Clinical significance of lung perfusion defects in children with post-infectious bronchiolitis obliterans

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ÖZET

Postinfeksiyöz bronşiyolitis obliteranslı çocuklarda akciğer perfüzyon defektlerinin klinik anlamı

Bronşiyolitis obliterans (BO)'lı çocuklarda segmental akciğer perfüzyon defektlerinin klinik önemi daha önce rapor edilmemiştir. Bu çalışmanın amacı; BO'lu çocuklarda akciğer perfüzyon defektlerinin klinik anlamının değerlendirilmesi ve izlem üzerine etkisinin açıklanmasıdır. Çalışmaya, yaşları 9-60 ay arasındaki (ortalama ± SD: 17.8 ± 13.4 ay) 38 BO'lu çocuk alındı. Tanı, altı haftadan uzun süren solunum yolu bulguları ve yüksek rezolüsyonlu bilgisayarlı tomografide oligemik-mozaik patern saptanmasıyla koyuldu. Akciğer grafisi, 24 saatlik pH monitörizasyonu, ter testi, immünglobulin düzeyleri ve solunum yolu viral paneli tüm çocuklarda değerlendirildi. Akciğer perfüzyon sintigrafisi, BO'nun ilk klinik bulguları ortaya çıktıktan en az üç ay sonra yapıldı. Perfüzyon defektleri skorlandı. Sintigrafi 24 (%63.2) hastada perfüzyon defekti gösterdi ama 14 (%36.8)'ünde normaldi. Perfüzyon defekti olan segmentlerin ortalama sayısı 2.9 ± 2.6 idi. İzlemin ilk yılında, ortalama alevlenme sayısı ve hastanede yatış gün sayısı sırasıyla 4.7 ± 4.4 ve 26.9 ± 29.8 gündü. Perfüzyon defektlerinin sayısının alevlenme sayısı ve hastaneye yatış süresi ile anlamlı korelasyon gösterdiği belirlendi (sırasıyla r= 0.66 ve p= 0.00). Sonuç olarak; BO'lu çocuklarda akciğer perfüzyon defektlerinin sayı ve yoğunluğu, klinik ağırlık ile koreledir. Bu nedenle, akciğer perfüzyon durumunun değerlendirilmesi hastalığın ağırlığı ve izleminin klinik olarak belirlenmesine yardımcı olabilir.

Anahtar Kelimeler: *Bronşiyolitis obliterans, yüksek rezolüsyonlu bilgisayarlı tomografi, perfüzyon sintigrafisi, oligemik mozaik patern, çocuk.*

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SUMMARY

Clinical significance of lung perfusion defects in children with post-infectious bronchiolitis obliterans

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Clinical significance of segmental lung perfusion defects in children with bronchiolitis obliterans (BO), have not been reported before. The aim of this study was to evaluate clinical significance of lung perfusion defects in children with BO and to reveal its impact on follow up. The study included 38 children aged 9 to 60 months (17.8 ± 13.4 months) with BO. Diagnosis was based on persistent respiratory findings beyond six weeks and oligemic-mosaic pattern in lung high resolution computerized tomography. Chest X-ray, 24 hour esophageal pH monitoring, sweat chloride test, immunoglobulin levels and respiratory viral screening were carried out in all. Lung perfusion scintigraphy was carried out at least three months after the first clinical sign of BO. Perfusion defects were scored. Scintigraphy demonstrated perfusion defects in 24 (63.2%) patients but was normal in 14 (36.8%). Number of segments having perfusion defects was 2.9 ± 2.6. Mean number of exacerbations and days of hospitalization during the first year of follow up were 4.7 ± 4.4 and 26.9 ± 29.8 respectively. It was detected that number of perfusion defects correlated significantly with the number of exacerbations and duration of hospitalization (r= 0.66 and p= 0.00). In conclusion, number and extent of segments with perfusion defects in lungs of children with BO are correlated with clinical severity. Therefore, evaluation of lung perfusion status may aid in clinical determination of disease severity and its follow-up.

Key Words: *Bronchiolitis obliterans, high resolution computerized tomography, perfusion, scintigraphy, oligemic mosaic pattern, child.*

Bronchiolitis obliterans (BO) is a chronic obstructive pulmonary disease that is caused by a potentially severe process of extensive airway scarring after acute or subacute lower airway injury especially during early childhood (1-3). Pathologically, it is characterized by chronic inflammation, granulation tissue and fibrosis in the peribronchiolar arterioles, bronchiolar wall and luminal face of bronchiole resulting in obliteration of small airways and vascular lumen (4,5). These changes lead to the athelactasis of small airways, vascular occlusion, perfusion insufficiency secondary to ventilation defects and finally pulmonary parenchymal atrophy (2,4,6). Most common etiological causes are infections with adenovirus (especially serotypes 3,7,21), respiratory syncytial virus (RSV), influenza, parainfluenza, cytomegalovirus (CMV), measles, mycobacteria and other uncommons (2,5-7). Connective tissue disorders, drugs, gastroesophageal reflux (GER), foreign body aspiration etc. have also been described in etiology (6).

Initial findings resemble acute bronchiolitis or pneumonia. However persistence of sign and symptoms with recurrent episodes and wheezing herald the development of BO (6). Chest X-ray is usually non-specific. However findings of high resolution computerized tomography (HRCT) including focal sharply demarcated areas of decreased lung attenuation associated with vessels of decreased caliber are the most commonly used non-invasive diagnostic clues. Combination of air trapping and oligemia lead to the typical appearance called “oligemic mosaic pattern” in HRCT (7). In lung scintigraphy, lung atenuation by decreased perfusion lead to moth-

eaten appearance of multiple defects is observed (2). Despite the findings reported previously, none of those have detected an association of lung perfusion defects with disease severity and clinical course. Therefore, the aim of this study was to evaluate clinical significance of lung perfusion defects in children with BO and to reveal its impact on follow up.

MATERIALS and METHODS

Subjects

Thirty eight patients (28 male, 10 female) aged between 9 months to 60 months (17.8 ± 13.4 months) diagnosed as having BO at pediatric pulmonology unit between 2000 and 2006 were included in the study.

Inclusion Criteria

The diagnosis of BO depended on persistence of respiratory findings including recurrent cough, wheezing, respiratory distress and persistent fine crackles on lung auscultation as well as the radiogical findings. Radiological findings included mosaic oligemic pattern, air trapping, wall thickening and bronchiectasis in HRCT. Diagnosis of cystic fibrosis, bronchopulmonary dysplasia, pulmonary tuberculosis, α1-antitripsin deficiency, immunodeficiency and congenital heart disease were excluded. Nine patients with gastroesophageal reflux documented by esophageal pH monitorization were included in this study. None of the patients were atopic as confirmed by normal IgE levels and negative results for serum specific IgE of common aero and food allergens mixtures (Alatop® and fx5®; DPC Co, New York, USA).

Study Design

Patients diagnosed as having BO between 2000 and 2006 were included in this study. Clinical features including physical examination findings of lower respiratory tract infection, number of exacerbations and days of hospitalization were recorded. Exacerbations were defined as deterioration of the persistent basal respiratory symptoms and signs. Chest radiograms and HRCT were performed. Screening laboratory examinations included sweat chloride test, Mantoux test, serum α1-antitrypsin levels, and serum immunoglobulins. Screening for common infectious agents for lower respiratory tract was carried out in all patients. Moreover, lung perfusion scintigraphy was performed. Additionally, all patients underwent 24 hour pH monitorization for gastroeosophageal reflux disease (GERD). Severity was evaluated on the basis of exacerbation rate and days of hospitalization. Predictive value of lung perfusion scintigraphy was evaluated on the basis of clinical findings.

Microbiological Methods

Respiratory secretions obtained by nasopharyngeal lavage were screened for the most common viral agents. RSV, adenovirus, influenza and parainfluenza viruses that are accepted to be the most common viral causes of respiratory infections were tried to be detected by the microimmunofluorescence technique. Moreover, Chlamydial antigens were screened in ocular secretions and serum chlamydial IgM and IgG levels were measured.

24 Hour pH Monitorization

All cases underwent 24 hour pH monitoring according to a standard protocol. An antimony catheter with a diameter of less than 2.1 mm and 2 sensors were placed nasally following an overnight fast (Synetics Medical AB, Stockholm, Sweden). Recorded pH data were downloaded in an IBM compatible computer and analyzed by a software (EsopHogram Software System). Fraction of time with pH for proximal and distal esophagus was considered abnormal if more than 1% and more than 4% respectively.

Chest Roentgenogram and HRCT

Two dimentional chest roentgenogram and HRCT were obtained from all patients. HRCT were evaluated especially for the presence of mosaic oligemic patern, air trapping, wall thickening and bronchiectasis by two radiologists blinded to the clinical findings. Diagnosis of BO was supported by HRCT images. Moreover, the number of lung segments involved in the disease process was recorded for each patient.

Lung Perfusion Scintigraphy

Lung perfusion scintigraphy was obtained at least 3 months later form the first clinical symp-

toms of BO. It was performed using 3mCi Tc^{99m} labelled macroaggregated albumin (MAA) with a radius of 10-50 μm. Six dimentional planar images were taken and were evaluated by two specialists in nuclear medicine. The number of segments displaying perfusion defects was recorded (0 to 8).

Treatment and Clinical Follow up

All patients diagnosed with BO were treated by nebulized corticosteroids (budesonide 1-2 mg/day) and intermittent bronchodilator (mainly salbutamol and ipratropium-bromide in resistant cases). Systemic corticosteroids (dexamethason or prednisolone) were used during acute exacerbations. Treatment of patients complicated with GER included conservative measures as well as a proton pump inhibitor (lansoprozole 1 mg/kg/day) and prokinetic agent (domperidon 0.3 mg/kg/day). Follow up examinations were performed at intervals of 6 weeks unless an exacerbation of the clinical symptoms led the family to present earlier. The numbers of exacerbation and hospitalization days with their all clinical data were recorded.

Statistical Analysis

Statistical analyses were performed by SPSS 11.0 (Chicago IL) computer program. Mann Whitney U test and Pearson's correlation test were used for the statistical analysis. p values less than 0.05 were regarded as statistically significant.

RESULTS

Clinical Findings

Post-infectious BO was diagnosed based on clinical and radiologic evidence in our patients. Initial findings of all subjects were similarities with acute bronchiolitis. All screening test such as sweat cloride test, levels immunoglobulin levels etc. were normal in the patients and Mantoux tests were negative.

Of the two patients that required emergency care, one had serologically proven adenoviral infection that presented with desquamative pneumonia and sepsis and the other had para-influenza virus infection. The first patient responded to treatment and his findings improved in two years. However, the second patient had a grave prognosis and was lost due to respiratory insufficiency. One of the patients who were detected to have chlamydia infection was also lost despite 15 months of treatment with antibiotics, inhaled steroids and bronchodilators and despite intensive care unit.

Mean number of exacerbations during the follow up was 4.7 ± 4.4 episodes. Additionally, mean days of hospitalization during the first year of follow up were and 26.9 ± 29.8 days.

Etiological Agents and Factors

The most common etiological agent detected either clinically or serologically were respiratory viruses leading to lower respiratory infection (Table 1). Adenovirus was detected in four patients and influenza was detected in 2 multiple viral agents were positive in three patients and these included RSV, influenza and adenovirus in one, parainfluenza and adenovirus in one and parainfluenza and influenza in one patient. Moreover, chlamydia trachomatis antigen was detected in nasopharyngeal aspirate of one patient.

GER was detected in 9 cases (23.7%). None of the patients had symptoms of GER prior to the initial episode of BO (Table 1).

Radiological Findings

Chest radiographs demonstrated specific findings as hyperlucency and athelectasis in 10 patients. The rest of the patients had non-specific or normal findings on chest X-ray (Table 2).

Table 1. Demographical and etiological characteristics of the study population.

Characteristic (n= 38)	
Age (month)(mean ± SD)	17.8 ± 13.4
Sex (F/M)	10/28
History of premature birth	28.9%
Presence of GER (%)	23.7%
History of a previous viral lower respiratory tract infection (%)	68.4%
Serologically proven viral agent (%)	24%

GER: Gastroesophageal reflux.

Table 2. Frequency of specific radiological findings in the study population.

	Normal		Pathological findings present	
Radiological finding	**n**	**%**	**n**	**%**
Chest X-ray	28	73.7	10	26.3
Perfusion scintigraphy	14	36.8	24	63.2
Thorax HRCT *	0	0	38	100

* High resolution computerized tomography.

Table 3. The correlation between the extent of perfusion defects and clinical severity assessed by the number of exacerbations and days of hospitalizations.

Clinical features	Perfusion defect (+)	Perfusion defect (-)	r[1]	p[2]
Number of exacerbations*	6.5 ± 5.4	3.5 ± 3.1	0.59	**0.002**
Days of hospitalizations*	36.1 ± 36.9	18.6 ± 23.9	0.66	**0.000**

* Mean ± standard deviation.
[1] Pearson's correlation coefficient.
[2] p value is significant less than 0.05.

However, HRCT demonstrated the specific diagnostic finding, oligemic mosaic patern, in all of the subjects (Table 2).

Lung Perfusion Scintigraphy

Scintigraphy demonstrated perfusion defects in 24 (63.2%) patients but was normal in 14 (36.8%) (Table 2). The mean number of segments shown to have perfusion defects in perfusion scintigraphy was 2.9 ± 2.6. It was detected that the number of segments displaying perfusion defects according to the sintigraphy results correlated significantly with the number of exacerbations and days of hospitalization (r= 0.59 and 0.66 respectively; p= 0.00 for both) (Table 3).

DISCUSSION

Bronchiolitis obliterans during childhood is usually post-infectious in etiology most commonly involving adenovirus, mycoplasma and chlamydia (4,6,1,8). Pneumonia is the most common initial lung insult in these cases and half are viral in etiology (9). In our study group, 26 patients reported a history of previous viral infection and nine of these had serologically demonstrated viral infection in etiology. This difference between history and serology was attributed to timing of serological testing which was carried out during the evaluation of the patient which was after the acute infection since the diagnosis of BO requires persistence of clinical findings for at least 30 days. Most commonly isolated pathogens were adenovirus, para-influenzavirus and RSV. This is in concordance with the fact that adenoviral infection is a risk factor for development of BO in children (10). Considering that adenoviral infection is a risk factor for BO, it can be concluded that serological assessment of children with viral bronchiolitis is essential to plan follow up for BO.

Previous research reported that GER is the etiology of BO in 60% of cases due to the aspiration of gastric contents (6). The frequency of GER was 23.7% in our study and treatment was observed to improve clinical course significantly in all these patients. GER frequency in patients with lower respiratory tract problems like non-atopic asthma was reported to be 76% and treatment was shown to cause significant clinical improvement (11). Therefore, 24 hour pH monitorization is indicated at the first clue of GER. However the frequency is lower in our study than that in the previous study. This difference may be due to the difference in diagnostic methods. Most previous research used scintigraphy while

we used 24 hour pH monitoring. Moreover, since the patients included in our study lacked history of GER findings before respiratory findings initiated, GER may be assumed to be the result of BO or treatment of the disease instead of a cause. However, since this finding depended only on clinical observation, direct comment on exact direction of causality can not be made.

HRCT is the most commonly used non-invasive diagnostic tool for BO. It is indicated in diagnosis and follow up of all the patients since it is highly sensitive in evaluation of small airway disease (4). HRCT findings in BO include defined areas of decreased parenchymal attenuation due to ventilation defects, attenuation of macroscopic pulmonary vascular structures, attenuation of the macroscopic pulmonary vasculature, some degree of bronchial thickening and dilatation, air trapping in end-expiratory phase as well as central bronchiectasis (10,12,13). Similar to the previous research by Cazzato et al. most commonly detected HRCT findings in this study included "mosaic oligemic pattern" that was followed by peribronchial thickening, hypoventilation and hypoperfusion (14). Sensitivity and specificity of mosaic perfusion as a diagnostic finding was 83% and 60% respectively (15-17). Thus, it has been reported as gold standard tool in non-invasive diagnosis of BO (16,17). Oligemic mosaic pattern was detected in HRCT of all the patients but perfusion defects in scintigraphy were absent in some.

Perfusion is impaired in BO due to hypoxic vasoconstriction in acute bronchiolar obstruction phase followed by vascular remodelling of the chronic phase. Moreover, inflamatory process that causes bronchiolar scarring may synchronously affect the adjacent pulmonary artery, thus causing vascular obliteration (12). Pulmonary perfusion defects are almost always detected in BO (5). Therefore, perfusion defects detected by scintigraphy may aid in determination of clinical severity and follow up. Sensitivity of pulmonary perfusion scintigraphy with intravenous infusion of macroaggregates is high (5). Matched ventilation perfusion defects were reported to be present in all cases of unilateral hyperlucent lung in a previous study (18). Perfusion scintigraphy was performed on all the patients in our study and it was detected that 63.2% of patients demonstrated perfusion defects in one or more pulmonary segments. Moreover, the number of hypoperfused segments was found to be significantly correlated with clinical parameters like number of exacerbations and days of hospitalization. This is an expected phenomenon since the limit and severity of inflammation is expected to determine perfusion defect. This result may aid in the use of perfusion scintigraphy in clinical evaluation of these patients as a clinical severity marker.

It was reported that clinical remission was observed in 22% of BO patients while 67% had persistent respiratory findings (6). Mortality rate in this study was 5.3%. The subjects who died had the highest perfusion defect scores. Clinical severity improved in the remaining 36 patients with antiinflammatory and bronchodilator therapy as well as etiology targeted treatment modalities including anti-GER treatment and antibiotics in selected cases. Mortality rate in this study was similar to the the value of 3.2% reported by a previous study (4). This may be attributed to the detection of cases at an early phase of disease activity by computed tomography results. There is no universally accepted protocol for the treatment of BO. Use of corticosteroid therapy in the early phase of the illness was proposed to modify the fibroblastic response. Clinical response to systemic corticosteroids was reported in 64.7% of patients (4). It has been reported that high dose systemic corticosteroid therapy in children with BO after bone marrow transplantation led to the stabilization of clinical findings preventing deterioration (19).

In conclusion, the results of this study suggest that extent of perfusion defects determined by scintigraphy may be used as a clinical severity marker in these children. Future studies to determine the significance of perfusion defects detected by more developed techniques such as lung magnetic resonance imaging may be useful in evaluation of pediatric BO cases. Finaly, treatment with antiinflammatory agents is beneficial in most cases but treatment of etiologies like bacterial infections and GER is more promi-

sing in modification of severity which is vital in the management of this disease with a potentially grave outcome.

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