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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

FACTORS AFFECTING MORTALITY AND MORBIDITY IN PATIENTS WITH BRONCHIECTASIS

BRONŞEKTAZİLİ HASTALARDA MORTALİTE VE MORBİDİTEYİ ETKİLEYEN FAKTÖRLER

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ÖZ

AMAÇ: Bronşektazide tekrarlayan bronş enfeksiyonları; akciğer fonksiyonlarında azalma, mortalite ve morbiditede artışa yol açar. Çalışmamızda bronşektazide mortalite oranlarını ve mortaliteye yol açan risk faktörlerini değerlendirmeyi amaçladık.

GEREÇ VE YÖNTEM: Çalışmaya yüksek rezolüsyonlu bilgisayarlı tomografisi (YRBT) olan 104 hasta dahil edildi. Demografik özellikleri, semptomları, fizik muayene bulguları, YRBT bulguları, solunum fonksiyon testleri, balgam analizleri ve kültür sonuçları, antibiyotik dirençleri, infeksiyon parametreleri, yoğun bakım ihtiyaçları ve mortalite oranları retrospektif olarak değerlendirildi.

BULGULAR: Ortalama yaş 59.5±15.1 idi. Hastaların % 65.4'ünün balgam şikayeti vardı, % 27.9'unda balgam kültüründe mikroorganizma saptandı. % 11.5 olguda antibiyotik direnci saptandı. Enfeksiyon sıklığı, antibiyotik direnci; yaş, sigara ve solunum yetmezliği mortalite ile ilişkili bulundu ($p<0.05$). Antibiyotik direnci olan ve olmayan hastalar arasında FEV_1%'de farklılık saptandı ($p<0.05$). FEV_1 ile antibiyotik direnci ($r=-0.257$, $p=0.02$), solunum yetmezliği ($r=-0.288$, $p=0.01$) ve infeksiyon sıklığı ($r=-0.329$, $p=0.003$) arasında negatif ilişki saptandı. Sık enfeksiyon geçirenlerde FEV_1 < % 60 olarak ölçüldü ($p=0.003$). Pulmoner hipertansiyon daha yaygın olarak tübüler ve bilateral bronşektazisi olan hastalarda bulundu (% 21.2).

SONUÇ: Bronşektazide ileri yaş, sigara içimi, enfeksiyon sıklığı, solunum yetmezliği ve antibiyotik direnci mortalite riskinin artması ile ilişkilidir. Çalışmamızda antibiyotik direnci saptanan hastalarda FEV_1 < % 60 olarak bulunmasının mortaliteyi artırdığını saptadık.

ANAHTAR KELİMELER: Bronşektazi, enfeksiyon, mortalite, pulmoner fonksiyon

ABSTRACT

OBJECTIVE: Recurrent bronchial infections lead to a decrease in pulmonary function and an increase in mortality and morbidity in patients with bronchiectasis. We aimed to evaluate mortality rate and identify risk factors in mortality in patients with bronchiectasis.

MATERIAL AND METHODS: In this study the records of 104 patients who underwent high resolution computed tomography (HRCT) were evaluated. Demographic variables, symptoms, physical examination findings, HRCT and pulmonary function test (PFT), culture and sputum analysis results, antibiotic resistance, infection markers, need to stay in intensive care unit and mortality rates were examined.

RESULTS: The mean age was 59.5±15.1 years. Sputum production was detected in 65.4% of the cases and in 27.9% a microorganism was identified on sputum culture. Antibiotic resistance was detected in 11.5% of the cases. Infection episode, antibiotic resistance, age, smoking and respiratory insufficiency were associated with mortality ($p<0.05$ for all). A significant difference was noted in FEV_1% between patients with and without antibiotic resistance ($p<0.05$). There was negative association between FEV_1 and antibiotic resistance ($r=-0.257$, $p=0.02$), respiratory insufficiency ($r=-0.288$, $p=0.01$) and infection episodes ($r=-0.329$, $p=0.003$). Number of infection episode was higher in patients with a FEV_1 <60% ($p=0.003$). Pulmonary hypertension was detected in 21.2% of the patients which was significantly more common in tubular and bilateral bronchiectasis.

CONCLUSIONS: Older age, smoking, infection episode, respiratory insufficiency and antibiotic resistance were associated with an increased risk of mortality. Our findings indicate that antibiotic resistance should be determined in patients with bronchiectasis who have a FEV_1 value <60% as these cases have increased mortality.

KEYWORDS: Bronchiectasis, infection, mortality, pulmonary function

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INTRODUCTION

Bronchiectasis is defined as chronic and irreversible dilatation of the bronchi and a decrease in lung function which manifests as coughing and sputum production. It is characterized by a repetetive cycle of inflammation followed by infections causing structural damage to the bronchi and bronchioles (19). Infections are the most common causes of bronchiectasis. If not diagnosed early and not treated on time bronchial destruction occurs. As a result impairment in lung function becomes evident leading to an increase in morbidity and mortality. High-resolution computed tomography (HRCT) scan of the lung is proven to be a high sensitivite and noninvasive technique for delineating the bronchiectatic segments (2). Patients with bronchiectasis are usually monitored clinically using reported symptoms and pulmonary function tests (PFTs). Airway obstruction is mild to-moderate in severity but may worsen over the time.

Literature about the mortality associated with bronchiectasis is limited (3). Therefore, in this study we aimed to investigate the type, degree of involvement and the factors associated with mortality and morbidity in patients with bronciectasis whose diagnoses were confirmed with HRCT.

MATERIALS AND METHODS

In this study the records of 104 adult patients (range 18-85 years) who underwent HRCT between 2000-2009 and identified as having bronciectasis were evaluated. Patients with HRCT findings compatible with interstitial lung disease, severe emphysematous disease, patients with known neoplasm, and cystic fibrosis were excluded. Diagnosis of bronchiectasis was established in all cases by chest HRCT scanning in sections of 1 to 1.5 mm every 10 mm. Standard HRCT criteria for diagnosing bronchiectasis are well estabilished (4). The most specific criteria are an internal diameter of bronchus wider than its adjacent artery and failure of the bronchi to taper. Based on HRCT findings bronchiectasis was classified and analyzed as cystic, tubular and traction type and analyzed. The etiology of bronchiectasis in the study group was not investigated.

Demographics, smoking history, systemic diseases, symptoms at admission, physical examination findings, and HRCT results were noted. Results of pulmonary function test (PFTs) which was performed when the patients were stable, arterial blood gas (ABG) analyses, transthoracic Doppler echocardiography were recorded. Laboratory results including leucocyte count, C-reactive protein and sedimentation rate were obtained. Pulmonary function tests had been obtained in the sitting upright position with a clinical spirometer (SensorMedics Vmax spectra 229, Bilthoven, The Netherlands). Forced vital capacity (FVC), volume of forced expiration in the first second (FEV_1), expiratory air flow rates in the middle segment of forced vital capacity (FEF25–75%), and FEV_1/FVC had been obtained. Carbon monoxide diffusing capacity (DLCO) had been measured by a single breath method. The DLCO value had been corrected for hemoglobin concentration. Spirometry results are expressed with standard gender and race specific prediction equations where appropriate (5). Arterial blood gas analyses had been done with the subjects breathing room air in an upright position at rest. A complete transthoracic echocardiographic evaluation including two-dimensional, continuous-wave color Doppler examinations had been performed. Using continuous wave Doppler the maximum tricuspid regurgitant flow (v) had determined. The modified Bernoulli equation was employed to estimate right ventricular systolic pressure (RVP) which had been considered to be equal to the systolic pulmonary artery pressure (SPAP) in the absence of right ventricular outflow obstruction or pulmonary valve stenosis (6). Patients had been diagnosed as having pulmonary hypertension (PH) when the Doppler echocardiographically had measured SPAP values were ≥30mmHg .

Culture and sputum analysis results, antibiotic resistance, infection markers, long term oxygen theraphy, need to stay in intensive care unit and mortality and factor affecting mortality rates were examined. Acute exacerbation of bronchiectasis was defined as change in sputum production, increased dyspnea, increased cough, fever (temperature > 37.8 C°), increased wheezing, fatigue or malaise, radiographic evidence of new infiltrate, change in breath sounds.

Infection episodes per year and mortality data were assessed based on patient interviews and medical records. Use of medications, short and long acting β_2 adrenergic agonist and inhaler steroid were noted.

Ethics Approval

The study protocol was approved by the Baskent University, Faculty of Medicine Ethics Committee.

STATISTICAL ANALYSIS

SPSS software (Version 10.0; SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Continuous variables were presented as mean ± SD or median and interquartile range, as appropriate. In order to compare continuous parameters, student t-test was performed. The chi-square test was used to compare non-parametric variables. Correlations were established with the Spearman rank correlation or Pearson product moment correlation analysis, as appropriate. All p-values were two-sided, and a pvalue <0.05 was considered to be statistically significant.

RESULTS

The mean age was 59.5 ± 15.1 years and %50 were male. Demographic variables and laboratory data are outlined in **(Table 1)**.

Table1. General characteristics of study patients with bronchiectasis

Demographic characteristics	n=104
Age (years)	59.5 ± 15.1 (18-85)
Sex (Female/Male)	52/52
Smoking history	39 (37.5%)
Smoking years (pack/years)	40.1 ± 33.4
History of lung infection	46 (44.2%)
COPD	39 (37.5%)
Asthma	15 (14.4%)
Respiratory insufficiency	13 (12.5%)
History of tuberculosis	7 (6.7%)
CRP mg/L (attacks/stable)	69.7/6.3
Leucocyte (thousand/uL) (attacks/stable)	10000/7035
Sedimentation (mm/h) (attacks/stable)	46.0/24.4
Mortality	12 (11.5%)

history of lung infection was identified in 46, and tuberculosis in 7 cases. The most common syptoms for admission to hospital were coughing, sputum production and dyspnea **(Table 2)**.

Table 2. Symptoms at admission

Admission symptom	n=104
Control	18 (17.3%)
Coughing	11 (10.6%)
Sputum production	4 (3.8%)
Dyspnea	19 (18.3%)
Coughing and sputum	22 (21.2%)
Coughing+dyspnea	5 (4.8%)
Coughing+sputum+dyspnea	25 (24%)

On physical examination at admission crackles were heard on both lung fields in 43.3%, left hemithorax in 13.5% and right lung in 8.7% of the cases. On HRCT, bronchiectasis was identified as bilateral in 63.5%, 20.2% right sided and in 16.3 left sided. With regard to type of bronchiectasis; it was classified as cystic in 50%, tubular in 27.9%, cystc and tubular 17.3% and traction in 4.8% of the study population. The findings of the sputum microscopy and culture results of the 68 patients with sputum production are summarized in **(Table 3)**.

Table 3. Sputum analysis and culture results

Sputum	n=68
Sputum microscopic evaluation results	
No microorganism, n (%)	42 (40.4)
Gram positive cocci, n (%)	13 (12.5)
Gram negative bacilli, n (%)	8 (7.7)
Diplococcus, n (%)	3 (2.9)
Gram positive cocci, gram negative bacilli, n (%)	2 (1.9)
Sputum culture results	
Pseudomonas aeruginosa, n (%)	6 (31.5)
α-Hemolytic Streptococcus, n (%)	3 (15.8)
Streptococcus pneumoniae, n (%)	2 (10.5)
Candida albicans, n (%)	2 (10.5)
Escherichia coli, n (%)	2 (10.5)
Staphylococcus aureus, n (%)	1 (5.3)

Sputum ARB was ordered in 37 patients and it was negative in all of them. In 19 of 68 patients with sputum culture a microorganism was isola-

ted, pseudomonas aeruginosa being the most common microorganism. PCO_2 was higher and FVC and FEV_1 values were lower in patients in whom pseudomonas aeruginosa was isolated. Ninety three patients had undergone PFT when in stable conditions. Obstructive pattern was noted in 50.5%, mixed in10.7%, restrictive in 2.2% and normal in 22.6% of the patients. Data about ABG analysis and PFT are provided in **(Table 4)**.

Table 4. Arterial blood gases and PFT parameters

Arterial blood gases (n=30)	
pH	7.4 ± 0.04
pCO_2 (mmHg)	39.0 ± 7.6
pO_2 (mmHg)	63.1 ± 15.1
HCO3 (mmol/L)	25.3 ± 4.1
SpO_2 (%)	92.5 ± 4.9
PFT parameters (n=93)	
FVC (%)	88.9 ± 23.6
FEV_1 (%)	72.4 ± 26.1
FEV_1/FVC	65.1 ± 14.2
$FEF\%_{25-75}$	43.1 ± 31.7
TLC (%)	90.3 ± 25.5
VC (%)	89.3 ± 23.3
RV (%)	96.2 ± 46.1
DLCO (%)	87.5 ± 22.4

Reversibility test was performed on 66 (63.5%) patients and it was positive in 11 (10.6%) of them. With regard to medications; 41 (39.4%) patients were on inhaler steroid, 37 (35.6%) on short acting β_2 adrenergic agonist, 56 (53.8%) on long acting β_2 adrenergic agonist. On Doppler echocardiographic examination PHT was detected in 21.2% of the cases. The prevalence of PH was higher in patients with tubular type and bilateral bronchiectasis and decresaed DLCO(%) ($P<0.05$). There was no association between type of bronchiectasis and respiratory failure. Respiratory failure and infection episodes were higher in patients with FEV1 <60%. Antibiotic resistance was identified in 12 of 19 patients with positive sputum culture. A significant difference in FEV1% was detected in patients with and without antibiotic resistance (53.6 ± 26.3% vs 74.8 ± 16.4% respectively; p=0.021). Mortality rate was higher in patient with antibiotic resistance (p=0.01, r=0.241), however no relation was noted between antibiotic resistance and extent of bronchiectasis.

By the end of the follow up, January 2010, (mean follow up= 4.2 years) 12 patients (11.5%) died. Four of the 6 patients admitted to intensive care unit were intubated and all of them died because of respiratory failure. Coexistince of coronary artery disease (CAD) and chronic obstructive pulmonary disease (COPD) were found to increase mortality ($p<0.05$). Duration of stay in hospital, infection episode, age and smoking were associated with mortality. CRP levels that were studied when the patients were stable were higher in patients who died than those who were alive (9.9 ± 4.6 vs 5.6 ± 4.5mg/dL respectively; p=0.02). Patients in whom pseudomonas was isolated on sputum culture had higher mortality rates compared to those with another microorganism (16.7% vs 4.3%; p=0.02). Non-smoking was associated with less pseudomonas isolation on sputum culture (p=0.03). Infection episode was higher in patients who were on inhaler steroid therapy than those were not (1.3 ± 1.0; 0.6± 0.8, $p<0.05$). There was no association between mortality and the type and localization of bronchiectasis and pulmonary hypertension (PH)

DISCUSSION

Pulmonary function test

Functional impairment in bronchiectasis is related to the etiology and extent of the disease. Patients may develop progressive decline in pulmonary function due to ongoing infection, inflammation, and destruction of bronchi if a delay in diagnosis and therapy occurs. Impaired lung function in patients with bronchiectasis usually leads to chronic airflow obstruction (7). The most prominent change in PFT is decreased FEV1/FVC due to airflow obstruction and there is a progresive decline in lung function over time with loss of FEV1. A decrease in vital capacity and residual volumes, restrictive pattern and a decrease in diffusion capacity might be observed in severe bronchiectasis because of atelectasis and restrictive abnormalities. It has been reported that the degree of airway obstruction is related to the extent of bronchiectasis on HRCT (8). Pulmonary function testing generally shows airflow obstruction ranging from modest to severe. A number of explanations have been offered to explain the finding of obstructive PFTs, including obliterative bronchiolitis, collapse of large airways on expiration, retention of endobronchial secretions, or concurrent asthma or emphysema, among others (9). In our study obstruction was identified in around half of the patients. The relation between airway obstruction and extent of bronchiectasis could not be evaluated

becaues of smoking history in the study group. Obstructive pattern on PFT may lead to a misdiagnosis of asthma. In a study by Grenier et al bronchiectasis was demonstrated on HRCT in around 30% of the patients with asthma (10). As bronchial hyperreactivity is prominent in bronchiectasis, bronchodilator testing when performing PFTs is recommended. Further tests should especially be ordered in patients having atypical symptoms with asthma. In our study reversibility was demonstrated in 10.6% of the cases with asthma symptoms and obstructive pattern. For this reason HRCT should be recommended in cases having atypical symptoms of asthma and abnormal lung graphy. The role of anti-inflammatory therapy in bronchiectasis is challenging. Martinez Garcia et al demostrated a significiant reduction in expectorated sputum and an improvement in health related quality of life as measured by the St George's Respiratory Questinnaire by fluticasone therapy (11). Tsang et al reported that inhaled fluticasone reduces sputum levels of inflamatory markers and the density of leukocytes (12). Because of the increased bronchial hyperreactivity and possible reversibility of the airflow obstruction in patients with bronchiectasis the use of bronchodilators could be part of their therapy. Since chronic inflammation is an ongoing process even in the stable phases of the disease it has been shown that inhaler steroid therapy is effective at reducing the symptoms, slowing the progression and supressing the inflammation (13). Although not supported by randomized controlled trials it might be argued that low doses of inhaler steroids be used. However, owing to the lack of firm data and the local side effects of this therapy their routine is not recommended. For these reasons an individualized approach is needed to optimally evaluate and treat individuals with bronchiectasis. The aim should be to improve life quality of the patients and to decrease exacerbations instead of just dealing with small changes in PFT parameters.

Microbiologic evaluation

Recurrent infections, sputum production and progressive lung tissue damage are the basic characteristics of bronchiectasis. It has been demostrated that even in asymptomatic and stable bronchiectasis patients bacterial colonization occurs (14). These microorganisms represent a potential risk for lung infections and may secrete several inflammatory mediators that cause progressive tissue damage and airway obstruction. Colonization with potential pathogenic microorganisms is identified in 60-80% of patients under stable clinical conditions. The two main pathogens isolated in patients with bronchiectasis are Haemophilus influenzae and Pseudomonas aeruginosa (14, 15). Infection with Pseudomonas aeruginosa presents a management problem and may produce a more rapid decline in lung function (16).

King at al found that the severity of disease correlated with the infecting agents: patients with the mildest disease had no pathogens, while those with the most severe disease were colonized with Pseudomonas species (17). Furthermore lung lesions are more diffuse and the abnormalities in pulmonary functions are more severe in patients colonized with these agents (18). Correlations between lung function, severity of disease on HRCT scan and infection with pseudomonas aeruginosa have previously been reported in bronchiectasis (19,20). In the present study pseudomonas was the most commonly isolated microorganism on sputum culture. And in these patients PCO_2 was higher and airway obstruction is more prominent. For these reasons to limit progressive tissue damage and to decrease airway obstruction the colonized microorganisms should be identified and accordingly the appropriate antibiotics should be administered. Sputum culture in this regard is an easy, cheap and a non invasive method of identifiying the colonized pathogens (14). Angrill et al demonstrated an association between airway colonization and FEV_1 below 80% of predicted and cystic-varicose type bronchiectasis on HRCT (14). In our patients there was no association between type of bronchiectasis and culture results, however the rate of positive sputum culture and infection episodes per year were higher in subjects with FEV_1 below 60% of predicted. Therefore we think that due to the high probability of airway colonization in patients with FEV1 <60% sputum culture should be obtained to diagnose and treat infection attacks for prevention of the progressive airway obstruction

and damage. In addition we suggest that because FEV1 below 60% and mortality is higher in patients with antibiotic resistance, sensitivity to antibiotics should be determined once the diagnosis of bronchiectasis is established.

Pulmonary hypertension

Pulmonary hypertension (PH) related to respiratory diseases is mostly mild to moderate, and the severity is associated with the category of respiratory disease (21). PH develops in patients with bronchectasis because of impaired pulmonary physiology as a result of structural changes in the lung. It is a common condition, especially in those with cystic bronchiectasis (22). In a study the prevalence of PH was reported as 32.9%, SPAP being higher in patients with cystic bronchiectasis. It has been shown that increasing SPAP was significantly correlated with a decline in DLCO percentage of predicted and correlated negatively with FEV_1 in patients with cystic bronchiectasis. High SPAP was associated with low pO_2 and high pCO_2 (19). In our study PH was diagnosed in 21.2% of the patients on echocardiographic examination. We identified that PH is significantly higher in patients with tubular bronchiectasis, bilateral bronchiectasis, hypoxia and respiratory insufficiency. These findings indicate that as a result of diffuse lung damage a decrease in diffusion capacity, hypoxia and respiratory insufficiency are seen, pulmonary vascular resistance increases and PH develops. PH may serve as a sign of lung parenchymal damage. For that reason in patients with PH, taking into account the symptoms and direct graphy findings, HRCT should be planned.

Mortality

Smoking is one of the major risk factor for the development of heart and lung disease. Abnormalities in cilia function and increase in mucus secretion lead to an increase in bacterial adherence and recurrent infections. In aggregate, these events lead to an increase in airway obstruction and parenchymal damage. It has been shown that development of COPD in bronchiectasis patients poses prognostic importance (23).

Finklea et al reported an association between smoking and mortality but no data is provided about the amount and time of exposure to smoking. In this study we found that both the time of exposure to smoking and amount in pack years were associated with an increase in mortality (24). Additionally we detected that mortality is higher in patients with bronchiectasis when COPD and CAD coexist. For this reason the first step should be to stop smoking in patients with bronchiectasis. Loebinger et al reported the factors independently associated with mortality were age, St George's Respiratory Questionnaire activity score, infection with Pseudomonas aeruginosa, total lung capacity (TLC), residuel volume/TLC and transfer factor coefficient (3). Mortality was substantially higher in patients with chronic colonization compared with noncolonized patients (25).

In our study isolation of pseudomonas on sputum culture and antibiotic resistance were identified as the predictors of mortality. Bacterial colonization was demonstrated as a contributing factor to increased mortality in patients with high serum CRP levels measured when the patients were stable. Wilson et al have reported that, there is an increase in the concentration of some acut phase reactants such as CRP, ESR, or IgA in patients with bronchiectasis that are correlated with decreased pulmonary function or extent of the disease (26). It has been proposed that systemic inflammation could be a spill-over phenomenon of local inflammatory markers from the lungs (27). For these reasons bronchiectasis should not be regarded as a localized disease and elevation of inflammatory markers, if not explained by another systemic disorder, the patients should be evaluated for colonization. Therefore early therapy might be advised to those cases with high CRP levels studied in stable conditions when harboring the other risk factors such as smoking, COPD.

In conclusion, when the diagnosis and treatment are delayed in bronchiectasis, inflammation and recurrent infections lead to a destruction in bronchi and a progressive decline in lung function. Pulmonary function testing should be routinelly performed and in those with FEV_1 <60% colonization and antibiotic resistance should be determined because of

increased infection risk and mortality. Identification of the microorganisms on sputum culture and determination of antiobiotic resistance should be done to give appropriate therapy. Older age, smoking, infection episode, respiratory insufficiency and antibiotic resistance were associated with an increased risk of mortality.

Limitations:

This study has several limitations. Inherent to its retrospective nature some tests were not available in all the cases. For example, sputum culture was not obtained in all the patients. Causes of bronchiectasis were not identified. Prospective studies with larger patient numbers and longer term follow up are needed to better clarify this issue.

Conflict Of Interest Statement

All support for this study came from institutional and departmental resources.

There is no conflict of interest to declare

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