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Misdiagnosis of Asthma in Patients with Anxiety/Depression

Anksiyete/Depresyon Hastalarında Yanlış Astım Tanısı

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ABSTRACT

Objective: *Anxiety/depression may lead to misdiagnosis of asthma if respiratory symptoms are prominent. In this study, we aimed to evaluate misdiagnosis due to anxiety and depression among patients diagnosed with asthma.*

Material and Methods: *This prospective study included patients who were previously diagnosed with asthma and evaluated by a psychiatrist through the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI). The patients were divided into two groups in terms of their BDI/BAI status as positive (mild, moderate or severe category) or negative (normal category). The groups were compared in terms of clinical characteristics, pulmonary function tests, asthma control tests (ACT), and atopy parameters.*

Results: *We identified 54 patients (32.7%) in BDI/BAI(+) group. Compared to that in BDI/BAI(+) group, patients in the BDI/BAI(-) group were more likely to have family history of asthma (37.0% vs. 65.7%, p<0.001). The mean ACT score in the BDI/BAI(+) group was significantly lower than that in the BDI/BAI(-) group (15.9 vs. 19.3, respectively, p<0.001). Significantly less patients in BDI/BAI(+) group had evidence of obstruction (14.8%) and reversibility (14.8%) compared to those in BDI/BAI(-) group (57.7% and 54.1%, respectively; p<0.001 for each). While total IgE and ACT were the tools with highest sensitivity (72% and 70%, respectively), skin prick test had the highest specificity (92%). Obstruction (88%) and reversibility (88%) had the highest positive predictive values.*

Conclusion: *The presence of dyspnea on the basis of asthma diagnosis may lead to misdiagnosis in some patients, especially in individuals with anxiety/depression. The history of patients presenting dyspnea symptoms should be taken carefully and examined in detail by spirometric and laboratory workup.*

ÖZET

Amaç: *Anksiyete/depresyon, solunum semptomlarının ön planda olması durumunda yanlış astım tanısına yol açabilir. Bu çalışmada astım tanısı alan hastalarda anksiyete ve depresyona bağlı yanlış astım tanılarını değerlendirmeyi amaçladık.*

Gereç ve Yöntem: *Bu prospektif çalışmaya daha önce astım tanısı konulan ve bir psikiyatrist tarafından Beck Anksiyete İndeksi (BAİ) ve Beck Depresyon İndeksi (BDİ) ile değerlendirilen hastalar dahil edildi. Hastalar BDİ/BAİ durumuna göre pozitif (hafif, orta ve şiddetli kategori) ve negatif (normal kategori) olmak üzere iki gruba ayrıldı. Gruplar klinik özellikler, solunum fonksiyon testleri, astım kontrol testleri (AKT) ve atopi parametreleri açısından karşılaştırıldı.*

Bulgular: *BDİ/BAİ(+) grubunda 54 (%32,7) hasta tespit ettik. BDİ/BAİ(+) grubuyla karşılaştırıldığında BDİ/BAİ(-) grubundaki hastaların ailede astım öyküsüne sahip olma olasılığı daha yüksekti (%37,0 vs. %65,7, p<0,001). BDİ/BAİ(+) grubu BDİ/BAİ(-) grubuna göre anlamlı derecede düşüktü (sırasıyla 15,9'a karşı 19,3, p<0,001). BDİ/BAİ(+) grubunda anlamlı olarak daha az hastada obstrüksiyon (%14,8) ve geri dönüşlülük (%14,8) bulgusu, BDİ/BAİ(-) grubuna (sırasıyla %57,7 ve %54,1; her biri için p<0,001) göre görüldü.).Total IgE ve AKT duyarlılığı en yüksek araçlar iken (sırasıyla %72 ve %70), özgüllüğü en yüksek olanı deri prick testiydi (%92). Obstrüksiyon (%88) ve reversibilite (%88) en yüksek pozitif öngörü değerlerine sahipti.*

Sonuç: *Astım tanısına dayalı nefes darlığının varlığı bazı hastalarda, özellikle de anksiyete/depresyon hastalarında yanlış tanıya yol açabilmektedir. Nefes darlığı semptomları gösteren hastaların öyküsü dikkatlice alınmalı ve spirometrik ve laboratuvar incelemeleriyle ayrıntılı olarak incelenmelidir.*

Keywords:
Misdiagnosis of asthma
Anxiety
Depression
Dyspnea
Pulmonary function test

Anahtar Kelimeler:
Yanlış astım tanısı
Anksiyete
Depresyon
Nefes darlığı
Solunum fonksiyon testi

INTRODUCTION

Asthma is a chronic airway inflammatory disease that develops against direct or indirect stimuli with different severity of airway obstruction. The clinical presentation of the diseaseand intensity of symptoms vary over time (1). Asthma is estimated to affect approximately 10% of the European population (2). While spirometric pulmonary function tests (PFTs), serum total IgE level and prick test may contribute to the diagnosis, it is mainly based on anamnesis: shortness of breath, wheezing, coughing, and chest tightness constitute critical features of asthma (3). Especially in the last 25 years, the number of patients diagnosed with asthma has increased significantly (4). However, this increase has been approached disputably, since a high prevalence of misdiagnosis of adult asthma has been reported in the literature (5). An estimated one-third of asthma patients are misdiagnosed. Evaluating the difference in healthcare resource use and costs between

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misdiagnosed and confirmed cases of asthma can inform assessments of the burden of asthma misdiagnosis (6). Evidence-based guidelines, including from the Global Initiative for Asthma, recommend the diagnosis of asthma be confirmed by objective tests demonstrating either reversible airflow limitation or increased airway hyperresponsiveness (1). Despite these recommendations, studies suggest that asthma is diagnosed solely based on symptom history in over half of physician-diagnosed cases (7,8). Asthma may be misdiagnosed due to a number of conditions, including chronic obstructive pulmonary disease (COPD), upper respiratory tract infections, acute bronchitis, obesity, heart failure, and psychiatric disorders (9-12).

The physiological symptoms of anxiety mimic many diseases and can be elaborated as palpitation, difficult and/or rapid breathing, feeling of suffocation, increased heart rate, and tremor in hands and feet. Apart from these, patients also experience psychological symptoms such as distress, excitement, and sense of impending doom (12). Depression is a common and serious illness that affects individuals' feeling, behaviors, and thoughts. Lack of energy, loss of interest or pleasure, lack of concentration, decreased self-confidence, feelings of guilt, pessimism, self-harm or suicidal thoughts, impaired sleep pattern, changes in appetite and decreased libido are common in depression (13). Anxiety, depression and panic attacks also cause asthma-like symptoms, confounding the diagnosis of asthma (1). Coexistence of psychiatric disorder and asthmamay compromise asthma control and deteriorate asthma status in affected individuals. This may result in unnecessary hospitalization and inpatient treatment costs (14). Infact, anxiety and depression are more frequent in asthmatic patients compared to the general population and drug treatments for two diseases may interact with each other (14).

Anxiety/depression may lead to a misdiagnosis of asthma if respiratory symptoms are prominent. Therefore, a carefull anamnesis is important in the diagnosis of asthma in such patients in addition to diagnostic tests (PFT, prick test, and reversibility test) (15).

In this study, we aimed to evaluate the misdiagnosis of asthma due to anxiety and depression.

MATERIAL AND METHODS

Study design and population

The study was planned in a prospective mannerat a single center. Ethical approval was obtained from the Ethics Committee of Dicle University Medical Faculty (Approval no: 206). All patients gave written informed consent. The study included 165 consecutive patients over the age of 18 years who were admitted to the pulmonary diseases outpatient clinic of ourhospital between 01/06/2020 to 01/12/2020 and were previously diagnosed with asthma. Individuals who were examined by a pulmonologist at least one month ago and diagnosed with asthma and had a history of using inhaled medications for at least one months were eligible for the study. In our institution, those patients were also examined independently by another pulmonologist and psychiatrist to re-assess asthma diagnosis. We defined asthma as a history of variable respiratory symptoms and evidence of variable expiratory airflow limitation. The dyspnea symptoms of the patients who applied to the outpatient clinic were questioned. If the patient's dyspnea was considered to be due to anxiety or diseases other than asthma, the patient was excluded from the study. Other exclusion criteria were as follows: being <18 years, respiratory infection or oral glucocorticoid use with in last month, concomitant anti-IgE medication or allergenic immunotherapy, current asthma attack, any accompanying condition with shortness of breath (e.g., heart failure, hypertension, hypothyroidism, anemia), coexisting diseases that may compromise respiratory function (e.g., COPD, tuberculosis, pneumonia, bronchiectasis), those who were incompatible and unable to undergo PFT or correctly and regularly use asthma medications, and pregnant women.

Data collection

Age, gender, smoking status, body mass index (BMI), asthma control test (ACT), PFT, obstruction, reversibility test, Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), history of asthma-related emergency room (ER) admission with in the last 1 year, and skin prick test (SPT) results were recorded. Total IgE levels were analyzed to evaluate the atopy status of the patients. The family history of asthma of the patients was recorded.

Scales and tests

Asthma Tests

Spirometry is the most widely used PFT (16). We used this tool to measure first-second forced expiratory volume (FEV1), peak flow rate (PEF), obstruction, and reversibility. ACT is a simple and reliable 5-item questionnaire that has five points for each. While a score of 25 points indicates full control, scores ≤19 points denotesthe state that the asthma is not under control (17). SPT is performed with commercially available respiratory and food allergens, latex or (more rarely) drugs. It is used in the diagnosis of allergic rhinoconjunctivitis, bronchial asthma, atopic dermatitis, contact urticaria, and food/drug allergies. SPT results were recorded as positive or negative (18).

Psychiatric Tests

BDI is a 21-item self-report scale to measure emotional, cognitive, somatic and motivational components. Each question was given a score of 0, 1, 2, 3.A total score of 0 to 9 points shows none/minimal depression whereas higher scores reveal increasing severity of depression (mild: 10-18 points, moderate: 19-29 points, severe: 30-63 points) (19). Similarly, Beck Anxiety Inventory (BAI) measures the frequency of anxiety symptoms experienced by an individual with 21-item scored between 0-3. While total score of 0-7 points is considered normal, 8-15 points is mild, 16-25 points is moderate, and 26-63 points is severe (20). The patients were divided into two groups in terms of their BDI/BAI status as positive (mild, moderate or severe category) or negative (normalcategory).

Statistical Analysis

Statistical analysis was performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). By calculating 0.05 margin of error and 0.80 effect power using G power, the minimum number of patient samples was determined and the number of samples greater than this number was reached. Descriptive statistics of continuous variables were shown with mean and standard deviation values. Shapiro-

Wilk test was performed to evaluate whether the data was distributed normally. Student t test was used to compare the BDI/BAI groups in terms of age, ACT, FEV1, BMI, PEF, and Total IgE levels. Categorical variables including SPT positivity, obstruction, reversibility, gender, smoking status, ER admission and presence of family history were compared via chi-square test. Statistically significant variables were tested through ROC curve analysis, where cut-off values, sensitivity, specificity, positive and negative predictive values were calculated.The hypotheses were bidirectional and an overall 5% Type-I error level of was used to infer statistical significance.

RESULTS

Comparison of the study groups

We identified that there were 54 patients (32.7%) in BDI/BAI(+) group and 111 patients (67.3%) in BDI/BAI(-) group. The groups did not differ inage, smoking status or BMI while there were significantly more women in BDI/BAI(+) group (87.0%) compared to that in the BDI/BAI(-) group (72.1%, p=0.05). Compared to that in BDI/BAI(+) group, patients in the BDI/BAI(-) group were more likely to have family history of asthma (37.0% vs. 65.7%, p<0.001) whereas the groups were similar in asthma-related ER admission during previous year (46.3% vs. 40.5%, p=0.50), (Table 1).

The mean ACT score in the BDI/BAI(+) group was significantly lower than that in the BDI/BAI(-) group (15.9 vs. 19.3, respectively, p<0.001).BDI/BAI(+) and BDI/BAI groups did not show difference in terms of the mean FEV1(87.7% vs.83.3%, respectively) and the mean PEF(84.7% vs. 79.0%, respectively) values. Significantly less patients in BDI/BAI(+) group had evidence of obstruction (14.8%) and reversibility (14.8%) compared to those in BDI/BAI(-) group (57.7% and 54.1%, respectively; p<0.001 for each).

Positive SPT results were significantly more common in BDI/BAI(-) group (25.2%) than that in BDI/BAI(+) group (7.4%, p=0.04). The mean total IgE level was also significantly higher (278.4IU/mL)in the BDI/BAI(-) group compared to that in the BDI/BAI (+) group (137.1 IU/mL, p<0.001), (Table 1).

Table 1: The comparison of the study groups by their demographic and clinical characteristics.

	BDI/BAI(+)	BDI/BAI(-)	p-value
n (%)	54 (32.7)	111 (67.3)	-
Age, yrs (mean ± SD)	39.3 ±11.5	39.3 ± 15.4	0.9
Female, n (%)	47 (87.0)	80 (72.1)	0.05
Smoking status			
Never, n (%)	32 (59.2)	69 (62.2)	0.6
Former, n (%)	13 (24.1)	20 (18.0)	
Current, n (%)	9 (16.7)	22(19.8)	
Family history of asthma, n (%)	20 (37.0)	73 (65.7)	<0.001
Asthma-related ER admission within last year, n (%)	25 (46.3)	45 (40.5)	0.5
Body mass index, kg/m2 (mean ± SD)	28.0 ± 6.8	27.4± 6.6	0.6
Total IgE, IU/mL (mean ± SD)	137.1 ± 204.3	278.4 ± 335.3	<0.001
Skin prick test positivity, n (%)	4 (7.4)	28 (25.2)	0.04
Asthma control test score (mean ± SD)	15.9± 4.6	19.3 ± 3.9	<0.001
FEV1, % (mean ± SD)	87.7 ± 18.5	83.3 ± 18.4	0.15
PEF, % (mean ± SD)	84.7 ± 21.3	79.0 ± 21.3	0.09
Obstruction, n (%)	8 (14.8)	64 (57.7)	<0.001
Reversibility, n (%)	8 (14.8)	60 (54.1)	<0.001

BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; SD, standard deviation; ER, emergency room;FEV1, forced expiratory volume during first second; PEF, peak expiratory flow.

Table 2: Effects of the significant parameters on asthma diagnosis by ROC curve analysis.

	Cut-off value	Sensitivity	Specificity	PPV	NPV
ACT score	17.5 points	70%	68%	82%	52%
Total IgE level	80 IU/mL	72%	77%	86%	57%
Family history	-	65%	62%	78%	47%
Obstruction	-	57%	85%	88%	49%
Reversibility	-	54%	85%	88%	52%
Skin prick test	-	25%	92%	87%	37%

ACT, asthma control test; PPV, positive predictive value; NPV, negative predictive value.

ROC Analyses

In ROC curve analyses, we determined cut-off values for ACT as 17.5 points and for total IgE as 80 IU/mL.Total IgE and ACT were the tools with highest sensitivity (72% and 70%, respectively), and SPT had the highest specificity (92%). While obstruction and reversibility had the highest positive predictive values with 88% for each, total IgE was the parameter with the highest negative predictive value of 57% (Figure 1, Table 2).

Patients who were misdiagnosed as asthma were referred to a psychiatrist. The patients were followed up for one year. Only seven of the patients who were misdiagnosed as inhalation needed to use an inhaler device.

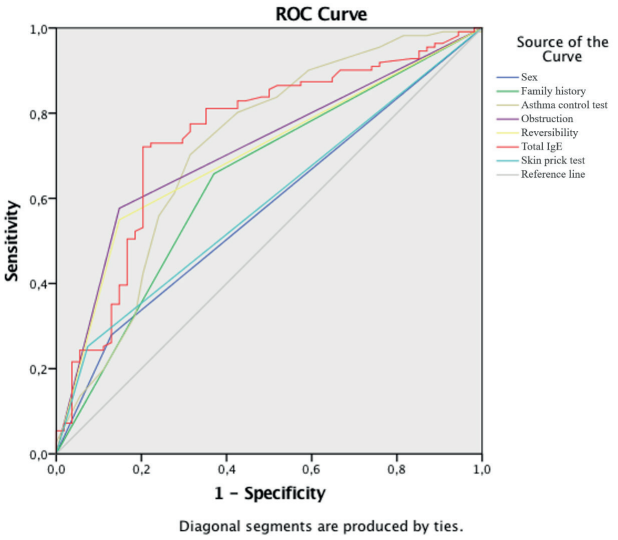

Figure 1: ROC curve analysis of sex, family history of asthma, ACT, obstruction, reversibility, total IgE, and skin prick test. AUCof sex: 575, p=0.1;AUC of family history:644, p=0.03;AUC of ACT: 719, p<0.001;AUC of obstruction: 714, p<0.001;AUC of reversibility: 701, p<0.001;AUC of total IgE: 748, p<0.001;AUC of skin prick test: 589, p=0.06. ACT, asthma control test; AUC, area under the curve.

DISCUSSION

We found that anxiety and depression patients were likely to be misdiagnosed as asthma. Although FEV1 and PEF values were similar in the study groups, the ACT measures of the well-being of patients with positive BDI/BAI values were lower. Thus, it can be suggested that the main cause of dyspnea was not due to loss of pulmonary function, but rather resulting from extrapulmonary factors. Consistently, our findings regarding obstruction, reversibility, prick test, total IgE levels, and family history were lower in the BDI/BAI positive group. These may suggest that asthma misdiagnosis occurs when dyspnea is prominent in patients with anxiety ordepression.

Asthma is a heterogeneous disease characterized by chronic airway inflammation associated with airway hypersensitivity to direct or indirect stimuli. It is characterized by respiratory symptoms such as wheezing, shortness of breath, chest tightness and/or cough, and limitation of expiratory airflow. Comorbidities also increase asthma-related symptoms while anxiety, depression, and panic attacks mimicasthma-like symptoms (1). In Canada, asthma was ruled out in 33% of people with physician-diagnosed asthma (21). There are many causes of misdiagnosis in asthma (22,23). Diagnosis of asthma is based on the combined presence of typical symptoms and objective tests of lung function. Objective diagnostic testing consists of two components: demonstration of airway obstruction and documentation of variability in degree of obstruction (1). As high as 30% of physician-diagnosed asthma that are based on symptoms may not be true asthma after measuring pulmonary function testing (11). In our study, obstruction and reversibility was present in 15% of patients in BDI/BAI(+) group while over half of those in BDI/BAI(-) group had evidence of obstruction and reversibility, which may re-emphasize the place of measuring pulmonary functions for the diagnosis of asthma.

Dyspnea originates from a variety of psychological, social, and environmental factors and may cause secondary physiological and behavioral responses (24). This creates a difficult environment to differentiate asthmatic symptoms from symptoms associated with psychological causes and diminishes the value of the control tests used in the follow-up of asthma patients (25,26). It was reported that even healthy individuals had respiratory complaints when they had psychological and mental disorders (anxiety, depression, fear, and cognitive impairment, etc.) (27). The relationship between asthma and anxiety/depression suggests that they usually coexist as comorbidities. Furthermore,they exhibit a vicious circle:anxiety and depression have a negative effect on asthma control test while asthma has a negative effect on anxiety/depression status. The quality of life and the ACT score of asthma patients improve with the treatment of anxiety/depression. Likewise, anxiety and depression are ameliorated in patients with adequate treatment of asthma (28-31). Consistently, mean ACT score was lower in depressed/anxious patients in our study, which might be attributed to the fact that dyspnea may result from extrapulmonary components. Contrary to all these studies, there are data suggesting that there is a weak correlation between asthma and ACT and it is not associated with anxiety/depression and mental health status (32,33).

Asthma is a heterogeneous disease, encompassing both atopic and non-atopic phenotypes. History of atopy in early life appears as one of the key factors of permanent asthma risk for affected individuals. In fact, numerous studies reported early and multiple sensitization to aeroallergens and some food antigens as a strong risk factor for the development of asthma. Atopic asthma is characterized by eosinophilic airway inflammation associated with IgE-mediated sensitization to various antigens, which could be verified by serology or SPT. A large population-based study in United States reported that 56.3% of asthma cases may be associated with atopy (34). Total IgE levels, SPT, and family history can be used to help diagnosis asthma. Consistently, these parameters were less common or lower in our patients with high BDI/BAI scores, which might support the fact that these patients were more likely to be

misdiagnosed as asthma.

In this study we have observed that the treatment success of accurately diagnosed asthma patients were higher compared to others. We also would like to state that the diagnosis should be supported by obstruction, reversibility test, serum total IgE level, family history, and SPT. Individuals with negative or low results in these parameters and ACT should be consulted for psychiatric problems. In fact, severe anxiety was reported to deteriorate the course of asthma and control of episodes (35).

Aaron et al. reported that 33% of patients did not need to use their asthma medication (23). Furthermore, Bryan Ng et al. emphasized that asthma was overdiagnosed with a consequent economic burden on the healthcare system in Canada (36). While we did not perform a pharmacoeconomic analysis, the fact almost one-third of our asthma patients had anxiety or depression may imply a substantial rate of asthma misdiagnosis, which could be potentially associated with unnecessary treatment expenditures and subsequent cost burden on the healthcare system.

There are certain limitations of this study. No asthma classification has been made regarding the severity of asthma in our patients. No bronchial provocation test and peak flow variability were performed in our patients. Subjects with anxiety or depression were included in the same group. Reactive airway dysfunction syndrome (RADS) was not considered in our article. Dyspnea isa subjective symptom and an objective evaluation could not be made.

In conclusion, we think that although asthma has been frequently reported as a concomittant disease with depression and anxiety, lack of analytical tests may contribute to the overrating of misdiagnosis. Dyspnea should be examined in detail by PFT, reversibility test, serum total IgE level, family history of asthma and SPT. The accuracy of the diagnosis of asthma should be re-evaluated in patients whose asthma cannot be controlled despite treatment, especially if the ACT is low.Since the pathogenesis of dyspnea in subjects with anxiety/ depression is different, they do not benefit from asthma treatmentwhich resultsin unnecessary drug use and medical costs. Psychological counselling may improve dyspnea-related complaints of asthma patients, who might be controlled with less medication. Asthma is diagnosed with clinical follow-up. Therefore, regular doctor control of patients is important. Further controlled studies are needed to clarify this subject.

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Ethics: This study was approved by the Dicle University Medical Faculty Non-Interventional Clinical Research Ethics Committee (Date: 20.09.2012, Number: 2012/206).

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