante. Houve predominância do sexo masculino (3:1). A média de idade no início dos sintomas foi de 7,5 meses e, por ocasião do diagnóstico, 21,8 meses. Os achados clínicos mais frequentes foram estertores/sibi-

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los, taquipneia, dispneia e deformidade torácica. A etiologia pós-infecciosa destacou-se como a principal causa de bronquiolite obliterante. As alterações encontradas com maior frequência à radiografia e à tomografia computadorizada de alta resolução de tórax foram espessamento peribrônquico e padrão de perfusão em mosaico, respectivamente. O tratamento instituído aos pacientes foi variável e individualizado. A maioria deles evoluiu com melhora clínica durante o seguimento, apesar da persistência da sintomatologia respiratória.

Conclusões: A presente casuística de bronquiolite obliterante mostrou predominância de pacientes do sexo masculino e de etiologia pós-infecciosa, corroborando os dados da literatura. Os achados tomográficos mais encontrados foram semelhantes aos descritos em trabalhos anteriores (perfusão em mosaico, espessamento peribrônquico e bronquiectasias). Ainda faltam evidências acerca do tratamento para esta doença. O diagnóstico de bronquiolite obliterante foi tardio, necessitando da suspeição clínica por parte dos pediatras frente a lactentes chiadores graves e perenes.

Palavras-chave: bronquiolite obliterante; criança; tomografia computadorizada espiral; pneumopatias obstrutivas.

RESUMEN

Objetivo: Describir las características clínico-radiológicas de los pacientes con bronquiolitis obliterante acompañados en el Ambulatorio de Pneumología Pediátrica del Hospital Infantil Albert Sabin en la provincia de Ceará (Brasil).

Métodos: Estudio descriptivo y retrospectivo. Se recogieron datos de pacientes diagnosticados con bronquiolitis obliterante entre 2004 y 2008. El diagnóstico se basó en criterios clínicos y tomográficos. Se evaluaron la historia previa, el cuadro clínico en el momento del diagnóstico, exámenes complementares y evolución.

Resultados: Se identificaron 35 pacientes diagnosticados con bronquiolitis obliterante. Hubo predominancia de los pacientes del sexo masculino (3:1). El promedio de edad en el inicio de los síntomas fue de 7,5 meses y, en el momento del diagnóstico, 21,8 meses. Los hallazgos clínicos más frecuentes fueron ruidos respiratorios/silbidos, taquipnea, disnea y deformidad torácica. La etiología post-infecciosa se destacó como la principal causa de bronquiolitis obliterante. Las alteraciones encontradas con más frecuencia a la radiografía y a la tomografía computadorizada de alta resolución del tórax fueron espesamiento peribrónquico y estándar de perfusión en mosaico, respectivamente. El tratamiento instituido a los pacientes fue variable e individualizado. La mayoría evolucionó con mejora clínica durante el seguimiento, a pesar de la persistencia de la sintomatología respiratoria en grados variables.

Conclusiones: La presente casuística de bronquiolitis obliterante mostró predominancia de pacientes del sexo masculino y de etiología post-infecciosa, corroborando los datos de la literatura. Los hallazgos tomográficos más encontrados fueron semejantes a los descriptos en trabajos anteriores (perfusión en mosaico, espesamiento brónquico y bronquiectasias). Todavía faltan evidencias sobre el tratamiento para esta enfermedad. El diagnóstico de bronquiolitis obliterante fue tardío, siendo necesaria la sospecha clínica por parte de los pediatras frente a lactantes silbadores graves y perennes.

Palabras clave: bronquiolitis obliterante; niño; tomografía computadorizada espiral; pneumopatías obstructivas.

Introduction

Bronchiolitis obliterans (BO) is an inflammatory disease of the small airways caused by an insult to the lower respiratory tract. The presence of inflammation and fibrosis of the terminal and respiratory bronchioles leads to a narrowing or full obliteration of the airway lumen and to the chronic obstruction of air flow[1,2]. Histologically, it is characterized by the presence of intraluminal granulation tissue in the airways or peri-bronchial fibrosis and lumen narrowing, which gives origin to scarring and obstruction[3]. The incidence of BO in the pediatric population is unknown, but it affects mostly male infants[4,5]. Some of the possible BO etiologies are: inhalation of irritant substance, aspiration syndromes, immunological abnormalities, collagen diseases (rheumatoid arthritis and Sjögren syndrome), organ transplantation, Stevens-Johnson syndrome and postinfection. Among children, postinfectious BO is the most frequent[6,7] and occurs mainly in the southern hemisphere (Argentina, Chile, New Zealand and Australia), which suggests that it might be associated with genetic factors. The expression of the HLA-DR8-DQB1*0302 antigen is high among children with BO in Argentina[3,7,8].

Currently, BO is diagnosed according to history of insult to the lower respiratory tract, usually infections, and persistent symptoms that do not respond to administration of systemic corticoids and bronchodilators for two weeks, tomographic (CT)

findings and exclusion of other diseases[2,9]. BO is a frequent disease that has a variable progression, but it often goes undiagnosed in Brazil and may be misdiagnosed as other childhood lung diseases, mainly wheezing syndromes. Epidemiological factors, treatment and disease prognosis should be more clearly defined to reduce morbidity and mortality.

This study described sociodemographic, clinical and radiological findings and diagnostic test results during the follow-up of patients with BO in the Pediatric Pulmonology Outpatient Department of Hospital Infantil Albert Sabin (HIAS) in Fortaleza, Brazil, and compared findings with data in the literature.

Method

This retrospective and descriptive study included 35 patients with a diagnosis of BO who were followed up in the Pediatric Pulmonology Outpatient Service of HIAS from October 2004 to October 2008, and was approved by the Ethics in Research Committee of the institution where it was conducted.

This study was conducted in two phases: in the first, we reviewed records to identify patients with a diagnosis of BO that were followed up in the Pulmonology Outpatient Service. A questionnaire about sociodemographic characteristics and history of diseases before the diagnosis was then applied to their parents or guardians. In the second phase, medical charts were reviewed to evaluate each patient's clinical and radiological findings.

The following criteria were used for the inclusion of a BO diagnosis: no respiratory disease from birth to acute disease onset; diagnosis of acute viral bronchiolitis or severe pneumonia in previously healthy child, requiring hospitalization and assisted ventilation; persistent obstructive symptoms with wheezing and rales for more than three months after first symptom; and recurrent aspirations with persistent respiratory symptoms; high-resolution chest tomography (HRCT) findings of a mosaic pattern or bronchiectasis; and exclusion of other diagnosis[4,10]. Patients with other diagnoses, such as asthma, congenital and acquired immunodeficiency, pulmonary tuberculosis, bronchopulmonary dysplasia, α-1-antitrypsin deficiency, cystic fibrosis and congenital heart disease were excluded in accordance with the outpatient service routine, after clinical and laboratory evaluation during follow-up.

The variables under analysis were: sex, age at acute phase of the disease, age at time of BO diagnosis, socioeconomic status, clinical characteristics at time of diagnosis (signs and symptoms, hospitalizations, mechanical ventilation and oxygen dependence), cause of BO, previous diagnoses, imaging studies (radiographs and HRCT), other diagnostic tests (transcutaneous oximetry, arterial blood gases, echocardiogram, lung perfusion scintigraphy and spirometry), treatment, outpatient progression (improvement or death) and follow-up duration. Aspiration syndromes and gastroesophageal reflux were diagnosed according to suggestive clinical history and upper gastrointestinal series.

HRCT was performed under sedation with chloral hydrate (20 to 40mg/kg) using a conventional scanner (Somaton Balance, Siemens, Germany, 2000) The parameters for image acquisition during inspiration and expiration were 1-mm thick sections at 5-mm intervals. Images were reviewed by the radiologist at the Pediatric Pulmonology Service of HIAS.

Oxygen saturation (SpO_2) was measured using a pulse oximeter (DX 2405, DixtalOxypleth, Brazil, 2005). Measurements were recorded during diagnosis and during the last outpatient visit. Oxygen (O_2) was supplied by the Extended Home Oxygen Therapy Program (ODP) of the Brazilian Unified Health System for patients with chronic hypoxemia (SpO_2<94%). Blood gases were measured in all patients at admission to the ODP, as well as before O_2 weaning.

Most patients (94%) underwent echocardiography to determine pulmonary artery pressure indirectly. Scintigraphy was performed in selected cases, and spirometry, in children older than 7 years that were cooperative. Patient progression was analyzed by comparing clinical findings and oxygen saturation at time of diagnosis and in the last outpatient visit. Follow-up lasted 12 to 112 months.

Results

Of the 35 patients, 26 were boys (3:1). Mean age at symptoms onset was 7.5 months (range: 1 to 24 months) and at BO diagnosis, 21.8 months (range: 6 to 107 months). Of all patient families, 83% had an income of one to two minimum wages, and 17%, less than one minimum wage. At the time of diagnosis, patients had tachypnea, dyspnea and wheezing or rales at auscultation; 27 (77%) had cough; 9 (26%), cyanosis; 7 (20%), clubbed fingers; and 22 (63%), chest deformity. Patients had to be hospitalized before the diagnosis (mean number of times: 5) due to acute viral respiratory infections. Eight (23%) had to receive mechanical ventilation during the first acute phase. At the time of diagnosis, 15 patients (43%) had oxygen saturation below

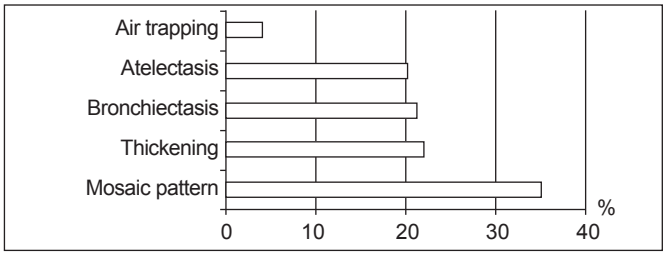

Figure 1 - High-resolution tomographic findings in patients with bronchiolitis obliterans

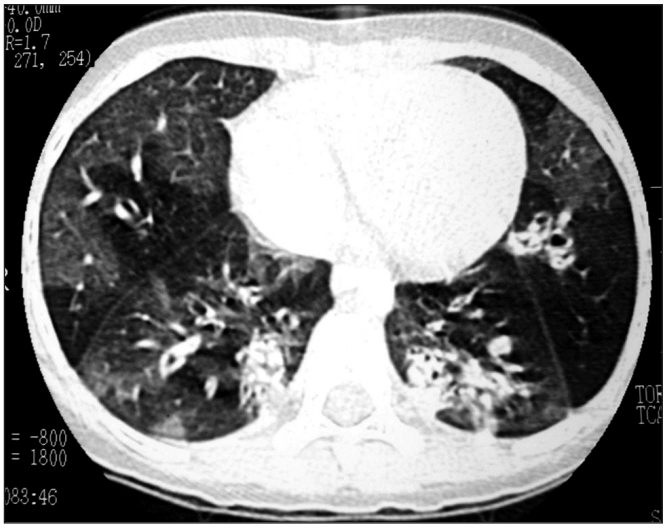

Figure 2 - Parameters axial high-resolution chest perfusion tomographic view of chest shows mosaic pattern of perfusion areas, peri-bronchial thickening and bronchiectasis in lower lobes

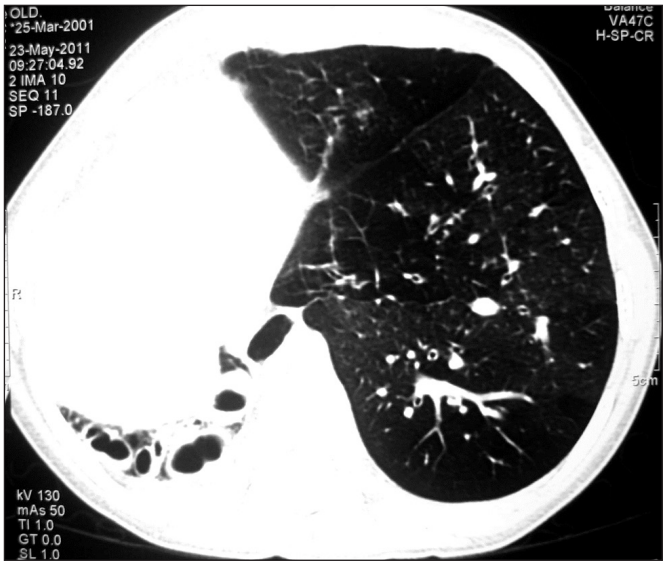

Figure 3 - High-resolution chest perfusion tomographic shows total pulmonary atelectasis on the right and destruction of pulmonary parenchyma; hyperinflated left lung, mosaic pattern of perfusion areas and bronchial wall thickening

94%, and 14 had arterial oxygen pressure (PaO_2) below 60mmHg, according to oximetry, and were oxygen dependent. Several degrees of pulmonary hypertension were found. The predominant causes were postinfectious BO in 31 cases (88%), BO associated with aspiration in 3 cases and BO after Stevens-Johnson syndrome in one case.

Before BO was diagnosed, patients had a diagnosis of other diseases during the acute phase of respiratory symptoms. Wheezing infant was the previous diagnosis of 13 patients (37%). The other diagnoses were: recurrent pneumonia (10), asthma (6), and others (6).

The most frequent chest X-ray findings of patients with BO were: peri-bronchial thickening (66%), pulmonary hyperinflation (54%), atelectasis (51%), alveolar opacity (34%), small or hyperlucent lung (3%), and localized hyperlucent areas (3%).Only two patients (6%) had a normal chest X-ray.

Regardless of age, all patients underwent HRCT. Figure 1 shows the most frequent findings: mosaic pattern (100%, Figure 2), peri-bronchial thickening (63%), bronchiectasis (60%) (Figure 2), atelectasis (57%), (Figure 3) and air trapping (11%).

An echocardiogram was requested to rule out heart disease and indirectly evaluate pulmonary arterial pressures of all patients, but was not performed in two cases due to social problems. Of the patients that underwent the test, 18 (31%) had normal mean pulmonary artery pressure (PmAP), and 15 (43%) had pressures higher than 25mmHg at rest, with variable degrees of pulmonary hypertension. One patient underwent spirometry; the others were younger than 7 years or uncooperative. Results showed severe obstruction and no response to bronchodilators. Four patients underwent lung perfusion scintigraphy when pulmonary resection surgery was considered. There was evidence of irregular and diffuse hypoperfusion in two patients and unilateral pulmonary exclusion in the others.

Treatments varied and were individualized. Mean doses (500μg/day) of inhaled corticosteroids (beclomethasone) were administered to 63% of the patients, and 14% received systemic corticosteroids (methylprednisolone or prednisone). Pulse therapy with methylprednisolone (30mg/kg/day IV for three consecutive days) was administered to selected cases depending on severity and to those with a diagnosis before the third month of the disease. The number of pulse therapy cycles varied according to individual responses. Those that were treated with oral corticosteroids received prednisone (1 to 2mg/kg/day) every other day, and the dose was gradually reduced until the medication was discontinued, according to clinical improvement. Steroid administration mode was chosen empirically, according to case severity.

In the acute respiratory phase, the antibiotics most often administered in the outpatient service were amoxicillin, azithromycin, and amoxicillin with clavulanic acid. Inhaled bronchodilators (short-acting ß-2) were administered to patients with exacerbations of the respiratory condition and in those that responded to it clinically. All patients' parents or guardians received information about respiratory therapy, nutritional support, vaccines (anti-influenza and anti-pneumococcal) and antiparasitic drugs. Continuous or intermittent home oxygen therapy was prescribed for the 15 (43%) patients with hypoxemia to keep SpO_2>94%.

Follow-up ranged from 12 to 112 months. Patients were seen at regular intervals of at least three months in the Pediatric Pulmonology Outpatient Service. In case of exacerbations, they should return to the outpatient service and not wait for the scheduled visits. Most patients had persistent, although less intense, respiratory symptoms. Of the 15 patients that were O_2 dependent and had pulmonary hypertension at diagnosis, only two remained so during follow-up. All patients had exacerbations of the pulmonary conditions during follow-up and had to receive clinical outpatient or hospital care. Three patients in the group died due to pulmonary complications.

Discussion

BO frequency in this study was greater among male infants, which confirms data in the literature[4,5]. Postinfectious BO is the most common, which was confirmed by the data in our study. Viruses are the main agents associated with the development of postinfectious BO. The most serious cases are associated with adenovirus infections, and types 3, 7 and 21 serotypes are responsible for the most severe conditions. Bacterial agents, such as *Mycoplasma pneumoniae*, type B *Streptococcus*, *Legionella pneumophila* and *Bordetella pertussis*, may also be associated with BO[3,11,12]. Virus infection is currently investigated by means of immunofluorescence in many centers, and the virus can be identified during the acute infection of the respiratory tract. As patients were referred only weeks or months after the acute infectious phase, it was not possible to isolate viruses in our study group. The three patients with a diagnosis of BP secondary to aspiration had chronic encephalopathy and a history of dysphagia and recurrent pneumonia. One case of BO was preceded by the Stevens-Johnson syndrome and developed after metamizole administration.

No protocol has been definitely established to confirm diagnoses in patients with signs and symptoms suggestive of BO. Biopsy or autopsy of children with a diagnosis of BO reveals that the most frequent histological pattern is constrictive, with variable degrees of inflammation[1,13]. Open pulmonary biopsy, the criterion standard, is currently not used to diagnose BO because it is invasive, poses greater chances of complications and may lead to inconclusive results. The distribution of pulmonary disease is heterogeneous and there may be no clinical or radiological correlation with the specimen examined by the pathologist[4,14,15].

BO diagnoses are currently made according to clinical and CT findings[2,9]. This disease stands out because of the persistence of respiratory symptoms that do not respond to different treatments, which may lead to the misdiagnosis of other lung diseases[9]. In this study, BO diagnoses were delayed a mean 14 months from symptom onset, and other diagnoses had been made previously.

The most frequent imaging abnormalities were compatible with the other findings in this study: peri-bronchial thickening and mosaic pattern on the radiographs and HRCT[2]. HRCT is the best test for the diagnostic investigation of BO[16]. In addition to defining the nature, location and extension of the bronchopulmonary lesions, it evaluates lesions in the small airways. Among the main CT findings, alternate areas of hypo- and hyperattenuation and few vessels, also called the mosaic pattern, formed the most evident sign of lesions in the small airways[17]. Bronchiectasis and bronchial wall thickening are also characteristic findings[16,18,19]. The most frequent abnormalities found in our study were: mosaic pattern, peri-bronchial thickening and bronchiectasis. In 20 patients, HRCT revealed areas of atelectasis, although this is not a common radiological finding in the literature. It may be associated with lung sequelae due to the delay in establishing a diagnosis.

Other tests may be included in the clinical evaluation of patients with BO, such as pulmonary function tests (PFT), lung scintigraphy and bronchoscopy[20]. PFT are important to define the type of ventilation disorder and to evaluate response to treatment and functional progression[20]. The typical spirometry finding in patients with BO is a fixed obstruction to air flow[21,22]. A Brazilian study showed a reduction in the capacity to practice physical exercises among children with a diagnosis of BO[22]. Because of the young age of the population under study, PFT were only performed in one of the patients, and results showed a severe obstructive disorder with no response to bronchodilators, which corroborated other findings in the literature[5]. Only four (11%) patients underwent lung perfusion scintigraphy, which showed the redistribution of lung circulation. The

others did not undergo this test because of technical problems and because it would not add any information to the HRCT findings. Bronchoalveolar lavage is not mandatory to make the diagnosis, but it may rule out other diseases. In postinfectious BO, there is a predominance of neutrophils and high IL-8 and IL-6 levels, in addition to an increase in T CD8+ lymphocytes[15,23].

BO treatment has not been universally defined. Current treatments aim at inflammation control because of the role of the immunological response in the physiopathology of this disease. Further studies should define the role of corticosteroids in inflammation in BO, as well as their capacity to prevent the disease progression[9]. The use of steroids is based on the reports of improvement of isolated cases, as well as on the empirical observation of improvement after their administration and deterioration when they are discontinued[9,20]. The use of corticosteroids in the initial phase of the disease may minimize inflammation. There is no consensus about the duration of use, administration mode, or evidence of results of treatment with inhaled or systemic corticosteroids[9,20].

Bronchodilators are empirically indicated and should be used in patients that have a clear response confirmed by pulmonary function tests or clinical examination[9]. In this study, they were used during pulmonary exacerbations, usually due to virus infections that led to bronchial hyperresponsiveness, and clinical responses varied.

Streptococcus pneumoniae, Haemophilus influenzae and *Moraxella Catharralis* are part of the most common microbiota of patients with BO and antimicrobial drugs should be directed to these agents when indicated[4,20]. The strategy in our service was to administer antibiotics to patients during the acute pulmonary phase (fever, increased cough, changes in viscosity, secretion amount or color). Some recent studies analyzed the role of azithromycin in the treatment of BO and showed that it reduces inflammatory markers in the bronchoalveolar lavage (BAL) and even improves pulmonary function[15,24,25].

Hypoxemia and oxygen dependence are common findings in the beginning of the disease and may persist in the most severe cases for a long time[26]. Oxygen therapy was used in patients whose oxygen saturation was below 94% to correct hypoxemia and prevent the development of pulmonary hypertension.

This disease may progress in different ways: it may range from mild and favorable forms to severe cases with fatal complications[4]. Most patients in our study improved clinically during follow-up: oxygen dependence disappeared and pulmonary hypertension was reversed, despite the variable degrees of respiratory dysfunction, which corroborated data in the literature[27]. Three patients (8.5%) died during the first hospitalization or in the first six months after the diagnosis. A prospective study with patients with pneumonia due to adenovirus infection had a mortality of 18.4% in the first acute phase and no death during the five-year follow-up of patients that had BO[12]. Rales at pulmonary auscultation were a constant finding during outpatient follow-up, and wheezing was frequent during the acute respiratory phase.

The prognosis of BO is variable and may be associated with several factors, such as its underlying cause and the need of mechanical ventilation during the acute phase[21]. It is not defined in the literature whether mechanical ventilation is a risk factor for BO or if it reflects the severity of the acute insult[26]. Although this study did not evaluate risk factor to define the severity of BO, 23% of the patients received mechanical ventilation in the initial phase, and most improved, probably because the most frequent cause was postinfectious BO, which tends to have a better progression[8].

The fact that pediatricians do not know about this disease may have contributed to the delays in the diagnosis of BO (mean 14 months from symptoms onset) and to misdiagnoses. BO should be included in the differential diagnosis when an infant has a chronic obstructive pulmonary disorder that does not respond to treatments so that an early diagnosis can be made, the treatment can be optimized and morbidity and mortality may be reduced. Clinical and CT findings are currently acceptable as sufficient data to confirm a diagnosis of BO[3,9].

The major limitation of this retrospective study was the fact that viruses were not isolated and treatments were not initiated during the first phase. However, the main cause of BO in children is respiratory infection, which is associated with high morbidity, frequent hospitalizations, hypoxemia, home oxygen therapy, and the frequent use of antibiotics and corticosteroids. Our study found a prevalence of postinfectious causes, characteristic CT findings and improvement of oxygen dependence and pulmonary hypertension.

The frequency of postinfectious BO in Latin America is relatively high, and multicenter studies should be conducted to better define diagnostic criteria, risk factors, prognosis and disease activity markers, as well as to standardize treatments.

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