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ORIGINAL ARTICLE

Factors Affecting Bronchial Hyperreactivity in Asthmatic Children

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Bronchial hyperresponsiveness (BHR), the exaggerated airway narrowing in response to nonspecific stimuli, is a common characteristic of asthma. One hundred thirty-five children who were diagnosed asthma in the outpatient clinic of Gazi University Hospital, Pediatric Allergy and Asthma Department between January 2007 and January 2008 were retrospectively analysed from the asthma database of the division. BHR was not found to be different according to sex. Younger the age of the patient, more severe was BHR ($p = 0.096$, $r = 0.164$). Younger the age at onset of the symptoms, the more severe was the BHR ($p < 0.001$, $r = 0.307$). Patients who had an asthmatic first degree relative and who were exposed to passive smoking at home, had more severe BHR ($p = 0.006$ and $p = 0.032$, respectively). There were more hospitalizations among the asthmatic children with moderate-severe BHR ($p = 0.027$) however no correlation was found between chronic asthma severity and the degree of BHR. In this study we found that age, age at onset of symptoms, having a parent with asthma, exposure to tobacco smoke and baseline lung function are related to BHR measured at referral. Serum levels of Ig E or skin prick test positivity were not found to have any effect on BHR severity. Considering BHR severity, we could not reveal any relation between atopic and nonatopic children. However among atopic subjects, the ones with indoor allergen sensitization had more severe BHR.

Keywords bronchial hyperreactivity, asthma, children

INTRODUCTION

Bronchial hyperresponsiveness (BHR), the exaggerated airway narrowing in response to nonspecific stimuli, is a common characteristic of asthma (1, 2). However, BHR is also present in 16% to 30% of children without respiratory symptoms in general population, and severity of BHR in a patient can show fluctuations, in time (1). Therefore, various factors are likely to have an impact on the severity of BHR. Both environmental and host factors may modify the individual's responsiveness to inhaled agents such as histamine and metacholine (1, 2).

Large epidemiologic studies have identified several risk factors for the development of BHR (2, 3). Studies have related nonspecific BHR to age, gender, atopy, identified as high concentrations of Ig E or positive skin test positivity against common allergens, severity of asthma, lung function, and environmental factors such as exposure to tobacco smoke and humidity (2, 3). Furthermore, the results of longitudinal studies demonstrated that lower lung function and the presence of atopy at presentation predicted a higher severity of BHR at the end of the follow up (4, 5). Awareness of the factors affecting BHR can not only help us in understanding the nature of asthma but also in primary prevention and management of asthma.

The aim of this study was to investigate the role of risk factors such as age, gender, duration of disease, age at onset of disease, sensitization to common allergens, serum total Ig

E level, and lung function upon presentation in determining the severity of BHR.

METHODS

Subjects

One hundred and thirty-five children diagnosed with asthma in the outpatient clinic of Gazi University Hospital, Pediatric Allergy and Asthma Department between January 2007 and January 2008 were retrospectively analysed using the asthma database of the division. According to the asthma follow-up protocol of our department, a detailed entry card including data on age at onset of disease, duration of symptoms on admission, frequency of asthma symptoms, seasonal effects, family history, home conditions, triggers for symptoms, presence of other atopic diseases, serum total Ig E, skin prick test and lung function test results is filled out for each patient. The data used in this study were obtained from these files. Asthmatic children whose FEV₁ was 75% of predicted or higher (probably of mild-to-moderate) severity were selected for the study. Most of the patients were newly diagnosed, and others had not been on steroid treatment for at least the last 2 months. According to American Thoracic Society criteria, BHR to metacholine was defined to be moderate-severe when PC20 was measured to be 1 mg/ml or lower, and mild, when it was higher. Asthma severity was determined according to the criteria suggested in Global Initiative for Asthma.

Spirometry

Spirometry was carried out using a computerized spirometer (Vmax20c, SensorMedics Co., Yorba Linda, California, USA), calibrated daily according to the current guidelines of American Thoracic Society. Before spirometry, the patients

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were asked to withhold short-acting β_2 -agonists for at least 6 h, long-acting β_2 -agonists for 12 h, theophyllines and leukotriene receptor antagonists for 48 h.

Metacholine Bronchial Challenge

Metacholine challenge was performed according to the guidelines of the American Thoracic Society (ATS). Briefly, after 3 reproducible FEV₁ and FVC measurements with the spirometer (Vmax20c, SensorMedics Co., Yorba Linda, California, USA), the patients inhaled from a mouthpiece attached to the nebulizer five inspiratory capacity breaths of aerolized metacholine chloride (Sigma, USA) in normal saline in increasing concentrations (from 0.01 to 8 mg/ml) at 5-min intervals after normal saline inhalation at the baseline. Aerosols were generated by a DeVilbiss 646 nebulizer (DeVilbiss Co., Somerset, PA, USA) attached to a dosimeter (KoKo Dosimeter, PDS Instrumentation Inc., Louisville, USA). Measurements of FVC, FEV₁ and FEF₂₅₋₇₅ were performed at least twice, 30 s, and 90 s after each dose, and the measurement with the best FEV₁ recording was used. The provocative dose of metacholine producing a fall in FEV₁ 20% (PC₂₀) was then calculated by a computer-assisted interpolation from the dose-response curve. All the challenges were made by the same technician at the same time of the day between 08:30 am and 11:00 am. The severity of BHR was defined according to ATS criteria as moderate to severe BHR with a PC₂₀ level of 1 mg/ml and mild BHR, with a PC₂₀ level between 1–16 mg/ml, and the patient characteristics of the two BHR groups were compared.

Skin Prick Tests (SPT)

The SPT was performed with a panel of 10 most common aeroallergens (Stallergens, France) by the use of standard prick method. Histamine hydrochloride 10 mg/ml and allergen diluents were used as positive and negative controls, respectively. Wheal diameters of at least 3 mm greater than those of the negative controls (15 min after administration) were considered positive. The arithmetic mean of the two widest diameters of the wheal was calculated for statistical purposes.

Statistical Analysis

The results are reported as mean value $\pm$ standard deviation (SD). Comparisons of means of variables between the groups of asthmatic children were made by the independent samples' *t*-tests. Correlations were assessed by Pearson's correlation test for normal distribution of variables and by Spearman's correlation test for data without normal distribution. The data were analyzed using Statistical Package for the Social Sciences, version 9.0 software.

RESULTS

One hundred and thirty-five children with a diagnosis of asthma were diagnosed with BHR between January 2007 and January 2008 in the outpatient clinic of Gazi University Hospital, Pediatric Allergy and Asthma Division. The average duration of symptoms and the mean age of the patients were 2.6 ± 2.4 years and 9.7 ± 2.1 years, respectively. The demographic characteristics of the patients have been presented in Table 1.

TABLE 1.—Demographic features of the patients.

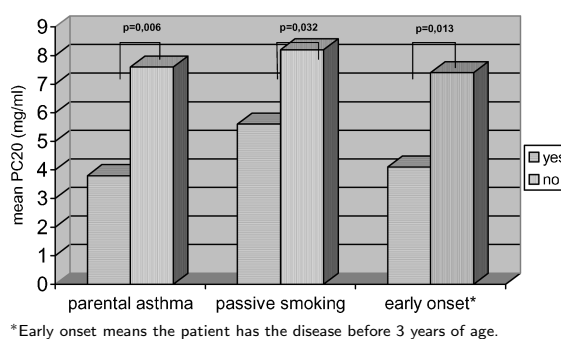
Sex, male/female, (n = 135)	72/63
Age at onset of disease (year)	7.3 ± 3.8
Duration of disease (year)	2.6 ± 2.4
FVC (%)	98.7 ± 12.3
FEV ₁ (%)	92.6 ± 11.4
FEF ₂₅₋₇₅ (%)	86.9 ± 19.9
FEV ₁ /FVC (%)	86.2 ± 7.5
Prick test, n, positive/negative (n = 135)	67/61
Passive smoking at home, positive/negative (n = 135)	71/64
Dampy house/sunny house (n = 135)	21/113
Indoor animal, positive/negative (n = 135)	19/116

BHR severity did not differ according to gender. BHR was more severe with younger age of the patient ($p = 0.096$, $r = 0.164$), and BHR was also more severe when the symptoms started at a younger age ($p < 0.001$, $r = 0.307$). The patients who had an asthmatic first-degree relative and who were exposed to passive smoking at home had more severe BHR ($p = 0.006$ and $p = 0.032$, respectively) (Figure 1). Among the atopic children, the patients with indoor allergen sensitization were found to have more severe BHR than the ones with outdoor allergen sensitization ($p = 0.024$). Among indoor allergens, only the mean house dust mite wheal size was reater in the patients with moderate-severe BHR. However, this difference was not statistically significant ($p = 0.148$). There were more hospitalizations among the asthmatic children with moderate-severe BHR ($p = 0.027$); however, no correlations were found between chronic asthma severity and the severity of BHR (Table 2).

The patients with a low FEV₁ upon presentation had more severe BHR ($p = 0.026$, $r = 0.192$). A similar relation was found between FVC and BHR severity ($p = 0.040$, $r = 0.177$). The patients who had severe-moderate BHR (PC₂₀ < 1) had a lower FEF₂₅₋₇₅ level ($p = 0.018$) (Figure 2).

DISCUSSION

The findings of this study indicated that age, age at onset of symptoms, having a parent with asthma, exposure to tobacco smoke, and baseline lung function were related to BHR measured upon presentation. Serum levels of Ig E or positive skin prick test did not have any effects on BHR severity. Considering the BHR severity, no relation between atopic and nonatopic children was established. However, among the atopic patients, those with indoor allergen sensitization had more severe BHR.



*Early onset means the patient has the disease before 3 years of age.

FIGURE 1.—Mean PC₂₀ values according to patient characteristics.

TABLE 2.—Patient characteristics according to BHR severity.

	PC 20 < 1	PC 20 ≥ 1	p
Age (year)	8.8 ± 0.3	10.2 ± 0.2	0.002*
Age at onset of disease (year)	5.7 ± 0.6	8.0 ± 0.4	0.001*
Duration of disease (year)	3.1 ± 0.4	2.2 ± 0.2	0.074*
Number of hospitalisations	1.6 ± 0.4	1.1 ± 0.9	0.027*
FVC (mg/ml)	2.1 ± 0.1	2.4 ± 0.1	0.068*
FEV ₁ (mg/ml)	1.8 ± 0.1	2.0 ± 0.6	0.018*
FEV ₁ /FVC	84.7 ± 1.4	86.7 ± 0.7	0.203
FEF _{25–75} (mg/ml)	1.9 ± 0.1	2.2 ± 0.7	0.018*
Total Ig E (mg/dl)	311.3 ± 116.3	290.6 ± 99.2	0.897
HDM square (mm)	1.3 ± 0.4	0.8 ± 0.1	0.135

BHR severity is reported to decline from childhood to adolescence, paralleling the increase in lung function during this period (6). The results of many studies suggest that younger children are more responsive to methacholine than are older children and adults (7–13). Similar to the findings of these reports, in our study, the younger children had more severe BHR although there are studies showing the contrary (14–17). Some investigators have recently questioned the interpretation of the relation between age and BHR because of the possibility that larger doses of agonists, in relationship to body size, are delivered to smaller children than to larger children and adults (5, 13, 18, 19).

In this study, a negative correlation was found between the age at onset of symptoms and the severity of BHR (Table 2). Accordingly, BHR was found to be more severe among the children whose symptoms started before 3 years of age (Table 3). Furthermore, age at onset of symptoms was correlated with PC20 values. Studies suggest that for children with asthma, environmental exposure and lung function deficits that develop during the early years are important factors in the development of persistent asthma, and characteristic pathologic features of asthma begin to develop between the ages of 1 and 3 years (15–20).

Exposure to passive smoking in the house is another important factor affecting asthmatic children (1). Exposure has been associated with aggravation and occurrence of increased prevalence of respiratory symptoms, acute respiratory infections, bronchial hyper-responsiveness, and asthma in children (21–23). Majority of parents of asthmatic children reported that cigarette smoking aggravated asthma of their children and that elimination of smoking generally led to improvement of symptoms (24). Similar observations were reported in other studies where asthma symptoms and their severity in children were related with the maternal smoking (25–27).

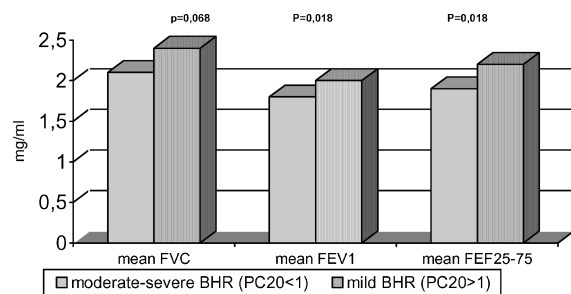


FIGURE 2.—Pulmonary function test results according to BHR severity.

TABLE 3.—Mean PC20 values according to patient characteristics.

		PC20	p
Sex	Male	6.5 ± 0.8	0.7–32
	Female	7.1 ± 1.0	
Parental Asthma	Positive	3.8 ± 0.7	0.015*
	Negative	7.6 ± 1.1	
Passive smoking at home	Positive	5.6 ± 0.9	0.031*
	Negative	8.2 ± 0.8	
Prick test positivity	Indoor allergens	5.1 ± 1.1	0.133
	Outdoor allergens	7.7 ± 0.8	
Home environment	Dumpy	4.8 ± 1.4	0.208
	Sunny	7.2 ± 0.6	
Atopy	Positive	6.4 ± 0.8	0.406
	Negative	7.2 ± 0.8	

These data may be related to the effect of ETS on BHR severity. Carlsen et al reported that passively smoking children had subclinical hyperreactivity at varying degrees, and some of them might turn out to be asthmatics (28). BHR and airways lability have been found by some to increase with ETS (20), but a comprehensive meta-analysis has concluded that an adverse effect of environmental tobacco smoke exposure on BHR in the general population has not been clearly established. Examining 15 studies, Cook et al observed a small increase in BHR among children of smoking mothers but argued that there might be an effect of publication bias (20). Only 3 of the studies used methacholine challenge, and all three included normal children besides asthmatics. In our study evaluating 135 asthmatic children, a significant relation was determined between ETS and BHR.

Lower level of prechallenge FEV₁, as an index of airway caliber, has a significant impact on the degree of BHR. This effect was confirmed in this study. The relation between BHR and airway caliber has been explained in several reports. Poiseuille's Law states that airflow resistance is inversely related to the fourth power of the radius of an airway. Thus, the same degree of airway constriction will lead to a greater increase in the airway resistance in the smaller airways than in the larger airways. Furthermore, increased thickness of the airway wall, as can be observed in asthma, leads to greater encroachment of the lumen for a given degree of airway constriction. Finally, the external load on the smooth muscle of the airway, including the relative stiffness of the bronchial cartilage and tethering effect of elastic recoil pressure, may oppose to a greater or lesser extent of the airway smooth muscle constriction. This may suggest that the presence of BHR in patients with airflow limitations is primarily an epiphenomenon of low baseline lung function, but not due to inherently increased sensitivity of the asthma to inhaled stimuli (1, 2, 29–32).

The small airways may play an important role in the clinical manifestations of asthma. A relation between BHR and small airway obstruction is less prominent. There are not many reports relating BHR and small airway obstruction (4, 33). Forced expiratory flow between 25% and 75% (FEF_{25–75%}) has been proposed as an approximate measure of the caliber of the distal airways. In our study, FEF_{25–75%} was found to be related with BHR. Consistent with our data, Ownby et al evaluated the data of 482 children in their epidemiologic study and revealed that % predicted FEF_{25–75%} to be related to the degree of methacholine responsiveness. There are two other studies (2, 5) that support this relationship. Investigators may

consider correcting methacholine responsiveness for baseline % predicted FEF_{25-75%} before analyzing data for age-related changes in such responsiveness.

Atopy is considered one of the important predictors of BHR although there are studies that did not find any relations between atopy and BHR (34–42). In their recent study, Bisgaard et al reported that atopy was not significantly related with BHR (43). Our data also supports these reports. However, Postma et al have reported that a gene governing BHR is located near a major locus regulating Ig E level. Interestingly, they could not determine a relation between BHR severity and Ig E level. They suggest that these data may imply the influence of multiple genetic and environmental factors on total Ig E level that does not have an effect on the development of BHR (40). These genetic and environmental effects may be responsible for the absence of a relationship between total Ig E level and BHR severity. One of these environmental factors may be the high prevalence of parasitic infections in our country. This hypothesis is also supported by another report from our country that did not find a relation between Ig E level and BHR severity (36).

Studies relating atopy and BHR explain the mechanism of this relation with the effect of cytokines released from the overexpressed Th2 lymphocytes, and it is noted that more severe BHR is associated with a more intense inflammatory profile in subjects with asthma (41). It must be taken into account that inflammation in asthma is not always the result of atopy, and BHR is reported to be associated with different cytokines among children with and without atopic sensitization (41, 42).

Some investigators report sensitization to indoor allergens, especially to HDM, rather than allergic sensitization itself being related to increased BHR (44, 46). The data supports the role of allergy to indoor allergens in childhood asthma, in at least aggravating and maintaining the symptoms. In our study, BHR of the children with positive skin test to indoor allergens were found to have more severe BHR than the children with no positive skin test, but the difference was not statistically significant.

The retrospective nature of our study can be considered a limitation, but the data were not obtained from verbal claims or patient notes, but from standardised cards designed for this purpose.

Asthma is a multifactorial heterogeneous syndrome comprising different phenotypes that manifest similarly with cough, wheeze, shortness of breath, and chest tightness. The patterns of inflammation and remodeling vary among individuals. Similarly, the clinical course of asthma varies substantially and is often quite unpredictable. Reasons for the variability in the clinical course of asthma have remained unknown. To shed some light on the issue, this study aimed to determine the risk factors for BHR, one of the hallmarks of asthma. Genetic and environmental factors are known to play an important role in the clinical picture. Thus, the study also aimed to reveal the features of BHR of asthmatic children in our country.

In summary, our data demonstrated that age at onset of symptoms, duration of the disease, parental asthma, ETS in the house and baseline scores of the lung function test have an impact on BHR of asthmatic children upon presentation. These findings suggest that risk factors for more se-

vere BHR can be considered warnings of severe attacks that need hospitalization. Thus, asthmatic children with maternal asthma, younger age, earlier disease onset, exposure to tobacco smoke, and low baseline pulmonary function should be monitored more closely. Better understanding of the nature of the main features of asthma, such as BHR, will help in monitoring and treatment of these patients.

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