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The Importance of Aeroallergen Sensitivity in Children with Cystic Fibrosis

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Abstract

Background: Cystic fibrosis (CF) is an inherited autosomal recessive disorder that causes chronic airway disease. In addition to genetic factors, environmental factors may affects the clinical phenotype of CF. In our study, the presence of aeroallergen sensitivity in our patients with CF and its effects on clinical findings were evaluated. Materials and Methods: Demographic characteristics, clinical and laboratory findings, skin prick test (SPT) results, and Modified Shwachman-Kulczycki (MSK) scores of patients diagnosed with CF followed in the Pediatric Respiratory and Allergy Clinic of Dokuz Eylul University Faculty of Medicine were evaluated. Results: We evaluated 51 patients with CF with a median age of 10 (6-18) years. The mean MSK score of the patients was 72.54±11.50, and the mean predictive value of forced expiratory volume (FEV1) in the first second of 41 patients was 80.43±19.50. According to SPT, aeroallergen sensitivity was detected in 17 (33.3%). The frequency of bacterial colonization and bronchiectasis was higher, MSK scores were lower in AF-sensitive patients (p[?]0.01). However, there was no similar difference in other allergen sensitivities. MSK scores and predictive FEV1 values of 25 (49%) patients with bacterial colonization were significantly lower than those without colonization (p=0.001, p=0.005, respectively). Conclusion: Aeroallergen sensitivity was detected in approximately 1/3 of CF patients. Although it has been emphasized in studies that environmental factors may have an impact on lung functions and clinical conditions in CF, the effect of allergens other than AF sensitivity may be less important compared to other environmental factors such as the presence of bacterial colonization.
Keywords: Cystic fibrosis, atopy, children, asthma, Aspergillus fumigatus, Pseudomonas aeruginosa

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive inherited disease that may damage the lungs caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[1]Another prevalent chronic childhood lung disease is asthma.[2] The fact that the clinical manifestations in patients with asthma and CF are similar, may be associated with difficulties in differential diagnosis and treatment.[3-5] It was reported for both the diseases that genetic factors and environmental factors, including infections and allergens, affected the lung function of the patients.[3,6] Relevant studies suggested that, in CF, allergens may invade the respiratory epithelium as a result of inflammation due to infections, allergic inflammation may cause the patients predisposed to colonization of pathogens, and CFTR mutations may turn individuals susceptible to atopy.[3,7] The most commonly reported allergen susceptibility among CF patients was associated with mold, and especially *Aspergillus fumigatus* (AF). AF may induce an allergic reaction, including allergic bronchopulmonary

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aspergillosis (ABPA).[8] Due to difficulties in differential diagnosis regarding asthma and/or special conditions, including comorbid ABPA, the asthma-specific treatments such as corticosteroids and omalizumab can be used in patients with CF.[3-5]

Allergen susceptibility and the prevalence of allergic diseases are increasing across the world.[9] Nevertheless, there are only a limited number of studies, which investigated the allergen susceptibility in patients with CF. Furthermore, the previous studies provide inconsistent reports with regard to the relationships between atopy and lung function.[6,10] Accordingly, this study aimed to investigate the prevalence of aeroallergen susceptibility in patients followed-up with a CF diagnosis in our clinic and to investigate the relationship between atopy and CF upon examination of clinical and laboratory findings in susceptible patients.

MATERIALS AND METHODS

The patients, who met the CF diagnostic criteria, followed up at the Department of Pediatric Respiratory and Allergy Department, Dokuz Eylül University (DEU) Hospital, between June 2019 and July 2020 were identified.[11] Patients aged between 6 and 18 years, who attended to control examinations at least 4 times a year, diagnosed with CF, and underwent a skin prick test (SPT) were included in the study.

The above skin prick test (SPT) included pollens (Grasses, Artemisia vulgaris, Alnus glutinosa, Populus alba, Betula, Fagus silvatica, Parietaria officinalis, Olea europaea); house dust mites (Dermatophagoides pteronysinus, Dermatophagoides farinae); animal epithelium (Felis domesticus, Canis familiaris, Blatella germanica); fungi (Alternaria alternata, Cladosporium herbarum, Aspergillus fumigatus) commercial extracts Alk-Abello®, Hørsholm, Denmark) . An induration diameter of 3 mm or above was considered positive for the purposes of SPT.

The demographic characteristics, CFTR gene mutations, medications in use, Total IgE, and blood eosinophil levels were retrieved from the file records of the patients. An eosinophil level of [?]470/uL were considered eosinophilia, where Total IgE of [?]77.7 IU/ml were considered high.[12,13]

The modified Shwachman-Kulczycki (MSK) score was used to rate the general activity, physical examination, nutritional status, and radiological findings of the patients based on a 0-25 point scale for each of the subdomains.[14,15] Accordingly, the patients were classified as excellent (86-100), good (71-85), average (56-70), poor (41-55) and severe (<40) based on the disease severity group. The patients were divided into 2 groups, including those with a MSK score of >70 and those with a MSK score of [?]70, which were simultaneously rated with SPT.

The spirometry analysis results of the patients, including the forced expiratory volume in 1 second (FEV_1) predicted values, forced vital capacity (FVC) values, and FEV_1/FVC ratio during their latest presentation were recorded. Spirometry reference values were based on NHANES III, Hankinson et al., and Wang et al.[16,17]

Phlegm cultures collected from the patients were examined. Chronic infection was investigated for *Pseudomonas aeruginosa* (Pa),*Staphylococcus aureus* (Sa), *Burkholderia cepacia complex*(Bcc), Atypical mycobacteria (Amb), *Aspergillus fumigatus* (AF),*Stenotrophomonas maltophilia* (Sm), *Escherichia coli* (Ec),*Haemophilus influenzae* (Hi) and *Klebsiella pneumoniae* (Kp) microorganisms. In cases where the same microorganism was detected in 2 or more samples in at least 4 samplings during the last year, this was considered a chronic infection of the microorganism.[18]

Patients were divided into classes based on the estimated mutation effect on CFTR function.[19] The 'minimal' function was defined as only the existence of class I, II or III mutations, while the 'Residual' function was defined as the existence of at least one mutation from Class IV or V. In case of at least 1 unknown mutation in the patients, these were classified as unclassified genotypes.

Allergic Bronchopulmonary Aspergillosis (ABPA) diagnosis was made pursuant to the Agarwall et al. criteria.[20]

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Allergic rhinitis (AR) was clinically diagnosed based on the presence of symptoms, including rhinorrhea, nasal congestion, nasal itching, and sneezing pursuant to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines.[21]

The patients were classified in accordance with their body mass index (BMI) during their most recent presentation as severely underweight (BMI)<16.5), underweight (BMI<18.5), normal weight (BMI=18.5–24.9,) overweight (BMI[?]25), and obese (BMI[?]30).[22] Patients were divided into 2 groups including patients with a BMI of <18.5 and with a BMI of [?]18.5 according to their respective BMI.

Ethics Committee

The required ethics committee approval for this study was obtained from the Local Ethics Committee of Dokuz Eylul University, School of Medicine (Approval number: 2020/21-28).

Statistical Analyses

The normality hypothesis was tested by Kolmogorov Smirnov test to decide the statistical methods to be used. The non-parametric test methods were used in case any of the groups did not meet the assumption of normality. Accordingly, the Mann-Whitney U test or Student's t-test was used in comparison of the variables obtained upon measurement in two independent groups, where the Chi-squared and Fisher exact tests were used in the analysis of the relationships between categorical variables or differences intergroup between. Pearson Correlation Test analysis was used to investigate the possible relationship between MSK scores, FEV_1 predictive value and age, Total IgE level, Absolute eosinophil count (AEC), and BMI. Statistical analyses of the study were conducted using the IBM Statistical Package for the Social Sciences (SPSS) for Windows, Version 25 and a p value of [?] 0.05 was considered statistically significant.

RESULTS

27 (52.9%) out of 51 patients included in this study were male and the median age was 10 years (min-max: 6-18 years), where the median age of CF diagnosis was 4 months (min-max:1-55 months). Minimal function and residual function CFTR gene mutations were detected in 15 (29.4%) and 16 (31.4%) patients, respectively. Identified in ten patients (19.6%), the Delta F508 mutation was the most prevalent gene mutation. 25 (49%) of the patients had bacterial colonization. Spirometry analysis could not be performed in 10 patients, who were not suitable for the procedure. The FEV_1 predicted value was [?]80% in 19 (46.34%), 60-80% in 16 (39.02%), and <60% in 6 (14.63%) patients out of 41 patients. Only 5 (12.19%) patients had early reversibility upon spirometry analysis. The MSK score regarding the severity of the disease was excellent in 7 (13.7%), good in 18 (35.3%), average in 20 (39.2%), and severe in 6 patients (11.8%). As regards the BMI, 20 (39.2%) patients were severely underweight, 16 (31.4%) were underweight, 12 (23.5%) were normal, and 3 (5.9%) were overweight. The 1st degree relatives of six patients (11.8%) had a remarkable history of atopic disease. There were elevated Total IgE and eosinophilia in 19 (37.3%) and 15 (29.4%) patients, respectively (Table 1).

17 (33.3%) patients had allergen susceptibility according to the SPT results. The most prevalent susceptibility were identified against fungi, 10 (19.6%); pollen, 8 (15.7%); animals, 5 (9.8%); and house dust mites, 4 (7.8%), respectively. AF was the most prevalent allergen with a rate of 17.6% (n=9). Three (5.9%) patients had ABPA.

Patients with allergen susceptibility based on the SPT results, had higher Total IgE levels and higher prevalence of eosinophilia ($p<0.001$, $p=0.011$, respectively). These patients more frequently used inhaled corticosteroids (ICS) and short acting beta agonists (SABA) ($p<0.01$). There was no difference between allergen susceptibility and genetic disorder, familial history of atopy, bacterial colonization, spirometry results, MSK scores, BMI, and bronchiectasis ($p>0.05$). The patients susceptible to AF had higher Total IgE levels and more prevalent eosinophilia ($p=0.001$, $p=0.030$, respectively). The prevalence of bacterial colonization and bronchiectasis was higher, and the MSK scores were lower ($p=0.010$, $p=0.001$, $p=0.007$, respectively). Similar differences were not identified in patients with pollen, house dust mite, and animal epithelial susceptibility ($p<0.05$) (Table 2).

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Ten (19.60%) patients had Allergic rhinitis (AR). There was no difference between the patients with and without AR by age (p=0.526), gender (p=0.835), genetic disorder (p=0.364), MSK score (p=0.298), FEV_1 predicted value (p=0.270), Total IgE level (p=0.286), and AEC (p=0.116).

The most prevalent bacterial colonization cases include *Pseudomonas aeruginosa* in 17 (33.3%) patients and *Staphylococcus aureus* in 11 (21.6%) patients. These patients had significantly higher rates of bronchiectasis compared to non-colonized (NC) patients (p= 0.043, p=0.001, respectively). Patients colonized with Pa had higher rates of positive SPT and AF susceptibility compared to the non-colonized patients (p=0.036, p=0.004, respectively). However, there was no similar difference with Sa colonization (p=1,000, p=0.385, respectively).

There was no difference between the patients' FEV_1 predicted values and the genetic disorders and positive SPT results (p>0.05). Nevertheless, the FEV_1 predicted value was lower in patients with bacterial colonization, comorbid bronchiectasis, without elevated Total IgE, and with lower BMI (p<0.05) (Table 3).

There was no relationship between the patients' genetic disorders and MSK scores, bacterial colonization, bronchiectasis, Total IgE level, AEC, and BMI (p=0.142; p=0.259; p=0.121; p=0.424; p=0.344; p=0.780, respectively). Bronchiectasis was more prevalent in patients with Delta F508 mutation (p=0.026).

There was no correlation between the MSK score and positive SPT results (p=0.133). Nevertheless, the MSK scores were lower in patients susceptible to AF compared to non-susceptible patients (p=0.007) (Table 3). The MSK scores were significantly lower in patients with fungal susceptibility (p= 0.030). There was no similar differences with the susceptibility to pollen, house dust mite, and animal epithelium (p=0.376, p=0.682, p=0.793, respectively). The MSK scores were lower in patients with minimally function mutations, bronchiectasis, bacterial colonization, SABA use, and BMI of [?]18.5 (p<0.05) (Table 4).

The MSK scores of patients were correlated moderately with the FEV_1 predicted value and weakly with BMI (r=0.616, p<0.001; r=0.473, p<0.001, respectively), and not correlated with age and Total IgE levels (p>0.05) (Figure 1). FEV_1 predicted value was moderately correlated with BMI (r=0.528, p<0.001).

All our patients received Dornase alfa therapy, pancreatic enzyme replacement, and supportive vitamin treatments. Furthermore, 35 (68.62%) patients were treated with SABA and 20 (39.21%) with ICS.

There was no difference by the MSK score (p=0.239), FEV_1predicted value (p=0.161), and BMI (p= 0.740) between the patients, who received and not received ICS treatment (p=0.150). Nevertheless, the total IgE level was higher [149 (min-max:2.40-1143) vs 21.1 (min-max:2.11-1030), p= 0.002].

Positive SPT results were more prevalent in patients on ICS compared to those, who did not use ICS (60% vs 25%, p=0.001). There was also no difference by MSK score and FEV_1 predicted value between the patients on ICS, with and without allergen susceptibility (p=0.583, p=0.539, respectively).

DISCUSSION

There are only a limited number of studies, which focused on environmental allergens, although the relevant literature reported the importance of environmental factors on the variability in lung function of the patients with CF.[6,23] Previous studies suggested that the prevalence of atopy in patients with CF was similar to the general population.[24,25] The ISAAC (The International Study of Asthma and Allergies in Childhood) Phase II study, which was conducted in Izmir, the prevalence of susceptibility to at least one aeroallergen was 8.8% in 2112 school-age children based on the SPT results.[26] In the present study, there was atopy in 33.3% of our patients with CF. This is indicative of the fact that the allergen susceptibility in children with CF is higher compared to the healthy children in Turkish society. Furthermore, it was suggested that environmental factors were more important regarding the prevalence of atopy compared to the genetic differences.[6] In the present study, there was no difference between the presence of atopy and CFTR gene mutations.

The patients susceptible to allergens had higher Total IgE levels, higher rates of eosinophilia, and higher rates of ICS and SABA use. There was no difference by bacterial colonization, FEV_1predicted value, bronchiectasis, BMI, and MSK scores between SPT positive and negative groups. Nevertheless, the prevalence of

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bronchiectasis was higher and MSK scores were lower in patients susceptible to AF. Patients with Pa colonization had a higher rate of positive SPT results compared to non-colonized patients, with manifest AF susceptibility. Nevertheless, there was no difference by Sa colonization. This may suggest that certain infectious agents are associated with atopy.

A study, which investigated 55 patients with CF in the adult population associated the presence of atopy in CF with rhinitis symptoms.[27] However, the present study did not identify any correlation between presence of atopy and AR. Based on the results of the study, we suggest that the effect of AR on CF clinical findings is not remarkable.

There was susceptibility to fungi (19.6%) followed by pollen (15.7%), while the most prevalent was the AF susceptibility. It was reported that 35% of children with CF had susceptibility to AF, 25% to grass pollen, and 13% to house dust mites.[8] Relevant studies suggested the association between susceptibility to AF and severe lung disease.[1,3,6,28] ABPA is defined as a clinical picture that may result in chronic lung disease due to a sudden hypersensitivity reaction to AF.[20] It was reported that 31-59% of the patients with CF were susceptible to AF and approximately 1-10% of those patients had ABPA.[1,3] In the present study, there were clinical findings suggesting ABPA in 3 patients susceptible to AF. There was susceptibility to fungi in one case and to pollen in another case. Although we had a small number of patients, we considered that additional allergen susceptibility might have an effect on the occurrence of ABPA. Relevant literature reported that atopy was an important risk factor for the occurrence of ABPA and ABPA was more prevalent in SPT positive individuals with CF, who were susceptible to at least one aeroallergen other than AF.[1,3]

It was also reported that all the pulmonary function parameters, including forced expiratory volume in 1 second (FEV_1), were lower in patients with ABPA, infected with Pa, and in atopic individuals with CF.[5] Certain studies suggested that the effect of atopy on respiratory function was insignificant.[25] In the present study, there was no significant difference between the FEV_1 predicted value and positive SPT results, eosinophilia, and ICS use. Whereas, the FEV_1 predictive value was significantly lower in patients with bacterial colonization, bronchiectasis, and lower BMI. Therefore, we considered that atopy had little effect on the respiratory function in patients with CF. Nevertheless, the prevalence of bacterial colonization and bronchiectasis was higher and MSK scores were lower in our patients susceptible to AF. Therefore, we suggest that AF is considered in patients with CF with severe clinical prognosis.

It is difficult to prove comorbid asthma in patients with CF. However, the term "CF asthma" was introduced for the patients with CF with airway obstruction attacks responsive to bronchodilators, personal atopy evidence, and eosinophilia. It was even suggested that the above definition represented a different phenotype.[29,30]While certain studies argued that higher Total IgE levels and eosinophilia might support the CF and asthma combination, other studies disagreed.[3,25,31] The Total IgE and eosinophil levels were higher in our atopic CF patients. Nevertheless, we were able to detect early reversibility in a very few patients by means of spirometry.

Relevant studies in the literature reported that 88.2% of the patients with CF used some sort of inhaled bronchodilator.[29]The rate of ICS prescription was reported as 10% in France, 12% in Germany, and 36% in the United Kingdom.[32] Although the ICS use is frequent in patients with CF, relevant studies found inconsistent results as regards the effects of ICS use on FEV_1.[33-35] The rate of ICS use was 39.2% in our patients. The prevalence of positive SPT results significantly higher in patients using ICS compared to those who did not use ICS, and the Total IgE levels were significantly higher. However, there was no difference by the FEV_1 predicted values and MSK scores. Similarly, there was no significant difference by FEV_1 predicted value and MSK score between atopic and nonatopic groups using ICS. Obviously, we believe that extensive studies are needed to assess the effectiveness of and requirement for ICS treatment in CF cases.

A Turkish study, which investigated 54 patients with CF, reported that the mean MSK scores of the patients aged between 6 and 22 years was 71+-18.7, where the mean BMI was 17.8+-3.57. Furthermore, it was demonstrated that there was a strong positive correlation between FEV_1 and MSK score ($r=0.778$, $p<0.01$).[15] Another study reported that there was a weak correlation between the pulmonary function and BMI in

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children with CF (r = 0.52, p <0.001).[36]

The mean MSK score of our patients was 72.54+-11.50, where the mean BMI was 17.47+-3.09. The patients' MSK scores were moderately correlated with FEV_1 predicted value and weakly correlated with BMI. Furthermore, the FEV_1 predicted values were moderately correlated with BMI.

Our study is based on the data collected from our clinic; the number of patients is limited and does not represent the total population of the patients with CF.

In conclusion; the importance of aeroallergens, which constitute an important risk factor for asthma and account for a different phenotype, is unclear as regards CF. Although the same may cause a new phenotype of CF, their effect on prognosis seem unremarkable, except for the mold allergens. Nevertheless, the relationship between CF and atopy should be closely observed for the fact that atopy in patients with CF may mediate the occurrence of ABPA. Furthermore, the individuals susceptible to AF should be closely monitored for bacterial colonization, bronchiectasis, ABPA, and poor clinical outcomes, regardless of other aeroallergens. Identification of the population, in which the ICS treatment aimed to prevent pulmonary exacerbation in CF may prove to be effective, may prevent unnecessary drug use. Extensive studies to investigate this topic will be useful.

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