Received: 28 November 2019 | Accepted: 4 February 2020

DOI: 10.1002/ppul.24690

ORIGINAL ARTICLE: OUTCOMES

PEDIATRIC PULMONOLOGY WILEY

Postinfectious bronchiolitis obliterans masked by misdiagnosis as asthma

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Abstract

Objectives: Asthma and postinfectious bronchiolitis obliterans (PIBO) have similar clinical findings, and PIBO may be misdiagnosed with asthma. This study aimed to determine the clinical features of PIBO in children and the causes of delay in its diagnosis.

Methods: We retrospectively evaluated all patients diagnosed with PIBO in four pediatric pulmonology centers between 2007 and 2018. In total, 64 PIBO patients were retrospectively reviewed. We compared the clinical and laboratory differences between PIBO patients who had initially been misdiagnosed with asthma and correctly diagnosed with PIBO.

Results: Of the 64 patients, 22 (34.4%) had initially been misdiagnosed with asthma. Adenovirus was the most common infectious agent in children. The age upon diagnosis was older, and the symptom duration was significantly longer in patients misdiagnosed with asthma ($P < .05$). There were no statistical differences in terms of sex, history of prematurity, duration of hospitalization, treatment, history of oxygen or mechanical ventilation support, pulmonary function test (PFT) results and asthma-predisposing findings between the two groups ($P > .05$).

Conclusions: Patients with PIBO who had initially been misdiagnosed with asthma were correctly diagnosed at older ages and had longer symptom duration. Asthma may mask PIBO diagnosis by the similarity of symptoms and the clinical response to inhaled β2-agonist or steroid treatment. PFTs may not help clinicians because of the age of children. The delay in the diagnosis of PIBO is probably attributable to the fact that some clinicians fail to include PIBO in the differential diagnosis when there is no clinical response to asthma medication.

KEYWORDS

asthma, children, postinfectious bronchiolitis obliterans

Abbreviations: API, asthma predictive index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computer tomography; LRTI, lower respiratory tract infection; MV, mechanical ventilation; PFT, pulmonary function test; PIBO, postinfectious bronchiolitis obliterans.

1 | INTRODUCTION

Asthma is the most encountered chronic disease in childhood. The observed frequency of asthma ranges from 1% to 18% across countries around the world.[1] It is usually related to airway inflammation and airway hyperresponsiveness to various stimuli.[2] The diagnosis of asthma is difficult, especially for children under the age of 5. Recurrent wheezing episodes can occur excessively in those children. Symptom patterns (wheezing, cough, and shortness of breath), the presence of risk factors for the development of asthma, and the response to treatment (low-dose inhaled corticosteroids) should be investigated for the diagnosis of asthma in children. The history of other allergic diseases (atopic dermatitis or allergic rhinitis) and a family history of asthma are also very important for the diagnosis.[1]

Bronchiolitis obliterans is a form of chronic lung disease that severely affects the small airways. It may cause both fibrosis and inflammation and lead to partial or complete luminal obstruction.[3] In children, bronchiolitis obliterans mostly begin with a severe lower respiratory tract infection (LRTI), in which case it is called postinfectious bronchiolitis obliterans (PIBO). The most frequent infectious agents in PIBO are adenovirus, influenza, parainfluenza, measles, and respiratory syncytial viruses, and *Mycoplasma pneumoniae*.[4] Adenovirus is the most frequent viral agent responsible for PIBO.[5] The real prevalence of the disease is unknown, but it is clear that it is related to LRTIs in early childhood. The diagnosis of PIBO is based on clinical criteria in children usually under the age of 3: (a) a history of acute and severe LRTI, (b) occurrence of persistent airway obstruction in physical examination or pulmonary function tests (PFTs) after an acute respiratory event, and (c) radiologic findings of obstructive lung disease such as hyperinflation, atelectasis, airway wall thickening, bronchiectasis, and mosaic pattern and/or air trapping in high-resolution computed tomography (HRCT) of the chest. Other chronic lung diseases such as tuberculosis, cystic fibrosis, bronchopulmonary dysplasia, immunodeficiencies, and severe asthma should be excluded for the diagnosis.[5]

PIBO is rarely observed in children, and its diagnosis is difficult. Therefore, several pediatric patients with PIBO can be misdiagnosed with asthma or other chronic lung diseases. Most patients who exhibit wheezing may be treated for asthma because of its higher prevalence, and some patients could respond to inhaled β2-agonist and steroid treatment. In our clinical practice, we have many patients with rare chronic lung diseases who had been misdiagnosed with asthma for many years. The aim of this study was to investigate the characteristics of patients diagnosed with PIBO, to compare them with those of patients with PIBO who had previously been misdiagnosed with asthma, and to determine the reasons for the misdiagnosis.

2 | METHODS

All patients diagnosed with PIBO at the Pediatric Pulmonology Department, Faculty of Medicine of Gazi University, Ankara, Turkey, the Pediatric Pulmonology Department, Meram Medicine Faculty of Necmettin Erbakan University, Konya, Turkey, the Pediatric Allergy and Immunology Department, Faculty of Medicine of Baskent University, Konya, Turkey, and the Pediatric Pulmonology Department, Faculty of Medicine of Erciyes University in Kayseri, Turkey between 2007 and 2018 were included in the study. Patients with cystic fibrosis, immunodeficiencies, primary ciliary dyskinesia, and bronchopulmonary dysplasia were excluded. In total, 64 PIBO patients were included.

PIBO was diagnosed by clinical and radiologic findings of patients according to the following diagnostic criteria: a history of LRTI, persistent airway obstruction in physical examination or PFTs (if performed), and radiologic findings such as hyperinflation, atelectasis, airway wall thickening, and bronchiectasis or mosaic pattern and air trapping in HRCT.[5] Demographic findings, complaints, history of birth, exposure to secondhand smoke, types of infection, microbiologic agents, physical examinations, hospitalization and mechanical ventilation (MV) history, administered treatments, asthma-predisposing factors, serum immunoglobulin E levels and percentages of eosinophil cells (if tests were performed) of the patients at the time of LRTI, and results of PFTs for those patients who could perform them at the time of PIBO diagnosis and/or after treatment, and all patients' HRCT findings at the time of PIBO diagnosis were recorded. The forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC ratio, and mean expiratory flow at 25 to 75 were recorded as percentages. The FEV_1/FVC ratio was assessed based on age, sex, and height. Patients with PIBO who had previously been misdiagnosed with asthma were categorized as group 1 and patients who had correctly been diagnosed with PIBO were classified as group 2. All findings of the two groups were compared.

The software SPSS Statistics 17.0 was used for statistical analysis. Categorical indicators were considered as absolute numbers and percentages, whereas numeric indicators were considered as average, standard deviation, median, minimum, and maximum. When investigating the differences between the two groups, a the χ^2 test was performed to assess the statistical significance of categorical differences. To assess the statistical significance of numerical differences, Student *t*-test was used when the assumption of normal distribution was satisfied for the sample, and a Mann-Whitney *U* test was performed when the normality assumption was not satisfied. A value of *P* less than .05 was considered statistically significant.

This study was approved by the Faculty of Medicine Ethics Committee of Gazi University (no. 43, 14 January 2019). Informed consent was not obtained from the patients because this was a retrospective study.

3 | RESULTS

In total 64 patients included in the study, 22 of them were in group 1 and 42 of them were in group 2. The majority were male and the median age upon diagnosis was 2.5 years (range, 0.3-13 years). Most of the patients' complaint was cough, and the most common type of infection was pneumonia. The most common microbiologic agent detected was adenovirus. All patients' characteristics and HRCT findings at the time of PIBO diagnosis are presented in Table 1.

TABLE 1 Clinical characteristics and HRCT findings of all PIBO patients

	n	%
Sex (male)	46	71.9
Prematurity	11	17.2
Consanguinity	22	34.4
Secondhand smoke exposure	22	34.4
Misdiagnosed with asthma	22	34.4
Complaint		
Cough	28	43.8
Wheezing	13	20.3
Shortness of breath	11	17.2
Recurrent LRTI	6	9.4
Cough + wheezing	6	9.4
Type of infection		
Pneumonia	41	64.1
Bronchiolitis	23	35.9
Microbiologic agent		
Respiratory syncytial virus	1	1.6
Adenovirus	6	9.4
Mycobacterium tuberculosis	1	1.6
Measles virus	1	1.6
Influenza virus	4	6.3
Metapneumovirus	1	1.6
Epstein-Barr virus	1	1.6
Rhinovirus	3	4.7
Physical examination findings		
Normal	9	14.1
Rales	28	43.8
Wheezing	14	21.9
Rales + wheezing	10	15.6
Decreased respiratory sounds	3	4.7
HRCT findings		
Mosaic pattern	48	75
Airway wall thickening	24	37.5
Atelectasis	18	28.1
Ground glass opacities	6	9.4
Consolidation	5	7.8
Bronchiectasis	3	4.7
Subpleural air cyst	1	1.6
Hospitalization	47	73.4
Oxygen support	33	51.6
Mechanical ventilation	23	35.9
	Mean ± SD	
Age of diagnosis, y	3.75 ± 0.51	
Symptom duration, mo	17.05 ± 3.31	
Hospitalization duration, d	26.15 ± 2.80	
Mechanical ventilation duration, d	11.12 ± 2.84	
Length of follow-up, mo	32.6 ± 4.6	

Abbreviations: HRCT, high-resolution computer tomography; LRTI, lower respiratory tract infection; PIBO, postinfectious bronchiolitis obliterans; SD, standard deviation.

At the time of severe respiratory tract infection, a significant number of patients needed MV and the majority of them (69.6%) were in group 2. Continuous oxygen support was provided to a considerable number of patients during the acute phase of the infection. In the follow-up period, only five patients with PIBO received oxygen support.

A comparison of the clinical features of patients between the two groups is shown in Table 2. Statistically significant differences were observed in terms of age upon diagnosis and symptom duration ($P < .001$).

All patients were reviewed for predisposing factors for asthma. A comparison of the predisposing factors, asthma predictive index (API) scores, immunoglobulin E levels, and eosinophil percentages between the two groups is shown in Table 3. No statistically significant differences were found in these respects.

PFTs were performed in 14 (21.9%) of the 64 patients both pretreatment and posttreatment, and nine (64.3%) of them were in group 1, five (35.7%) of them were in Group 2. Nine patients performed reversibility tests before treatment and four patients performed after treatment with systemic steroids and/or inhaled steroids and/or β2 agonists. There were no differences in terms of reversibility positiveness before and after treatment between the two groups. A comparison of PFT findings between the two groups at the time of diagnosis and after treatment is shown in Table 4 and there was no statistically significant difference between the two groups.

4 | DISCUSSION

PIBO is a clinical syndrome that affects the small airways with obstruction, fibrosis, and inflammatory changes in the lung, and it is usually diagnosed in children aged under 3 years.[5,6] LRTI, asthma, and recurrent wheezing are common in this age group. The purpose of this study was to investigate the clinical features of PIBO in children and difficulties in its diagnosis. In this way, factors that cause PIBO patients to be misdiagnosed with asthma may be understood. Early diagnosis of PIBO and timely treatment initiation are important to prevent irreversible peribronchial fibrosis. PIBO is difficult to diagnose because its clinical manifestations are not specific. Patients who have prolonged LRTI symptoms can be regarded as potential candidates for PIBO because all PIBO patients have LRTIs. Previous studies have shown that most patients with LRTIs had cough or wheezing or both.[7] In our study, a significant number of patients had a chronic cough, wheezing and crackles in their physical examination, in line with Chiu et al[6] and Wang et al.[8]

The prevalence of PIBO in children is not known definitely. However, it is known to be directly related to the frequency of LRTIs. Although children recover from adenovirus LRTIs, severe cases can result in considerable morbidity and mortality. It is known that 14% to 60% of children with documented adenovirus LRTIs have some degree of pulmonary sequelae.[9] Wang et al[8] found that adenovirus and *M. pneumoniae* were the most common etiologic agents of PIBO. Similarly, we found that adenovirus was the most common infectious agent giving rise to PIBO; there was one patient with adenovirus infection in group 1 and five patients in group 2. The detection of

TABLE 2 Comparison of the clinical features between group 1 and group 2

	Group 1 (n = 22)	Group 2 (n = 42)	P
Age of diagnosis, y	6.3 ± 4.1	2.8 ± 3.2	<.001
Gender (male)	15 (68.2%)	31 (73.8%)	>.05
Prematurity	4 (18.2%)	7 (16.7%)	>.05
Secondhand smoke exposure	7 (31.8%)	15 (35.7%)	>.05
Consanguinity	11 (50%)	11 (26.2%)	>.05
Symptom duration, mo	30.9 ± 35.1	9 ± 14.7	<.001
Hospitalization duration, d	28.8 ± 18.7	24.7 ± 19.4	>.05
Treatment duration, mo	6.5 ± 9.4	5.1 ± 6.9	>.05
Follow-up duration, mo	40.5 ± 28.8	28.5 ± 33.4	>.05
Oxygen support	11 (50%)	22 (52.4%)	>.05
MV support	7 (31.8%)	16 (38.1%)	>.05
MV duration, d	11.6 ± 12.2	10.9 ± 12	>.05
Use of β2 agonists	22 (100%)	38 (90.5%)	>.05
Use of inhaled steroids	13 (59.1%)	17 (40.5%)	>.05
Use of systemic steroids	8 (36.4%)	20 (47.6%)	>.05

Abbreviation: MV, mechanical ventilation.

TABLE 3 Comparison of predisposing factors for asthma between group 1 and group 2

	Group 1 (*n* = 22)	Group 2 (*n* = 42)	P
Family history of asthma	36.3%	16.6%	>.05
Family history of allergies	10.5%	2.6%	>.05
Atopy	0	10.8%	>.05
Skin prick test positivity	11.7%	6.4%	>.05
Allergic rhinitis	0	6.2%	>.05
API positiveness	36.3%	21.4%	>.05
Immunoglobulin E, IU/L[a]	78.6 ± 119.7	53.9 ± 107.3	>.05
Eosinophils (%)[b]	2.2 ± 2.4	2.5 ± 2.2	>.05

Abbreviation: API, asthma predictive index.
[a]Immunoglobulin E levels were measured in 20 patients in group 1 and 32 patients in group 2.
[b]Eosinophil percentages were measured in 19 patients in group 1 and 39 patients in group 2.

adenovirus in only one patient in group 1 could be one of the reasons for misdiagnosis and late correct diagnosis in group 1, as it is known that adenovirus infections are frequently related to PIBO, and the presence of the virus is an important clue in diagnosing the disease.

PIBO is mostly seen in early childhood because of the high rate of LRTIs. In the Republic of Korea, Yoon et al[10] found that the median age of 17 patients at the time of diagnosis was 4 years, and Li et al[11] reported a median age of 2.32 years (range, 0.8-5.7 years). Our results support these findings. When comparing the difference in the age upon diagnosis between groups 1 and 2, we found a significant delay in diagnosis in group 1. Also, the symptom duration in group 1 was significantly longer than in group 2. This could be explained by the similarity of symptoms of PIBO and asthma, as well as the partial response to inhaled β2-agonist and steroid treatment in PIBO.

Children who develop PIBO are known to have a more compromised respiratory system and are more likely to require intensive care unit admission and MV and oxygen support during an LRTI than those who do not develop PIBO.[9] MV support is known as a risk factor for PIBO.[9,12] It is rarely necessary for asthma: only 2% to 4% of the patients with asthma hospitalized because of severe exacerbation require it.[13] In our study, 7 of 22 (31.8%) patients in group 1 and 16 of 42 (38.1%) patients in group 2 required MV. Also, 11 of the 22 patients in group 1 and 22 of the 42 patients in group 2 received oxygen support. However, there were no significant differences between the two groups in terms of oxygen support, hospitalization duration, MV support, treatment duration, and follow-up duration.

In the diagnosis of asthma, asthma-predisposing factors (such as a family history of asthma or allergies, a history of atopy, skin prick test positivity, high immunoglobulin E levels, and eosinophil percentages) could be helpful to physicians.[14] In our study, there were no statistically significant differences in asthma-predisposing factors between the two groups. The fact that PIBO is more likely to be seen in preschool children, who suffer from LRTIs more frequently, explains why most of the patients in our study could not perform PFTs. There were no statistical differences between patients who could perform PFTs and reversibility tests in two groups. While PFTs and API scores may help physicians in the diagnosis of asthma in older children, our findings indicate that they were not helpful in the diagnosis of PIBO and the differentiation between PIBO and asthma during the early stages of childhood.

Recurrent wheezing and chronic cough are typical symptoms of asthma. For this reason, children who exhibit wheezing and cough tend to be diagnosed with asthma. However, patients who display these symptoms could also have PIBO, as these two diseases are characterized by similar symptoms. PIBO is clinically characterized by severe and persistent airway obstruction despite the use of bronchodilators such as inhaled β2- agonists and systemic/inhaled steroids.[9] On the other hand, patients with either asthma or PIBO could respond to inhaled β2-agonist or steroid treatment or both, which is another source of confusion in the diagnosis.[2,12] In our study, there was no difference between the two groups in terms of steroid and inhaled β2-agonist use. One reason for this is the variation in the findings of histologic studies on PIBO, ranging from minimal bronchiolar inflammation to peribronchiolar fibrosis and complete occlusion of the bronchiole lumen.[9] In

TABLE 4 PFT findings of group 1 and group 2

	Group 1			Group 2			
	Pretreatment n = 9	Posttreatment n = 9	P^a	Pretreatment n = 5	Posttreatment n = 5	P^b	P^c
FEV_1 (%)	63.4 ± 19.8	72.6 ± 22.5	>.05	68.6 ± 23.5	69.2 ± 20.3	>.05	>.05
FVC (%)	66.6 ± 18.7	72.0 ± 24.2	>.05	67.8 ± 24.3	72.8 ± 17.2	>.05	>.05
FEV_1/FVC ratio	87.7 ± 16.0	86.6 ± 16.5	>.05	94.4 ± 10.6	89.4 ± 14.2	>.05	>.05
MEF_{25-75} (%)	47.7 ± 21.4	53.9 ± 22.1	>.05	52.6 ± 22.6	48.8 ± 19.3	>.05	>.05

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MEF_{25-75}, mean expiratory flow at 25-75; PFT, pulmonary function test.

[a]Comparison of pretreatment and posttreatment PFT findings of group 1.

[b]Comparison of pretreatment and posttreatment PFT findings of group 2.

[c]Comparison of PFT results between group 1 and group 2.

addition, steroid treatment for PIBO patients who are misdiagnosed with asthma may mask the characteristic symptoms of PIBO and prevent physicians from identifying it early and accurately. Early diagnosis of PIBO could help clinicians in disease management and prevention of respiratory function impairment.[15]

Despite the large number of patients-given the rarity of the disease- and the long follow-up duration, our study had some limitations. Due to the age of patients, many of them could not perform PFTs, and since this was a retrospective study, the quality of life, hospitalization rates, and exacerbations were not recorded.

In conclusion, physicians tend to think of asthma as a preliminary diagnosis in patients with cough or wheezing. The presence of severe respiratory disease, a history of LRTI especially by adenovirus, a poor response to inhaled β2-agonist and inhaled steroid treatment, and a history of MV and oxygen support may be clues to PIBO. Misdiagnosis as asthma may mask the PIBO diagnosis and cause a delay in initiating the appropriate treatment. This is probably attributable to the fact that some clinicians do not include PIBO in the differential diagnosis when there is no clinical response to asthma medication.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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How to cite this article: Onay ZR, Ramasli Gursoy T, Aslan AT, et al. Postinfectious bronchiolitis obliterans masked by misdiagnosis as asthma. *Pediatric Pulmonology*. 2020;55:1007–1011. https://doi.org/10.1002/ppul.24690