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Associated Markers for Adult-onset Allergic Asthma

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ABSTRACT

The clinical behavior of asthma varies with age at onset. This study was undertaken to identify associated markers of adult-onset allergic asthma (age ≥20 years).

This cross-sectional study compared two groups: 58 patients with asthma onset at <20 years and 66 with onset at ≥20 years. They were compared depending on results of clinical history, and body mass index (BMI), aeroallergen sensitization, total serum IgE, eosinophil count, asthma control test, and asthma severity level.

Ages at first asthma episode were 10.0±6.6 and 33.4±10.5 (p<0.001) in the <20 and ≥20 group, respectively. BMI was higher in adult asthmatic subjects (29.8 versus 27.1, p= 0.017), but BMI ≥30 kg/m² was not associated with asthma onset in ≥20 years (odds ratio [OR]=1.56, 95% confidence interval [CI] 0.759 to 3.211; p=0.227). After multivariate analysis, allergic rhinitis and IgE ≥150 IU/mL were negatively correlated with asthma onset in ≥20 years old (OR adjusted [ORa]=0.255, 95% CI 0.078 to 0.837, p=0.024, and ORa=0.385, 95% CI 0.175 to 0.849, p=0.018, respectively).

Adult-onset allergic asthma was not different from early-onset asthma.

Keywords: Adult; Asthma; Biological markers; Immunoglobulin E

INTRODUCTION

Asthma is a heterogeneous disorder characterized by chronic inflammation of the airways, and different phenotypes, including allergic and non-allergic asthma, late-onset asthma, fixed airflow limitation asthma, and obesity and asthma, have been described.[1] Production of specific IgE directed against aeroallergens defines allergic asthma, and frequency ranges from 61.5% to 81.2% of patients in adulthood.[2,3] The clinical course of this phenotype differs from that of non-allergic

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asthma.[4] Age at onset plays a significant role in the behavior of asthma since adult onset asthma has been associated with greater decline in pulmonary function tests, worse control of the disease, higher number of hospitalizations for asthma in the previous year, and increased severity.[4,5]

Differences are common between patients with allergic asthma and those with non-allergic asthma. However, the clinical course of allergic asthma according to age at onset has rarely been addressed. The aim of this study was to identify associated markers of adult-onset allergic asthma with regard to early-onset asthma.

METHODS AND PATIENTS

Study Patients and Design

In a cross-sectional comparative study, asthmatic subjets were recruited consecutively from October 2012 to March 2014. Participants were residents of Guadalajara (Mexico), had no history of skin tests with allergens, and had not used systemic steroids the previous month of study. Patients were classified according to age at onset of symptoms of asthma; onset was classified as adult when it started at the age of ≥20 years. Groups were compared according to demographic and clinical characteristics, asthma severity, asthma control, sensitization to inhalant allergens, and total serum IgE levels.

Diagnosis and Classification of Asthma

To establish a diagnosis of asthma, Global Initiative for Asthma (GINA) guidelines were considered:[1] presence of episodic dyspnea, wheezing, coughing, and tightness in the chest accompanied by forced spirometry consistent with airflow limitation and reversibility. According to the results of the clinical interview and respiratory function tests, each patient was classified by the level of severity (intermittent, mild persistent, moderate, or severe).

Atopic Comorbidities

Diagnosis of atopic comorbidities of all subjects was performed by the same allergologist, who considered the personal history and the following recommendations: (a) allergic rhinitis is defined as an inflammatory disorder of the nasal mucosa, induced by an IgE-mediated reaction following exposure to an allergen;[6] (b) atopic dermatitis, whose diagnosis was based on the presence of pruritus, chronic, or relapsing eczematous lesions with typical morphology and distribution in patients with a history of atopy;[7] (c) hypersensitivity to food; and (d) drugs were considered in the presence of reproducible signs/symptoms initiated by exposure to a food or drug in which immunological mechanisms are involved or not.[8]

Technique of Skin Prick Tests

Skin tests against aeroallergens of the region were made by the puncture method using a calibrated lancet (Mizollen®, Sanofi, Hamburg, Germany); histamine was used as positive control, and 50% glycerol solution as negative control. Allergens were placed on both volar regions of the forearms. The largest diameter of the papule was measured 15 minutes after puncture; if it was at least 3 mm with respect to the negative control, the reaction was considered positive.[9] Allergic status was determined by the presence of at least one positive reaction to allergens: pollens, mold spores, house dust mites, cockroach mixture, epithelia, and feather mixture.

Forced Spirometry Technique

All tests were done in the morning, the subject was seated, and a nose clip and a disposable mouthpiece were used. Flow-volume curves were performed with a spirometer (MasterScreen Body PFT, Jaeger®, CareFusion, Baesweiler, Germany). Spirometry technique and interpretation were based on American Thoracic Society/European Respiratory Society recommendations.[10]

Asthma Control

The asthma control test (ACT) was conducted through direct questioning[11] and consisted of five questions related to asthma symptoms and use of asthma medication in the previous 4 weeks. The score for each item ranged from 1 (poor control) to 5 (best control), and the sum showed the ACT score (possible scores ranged from 5 to 25). Poor asthma control was defined as score of ≤19.

Total Serum IgE and Blood Eosinophil Count

IgE quantification was made by chemiluminescence by paramagnetic particles (AccessTotal IgE®, Beckman Coulter, Pasadena, CA, USA). A value of ≥150 IU/mL was measured as cutoff; eosinophil count in blood was made routinely; both studies were conducted in the

clinical laboratory of our hospital. Height and weight were measured the day pulmonary function tests were performed. Obesity was defined as body mass index (BMI) ≥30 kg/m^2.

The ethics and research committees of the hospital approved this study. Participants gave informed consent for inclusion in the study.

Statistical Analysis

Categorical variables were reported as percentage, and continuous variables as mean and standard deviation or median and interquartile range. Proportions were compared by chi-square test, and continuous variables of independent groups were compared by Student *t* test or the Mann-Whitney *U* rank test according to distribution. The relationship between variables was measured by odds ratio (OR) and 95% confidence interval (CI). We performed univariate analysis by introducing every independent variable separately. We used logistic regression to perform a multivariate analysis; the dependent variable was adult-onset allergic asthma, and covariates were obesity, allergic rhinitis, food hypersensitivity, IgE levels, and male gender. Two multivariate models were developed by using the "Enter" and "Forward conditional" methods. *P* values of ≤0.05 were considered statistically significant. For data analysis, we used SPSS version 20.0 for Windows (IBM, Armonk, NY, USA).

RESULTS

A comparison of characteristics of patients according to age at asthma onset (<20 versus ≥20 years) is shown in Table 1. Overall, 75% were female, and mean current age was 35.8±12.4 years. The mean age at the first episode of asthma was 22.5±14.7 years; in the asthma group with onset at ≥20 years, the mean was significantly higher, 33.4±10.5 years (p<0.001). BMI was higher in the adult-onset asthma group (p=0.017). However, the frequency of obesity did not differ between the two groups (p=0.226). Allergic rhinitis an food hypersensitivity were significantly more common in patients with asthma onset <20 years comparared to those with with allergic asthma adult-onset (p=0.015 and 0.019, respectively). All patients had persistent asthma according to the GINA criteria. No significant differences in the frequency of current smoking status, asthma control, and history of hospitalization for asthma in the previous year were observed, and this was similar to the results of spirometry test. The subjects with asthma onset at <20 had a higher total IgE and a higher proportion of IgE ≥150 IU/mL compared to age ≥20 years.. There were no differences in total eosinophil count, frequency of sensitization to aeroallergens, or median of positive skin tests between the two groups.

Univariate analysis showed that allergic rhinitis, food hypersensitivity, and serum IgE levels ≥150 IU/mL were negatively associated with adult-onset allergic asthma (Table 2). In multivariate analysis, allergic rhinitis and serum IgE ≥150 IU/mL remained significantly associated with asthma onset at <20.

DISCUSSION

Our results suggest that the personal history of allergic rhinitis and serum IgE ≥150 IU/mL were less common in adult-onset allergic asthma compared to with asthma onset at <20 years. Different distribution models of asthma have emerged since the phenotypic classification proposed by Rackemann.[12] Defining adult-onset asthma and its characteristics has been controversial. Adult-onset asthma has been defined as asthma that begins at 12 years of age and that is accompanied by greater sensitivity to allergens, increased number of allergic symptoms, and worse lung function.[5] Other authors have used a later age (16 and older) and characterized adult-onset asthma by its association with occupational dust or fumes and greater prevalence in women.[13] A higher cutoff point of ≥40 years has also been proposed for adult-onset asthma.[14] This last criterion was able to document five clusters; group 3 was characterized by its predominance in adulthood and is more common in obese women; group 5 showed a higher predominance of late onset. In our study, we defined adult-onset asthma according to the biological definition of adult (age ≥20 years).[15] Therefore, we integrated two distinct groups that were significantly different in age at asthma onset to allow us to visualize the role of age at onset.

Our results indicated that age at onset of allergic asthma did not appear to be associated with its clinical behavior, and allergic asthma was a more homogenous phenotype (it tended to be more common in women and did not differ in effect on respiratory function, the severity of asthma, and the types of allergic sensitivity), and that non-allergic asthma was substantially different from allergic asthma.

Table 1. Demographical and clinical characteristics of subjects

	Total n=124	Age at onset of asthma		*p* value
		<20 years n=58	≥20 years n=66	
Female, n (%)	93 (75.0)	44 (75.9)	49 (74.2)	0.835
Current age in years, mean ± SD	35.8±12.4	28.5±9.7	42.3±10.9	<0.001
Age at asthma onset in years, mean ± SD	22.5±14.7	10.0±6.6	33.4±10.5	<0.001
Current BMI in kg/m^2, mean ± SD	28.6±6.2	27.1±5.9	29.8±6.3	0.017
BMI ≥30, n (%)	52 (41.9)	21 (36.2)	31 (47.0)	0.226
Atopic comorbidities, n (%)				
Allergic rhinitis	105 (84.7)	54 (93.1)	51 (77.3)	0.015
Food hypersensitivity	18 (14.5)	13 (22.4)	5 (7.6)	0.019
Atopic dermatitis	7 (5.6)	5 (8.6)	2 (3.0)	0.178
Drug hypersensitivity	19 (15.3)	7 (12.1)	12 (18.2)	0.346
Persistent asthma severity, n (%)				0.935
Mild	42 (33.9)	20 (34.5)	22 (33.3)	
Moderate	48 (38.7)	23 (39.7)	25 (37.9)	
Severe	34 (27.4)	15 (25.9)	19 (28.8)	
Current smoking, n (%)	6 (4.8)	3 (5.2)	3 (4.5)	0.871
Asthma control test, mean ± SD	14.8±5.8	13.8±5.4	15.7±5.8	0.061
Hospitalization for asthma/previous year, n (%)	47 (37.9)	18 (31.0)	29 (43.9)	0.139
Baseline lung function				
FVC % predicted	87.2±18.1	89.2±17.4	85.5±18.7	0.257
FEV_1 % predicted	70.2±20.2	69.7±20.4	70.6±20.1	0.796
FEV_1/FVC	66.8±10.8	67.3±11.1	66.4±10.6	0.659
Maximal lung function				
FVC % predicted	96.4±15.5	97.8±14.5	95.2±16.3	0.349
FEV_1 % predicted	84.1±20.2	84.2±20.9	83.9±19.8	0.943
FEV_1/FVC	73.3±10.9	74.8±11.2	72.1±10.6	0.174
Total eosinophil × $10^3/\mu L$, median (IQR)	330 (210-580)	355 (212-595)	290 (165-572)	0.378
Total IgE, IU/mL, median (IQR)	307.9 (95.0-590.5)	370.4 (167.3-892.3)	189.8 (72.5-498.9)	0.010
IgE ≥150 IU/mL, n (%)	93 (75)	44 (75.9)	36 (54.5)	0.013
Sensitization to aeroallergens, n (%)				
House dust mites	83 (66.9)	43 (74.1)	40 (60.6)	0.110
Cockroaches	66 (53.2)	36 (62.1)	30 (45.5)	0.064
Trees	64 (51.6)	33 (56.9)	31 (47.0)	0.270
Weeds	63 (50.8)	27 (46.6)	36 (54.5)	0.374
Cat or dog	56 (45.2)	28 (48.3)	28 (42.4)	0.514
Grasses	46 (37.1)	21 (36.2)	25 (37.9)	0.848
Mold	15 (12.1)	4 (6.9)	11 (16.7)	0.096
Total number of positive skin tests, median (IQR)	5 (3-8)	5 (3-9)	5 (2-8)	0.403

p value obtained by chi-square or Student *t* test or Mann-Whitney *U* test as appropriate. BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; n, number of subjects with the characteristic of interest; SD, standard deviation.

Table 2. Univariate and multivariate analyses of allergic asthma-associated markers of onset in adulthood

	Univariate analysis			Multivariate analysis					
				Unadjusted model			Adjusted model		
	OR	95% CI	*p* value	OR*	95% CI	*p* value	OR*	95% CI	*p* value
Obesity	1.561	0.759-3.211	0.227	1.468	0.648-3.326	0.357	-	-	0.663
Allergic rhinitis	0.252	0.078-0.809	0.021	0.344	0.100-1.179	0.090	0.255	0.078-0.837	0.024
Food hypersensitivity	0.284	0.094-0.853	0.025	0.311	0.095-1.012	0.052	-	-	0.065
Total IgE ≥150 IU/mL	0.382	0.176-0.827	0.014	0.405	0.181-0.909	0.028	0.385	0.175-0.849	0.015
Male**				1.17	0.488-2.806	0.725	-	-	0.776

OR: odds ratio; 95% CI, confidence interval of 95%. The comparison groups were patients aged <20 years.

*ORs obtained by logistic regression.

**Only calculated for multivariate analysis.

Adjusted model for the variables: obesity, food hypersensitivity and sex.

The frequency of allergic rhinitis in the group with asthma onset at ≥20 years was significantly lower than in the complementary group. Epidemiological studies have shown wide variations in the prevalence of allergic rhinitis coexisting with asthma in adults. Up to 60.8% of adults were reported to have allergic rhinitis;[16] another study reports a slightly lower prevalence (55.2%).[17] Our data show that a very high proportion of patients had concomitant allergic rhinitis, conceivably because all asthmatics were allergic populations behaving more like those analyzed by Linneberg *et al*., who showed that 89% to 100% of participants with atopic asthma had allergic rhinitis.[18] In our study, >20% of subjects with adult-onset asthma had no allergic rhinitis; this clinical behavior was described by Greisner et al., who documented that 35% of participants in a cohort developed asthma before allergic rhinitis.[19] The mechanisms that explain this course of action have not been fully clarified; means of sensitization besides air spread could be assumed. Also, the existence of aeroallergen fragmentation which facilitates entry into the lower airway by reducing aerodynamic size has been postulated.[20]

The association between food hypersensitivity and asthma in this study was 14.5% and was less common in patients with ≥20 years of age. Prevalence of food hypersensitivity in adults varied from 3% to 35%.[21] These oscillations can be partially explained by differences in data collection techniques. However, even when the same methodology is applied, this behavior persists; an example is the European Community Respiratory Health Survey, an investigation in which 15 countries participated and the prevalence of food hypersensitivity ranged from 4.6% to 19.1%.[22] Although the frequency of food hypersensitivity was obtained through medical history, our results are consistent with previous evidence.[23,24]

We found a decrease in total serum IgE levels related to age at asthma onset; this finding is consistent with a cohort study[5] in which increased levels of IgE were observed in adults with asthma onset in childhood (124.3 IU/mL) compared with adult-onset asthma (65.7 IU/mL) (p=0.001).[25] Another study showed a significant decrease in total and specific IgE in serum according to age in patients with allergic rhinitis, asthma, and insect allergy.[26]

Our study revealed significant differences in age at asthma onset in relation to BMI. However, categorizing patients according to frequency of obesity did not yield differences. During the last 12 years, a growing obesity epidemic has been documented in Mexico.[27] Meanwhile, the health-care needs of asthma have not been substantially modified.[28] Recent data from our country have not been able to document a relationship between obesity and asthma.[29] Therefore, prevalence, severity, and control of asthma in relation to obesity remains controversial.

With respect to the prevalence of sensitization to aeroallergens, the two asthma groups did not differ from one another; they showed behavior that was consistent with previous data from our geographical region, where sensitization to dust mites or cockroaches and (to a lesser extent) fungus spores predominated.[2]

Our research had some limitations. For example,

only the results obtained should be extrapolated to patients with allergic asthma. Similarly, recall bias may be present, given that patients with a history of asthma at an early age may not be able to recall it during medical examination. Other limitations could result from how the subjects were selected and from the relatively small sample size studied.

In summary, although the clinical behavior of allergic asthma with adult onset did not differ markedly from that seen in earlier-onset asthma, markers such as lower frequency of allergic rhinitis and lower levels of total serum IgE, which predominated in the ≥20 year asthma group, put into perspective the minimal participation of atopy in the clinical behavior of adult asthma.

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