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FULL PAPER

Post-infectious bronchiolitis obliterans in children: CT features that predict responsiveness to pulse methylprednisolone

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Objective: Intravenous pulse methylprednisolone therapy (IPMT) is an important treatment option for post-infectious obliterative bronchiolitis (OB), although it must be used carefully and only in selected patients because of its drawbacks. This study evaluated whether CT and clinical features of children with post-infectious OB can predict their responsiveness to IPMT.

Methods: We searched the medical records for patients (less than 18 years of age) who were diagnosed with post-infectious OB between January 2000 and December 2011. 17 children who received IPMT were included in this study. All underwent chest CT before and after IPMT. The radiological features seen on pre-treatment CT were recorded. The air-trapping area percentages on pre- and post-treatment CT images were determined. The nine patients who exhibited decreased air trapping on post-treatment CT scans relative to

pre-treatment scans were classed as responders. The patient ages and time from initial pneumonia to IPMT were recorded.

Results: All responders and only four non-responders had thickened bronchial walls before treatment ($p = 0.029$). The two groups did not differ significantly in terms of bronchiolitis, bronchiectasis or the extent of air trapping, although the responders had a significantly shorter median interval between initial pneumonia and IPMT (4 vs 50 months; $p = 0.005$) and were significantly younger (median, 2.0 vs 7.5 years; $p = 0.048$).

Conclusion: Immediate IPMT may improve the degree of air trapping in children with post-infectious OB if they show a thickened bronchial wall on CT.

Advances in knowledge: Children with post-infectious OB may respond favourably to IPMT when pre-treatment CT indicates bronchial-wall thickening.

Post-infectious obliterative bronchiolitis (OB) is an uncommon and severe form of chronic obstructive lung disease that follows a microbiological insult to the lower respiratory tract. At the pathological level, it is characterized by a fibrosing inflammatory process around the lumen of the bronchioles that results in concentric narrowing and obliteration of the small airways.^{1,2} Consequently, areas of hypoventilation with air trapping, bronchiectasis and atelectasis can develop.³ The clinical severity of post-infectious OB correlates with the degree of air trapping and the amount of inflammation. The prognosis is not favourable, and the prospective observational study of Zhang et al⁴ of 31 post-infectious OB cases revealed that while clinical remission occurred in 22.6%, persistent respiratory signs and symptoms occurred in 67.7% and 9.7% died.

Post-infectious OB is considered to be an irreversible airway obstruction; thus the principal treatment is supportive. Important general supportive treatment options include avoidance of second-hand smoking and other inhaled irritants, annual influenza vaccination, airway clearance techniques, adequate nutritional intake and supplemental oxygen for patients with hypoxaemia. A drug that may be effective is azithromycin, a macrolide antibiotic, and although its usefulness in post-infectious OB has not been tested, it is effective in other chronic obstructive diseases, including diffuse panbronchiolitis and cystic fibrosis, and in OB syndrome after lung or bone marrow transplantation.⁵⁻⁸ Inhaled corticosteroids and bronchodilators are also recommended for patients whose airway obstruction is improved after using bronchodilators. Systemic corticosteroids are also frequently used, although their effectiveness in improving the outcome

in patients with post-infectious OB is as yet unknown. Intravenous pulse methylprednisolone therapy (IPMT) is currently the preferred method of treatment. However, this approach necessitates frequent hospital admissions during treatment and has high rates of side effects. For this reason, IPMT must be used with care and only in selected patients with post-infectious OB.^{2,5}

CT is an effective and widely used, non-invasive method for confirming the diagnosis of post-infectious OB, as it is more sensitive than chest radiography. We hypothesized that it might be possible to predict a patient's responsiveness to IPMT by analysing pre-treatment CT findings, thereby reducing the risk of unfavourable side effects from IPMT. Therefore, the purpose of this study was to evaluate whether CT and clinical features of children with post-infectious OB are predictive of their responsiveness to IPMT.

METHODS AND MATERIALS

Patients

This retrospective cohort study was approved by the Institutional Review Board of Asan Medical Center, Seoul, Republic of Korea. The computerized hospital medical records of our large tertiary care hospital in Seoul, Republic of Korea, were searched for all patients who were less than 18 years of age and were diagnosed with post-infectious OB between January 2000 and December 2011. Suspicion of post-infectious OB was based on clinical features, namely, more than 6 weeks of continuous wheezing, coughing and tachypnoea. In total, 65 children were diagnosed with post-infectious OB during the study period. The 17 patients who had received IPMT were included in the present study.

The median ages of the 17 patients (13 boys and 4 girls) at the time of initial diagnosis and the first episode of pneumonia were 4 years (range, 9 months–9 years) and 20.5 months (range, 8–60 months), respectively. Eight of the children were diagnosed with post-infectious OB by open-lung biopsy. The remaining nine patients were diagnosed with post-infectious OB on the basis of their clinical data, namely, a history of pneumonia in the first 3 years of life, persistent airway obstruction and the presence of radiological abnormalities such as hyperinflation, atelectasis, bronchial wall thickening and a mosaic pattern seen on the chest radiograph and/or chest CT.

Treatment

All study subjects underwent supportive treatment, including avoidance of second-hand smoking and other inhaled irritants, annual influenza vaccination, airway clearance, adequate nutritional intake, supplemental oxygen and treatment with roxithromycin, macrolide antibiotics and an inhaled bronchodilator.

The patients were treated with a systemic corticosteroid by infusing IPMT (20–30 mg kg⁻¹; maximum, 1 g) for 1 h daily for three consecutive days. This pulse therapy course was repeated on a monthly basis in patients who continued to have symptoms. The median number of IPMT sessions was 12 (range, 1–36).

CT scans and review

The chest CT scans of the study group patients were retrieved from the digital archives. Chest CT was performed in all children

at the time of their initial diagnosis, and follow-up CT was performed in all cases depending on the physician's decision that was based on the patient's clinical symptoms. Two radiologists (JSL and HMY) analysed in consensus the chest CT scans obtained before and after IPMT. The mean thickness $\pm$ standard deviation of the pre-treatment CT scans was 2.0 ± 1.0 mm (range, 1–4 mm), and the post-treatment CT scans was 3.1 ± 1.3 mm (range, 1–4 mm). The reviewers were blinded to the patients' clinical information.

The percentages of the area of air trapping in the pre- and post-treatment CT images were determined by visual assessment with a 10% interval on the supine position. To estimate the percentage of air trapping, the reviewers evaluated all available images, including the inspiratory and expiratory scans. Patients were classified into the responder group if the extent of air trapping dropped after treatment or into the non-responder group if the extent of air trapping remained the same or increased after treatment.

The pre-treatment CT images were also assessed for the presence of the following: bronchial wall thickening, inflammatory bronchiolitis, bronchiectasis and the CT attenuation value in the area of air trapping. Bronchial wall thickening was quantified relative to the accompanying pulmonary arteries as follows: absence, non-visualization of the bronchial wall or as thin as a pencil drawing; mild, the bronchial wall thickness half or less than half of the adjacent pulmonary artery diameter; severe, the bronchial wall thickness is more than half of the adjacent pulmonary artery diameter.⁹ The presence of inflammatory bronchiolitis was defined when severe bronchial wall thickening with a blurred margin, ill-defined centrilobular nodular opacities, and/or patchy consolidation were seen on CT images. For the latter, the CT attenuation values (Hounsfield units) in areas of hypoattenuation in three different regions were measured by placing 30×30 pixel-sized regions of interest on the pre- and post-treatment CT images.

Follow-up and clinical information

The mean follow-up duration was 30.4 ± 20.6 months (range, 11–95 months). The follow-up interval was determined by a paediatrician on the basis of severity of the clinical symptoms. The medical records of the 17 patients were retrieved, and the following data were recorded: age at the start of IPMT; the interval between the initial episode of pneumonia and the start of IPMT; and the interval between the diagnosis of post-infectious OB and the start of IPMT. The aetiological agent of the initial pneumonia episode was also determined by reviewing the medical records and was identified in 12 children. *Mycoplasma pneumoniae* was the most common aetiological agent (6/12), followed by adenovirus (5/12). Two of these children were coinfecting by *M. pneumoniae* and adenovirus. Influenza was seen in one patient.

Statistical analysis

All statistical analyses were performed using SPSS® for Windows v. 18.0 (SPSS Inc., Chicago, IL). The two groups were compared using Fisher's exact test and the Mann–Whitney *U* test. A *p*-value <0.05 was considered to indicate statistical significance.

Table 1. Clinical and radiological features of 17 patients with post-infectious obliterative bronchiolitis

Clinical and radiological features	Responder	Non-responder	<i>p</i> -value
Bronchial wall thickening	9 (100%)	4 (50%)	<0.05
Inflammatory bronchiolitis	6 (66.7%)	2 (25%)	>0.05
Bronchiectasis	6 (66.7%)	3 (37.5%)	>0.05
Mean CT attenuation value (HU)	−868.8 (43.6)	−888.4 (42.0)	>0.05
Interval between the initial pneumonia episode and the start of IPMT (months)	4 (2–7)	50 (31.3–74.8)	<0.05
Interval between post-infectious obliterative bronchiolitis diagnosis and the start of IPMT (months)	1 (1–2)	5.5 (1–14.5)	>0.05
Median patient age at the start of IPMT (years)	2 (1–5)	7.5 (4.5–9.3)	<0.05

IPMT, intravenous methylprednisolone therapy.

The data are expressed as number (%), mean (standard deviation) or months/year (quartiles).

Intraclass correlation coefficient (ICC) statistics was used to analyse the interobserver agreement for estimating the extent of air trapping seen on pre- and post-treatment CT scans. The ICC value was interpreted as follows: ICC of <0.20, slight agreement; ICC of 0.21–0.40, fair agreement; ICC of 0.41–0.60, moderate agreement; ICC of 0.61–0.80, substantial agreement; and ICC of 0.81–1.0, good agreement. The results are expressed as mean $\pm$ standard deviation.

RESULTS

The average extent of air trapping seen on the pre- and post-treatment scans was $51.8 \pm 20.4\%$ and $45.3 \pm 16.2\%$, respectively. Nine patients were classified as responders and the remaining eight were considered to be non-responders (Table 1). There was good interobserver agreement for estimating the percentage of area of air trapping between pre- and post-treatment scans (ICC = 0.823).

Further analysis of the pre-treatment scans revealed that all nine (100%) responders and four (50%) non-responders had bronchial wall thickening. Six (66.7%) responders and two (25%) non-responders had inflammatory bronchiolitis and six (66.7%) responders and three (37.5%) non-responders had bronchiectasis. The responder group was significantly more likely to have bronchial wall thickening than the non-responder group ($p = 0.029$) (Figures 1 and 2). However, the two groups did not differ in terms of the bronchiolitis and bronchiectasis frequency ($p = 0.419$ and 0.109 , respectively). They also did not differ in terms of the pre-treatment mean CT attenuation value (-868.8 ± 43.6 vs -888.4 ± 42.0 HU; $p = 0.185$).

The responder group had a significantly shorter median interval between the initial pneumonia episode [4 months (quartiles = 2 and 7)] and the start of IPMT than did the non-responder group [50 months (quartiles = 31.3 and 74.8); $p = 0.005$]. The responder

Figure 1. Improvement of post-infectious bronchiolitis obliterans after intravenous pulse methylprednisolone therapy (IPMT). (a) The pre-treatment CT image of a 1-year-old, male child shows multifocal thickening of the bronchial walls (arrows) and multifocal lower-density areas of air trapping, primarily in the paramediastinal area. (b) A post-treatment CT obtained after 1 year of treatment with IPMT indicates that the extent of the lower-density area of air trapping (open arrows) has markedly decreased. The thickening of the bronchial wall has also improved.

Figure 2. Aggravation of post-infectious bronchiolitis obliterans after intravenous methylprednisolone therapy (IPMT). (a, b) Pre-treatment CT images of an 8-year-old, male child show multifocal, lower-density areas of air trapping in the left lung. Bronchial wall thickening is not present. (c, d) A post-treatment CT obtained after 1 year of treatment with IPMT demonstrates that the extent of the lower density area of air trapping (open arrows) has increased.

group was also significantly younger at the time IPMT started [median = 2 years (quartiles = 1 and 5)] than the non-responders [7.5 years (quartiles = 4.5 and 9.3); $p = 0.048$]. However, the two groups did not differ significantly in terms of the interval between the diagnosis of post-infectious OB and the start of IPMT [1 month (quartile = 1 and 2) vs 5.5 months (quartiles = 1 and 14.5); $p = 0.107$].

DISCUSSION

This retrospective cohort study showed that the presence of bronchial wall thickening on the pre-treatment CT could be predictive of a favourable response to IPMT as all responders, but only 50% of the non-responders, exhibited this CT feature. Bronchial wall thickening is the result of inflammation and fibrosis of the wall of bronchioles and leads to fixed obstruction and occasional airway occlusion. Corticosteroid is a potent anti-inflammatory drug that has been used to treat respiratory disease

since 1950.¹⁰ Although the effectiveness of systemic corticosteroids for patients with post-infectious OB is still unknown, we speculated that the difference between the responders and the non-responders, in terms of bronchial wall thickening, may indicate that systemic corticosteroids decrease the peribronchial inflammation and early fibroblastic proliferation and fibrosis that results in bronchial wall thickening, therefore reducing air trapping.

The responders also had a significantly shorter interval between the initial pneumonia episode and the start of IPMT than did the non-responders. This may indicate that the disease in the responders had not yet progressed to an irreversible stage, unlike that in the non-responders. Indeed, it has been shown that while initial insults to the small airways result in derangements in epithelial cell function or local necrosis, these lesions can eventually progress to near-circumferential scarring or fibrosis.²

Therefore, it is likely that the extent and severity of inflammation is greater and more profound in the early stages of post-infectious OB, although in the later stages this has progressed into irreversible fibrosis around the small airways. Therefore, starting IPMT at an early stage of post-infectious OB may yield more favourable outcomes.

It is possible that the greater responsiveness of patients with a thickened bronchial wall or a short interval between the initial pneumonia and the start of treatment only reflects the anti-inflammatory effect of the corticosteroid on the residual peribronchial active inflammation caused by the initial pneumonia. However, this is unlikely to be the reason for the improvement in most responder cases because the median interval between the initial pneumonia and the start of IPMT in the responder group was 4 months. Therefore, it is more likely that the IPMT treatment achieved a response in the responders by decreasing the early fibroblastic proliferation.

The responders were younger when IPMT treatment started than were the non-responders, and this may reflect the fact that normal lung maturation terminates around the age of 8 years.¹¹ Starting the treatment before lung maturation finishes may, therefore, significantly reduce the occurrence of sequelae such as bronchiectasis, air trapping or lung fibrosis.

To the best of our knowledge, this is the first study to show that CT findings may be useful for predicting which children with post-infectious OB are likely to respond to IPMT. Our results suggest that prompt application of IPMT will improve air trapping if the pre-treatment CT images reveal the presence of

a thickened bronchial wall, if the first episode of pneumonia is recent or if the patient is relatively young at the start of therapy.

Our study has several limitations. First, it is a retrospective study and the number of the patients was small. Second, clinical data such as the symptom scores or pulmonary function test were not included in this study. However, we believe that such clinical data would have been relatively unreliable because our patients were quite young (the median age of our study population was only 4 years). However, well-designed prospective studies that include clinical findings are needed to confirm our results. Third, we did not consider the effect of other treatments. However, as all patients received supportive treatment using a relatively standard protocol in the Asan Medical Center, we believe that other treatments had a negligible impact on the outcomes of this study.

In conclusion, children with post-infectious OB may be more likely to respond favourably to IPMT if their pre-treatment CT indicates bronchial wall thickening, the interval between the initial pneumonia and their treatment is relatively short, and the patient is relatively young at the beginning of therapy. These factors may be helpful when deciding whether to treat children with post-infectious OB who are seen in clinical practice with IPMT.

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