Effect of pediatric asthma complicated by respiratory virus infection on airway remodeling and inflammation

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Objective: To study the effect of pediatric asthma complicated by respiratory virus infection on airway remodeling and inflammation. Methods: A total of 41 children with asthma complicated by respiratory virus infection who were treated in our hospital between May 2012 and March 2016 were collected as observation group, and 50 children with asthma alone who were treated in our hospital during the same period were selected as control group. High-resolution CT was used to determine the right upper lobe apical segment (RB1) and the left lower lobe posterior basal segment (LB10) airway remodeling parameters of two groups of patients, and serum airway remodeling index and inflammatory factor contents were detected. Results: LA, WA and TA levels of RB1 and LB10 of observation group were significantly lower than those of control group, serum airway remodeling indexes TGF-β1, Smad3, P1NP and PIIINP contents were higher than those of control group, serum inflammation indexes IL-4, IL-5 and TNF-α contents were higher than those of control group. Conclusion: Complication of respiratory virus infection can aggravate the airway remodeling and systemic inflammation in children with asthma.

1. Introduction

Bronchial asthma is a chronic inflammatory airway disease that is common in children, it is mainly characterized by repeated cough, wheezing and dyspnea, and it can affect the normal growth and development as well as study and life of children[1,2]. Study has shown that more than 50% of asthma children are with frequent respiratory virus infections, and the primary mechanisms of respiratory viral infections to cause acute asthma attack include that the virus directly damages the airway epithelial cells and leads to airway hyperresponsiveness, and respiratory tract infection reduces children’s ability to fight infection and aggravates airway inflammation, etc[3,4]. Many current studies have shown that recurrent respiratory virus infection can increase asthmatic disease, but little specific research is carried out. In the study, children with asthma alone and children with both asthma and respiratory virus infection were selected as the research subjects, and the differences in airway remodeling and systemic inflammatory response were compared between the two groups in order to confirm the effect of respiratory virus infection on asthma condition and the specific mechanism.

2. Case information and detection indexes

2.1 Case information

A total of 41 children with asthma complicated by respiratory virus infection who were treated in our hospital between May 2012 and March 2016 were collected as the observation group, and 50 children with asthma alone who were treated in our hospital during the same period were selected as control group, and children's families learned about the research process and signed the informed consent. Observation group included 20 male cases and 21 female cases, they were 3-8 years old and (5.69±0.74) years old in average, and the asthma course was 1-4 years and (2.61±0.48) years in average; control group included 24 male cases and 26 female cases, they were 3-9 years old and (5.99±0.72) years old in average, and the asthma course was 1-4 years and (2.53±0.46) years in average. Two groups of children were not statistically different in gender,
age and asthma course distribution ($P>0.05$), and the hospital ethics committee members discussed and approved the study.

2.2 Detection indexes

2.2.1 CT airway remodeling parameters

Immediately after admission (before treatment), the 256-slice iCT scanner (Philips offerings) was used for lung scanning of two groups of children, children took supine position with arms upward, and the scanning range was from thorax to diaphragm, and children were trained to hold breath at end inspiration before scanning. The original images from inspiratory phase CT scanning were transmitted to fully automated airway evaluation software (researched and developed by Apollo company, USA) for three dimensional quantitative analysis, and apical segment of right upper lobe (RB1) and left posterior basal segment of lower lobe (LB10) were selected as the target bronchi to calculate the airway remodeling-related parameter levels, including the airway lumen area (LA), airway wall area (WA) and total airway area (TA), which were all corrected with surface area.

2.2.2 Serum airway remodeling indexes

Immediately after admission (before treatment), 1.0 mL fasting peripheral venous blood was extracted from two groups of children, added in anticoagulant and centrifuged at low speed to get supernatant, and RIA kits were used to detect airway remodeling index levels in it, including transforming growth factor β1 (TGF-β1), Smad3, collagen type I (P I NP) and collagen type III (P III NP). RIA kits were purchased from Beijing Furui Runkang Biotechnology Co., LTD., and the article number was MS782, HT626, LK862 and BS516 respectively.

2.2.3 Inflammation indexes

Immediately after admission (before treatment), peripheral blood serum was obtained from two groups of children in the same way, ELISA kits were used to detect inflammation index levels in it, including interleukin-4 (IL-4), interleukin-5 (IL-5) and tumor necrosis factor alpha (TNF-α). Elisa kits were purchased from Shanghai Jingkang Biological Engineering Co., LTD., and the article number was 09272, 52771 and 87372 respectively.

2.3 Statistical methods

Statistical software SPSS 21.0 and one person with professional statistical knowledge were selected, measurement data in the study was in terms of ($\bar{x}\pm s$) and comparison between groups was by grouping $t$ test. $P<0.05$ was set as the standard of statistical significance in differences.

3. Results

3.1 CT airway remodeling parameters

Comparison of RB1 and LB10 CT airway remodeling parameters LA, WA and TA levels between two groups of children was as follows: LA, WA and TA levels of RB1 and LB10 of observation group were significantly lower than those of control group. Differences in RB1 and LB10 CT airway remodeling parameters LA, WA and TA levels were statistically significant between two groups of children ($P<0.05$), shown in Table 1.

3.2 Serum airway remodeling index contents

Comparison of serum airway remodeling indexes TGF-β1 (μg/mL), Smad3 (μg/mL), P I NP (μg/L) and P III NP (μg/L) contents between two groups of children was as follows: serum TGF-β1, Smad3, P I NP and P III NP contents of observation group were significantly higher than those of control group. Differences in serum TGF-β1, Smad3, P I NP and P III NP contents of observation group were significantly higher than those of control group. Differences in serum TGF-β1, Smad3, P I NP and P III NP contents were statistically significant between two groups of children ($P<0.05$), shown in Table 2.

3.3 Serum inflammation index contents

Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>LA</th>
<th>WA</th>
<th>TA</th>
<th>RB1</th>
<th>LA</th>
<th>WA</th>
<th>TA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>50</td>
<td>11.94±2.51</td>
<td>19.26±2.17</td>
<td>29.16±3.42</td>
<td>12.18±1.64</td>
<td>19.13±2.05</td>
<td>29.54±3.12</td>
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</tr>
<tr>
<td>Observation group</td>
<td>41</td>
<td>10.05±1.82</td>
<td>17.15±1.93</td>
<td>27.53±2.85</td>
<td>10.94±1.63</td>
<td>17.47±2.13</td>
<td>28.09±3.11</td>
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</tr>
<tr>
<td>$T$ value</td>
<td></td>
<td>6.492</td>
<td>7.982</td>
<td>8.463</td>
<td>7.293</td>
<td>8.192</td>
<td>6.583</td>
<td></td>
</tr>
<tr>
<td>$P$ value</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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</tr>
</tbody>
</table>

Table 2.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>TGF-β1 (μg/mL)</th>
<th>Smad3 (μg/mL)</th>
<th>P I NP (μg/L)</th>
<th>P III NP (μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>50</td>
<td>38.49±4.51</td>
<td>231.28±28.94</td>
<td>30.71±4.35</td>
<td>4.85±0.61</td>
</tr>
<tr>
<td>Observation group</td>
<td>41</td>
<td>58.21±6.83</td>
<td>319.37±35.88</td>
<td>42.54±5.48</td>
<td>5.73±0.72</td>
</tr>
<tr>
<td>$T$ value</td>
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<td>9.213</td>
<td>14.381</td>
<td>7.583</td>
<td>6.293</td>
</tr>
<tr>
<td>$P$ value</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Comparison of serum inflammation indexes IL-4 (pg/mL), IL-5 (pg/mL) and TNF-α (μg/L) contents between two groups of children was as follows: serum IL-4, IL-5 and TNF-α contents of observation group were significantly higher than those of control group. Differences in serum IL-4, IL-5 and TNF-α contents were statistically significant between two groups of children ($P<0.05$), shown in Table 3.

### Table 3.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>IL-4 (pg/mL)</th>
<th>IL-5 (μg/L)</th>
<th>TNF-α (μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>50</td>
<td>12.18±1.95</td>
<td>1.83±0.29</td>
<td>18.24±2.74</td>
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<tr>
<td>Observation group</td>
<td>41</td>
<td>25.47±4.31</td>
<td>2.71±0.34</td>
<td>27.96±4.51</td>
</tr>
<tr>
<td>$T$ value</td>
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<td>9.21</td>
<td>5.83</td>
<td>11.52</td>
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<tr>
<td>$P$ value</td>
<td></td>
<td>$&lt;0.05$</td>
<td>$&lt;0.05$</td>
<td>$&lt;0.05$</td>
</tr>
</tbody>
</table>

#### 4. Discussion

There are many causes for pediatric asthma, including genetics, climate, interior decoration, life level and so on, and research has shown that more than 80% of pediatric acute asthma attack is induced by respiratory virus infection, so the study has been gradually carried out about the influence of respiratory virus infection on asthma progression. A longitudinal cohort population study has shown that virus infection before the age of 13 can directly increase the incidence of occasional wheezing in children with asthma, the incidence of recurrent wheezing are (3.2 times and 4.3 times respectively), but there was no evident difference after the age of 13, confirming that the respiratory virus infection is the independent risk factor for allergic asthma aggravation[5]. At present, there is not much research about the effect of respiratory virus infection on airway anatomy changes and systemic inflammation in children with asthma, children with asthma alone and children with asthma complicated by respiratory virus infection were selected as the research subjects of the study respectively, and the differences between the two were elaborated from airway remodeling and inflammation.

Airway remodeling is a kind of complex airway geometry change, it may occur in a variety of chronic inflammatory respiratory diseases, it is caused by the airway epithelial inflammatory damage - repair - re-damaged - re-repair, and patients with airway remodeling can be clinically characterized by irreversible airway ventilation disorders and airway hyperresponsiveness[6,7]. The airway remodeling illness is usually mild in children with asthma, but when asthma is complicated by respiratory virus infection, the recurrent airway inflammation can accelerate the pathological changes of trachea and epithelial cells and increase airway hyperresponsiveness, ending up with the qualitative change of airway geometric representation[8,9]. High-resolution CT is the gold standard to intuitively reflect the airway changes in asthma children, apical segment of right upper lobe and left posterior basal segment of lower lobe were selected as the target bronchi in the study, the airway area parameters were compared between two groups of children, and the results showed that LA, WA and TA levels of RB1 and LB10 of observation group were significantly lower than those of control group, it indicates that complication of respiratory virus infection can aggravate the patient's airway remodeling process, and this is mainly because that the repeated respiratory infection causes acute asthma attack and gradually leads to respiratory bronchiolectasis and damage. Many studies have shown that TGF-β / Smad signaling pathways are involved in airway remodeling process of patients with asthma, and the massively secreted TGF-β, and Smad mediate fibrous protein and collagen formation[10]. PⅠNP and PⅠIINP are the main components of collagens in pulmonary extracellular matrix and account for over 90% of the total amount, and their deposition is the main cause of the airway remodeling[11,12]. In the study, the serum airway remodeling index levels were further compared between two groups of children, and it was found that serum airway remodeling indexes TGF-β, Smad3, PⅠNP and PⅠIINP contents of observation group were higher than those of control group, indicating that complication of respiratory virus infection and recurrent acute airway inflammation can hasten the collagen deposition in the pediatric airway and accelerate airway remodeling process.

The mechanism of airway remodeling is directly related to the pro-inflammatory factors released by inflammatory cells in airway, and Th2 cells massively secrete IL-4 and IL-5, stimulate B cells to differentiate and synthesize IgE, and mediate immune reaction[13,14]. TNF-α is mainly secreted by mononuclear macrophages, and a variety of pathogen infections can increase the TNF-α synthesis and optimize acute asthma attack[15,16]. In the study, above serum inflammatory factor levels of two groups of patients were detected, and it was found that serum inflammation indexes IL-4, IL-5 and TNF-α contents of observation group were higher than those of control group, it indicates that the complication of respiratory virus infection can directly increase the local and systemic inflammatory factor secretion, and this is the important cause of acute asthma attacks, and also one of the important causes of worse airway remodeling.

Airway remodeling and systemic inflammatory response are more severe in children with asthma complicated by respiratory virus infection, and recurrent respiratory virus infections can exacerbate asthma and is expected to become important precipitating factor of the long-term adverse outcomes. For asthmatic children with recurrent respiratory virus infection, early intervention should be...
taken to control the disease and guarantee children’s normal life as well as growth and development.

References


