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RESEARCH ARTICLE
KLİNİK ÇALIŞMA

Asthma-like symptom or "cystic fibrosis asthma"?

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ABSTRACT

Asthma-like symptom or "cystic fibrosis asthma"?

Introduction: *The diagnosis of asthma is still a difficult problem in cystic fibrosis. There is no consensus on how to define "CF asthma". The aim of this study was to determine the role of bronchodilator response and laboratory evidence of allergy in "CF asthma".*

Materials and Methods: *Patients aged ≥6 years with evaluated bronchodilator response and characteristics of atopy were included in the study. Patients diagnosed with Allergic Bronchopulmonary Aspergillosis or pulmonary exacerbation were excluded.*

Results: *A total of 204 CF patients were evaluated, and 40 who met the criteria were included. Asthma had been diagnosed in ten patients. A positive bronchodilator response was present in 47.3% of the patients tested. Aeroallergen sensitization was present in 52.5% of the patients. While the frequency of recurrent/history of wheezing, family history of atopy and elevated total immunoglobulin E were similar (p> 0.05), the frequencies of inhaled medication use and coexistence of asthma were statistically higher in the group with positive allergen sensitization (p< 0.05). The frequencies of positive bronchodilator response (77.7% versus 37.9%) and a family history of asthma/atopy (40% versus. 23%) were found to be similar in CF asthma and CF. There were significant increases in total IgE and allergen-specific IgE and an increase in the frequency of aeroallergen sensitization in CF asthma compared to CF (p< 0.05).*

Conclusion: *Although not routinely used in the evaluation of patients, allergen specific-IgE and skin prick test for aeroallergen sensitization may be used as an adjunctive test in patients with suspected clinical findings. The recognition of CF asthma may facilitate the development of targeted therapies.*

Key words: *Cystic fibrosis; asthma; bronchodilator responsiveness; atopy*

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ÖZ

Astım benzeri semptom mu veya “kistik fibrozis astım” mı?

Giriş: *Kistik fibrozis hastalığında astım tanısının konulmasında hala sorunlar yaşanmaktadır. Kistik fibroziste astımın tanımlanmasına yönelik herhangi bir fikir birliği bulunmamaktadır. Çalışmamızda astım eşlik eden kistik fibrozis hastalarında bronkodilatör cevabının ve alerji açısından laboratuvar kanıtlarının rolünün belirlenmesi amaçlandı.*

Materyal ve Metod: *Çalışmaya altı yaşın üzerinde, bronkodilatör yanıtı ve atopi özellikleri değerlendirilmiş kistik fibrozis tanısı ile takip edilen hastalar dahil edildi. Alerjik Bronkopulmoner Aspergilloz ve pulmoner alevlenme tanısı alan hastalar çalışma dışı bırakıldı.*

Bulgular: *Toplam 204 hastanın dosyası incelendi. Kriterlere uyan 40 hastanın sonuçları değerlendirildi. On hastaya astım tanısı konulmuştu. Hastaların %47,3'ünde pozitif bronkodilatör yanıtı ve %52,5'inde aeroallerjen duyarlılığı bulunmaktaydı. Pozitif aeroalerjen duyarlılığı olan grupta astım birlikteliği ve inhalasyon ile ilaç kullanım sıklığı istatistiksel olarak yüksekken (p< 0,05), hışıltı/tekrarlayan hışıltı, ailede atopi ve IgE yüksekliği sıklığı her iki grupta benzer (p> 0,05) saptandı. Astım olan ve olmayan hasta gruplarında pozitif bronkodilatör cevabı (%77,7 ve %37,9) ve ailede astım/atopi sıklığı (%40 ve %23) benzer olarak belirlendi. Astım eşlik eden grupta, eşlik etmeyen grup ile karşılaştırıldığında IgE ve alerjen spesifik IgE yüksekliği ve aeroalerjen duyarlılığı sıklığı daha fazlaydı (p< 0,05).*

Sonuç: *Kistik fibrozis hastalarında rutin olarak kullanılmayan, alerjen spefisik IgE ve deri prick testi şüpheli klinik bulgulara sahip hastalarda yardımcı test olarak kullanılabilir. Bu hastalarda astımın tanınması, hedefe yönelik tedavilerin geliştirilmesini kolaylaştırabilir.*

Anahtar kelimeler: *Kistik fibrozis; astım; bronkodilatör cevabı; atopi*

INTRODUCTION

The diagnosis of asthma is still a problem in cystic fibrosis (CF). Asthma is a disease characterized by varying degrees of airway limitation due to chronic inflammation of the airways. Asthma, which is seen in 1-18% of people generally varying according to the population, is also seen in CF in this frequency range (1). There is no consensus on how to define CF asthma, which causes difficulties in the definition of asthma in CF.

Wheezing, shortness of breath, and cough are the main symptoms of asthma (2). The symptoms are unhelpful for defining CF asthma; however, as wheezing and cough are common findings in CF. Varying degrees of bronchodilator response is observed in approximately 40% of CF patients, whether they have CF asthma or not. In addition, reversible airway obstruction is not correlated with atopy in CF (3). There is little evidence of high incidence of atopy among asthmatic children, such as from positive allergen skin tests or family history of atopy in CF, when compared to non-asthmatic children. A strong family and personal history of atopy may help the diagnosis of CF asthma (4-6). Unfortunately, these criteria are often not useful. The diagnosis of CF asthma is mainly clinical.

The prevalence of asthma in CF patients, despite many studies, is still unknown due to the diagnostic difficulties. “CF asthma” was reported by the European Epidemiologic Registry of Cystic Fibrosis (ERCF) as a combination of asthma-like symptoms and bronchial hyperreactivity (7). In the North American Epidemiologic Study of Cystic Fibrosis (ESCF), asthma diagnosis is suggested by the following: episodes of acute airway obstruction reversed by bronchodilators, a strong family history of asthma and/or evidence of atopy, or laboratory evidence of allergy. In line with these recommendations, the aim of this study was to determine the role of bronchodilator response and aeroallergen sensitization in CF asthma. The recognition of CF asthma may facilitate the development of targeted therapies.

MATERIALS and METHODS

Study Design

This was a cross-sectional retrospective study. Patients with CF followed up in our department between 2016 and 2019 were evaluated. The study was approved by the local ethics committee (19.9.1T/3). The diagnosis of CF was established according to either a sweat chloride level of >60 mmol/L or a known genotype and compatible symptoms. CF asthma was diagnosed by the combination of asthma-like symptoms and episodes of acute airway obstruction reversed by bronchodilators, a strong family history of asthma and/or evidence of atopy, or laboratory evidence of allergy.

Inclusion Criteria

In our unit, patients are routinely evaluated annually for CF complications. Bronchodilator response and

total immunoglobulin E (IgE) are examined, and patients with eosinophilia, positive bronchodilator response and elevated total IgE are evaluated for accompanying atopy with allergen-specific IgE and skin prick test (SPT).

Patients aged ≥6 years with evaluated bronchodilator response and characteristics of atopy were included in the study. The data collected from each patient included 1) recurrent wheezing and history of wheezing, 2) family history of asthma and/or atopy, 3) laboratory tests for allergy (eosinophil count, total IgE and allergen-specific IgE), and 4) aeroallergen sensitization, at the time of selected inclusion criteria.

Exclusion Criteria

Patients were excluded with decreased pulmonary function tests (PFTs) (decreased forced expiratory volume in one second [FEV_1] and forced vital capacity [FVC] >10%), symptoms suggestive of acute pulmonary exacerbation (new or increased productive cough, changes in sputum, hemoptysis, dyspnea, chest pain, fever, weight loss, fatigue, loss of appetite, etc.), physical examination findings (changes in auscultation or new additional sounds), and/or new changes in chest X-ray and along with patients diagnosed with Allergic Bronchopulmonary Aspergillosis (ABPA).

Pulmonary Function Tests

FVC and flow rates were measured by spirometry (Flowhandy ZAN100, Germany) according to the criteria of the American Thoracic Society (ATS) (8). In our unit, PFTs are repeated 15-20 minutes after inhalation of short-acting bronchodilator (200 µg salbutamol) to evaluate bronchodilator response in stable patients with newly developed airway obstruction. Laboratory protocol for evaluating the response to bronchodilator required at least six hours after short-acting beta-agonist (SABA) and at least 24 hours after long-acting beta-agonist (LABA) or combined LABA-inhaled corticosteroid (ICS) inhalation.

Definitions

A positive bronchodilator response was defined as an increase of ≥12% for change in FEV_1 and an increase of ≥25% for change in flow rate in the middle of forced expiration (FEF_{25-75}) (9). ABPA is defined in accordance with the "CF Foundation"s consensus criteria (10).

Laboratory and Immunological Evaluation

Total IgE was measured by radioimmunoassay, with results expressed as kU/L and taking a normal range as <100 kU/L. Allergen-specific IgE was determined by radioallergosorbent test (RAST) to environmental aeroallergens: grass pollens (Anthoxanthum odoratum, Lolium perenne, Phleum pretense, Secale cerale, Holcus lanatus), tree pollens (Alnus incana, Betula verrucose, Corylus avellane, Quercus alba, Sallix caprea), weed pollens (*Artemisia vulgaris*, *Plantago lanceolate*, *Chenopodium album*, *Solidago virgaurea*, *Urtica dioica*), molds (*Penicillium notatum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Alternaria alternata*), mite (*Dermatophagoides pteronyssinus*), and cat, horse, and dog epithelium. Aspergillus-specific IgE was measured by ImmunoCap method. Skin prick test (SPT) was applied for 38 environmental aeroallergens, including house-dust mites, animal epithelium, grasses, weeds, trees, and molds. The tests were performed as previously described (11).

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences Statistics Package V.20.0. The Shapiro-Wilk test was used to test the normality of data distribution. Continuous variables are presented as mean ± SD and median (minimum-maximum). Categorical variables are presented as percentages. Pearson chi-square and Fisher's exact chi-square test were used for categorical data. Two independent samples t-test and Mann-Whitney U test were used for group comparisons. Statistical significance was accepted as $p< 0.05$.

RESULTS

Of the 204 evaluated CF patients, five patients had ABPA. Twenty-two patients with positive bronchodilator response were excluded because of acute exacerbation. Forty patients who met the criteria were included in the study. Mean age was 145.5 ± 51.9 months, 22 (55%) were males. Characteristics of the study population are shown in Table 1.

Thirty-two patients had recurrent wheezing and history of wheezing. Nasal polyps were detected in 8 of 11 patients with rhinitis symptoms. Family history of atopy was present in 11 patients (27.5%). Elevated IgE was detected in 20 (50%) patients and elevated allergen-specific IgE in 12 (30%). Inhaled medication was used by 11 patients. The most common positive

Table 1. Patient characteristics

	n= 40
Age, months (mean ± SD)	145.5 ± 51.9 (72-276)*
Sex	
F/M	18/22
Mutation (%)	
F508del homozygous	7 (17.5)
F508del heterozygous	12 (30)
Other mutations	21 (52.5)
Colonization %	29 (72.5)
Microorganism	
Staphylococcus aureus	19
Pseudomonas aeruginosa	22
Aspergillus spp.	6
Others**	2

* Minimum-maximum
**Others; *Escherichia coli, Stenotrophomonas maltophilia, Haemophilus* influenzae type b

allergens in SPTs were molds (n= 12, 30%), grasses pollens (n= 9, 22.5%) and house-dust mites (n= 8, 20%). Atopy characteristics, laboratory findings, and aeroallergen sensitizations of the patients are shown in Table 2.

Bronchodilator response was evaluated in 38 patients and found to be positive in 47.3%. The mean age of the patients with positive and negative bronchodilator response was similar (p> 0.05). PFTs were significantly lower in the group with positive bronchodilator response (mean FEV_1 61.3 ± 21.2% versus. 74.5 ± 18.1%, p= 0.04 and mean FEF_{25-75} 50.1 ± 26.8% versus. 75.6 ± 35.4%, p 0.01). There was no significant difference between the mean eosinophil count and median total IgE of the two groups (p> 0.05). The frequency of recurrent/history of wheezing and family history of atopy were similar in patients with positive and negative bronchodilator response (p> 0.05). No significant difference was found between the two groups for the ratio of patients with the elevated IgE and the elevated allergen-specific IgE (p> 0.05). The frequency of positive SPT was also similar in both groups (Figure 1). In 38.8% of patients with positive bronchodilator response and in 10% of patients with negative bronchodilator response, inhaled medication was used. There was no significant difference between the two groups in terms of inhaled medication use (p> 0.065). Although the coexistence of asthma was higher in the group with positive bronchodilator response (38.8% versus 10%), the difference was not statistically significant (p> 0.05) (Table 3).

Table 2. Atopy characteristics, laboratory data and aeroallergen sensitization of the patients

	n= 40
Symptoms, n (%)	
Rhinitis	11 (27.5)
Wheezing	32 (80)
Ages	7 (17.5)
3-6 ages	11 (27.5)
>6 ages	4 (10)
Persistent	10 (25)
Nasal polyps, n (%)	8 (20)
Family history of atopy, n (%)	
+/-	11 (27.5)/29 (72.5)
Laboratory	
Eosinophils/µl*	175 (20-690)
Elevated IgE, n (%)	20 (50)
IgE, kU/L*	94.4 (2.4/2499)
Elevated allergen-specific IgE, n (%)	12 (30)
Aspergillus specific-IgE, n (%)	13 (32.5)
Aeroallergen sensitizations, n (%)	21 (52.5)
Mites, n	8
Animal epithelium, n	3
Grass pollens, n	9
Weed pollens, n	2
Tree pollens, n	6
Molds, n	12
Aspergillus fumigatus	12
Others+	6
Monosensitization, n (%)	14 (66.6)
Polysensitization, n (%)	7 (33.3)
Medications, n (%)	11 (27.5)
β2-agonist	3
ICS	3
LABA+ICS	5

*Median (minimum-maximum). +Others; *Alternaria alternata, Cladosporium herbarum, Penicillium notatum*.
Polysensitization; defined as more than one kind of allergen sensitization.
ICS: Inhaled corticosteroid, LABA: Long-acting beta-agonist.

Aeroallergen sensitization was present in 21 of the 40 (52.5%) patients. When the groups with and without aeroallergen sensitization were compared, the mean ages of patients were found to be similar (p> 0.05). Eosinophil counts, total IgE levels, and the frequency of elevated allergen-specific IgE were significantly higher in the group with positive aeroallergen sensitization (p< 0.05). PFTs, the frequency of positive bronchodilator response, and presence of microorganism colonization were similar in both groups (p>

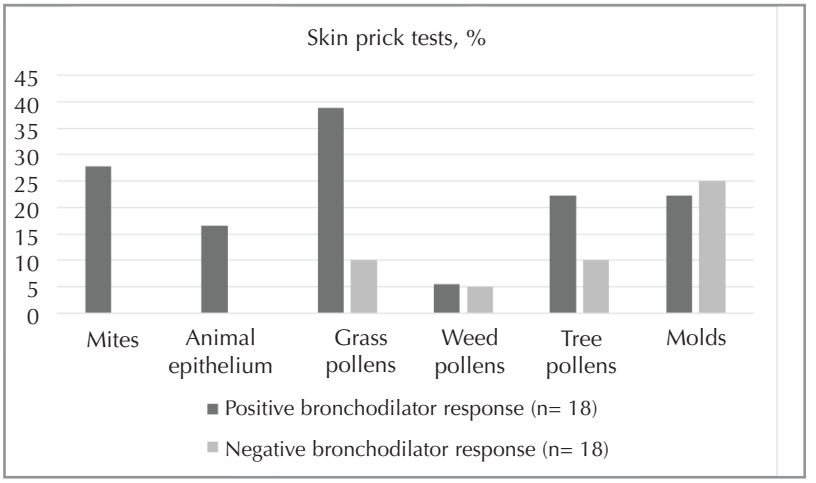

Figure 1. Frequency of aeroallergen sensitivity by skin prick test in cystic fibrosis with positive and negative bronchodilator response.

0.05). While the frequency of recurrent/history of wheezing, family history of atopy, and elevated total IgE were similar (p> 0.05), the frequency of inhaled medication use and coexistence of asthma were higher in the group with positive allergen sensitization (p> 0.05) (Table 3).

Asthma had been diagnosed in 10 patients. When the patients were divided into two groups, as CF with asthma (CF asthma) and without asthma (CF), no significant difference between them was found in terms of age, eosinophil counts, and PFTs (p> 0.05). Total IgEs in the CF asthma group (median 229.5 kU/L) were significantly higher than those without asthma (median 80.5 kU/L) (p< 0.05). The frequency of recurrent/history of wheezing, family history of atopy, and elevated total IgEs was similar in both groups (p> 0.05). Aeroallergen sensitization was present in all CF asthma patients and 36.6% of just CF (Figure 2). Allergen-specific IgE was positive in all CF asthma patients, and there was a statistically significant difference between the two groups (100% versus 6%) (p< 0.05). The frequencies of patients with positive bronchodilator responsiveness and patients with colonized microorganisms was similar in both groups. The use of inhaled medication was significantly higher in the CF asthma group (p< 0.05) (Table 4).

DISCUSSION

In this study, a positive bronchodilator response and a family history of asthma/atopy, which is frequently emphasized in the literature and indicated to be a guide in the diagnosis of asthma in CF patients, were found to be similar in CF patients with and without asthma. There was a statistically significant increase in total IgE and allergen-specific IgE and an increase in the frequency of aeroallergen sensitization in CF to be diagnosed with asthma. Elevated total IgE was present in 50% of patients without asthma, which was similar in both groups. With these results, elevated total IgE was thought that to be a helpful marker in asthma diagnosis, although insufficient alone. The eosinophil count was high in CF asthma, but there was no significant difference between the two groups. Also, similar to other studies, the frequency of recurrent wheezing/history of wheezing and PFTs in the two groups were similar. Inhaled medication was more frequent in the presence of aeroallergen sensitization.

Although neutrophil-dominated, airway inflammation in CF has a mixed pattern, Th2-rich inflammation and tumor necrosis factor α (TNFα), interleukin-8 and interleukin-13 mediated inflammation in CF is responsible for increased airway smooth muscle contractility and increased smooth muscle mass. Ion transport deficiency due to CF transmembrane conductance regulator (CFTR) defect and inflammation in this mixed pattern are thought to cause asthma-like symptoms in CF patients (12). In this interplay of factor, asthma-associated mediators are difficult to detect and differentiate from CF-associated inflammation. There are still no gold standard criteria for the diagnosis of asthma in CF patients.

Table 3. Bronchodilator response and aeroallergen sensitization

	$\Delta FEV_1 \geq \%12$ $\Delta FEF_{25-75} \geq \%25$ (n= 18)	$\Delta FEV_1 < \%12$ $\Delta FEF_{25-75} < \%25$ (n= 20)	p	Positive aeroallergen sensitization (n= 21)	Negative aeroallergen sensitization (n= 19)	p
Ages, months (mean ± SD)	150.5 ± 49.7	148.4 ± 52.2	0.89	139.23 ± 46.27	152.52 ± 58.14	0.42
Eosinophils/µl (mean ± SD)	204 ± 162	171 ± 105	0.46	251 ± 157	136 ± 93	<0.001
Total IgE, kU/L*, (median (minimum - maximum))	146.5 (2.4/2499)	80 (2.4/635)	0.18	295.9 (2.4/2499)	87.9 (2.4/635)	<0.001
Pulmonary function test +, % (mean ± SD)						
FEV_1	61.3 ± 21.2	74.5 ± 18.1	0.04	64.6 ± 20.4	71.8 ± 20.5	0.28
FVC	62.6 ± 18.8	72.1 ± 17.2	0.11	63.0 ± 18.3	71.4 ± 18.1	0.20
PEF	68.0 ± 20.7	76.3 ± 17.1	0.18	70.5 ± 18.9	74.6 ± 19.5	0.46
FEF_{25-75}	50.1 ± 26.8	75.6 ± 35.4	0.01	55.8 ± 25.5	71.1 ± 39.6	0.16
n (%)						
Recurrent/ history of wheezing	14 (77)	16 (80)	0.58	19 (90.5)	13 (68.4)	0.12
Family history of atopy	4 (22.2)	6 (30)	0.43	7 (33.3)	4 (21.1)	0.48
Elevated IgE	11 (61.1)	8 (40)	0.33	13 (61.9)	7 (36.8)	0.20
Elevated allergen-specific IgE	8 (44.4)	3 (15)	0.07	12 (57.1)	0 (0)	<0.001
Aeroallergen sensitization	11 (61.1)	8 (40)	0.16	-	-	-
Positive bronchodilator responsiveness	-	-	-	11 (57.8)	7 (36.8)	0.33
Colonization of microorganisms	14 (77)	15 (75)	0.57	15 (71.4)	14 (73.7)	0.57
Pseudomonas aeruginosa	9 (50)	12 (60)	0.38	12 (57.1)	9 (47.4)	0.75
Inhaled medication	7 (38.8)	2 (10)	0.06	9 (42.9)	2 (10.5)	0.03
Asthma	7 (38.8)	2 (10)	0.06	10 (47.6)	0 (0)	0.01

*Mann-Whitney U test.

+ Positive aeroallergen sensitization n= 19, negative aeroallergen sensitization n= 19.

FEV_1: Forced expiratory volume in one second, FVC: Forced vital capacity, PEF: Peak expiratory flow, FEF_{25-75}: Forced expiratory flow during the middle half of FVC.

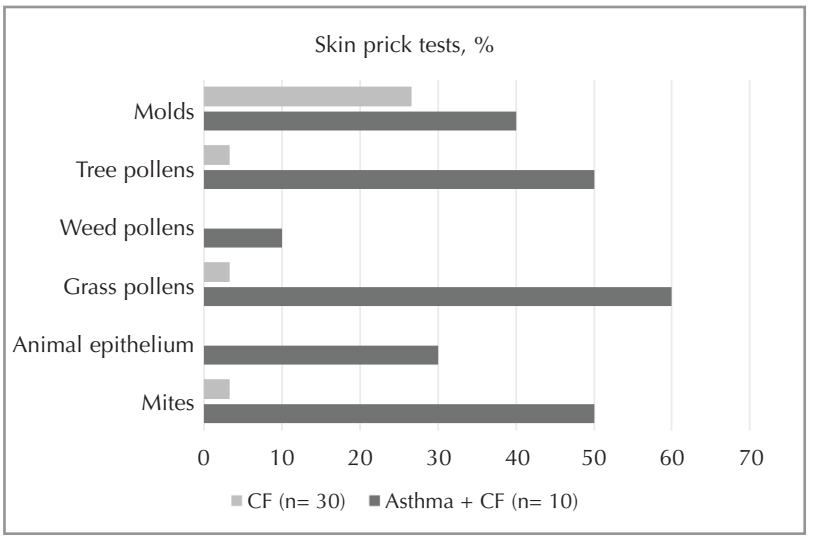

Figure 2. Frequency of aeroallergen sensitization by skin prick test in cystic fibrosis with and without asthma.

Table 4. Comparison of CF and Asthma + CF

	CF + Asthma (n= 10)	CF (n= 30)	p
Ages, months (mean ± SD)	153.60 ± 47.93	142.86 ± 53.78	0.57
Eosinophils/µl (mean ± SD)	288 ± 192	166 ± 108	0.08
Total IgE, kU/L*, (median (minimum - maximum))	229.5 (48.2/2499)	80.5 (2.4/635)	<0.001
Pulmonary function test +, % (mean ± SD)			
FEV_1	62.6 ± 19.0	70.0 ± 20.9	0.35
FVC	63.0 ± 15.7	69.0 ± 19.1	0.39
PEF	66.3 ± 17.8	74.2 ± 19.4	0.28
FEF_{25-75}	51.2 ± 24.2	67.3 ± 35.7	0.21
n (%)			
Recurrent/ history of wheezing	10 (100)	22 (68.7)	0.07
Family history of atopy	4 (40)	7 (23.3)	0.26
Elevated IgE	8 (80)	12 (40)	0.06
Elevated allergen-specific IgE	10 (100)	2 (6)	<0.001
Aeroallergen sensitization	10 (100)	11 (36.6)	<0.001
Positive bronchodilator responsiveness	7 (77.7)	11 (37.9)	0.06
Colonization of microorganisms	6 (60)	23 (76.6)	0.19
Pseudomonas aeruginosa	5 (50)	16 (53.3)	0.57
Inhaled medication	6 (60)	5 (16.6)	0.01

*Mann-Whitney U test.

+CF + Asthma n= 9, CF n= 29.

FEV_1: Forced expiratory volume in one second, FVC: Forced vital capacity, PEF: Peak expiratory flow, FEF_{25-75}: Forced expiratory flow during the middle half of FVC.

Reversible airway obstruction is a frequently used method in the diagnosis of asthma in children. Airway edema due to chronic inflammation, airway collapse, smooth muscle contraction due to mediators released by infection and chronic inflammation, and bronchiectasis may all cause various degrees of airway obstruction in CF (13). Several studies have shown that 50-60% of CF patients have reversible airway obstruction after bronchodilator inhalation (13-16). Reversible airway obstruction has been shown to be common but not associated with asthma characteristics (family history of asthma, serum IgE,

blood eosinophils) in adult CF patients (3). Among pediatric patients, no correlation was found between bronchodilator response and atopy (17). Contrary to other studies, Ormerod et al. (18) have emphasized that all patients with significant airway obstruction were atopic. In this study, a positive bronchodilator response was present in 47.3% of the patients. No increased prevalence of laboratory evidence of atopy and a or family history of asthma/atopy in those with positive reversible airway obstruction was found. In contrast to studies showing reversible airway obstruction to be associated with younger age, mean ages of the patients with positive and negative bronchodilator responses were similar (3). Mean FEV_1 and FEF_{25-75} were significantly lower in the group with positive bronchodilator response than the one with negative bronchodilator response (mean FEV_1 61.3 ± 21.2% versus 74.5 ± 18.1%, mean FEF_{25-75} 50.1 ± 26.8% versus 75.6 ± 35.4%), while the use of inhaled medication (38.8% and 10%, respectively) was similar. Lower PFTs and positive bronchodilator response may lead to an increase in the use of inhaled medication by clinicians. Many centers use response to inhaled medication as a criterion for diagnosis because of the difficulties in diagnosing CF asthma. In a study with 48 pediatric patients, bronchodilator response has been found to be positive in 29% of the patients, where SPT was positive in all patients. Although PFTs of the patients with positive and negative bronchodilator responses were similar, PFT improvement was observed with treatment in patients without a history of atopy but with significant reversibility in the test (18). The determination of patients with positive bronchodilator response who should receive treatment is still controversial. In this study, although bronchodilator response was not significant in the diagnosis of asthma, it is suggested that asthma may accompany patients with seasonal worsening of symptoms and PFTs.

Allergen sensitization mediated by multiple mechanisms may be seen in patients with CF. These mechanisms include increased permeability due to bronchial epithelial barrier dysfunction, cilia dysfunction and inability to remove antigens due to mucus hypersecretion, and defect in secretory IgA. All these mechanisms cause allergen accumulation in the respiratory tract and sensitization (19-21). Studies in pediatric patients have been shown sensitization to house-dust mites to be the most common (22,23). The most common allergen sensitization in this study was against molds, grass pollens, and house-dust mites. In 66.6% of our patients with aeroallergen sensitization, monosensitization (most common molds and house-dust mites) and in 33.3% polysensitization (most common grass pollens and tree pollens) were detected. Three monosensitized patients with house-dust mites and seven patients with polysensitization were diagnosed with asthma. The rate of allergy to *Aspergillus* (30%) in this study was similar that reported in studies of children and adolescents with CF (22,24). No patients diagnosed as asthma had only *Aspergillus* sensitization. The presence of *Aspergillus* sensitization alone does not always indicate atopy. Therefore, screening is not recommended for these patients (5). The presence of allergy may contribute to airway inflammation and be associated with lower pulmonary function and increased pulmonary exacerbation in CF (6). In this study, aeroallergen sensitization was found to be positive in 50% of the patients who underwent PFTs. Mean FEV_1 was 64.68 ± 20.45%, FVC 63.78 ± 18.31%, PEF 70.05 ± 18.98% and FEF_{25-75} 55.89 ± 25.58% in patients with positive aeroallergen sensitization. In the group with negative aeroallergen sensitization, the mean FEV_1 was 71.84 ± 20.50%, FVC 71.42 ± 18.17%, PEF 74.68 ± 19.55% and FEF_{25-75} 71.15 ± 39.66%. There was no statistically significant difference between the two groups in terms of PFTs ($p > 0.05$). Thus, this study suggests that lung function is not altered by the presence of allergy in CF. However, the sample was not large enough to adequately adjust for factors such as age, presence of bronchodilator response, genotype, or use of medications that could confound the relationship between allergy and lung function in CF.

There are three different theories for total IgE elevation in CF: persistent antigenic stimulation from the respiratory tract, Pseudomonas colonization, and recurrent pulmonary infection. Recurrent pulmonary infections are thought to affect allergen sensitization (6,21). In addition, Th2-mediated inflammation of the respiratory tract has been found to be higher in chronic Pseudomonas infection, which may a risk factor for atopy (25). In this study, while the frequency of microorganism colonization was similar in the CF asthma and CF groups, total IgE was found to be significantly higher in the group with asthma. There was no statistically significant difference between the groups for Pseudomonas colonization, which was found in 50% of the CF asthma group and 53% of the

CF. A similar age, frequency of colonization, and PFTs suggest that total IgE in CF asthma may be due to atopy. However, the similar frequency of elevated total IgE in the CF asthma and CF groups suggests that it can be used as an adjunct test in the diagnosis of CF asthma. Elevated allergen-specific IgE was found to be statistically significant higher in CF asthma. Allergen-specific IgE may be more sensitive to atopy in CF asthma than elevated total IgE. Although not routinely used in the evaluation of patients, therefore, specific IgE may be used as an adjunctive test in patients with suspected clinical findings, family history of atopy, and or seasonal bronchodilator response.

There were several limitations in the study. One was bronchial-hyperresponsiveness (BHR), which has been reported more frequently in cases with a history of atopy and aeroallergen sensitization. BHR was not evaluated here because it is not preferred for the diagnosis of asthma in pediatric patients in routine practice. The retrospective design of the study precluded, monitoring of seasonal worsening in symptoms and signs and change in PFTs. The small sample size of the study prevented the examination of additional factors, such as treatment choice and treatment response, differential diagnosis, and non-atopic asthma, which may affect the asthma relationship in CF.

According to the results of this study and the others in the literature, there are not enough data to diagnose CF asthma; however, there are clues to suggest suspicion of asthma. In this study, only laboratory evidence of allergy (allergen-specific-IgE and aeroallergen sensitization) as listed among the North American ESCF asthma diagnostic criteria was found to be significantly higher in patients with asthma. The presence of symptoms and signs for asthma diagnosis in the natural course of CF disease, a positive bronchodilator response, and the lack of a family history for atopy all indicate that further studies are needed for asthma in CF patients. The diagnosis and treatment strategies of CF asthma in childhood is a topic that needs to be re-examined with the development of new treatments in CF patients.

Ethical Committee Approval: The study was approved by the Clinical Research Ethics Committee of Ege University Faculty of Medicine (19.9.1T/3 and 25.09.2019).

CONFLICT of INTEREST

The authors of this meta-analysis declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: GKÖ, AE, ED, FG

Analysis/Interpretation: GKÖ, AE, ED, FG

Data Acqusition: GKÖ, AE, FG

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Clinical Revision: GKÖ, AE, ED, FG

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