

Clinical analysis of adenovirus postinfectious bronchiolitis obliterans and nonadenovirus postinfectious bronchiolitis obliterans in children

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ABSTRACT

Background and Objective: Postinfectious bronchiolitis obliterans (PIBO) is an uncommon and severe form of chronic obstructive lung disease in children. Adenovirus (ADV) is the main pathogen of PIBO in children. However, the risk factors of ADV-PIBO are not fully understood. This study aims to analyze the clinical characteristics of PIBO caused by ADV and compared with non-ADV-PIBO. **Materials and Methods:** A retrospective study of children under the age of 14 years diagnosed PIBO was performed in 56 ADV-PIBO cases, 29 non-ADV-PIBO, and 39 healthy controls to determine clinical characteristics of PIBO. **Results:** There was no difference between ADV-PIBO and non-ADV-PIBO cases in gender, age, individual and family atopy or history of asthma, and previous history of wheezing and no difference in the clinical manifestations and signs between the two groups. However, the hospital stay, duration of ventilator use, and multifocal pneumonia incidence of ADV-PIBO group have a significant differences compared with non-ADV-PIBO. Notably, inflammatory markers lactic dehydrogenase (LDH), interleukin 8 (IL-8), and interferon-gamma (IFN- γ) were significantly increased in PIBO patients, and those expressed in ADV-PIBO patients were higher than those in non-ADV-PIBO patients. In addition, ADV-PIBO children required a longer duration of oral prednisone and azithromycin than non-ADV-PIBO cases. **Conclusions:** Compared with non-ADV-PIBO, ADV-PIBO has a longer hospital stay, longer duration of ventilator use, increased LDH, IL-8, and IFN- γ expressions, and longer duration of oral prednisone and azithromycin treatment. Further research is needed to determine why PIBO caused by ADVs are more severe than those caused by other pathogens.

KEY WORDS: Adenovirus, interferon-gamma, interleukin-8, lactic dehydrogenase, postinfectious bronchiolitis obliterans

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INTRODUCTION

Bronchiolitis obliterans (BO) is a clinical syndrome of chronic airflow obstruction caused by chronic inflammatory lesions of small airways. It can be caused

by severe lower respiratory tract infection, connective tissue disease, heart and lung transplantation, bone marrow transplantation, Stevens–Johnson syndrome, and inhalation or ingestion of toxic substances.^[1-3] Among

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them, BO caused by respiratory tract infection is also known as postinfection BO (PIBO), PIBO is the main type of pediatric BO.^[4-6] The incidence of PIBO is low, and its overall incidence is rarely reported worldwide.^[7] At present, there are some reports comparing PIBO with healthy controls. However, there are few studies on the correlation between PIBO caused by adenovirus (ADV) and other pathogens. Therefore, this study will compare the differences in clinical characteristics and associated inflammatory indicators between ADV-PIBO and non-ADV-PIBO, in an attempt to identify the possible pathogenesis of PIBO caused by ADV.

MATERIALS AND METHODS

Patients

A total of 97 children with PIBO were selected from January 2016 to March 2020 using the computerized management system of medical records, which includes patients who were first diagnosed with PIBO in the outpatient or inpatient department of the First Hospital of Jilin University. Inclusion criteria: (1) children under 14 years of age; (2) definitely diagnosed as PIBO; (3) there is a clear history of LRTI with a specific pathogen before the diagnosis of PIBO; and (4) a well-documented history of severe pneumonia associated with PIBO and follow-up at least 12 months after PIBO was diagnosed. Exclusion criteria: (1) incomplete medical records (partial clinical data records are incomplete); (2) previous organ transplantation, connective tissue disease, toxic drug intake history, and other special medical history. Diagnostic criteria of PIBO:^[7,8] (1) continuous or repeated coughing and wheezing for 6 weeks after the infection; (2) evidence of obstructive pulmonary disease on computed tomography (CT) examination imaging such as hyperventilation, atelectasis, bronchial wall thickening, bronchiectasis and mosaic perfusion, and air trapping (two fixed radiologists performed imaging reports); (3) excluding other chronic pulmonary diseases such as tuberculosis, cystic fibrosis, bronchopulmonary congenital dysplasia, and primary immune deficiency. According to the pathogen, PIBO can be divided into ADV-PIBO and non-ADV-PIBO. Finally, 85 children with PIBO meeting the standards were included in the study.

Evaluation index

Data of age of onset, gender, previous history of wheezing, length of hospital stay (this refers to the length of hospital stay for severe pneumonia clearly associated with PIBO before the diagnosis of PIBO), duration of ventilator use (this refers to the presence and duration of mechanical ventilation during severe pneumonia which has a clear correlation with PIBO before diagnosis of PIBO), wheezing in severe pneumonia, image of high-resolution CT, and lung function test when PIBO are diagnosed and the level of lactic dehydrogenase (LDH) in severe pneumonia were collected.

Etiological detection

All of the patients had documented results of the etiologic agent causing the original lower respiratory tract infection. The antigen expressions of ADV, respiratory syncytial virus (RSV), and parainfluenza virus in nasopharyngeal aspirates was detected by indirect immunofluorescence assay. *Pneumoniae*-IgM, *Chlamydia pneumoniae*-IgM, and *Legionella pneumophila*-IgM in serum were detected by ELISA.

Detection of cytokine expression

The production of IL-8 and interferon-gamma (IFN- γ) in peripheral blood of PIBO children was measured 1 month after the oral hormone was discontinued during the follow-up period by specific enzyme-linked immunosorbent assay (ELISA) kits (eBioscience, San Diego, CA, USA); samples from the healthy control group were collected together when clinical characteristics were recorded in the outpatient physical examination. The operations are according to the manufacturer's instructions.

Statistical analysis

SPSS 21.0 software (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Quantitative data were expressed as $x \pm s$, and *t*-test was used for comparison between groups. Enumeration data were analyzed using the Chi-squared test or Fisher's exact probability test. The $P \leq 0.05$ is considered statistically significant for a confidence interval of 95%.

RESULTS

Eighty-five children with PIBO met the inclusion criteria including 56 ADV-PIBO cases, 29 non-ADV-PIBO cases, and 39 children were randomly selected from outpatient health checkups as healthy controls. Clinical characteristics showed that there was no difference in gender structure and previous history of wheezing between healthy controls and ADV-PIBO group and non-ADV-PIBO group. In 29 non-ADV-PIBO cases, RSV-specific IgM was positive in 14 patients, *M. pneumoniae*-specific IgM was detected in ten patients, *C. pneumoniae*-IgM was positive in three patients, and influenza A virus-IgM and Influenza B virus-IgM were positive in one patient, respectively. Of the 56 ADV-PIBO cases, 22 cases were tested for ADV typing, and the results showed that 12 cases were ADV7, eight cases were ADV3, one case was ADV 1, and one case was ADV 14. There was no significant difference between the ADV-PIBO and non-ADV-PIBO in the clinical manifestation including cough, wheezing, activity intolerance, dyspnea, and tri-retraction sign positive [Table 1, $P > 0.05$] in the active phase of the disease. In addition, there was no significant difference in the age of onset, gender composition, previous history of wheezing (before the occurrence of PIBO, a specialist determined wheezing by auscultation of the lungs),

Table 1: The clinical manifestation in adenovirus-postinfectious bronchiolitis obliterans and nonadenovirus-postinfectious bronchiolitis obliterans patients

	ADV-PIBO (n=56)	Non-ADV-PIBO (n=29)	Fisher's exact test	P
Cough	48 (85.7)	26 (89.7)	NS	0.7418
Exercise intolerance	51 (91.1)	24 (82.8)	NS	0.2984
Wheeze	54 (96.4)	26 (89.7)	NS	0.3322
Dyspnea	48 (85.7)	23 (79.3)	NS	0.5406
Tri-retraction sign positive	36 (64.3)	15 (51.7)	NS	0.3507

ADV-PIBO: Adenovirus-postinfectious bronchiolitis obliterans, NS: Not significant

Table 2: The clinical characteristics in adenovirus-postinfectious bronchiolitis obliterans and nonadenovirus-postinfectious bronchiolitis obliterans patients

	ADV-PIBO(n=56)	Non-ADV-PIBO(n=29)	Hcs (n=39)	P-value
General characteristic				
Age of onset	17.61 (7- 91)	15.14 (5- 86)		>0.05
Sex (female/male)	21/35	13/16		>0.05
Previous history of wheezing (%)	12 (21.4)	7 (24.1)		>0.05
Length of hospital stay (day)	19.6±9.3	13.3±10.7		<0.05
Duration of ventilator use (day)	7.5±6.2	4.2±3.5		<0.05
Multi-focal pneumonia (%)	37 (66.1)	12 (41.4)		<0.05
Atopy and asthma				
Atopy in children (%)	13 (23.2)	5 (17.2)	7 (17.9)	>0.05
Asthma in children (%)	2 (3.8)	0 (0)	1 (2.6)	>0.05
Atopy in family (%)	15 (26.8)	8 (27.6)	6 (15.4)	>0.05
Asthma in family (%)	1 (1.8)	0 (0)	1 (2.613)	>0.05
IL-8, IFN-γ and LDH				
LDH (U/L)	1278.5±937.4	763.8±506.2	106.27±12.55	<0.05
IL-8 (pg/mL)	43.66±15.42 (n=51)	35.19±11.05 (n=27)	24.01±1.61 (n=35)	<0.05
IFN-γ (pg/mL)	3.42±1.37 (n=51)	2.37±1.19 (n=27)	1.58±0.09 (n=35)	<0.05
The treatment time				
Oral prednisone (day)	137.3±34.6	105.7±29.3		<0.05
Oral azithromycin (day)	145.7±27.4	132.1±31.8		<0.05
Long-term oxygen therapy (%)	6 (10.7)	2 (6.9)		>0.05

Long-term oxygen therapy: After discharge, he still needs intermittent oxygen therapy at home. ADV-PIBO: Adenovirus-postinfectious bronchiolitis obliterans, LDH: Lactic dehydrogenase, IFN-γ: Interferon-gamma, IL: Interleukin

and complications between the two groups [Table 2, $P > 0.05$]. Furthermore, we compared the individual and family history of atopy and asthma in ADV-PIBO children, non-ADV-PIBO children, and healthy controls; there was no significant difference in atopy or incidence of asthma among the three groups.

Hospital stay and mechanical ventilation time

Compared with the non-ADV-PIBO children, the ADV-PIBO patients have a longer hospital stays and mechanical ventilation time, and the proportion of multifocal pneumonia was also higher [Table 2, $P < 0.05$].

The levels of lactic dehydrogenase, interleukin-8, and interferon gamma

LDH, interleukin 8 (IL-8), and IFN-γ expression were significantly higher in both ADV-PIBO and non-ADV-PIBO than in healthy controls. Further tests confirmed that the levels of LDH in severe pneumonia in ADV-PIBO patients were all distinctly increased compared with those in non-ADV-PIBO patients [Table 2, $P < 0.05$]. Furthermore, the expression levels of IL-8 and IFN-γ in 51 ADV-PIBO patients and 27 non-ADV-PIBO patients were conducted 1 month after withdrawal of the oral prednisone during the follow-up.

Lung function

Airway obstruction was defined using tidal breathing analysis (in children aged <3 years) or impulse oscillometry (in children aged 3-6 years) or routine measurement of pulmonary ventilation function (in children aged >6 years). The tidal breathing analysis revealed a decreased $t_{PTEF\%} t_E$ both in ADV-PIBO ($n = 52$) and non-ADV-PIBO ($n = 26$) ($21.2\% \pm 4.5\%$, and $23.3\% \pm 4.7\%$, respectively, $P > 0.05$, normal: more than 40%) or in $V_{PEF\%} V_E$ ($18.5 \pm 3.8\%$ and $21.5 \pm 4.6\%$, respectively, $P > 0.05$, normal: more than 40%), suggesting obstructive airway dysfunction. The impulse oscillometry results showed abnormally increased values for Z5 both in ADV-PIBO ($n = 3$) and non-ADV-PIBO ($n = 3$) ($158.6\% \pm 16.0\%$ and $150.6\% \pm 11.3\%$ of the predicted value, respectively, $P > 0.05$, normal: less than 120% of the predicted value), R5 ($159.3\% \pm 9.4\%$ and $152.7\% \pm 12.1\%$ of the predicted value, respectively, $P > 0.05$, normal: less than 120% of the predicted value), and X5 ($197.6\% \pm 58.7\%$ and $189.2\% \pm 42.9\%$ of the predicted value, respectively, $P > 0.05$, normal: Less than 120% of the predicted value), suggesting increased peripheral airway resistance. Notably, pulmonary ventilation function in a patient with ADV-PIBO showed: That FEV1, peak expiratory flow and FEF 25-75 were significantly lower suggestive of severe obstructive

ventilatory dysfunction. Both groups had a significant obstructive ventilation dysfunction, but there was no difference in the degree of obstruction between the two groups.

Treatment

The treatment protocol for PIBO included oral prednisone and azithromycin, six cases of ADV-PIBO and two cases of non-ADV-PIBO required long-term oxygen support. Compared with the non-ADV-PIBO children, the ADV-PIBO children received oral prednisone and azithromycin for a longer period of time, but there was no significant difference in oxygen duration between the two groups.

DISCUSSION

Some studies have pointed out that ADV is the most common pathogen among the causes of PIBO.^[9] ADV infection is an important cause of BO, and severe pneumonia caused by ADV infection is more likely to develop into BO. Previous studies have found that ADV infection is one of the most dangerous factors for BO.^[10] In this study, 65.9% of children with PIBO were caused by ADV, whereas other PIBO were mainly caused by RSV, mycoplasma pneumoniae, chlamydia pneumoniae, influenza virus, etc., In the serotype of ADV, ADV3 and ADV7 are the most common types that cause severe ADV pneumonia and further develop into PIBO, especially Type 7 with a high fatality rate and many sequelae.^[11,12] Our study is consistent with previous studies showing that serotypes 3 and 7 remain important serotypes, leading to ADV-PIBO. Pulmonary function results showed that both groups had significant obstructive ventilation dysfunction, and there was no significant difference between the two groups.

Currently, there have no ideal treatments for PIBO, so understanding the pathogenesis of PIBO, especially the mechanism of ADV infection, will help to find effective treatment. Previously, studies demonstrated that independent risk factors for PIBO acute stage death included mechanical ventilation, multifocal pneumonia, hypercapnia, coagulation dysfunction, neurological symptoms, and combined measles virus infection.^[13] Among the risk factors monitored in this study, length of hospital stay, duration of ventilator use, and the proportion of multifocal pneumonia in ADV-PIBO are remarkable higher than those in non-ADV-PIBO. Previous studies indicate that the timing of use of ventilator for severe ADV pneumonia is very important, and prolonged maintenance of invasive mechanical ventilation means that the children have more severe lung lesions. Therefore, most PIBO children have a history of mechanical ventilation. Clinically, children with PIBO have multiorgan dysfunction, which is further aggravated by hypoxia, respiratory support can effectively relieve hypoxia and reduce the occurrence of multiorgan dysfunction. Therefore, mechanical ventilation is an important supportive therapy. It is worth noting

that high-resolution CT showed PIBO often involved multilobar lesions. Moreover, the multilobar lesions involvement of PIBO caused by ADV was more than that caused by other pathogens; it further suggests that ADV infection may be more likely to cause multifocal pneumonia, which may be an important cause that it is liable to develop into PIBO. It is worth noting that severe pneumonia can also cause extrapulmonary complications such as toxic encephalopathy, diarrhea, liver damage, myocardial damage, anemia, neutropenia, and disseminated intravascular coagulation; our study found that there was no difference in the incidence of the above complications between the ADV-PIBO and non-ADV-PIBO.

The pathogenesis of PIBO mainly involves the infiltration of inflammatory cells around the airway; infection recruits a large number of inflammatory cells and cytokines, which result in excessive inflammatory response and form airway constriction and occlusion.^[14] Currently, the leading therapeutic drugs for BO, whether it is glucocorticoids or azithromycin, both depend on their anti-inflammatory properties, which can effectively reduce the airway hyperreactivity and airway stenosis.^[2,4] This study mainly detected and analyzed the expressions of LDH, IL-8, and IFN- γ . LDH is a kind of biological active enzyme ubiquitous in the body and highly expressed in the heart, skeletal muscle, and kidney, followed by liver, pancreas, and lung; the LDH level could partly reflect the severity of organ damage in the body. When the lung tissue is hypoxic and necrotic, the cell membrane permeability increases, and the enzyme is released from the cell to the blood, which makes the serum LDH increase. Therefore, serum LDH is also used in the clinic as a routine detection index reflecting lung diseases. The study of Tasaka *et al.* showed that the elevation of LDH more reflects the severity of lung tissue injury.^[15] In this study, it was found that LDH of PIBO increased significantly compared with the healthy controls, and LDH in ADV-PIBO remarkable increased than in non-ADV-PIBO. IL-8 has an obvious chemotactic effect on neutrophils, helping them to penetrate vascular endothelial cells to reach inflammatory areas. It was reported that the level of IL-8 in BLAF increased significantly about 300 days before BO diagnosis after lung transplantation.^[16] A large number of studies have reported that IL-8 is secreted by damaged respiratory epithelial cells, which is closely related to the pathological mechanism of airway damage. Animal studies have found INF- γ expression was correlated with airway obliteration.^[14,17] IFN- γ was significantly increased in CD8⁺ T intraepithelial lymphocytes, NK T-like and NK cells in patients with lung transplant-related BOS compared with stable transplant patients and healthy controls.^[18] This study showed that the expressions of IL-8 and INF- γ were significantly increased in PIBO children. In addition, the levels of IL-8 and INF- γ in ADV-PIBO were higher than those of non-ADV-PIBO. Accordingly, this study showed that oral prednisone and azithromycin were

administered for a longer time in ADV-PIBO children than in the non-ADV-PIBO children.

CONCLUSIONS

ADV is the most important etiology causing PIBO; the expression levels of LDH, IL-8, INF- γ , and the duration of prednisone and azithromycin administration were significantly higher in ADV-PIBO than those of non-ADV-PIBO, which may be an important reason why ADV-PIBO is more serious than non-ADV-PIBO. The difference of the mechanisms of pathogenesis in the two etiologies should be further explored.

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Conflicts of interest

There are no conflicts of interest.

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