Bronchial Hyperreactivity in Non-Cystic Fibrosis Bronchiectasis

Kistik Fibrozis Dışı Bronşektazide Bronş Aşırı Duyarlılığı

Bronşektazide Bronş Aşırı Duyarlılığı / Bronchial Hyperreactivity in Bronchiectasis

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Özet

Amaç: Bronşektazi tekrarlayan hava yolu enfeksiyon ve inflamasyonları nedeniyle, bronş ve bronşiollerin anormal dilatasyonudur. Bronşektazide bronş aşırı duyarlılığı (BHR) varlığını destekleyen sınırlı sayıda çalışma mevcuttur. Bu çalışmada biz bronşektazi hastalarında BHR varlığını ve bunu etkileyebilecek olası faktörleri araştırdık. Gereç ve Yöntem: Çalışma bronşektazi hastaları takip polikliniğinde gerçekleştirildi. Yüksek çözünürlüklü bilgisayarlı tomografi (HRCT) ile bronşektazi tanısı konulmuş 69 hasta çalışmaya alındı. Kistik fibrozis, immune yetmezlik ve astım tanılı hastalar çalışma dışı bırakıldı. Bronş provakosyon testi, cinsiyet, hastalık süresi, sigara öyküsü, solunum fonksiyon testleri, radyolojik dağılım derecesi, bronşektazi tipi, bakterial kolonizasyon varlığı ve atopi arasındaki ilişki araştırıldı. Bulgular: Bronşektazi tanılı hastalarda bronş aşırı duyarlılığı literatürde olduğundan çok daha düşük oranda (%29) saptandı. Kadın cinsiyet ve düşük FEV_1 düzeyi bronş aşırı duyarlılığı gelişimini etkileyen iki önemli faktör olarak bulundu ($p<0.05$). Sonuç: Sonuç olarak, bronşektazi hastalarında kadın cinsiyet ve bronşial obstrüksiyon derecesi bronş aşırı duyarlılığı gelişimini etkileyen iki önemli faktör gibi görünmektedir.

Anahtar Kelimeler

Bronşektazi; Bronş Aşırı Duyarlılığı

Abstract

Aim: Bronchiectasis is an abnormal dilatation of bronchi and bronchioles due to repeated cycles of airway infection and inflammation. There is a limited data that support the existence of bronchial hyperreactivity (BHR) in bronchiectasis. In the present study we investigated the existence of BHR and possible factors that could affect the BHR in bronchiectasis patients. Matherial and Method: Study performed in bronchiectasis outpatient clinic. We included 69 patients in which the diagnosis of bronchiectasis was made by high-resolution computed tomography (HRCT). Patients with cystic fibrosis, immune deficiency and asthma were excluded. We evaluated the relationship between the results of bronchial provocation test (BPT) and gender, duration of disease, smoking history, lung function tests, degree of radiologic distribution, type of broncіectasis, existence of bacterial colonisation and atopy. Results: We found that, bronchial hyperreactivity was detected in a much smaller proportion (29%) of patients with the diagnosis of bronchiectasis than the existing literature. Female gender and low FEV_1 value were found to be important two factors to influence the development of bronchial hyperreactivity ($p<0.05$). Discussion: In conclusion, female gender and the degree of bronchial obstruction seem to be important two factors to influence the development of bronchial hyperreactivity in patients with bronchiectasis.

Keywords

Bronchiectasis; Bronchial Hyperreactivity

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Introduction

Bronchiectasis is an abnormal dilatation of bronchi and bronchioles due to repeated cycles of airway infection and inflammation [1].

Most frequent causes of bronchiectasis are respiratory infections like pertussis, measles and tuberculosis. Genetic diseases such as cystic fibrosis, primary ciliary dyskinesia, α-1 antitrypsin deficiency; immune deficiencies such as primary hypogammaglobulinemia; immune-related diseases such as allergic bronchopulmonary aspergillosis (ABPA), collagen vascular diseases, and inflammatory bowel diseases may all contribute to the development of bronchiectasis [1].

There is a limited data that supports the existence of bronchial hyperreactivity (BHR) in bronchiectasis. BHR is defined as an exaggerated bronchoconstriction response to small amounts of irritants that normally does not effect healthy humans. Still the pathogenesis of BHR is unclear. Patients with bronchiectasis, even in stable condition, present an active neutrophilic inflammation in the airways through the presence of myeloperoxidase, tumour necrosis factor-alpha (TNF-α) and interleukin-8 (IL-8) [2, 3]. This persistent neutrophilic inflammation is the probable one of the leading causes of bronchial hyperreactivity deteriorating the pulmonary functions in patients with bronchiectasis. In addition, also bronchial hyperreactivity may also be related to narrowing of bronchial lumen [4]. It is speculated that recurrent bacterial infections rich in neutrophils or hypertrophied mucosal glands causes BHR in bronchiectasis. Eventually bacteria like Pseudomonas may increase BHR by secreting materials that could stimulate mucous secretion, destroy the mucosa and the diminish the ciliary activity [5].

In the present study we investigated the existence of BHR and possible factors that could affect the BHR in bronchiectasis patients.

Material and Method

Study design

This study was performed in a bronchiectasis outpatient clinic. In this clinic, HRCT, spirometry, bronchial provocation test, sputum examination, sputum culture are performed as a routine to patients with bronchiectasis. In this study, the data of these patients were evaluated retrospectively. All included patients were in a clinically stable phase. They were free of any infectious exacerbation for at least 8 weeks prior to the start of the study. The relationship between bronchial provocation test (BPT) results and age, gender, duration of disease, smoking history, lung fuction tests, degree of radiologic distribution, type of bronchiectasis, existence of bacterial colonisation, and atopy were evaluated.

Subjects

We included 69 patients in which the diagnosis of bronchiectasis was made by high-resolution computed tomography (HRCT). Protein electrophoresis, serum levels of Ig E,Ig A, Ig G,Ig M and alfa1 antitrypsin levels were measured and skin prick tests against most common allergens were performed. If the patient had a history of disease started during childhood, sweat NaCl test was performed. Patients with cystic fibrosis and asthma were excluded. Immune deficient or ABPA patients were not included in the study.

Clinical Evaluation

Age, gender, status and duration of the disease were evaluated. In symptomatic patients, the onset of the symptoms was accepted as the starting time of the disease. In asymptomatic patients, we accepted the first time of radiographically proven bronchiectasis as the starting time of the disease. Patients were considered to be smokers if they were smoking daily at least for one year. Level of smoking was expressed as package-year. If the patient quit smoking at least one year before the study, he was accepted as ex-smoker.

Radiological Evaluation

All patients underwent thorax HRCT and were divided into two groups as 1) patients with disease limited to upper lobes and 2) patients without upper lobe involvement. Patients were also evaluated according to presence or absence of cystic and/or varicose bronchiectasis, as these two types have more serious effects on the bronchial anatomy. The total number of lobes with bronchiectasis were also documented.

Spirometric Evaluation

All patients underwent spirometric evaluation during the stable phase by Sensor Medics Vmax series 22 device. Spirometry was performed according to the criteria of American Thoracic Society [6].

Measurement of BHR

BHR was evaluated by 1% methacholine bronchial provocation test. Test was done according to the rules of American Thoracic Society (ATS) [7]. We used the Sensor Medics V max series 22 lung function test device and Mediprom nebulizer. Bronchial hyperreactivity was defined as a PD 20 of ≤ 16mg/ml.

Microbiological Evaluation

Bronchial colonisation was investigated in all patients. The patients were free of an infectious exacerbation for at least 8 weeks prior to the start of the study. All the sputum samples which had less than 10 epithelial cells in microscopic examination with x100 magnification, were accepted as valid sputum samples and underwent further analysis [8]. Samples were embedded to 5% sheep bloody agar, chocalate and Mc Conkey agar. All samples were stained for Gram and Ehrlich Ziehl Nielsen (EZN) preparations. If a microrganism was dominant both in Gram preparations and sputum culture, it was accepted as the causative agent. Bacterial colonisation was defined as the isolation of the same pathogen in sputum taken in two clinically stable periods at least 6 weeks apart from each other. Patients with no pathogens isolated from their sputum were considered as having no bacterial colonisation.

Skin Prick Tests and Total Ig E measurement

Skin Prick tests were applied to 64 patients. Patients were reguired to withhold any short acting antihistamines for 48 hours and long acting antihistamines for 2 months prior to study. Total Ig E measurements were performed in 56 patients with nephelometric assay.

Statistical Analysis

In order to asses factors affecting bronchial hyperreactivity we used chi square, Mann Whitney U test and logistic regression test. For evaluating the relation of lung function test and PD20 levels in BPT test we used Pearson correlation test, p value smaller than 0.05 was accepted as significant.

Results

Out of 69 patients 38 were male (55.1%) and 31 of them were female (44.9%). Mean age was 50±16 years. Bronchiectasis was diagnosed for 15±16 years (median 10 years). 25 patients (36.2%) had smoking history of 31±25 package/years. Among them 18 patients were ex-smokers for 8±8 years (median 5 years).

20 patients (29%) had positive bronchial provocation test with methacholine. Mean PD20 value for these patients were 6.81±5.67 (minimum 0.1 mg, maximum16 mg).

Bacterial colonisation was detected in 10 patients. Among these 5 had grown Pseudomonas aeruginosa, 1 had Pseudomonas alcaligenes, 3 had Haemophilus influenzae and 1 had Nocardia species. While colonisation could not be evaluated in 39 patients, 20 patients had no colonisation.

FEV_1 (pred %), FVC (pred %) and FEV_1/FVC (%) values are statisticaly significantly lower (p=0.01; p<0.001; p=0.002) among bronchiectasis patients with BHR than without BHR (Table-1)

When we analysed the factors affecting BHR among bronchiectasis patients by using logistic regression analysis, gender and FEV_1% were found statistically significant (P<0.05) (Table-2).

Table 1. Comparison of bronchiectasis patients with and without BHR (NS=Non-significant).

	BHR (+)	BHR (-)	p
Age (Mean ± SD years)	55 ± 15	48 ± 17	NS
Gender (M/F)	6/14	32/17	0.007
Duration of disease (years)	22 ± 20	12 ± 13	0.01
Smoking status	%30	%38.8	NS
TB history	%20	%40.8	0.1
Cystic and/or varicose bronchiectasis	%50	%20.4	0.01
Bronchiectasis limited to upper lobes	%20	%20.4	NS
Number of lobes involved	3 ± 1	2 ± 1	NS
Bronchial colonisation (+/-)	3/11	7/19	NS
Pseudomonas colonisation (+/-)	3/11	3/23	NS
FVC (Pred %)	83 ± 16	93 ± 15	0.01
FEV_1 (Pred %)	64 ± 16	82 ± 19	<0.001
FEV_1/FVC (%)	67 ± 7	75 ± 11	0.002
Prick test (+/ -)	1/18	6/39	NS
Total IgE high/normal	3/12	10/31	NS

Table 2. Results of logistic regression analysis

	P
Gender (M/F)	0.016
Duration of disease	NS
Tuberculosis history	NS
Cystic and/or varicose bronchiectasis	NS
FVC (Pred %)	NS
FEV_1 (Pred %)	0.023

Discussion

We found 29% BHR in bronchiectasis patients without cyctic fibrosis, ABPA, immunsupression and asthma. Bronchial hyperreactivity was reported between 20% -69% in different studies. A study conducted in 1978, showed BHR in 50% of bronchiectatic patients. However their group of patients contained 43% asthma [9]. In a study of Bahous et al. [10], performed with 29 bronchiectasis patients without tuberculosis and immunsupression yielded 69% BHR. A relationship was found between BHR and the presence of bronchial obstruction and asthma. Ip et al. [11] found BHR in 45% among 47 bronchiectasis patients with no concomittant cystic fibrosis. 52% of these patients were clinically accepted as having asthma . Koh et al [12] investigated the effects of roxithromycin in patients with bronchiectasis. In 43% of cases BHR was determined. None of the patients had ABPA, cystic fibrosis and immune deficiency. 30% of the provoked patients were accepted as asthma [12].

None of the above mentioned studies excluded asthmatic patients as a rule. As BHR is a dominant feature of asthma, the high BHR rates coming from these studies may not reflect the real status in pure bronchiectatic population. We carefully excluded asthmatic patients from the study and detected BHR in 29%. The study of Pang et al. [13] supported our findings. They reported the rate of BHR as 20% in 30 bronchiectatic patients and only one patient was diagnosed as asthma.

It is also remarkable that in studies where BHR ratio is found to be high in bronchiectasis, the PD20 value is higher than accepted today. This may explain the exaggerated values in these reports.

In the present study it was detected that female gender and low FEV_1 correlated with BHR. It is not easy to explain higher rates of BHR in female subjects. Giamarchi included 28 women with uterine fibroma in their study to investigate bronchial hyperreactivity [14]. Carbachol BHR was found in 8/28 persons (28%), but with no clinical manifestations. None of the patients were smokers and only one suffered from mite-allergic rhinitis-conjunctivitis without asthma. The researchers commented that this may suggest a possible link between hormonal malfunction and BHR in women. We may speculate that some hormonal factors may be important in the development of BHR.

It is obvious that the degree of obstruction in lung function tests correlate with BHR. This finding parallels to the opinion that diminishing of bronchial calibre may induce BHR. The study of Ip supports our findings [11]. In their results, presence of BHR was positively associated with low baseline spirometric values.

We did not find a relationship between the development of BHR and age, duration of the disease, presence of atopy, disease limited to upper lobes, presence of cystic and/or varicose bronchiectasis, size of the affected area and restriction parameters. Also, we did not find a relationship between BHR and bacterial colonisation. Our study does not support the hypothesis that pseudomonas type bacteria do secrete some mediators that cause BHR.

In conclusion, when asthma, cystic fibrosis and immune deficiency are excluded, bronchial hyperreactivity was detected in a much smaller proportion than the existing literature. Female gender and the degree of bronchial obstruction seem to influence the development of bronchial hyperreactivity in patients

with bronchiectasis. These two determinants are general factors associated with the development of bronchial hyperreactivity.

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