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ORIGINAL ARTICLE

Triggers in Intrinsic Asthma in the EGEA Study

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ABSTRACT

The objective of the study was to compare triggers for asthma attacks in a group of intrinsic (IA) and extrinsic asthmatic (EA) subjects. We included 205 asthmatic patients divided, according to skin-prick tests, in a group ($n = 63$) of IA and a group ($n = 142$) of EA. The questionnaire provided information on associated conditions (nasal polyps and intolerance to aspirin) as well as on allergenic and nonallergenic triggers. Data analysis demonstrated that in IA, some airborne nonallergenic factors were significantly more often involved. In addition, this association did hold true when comparing subgroups of patients with normal baseline FEV₁ values. For those subjects, PC₂₀ and the slopes of the dose-response curves to metacholine were comparable. In conclusion, the higher sensitivity of a group IA subjects to some nonallergenic factors is not related to a lower baseline spirometric value in this subgroup. It may be hypothesized that, in these patients, sensitivity of airways irritant receptors might be increased.

Key Words: Asthma; Intrinsic asthma; Nonallergic asthma; Triggers; Triggering factors; Etiology.

The wording “intrinsic” asthma was introduced by Rackemann in 1940 (1) to emphasize that this type of asthma differs from allergic extrinsic asthma with respect to the absence of an obvious precipitating exogenous cause. In the chapter “Asthma: classification

and pathogenesis” by C.E. Reed and R.G. Townley in the 1983 book: *Allergy—Principles and Practice* (2), intrinsic asthma is not identified as such. The text makes reference to “nonallergic” asthma and it is stated that stimuli such as irritants, exercise,

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and infections affect everyone with asthma. The 1993 edition does not include any comment on triggering factors of nonallergic asthma. In the field of rhinitis, there have been several studies (3,4) demonstrating that patients with nonallergic rhinitis are more sensitive to colds and other infections. However, a similar proportion of subjects with allergic rhinitis and vasomotor rhinitis reported symptoms when exposed to other nonspecific irritants, such as cigarette smoke and perfumes (5). In the field of asthma no such study has been performed. The goal of this study was to compare triggers for asthma attacks in a group of intrinsic and extrinsic asthmatic subjects.

MATERIAL AND METHODS

This study has been performed within the framework of EGEA (Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy). Design (6) and phenotypic issues (7) have been published elsewhere. Briefly, EGEA was planned to assess genetic and environmental risk factors and their interaction for asthma occurrence, and two related parameters, bronchial hyperresponsiveness and atopy. EGEA combines a case-control and a family study of adults and pediatric asthmatic probands, using a standardized methodology mostly based upon the European Community Respiratory Health Survey. In this part of the study, only adult asthmatic patients were considered. Inclusion criteria were place of birth, area of residence, age, family structure, and, for proband cases, positive answer to four standardized questions: Have you ever had attacks of the breathlessness at rest with wheezing? Have you ever had asthma attacks? Was this diagnosis confirmed by a physician (diagnosis of asthma)? Have you ever had an asthma attack in the past 12 months? Asthmatic probands were recruited from chest clinics of six university hospitals. Controls were mostly population-based

(electoral rolls). Data involved a standardized questionnaire including, among others, questions on triggers and medication requirements, a spirometric examination, a metacholine test, a blood sampling, and a battery of 11 skin-prick tests. The same spirometer (Biomedin, Italy) was used in all clinical centers. It is an ATS- and ERS-certified spirometer. We used the ATS quality control criteria to ensure a proper spirometric measurement. We did not perform the test within 1 hour after a heavy meal. We asked the patients to avoid taking long-acting bronchodilators within the 48 hours before the test and short-acting bronchodilators on the same day. A nonspecific bronchial challenge to metacholine was performed using increasing dosages in patients whose baseline FEV₁ was equal or greater than 80% of the predicted value. A test was considered positive if the mean diameter of the wheal was larger than 3 mm, compared to the negative control test. Questions considered if asthma attacks or cough were triggered by exposure to dust, feathers or wool, humidity, pollens, mowing, humid leaves, air conditioning, exercise, stress, fatigue, laughing, strong smells, meals, alcohol intake, occupation, air pollutants, certain climatic conditions, weather changes, altitude, cold air, moving into a new house, colds, and, for women, menstruation.

In this part of the study, we will only consider 205 adult asthmatic probands who were subdivided into two subgroups according to the results of skin-prick tests: 63 had negative skin tests and were considered to belong to the "intrinsic asthma (IA)" group, whereas 142 had at least one positive skin test and belonged to the "extrinsic asthma (EA)" group. Table 1 provides some characteristics of the two groups. In the analysis, other phenotypes, apart from skin tests, were considered: IA plus perennial (at least 3 months during the last 12 months) rhinitis, IA plus history of surgery for nasal polyps, and IA plus history of aspirin-induced asthma attacks. Data were analysed using an SAS package. In this article, we performed comparisons of the percentage using

Table 1. Demographic and spirometric characteristics of the study groups.

Group	IA (n = 63)	EA (n = 142)	P value
Sex (M/F)	27/36	79/63	NS
Age (m ± SD) yrs	47 ± 12	35 ± 14	.000
Age when asthma started (m ± SD)	34.7 ± 13.5	19.7 ± 15.5	.0001
FEV ₁ (% predicted)	80.6 ± 23.0	90.4 ± 19.4	.002
PD ₂₀ ≤ 4 mg	87%	89%	NS

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the chi-square test and, when appropriate, the Fisher exact test. We also used logistic regression analysis to evaluate the role of the type of asthma and a covariate on the trigger involved. A *P* value less than .05 was considered to be statistically significant.

RESULTS**Groups Defined According to Skin Tests Only**

Table 2 shows that allergenic exposure was more often considered as a trigger in extrinsic than in IA (except for altitude, which did not act as a protective factor in asthmatic patients). In contrast, in intrinsic asthmatics, some nonallergenic factors such as air conditioning, strong smells, passive smoking, air pollutants, and aspirin intake were more often involved as triggers for asthma attacks than in EA.

Because intrinsic asthmatics have lower mean FEV₁ levels, the question arose whether those patients might be more sensitive to nonallergenic stimuli because they have more severe asthma (8). To address this question, we compared baseline

mean FEV₁ in asthmatic patients who acknowledged nonallergenic triggering factors. Because most patients acknowledged at least one trigger, we compared baseline FEV₁ in patients who had at least two triggering factors (*n* = 158) and in those who had none and only one triggering factor (*n* = 47). Mean ($\pm$ SD) FEV₁ was equal to 3.018 ($\pm$ 0.966)l in the first group and 2.947 ($\pm$ 0.982)l in the second group, a difference that was not statistically significant (*P* = .9). We also performed a logistic regression analysis including the trigger (yes/no) as the predicted variable and type of asthma (IA vs. EA) and FEV₁ as predicting variables. Exposure to strong smells, passive smoking, and air pollutants were linked to an increased risk of asthma attacks in IA compared to EA, after correcting for the FEV₁ influence. Then, we compared triggers in the subgroup of IA vs. EA patients who underwent the metacholine challenge. Among those patients, the ratio of mean FEV₁ values to expected values was equal to 101.9% in the IA group and 99.9% in the EA group, a nonsignificant difference. Allergenic triggers, such as exposure to "dust, feathers, or wool" and exposure to pollen were more often involved in EA. In the IA group, exposure to air conditioning (*P* = .035), air pollutants

Table 2. Triggering factors (expressed in %) for asthma attacks.

Exposure	Negative skin tests	Positive skin tests	OR (95% CI)	<i>P</i> value
Dust, feathers or wool	38	73	0.22 (0.12–0.43)	.00
Pollens	28	62	0.24 (0.13–0.47)	.001
Mowing	17	31	0.44 (0.20–0.95)	.033
Moving house	11	27	0.36 (0.15–0.86)	.017
Altitude	24	16	1.61 (0.76–3.43)	NS
Air conditioning	35	21	2.04 (1.04–4.00)	.037
Exercise	67	67	0.99 (0.52–1.88)	NS
Emotional stress	64	53	1.63 (0.87–3.07)	NS
Fatigue	52	38	1.82 (0.98–3.38)	NS
Laugh	35	35	1.01 (0.53–1.91)	NS
Strong smells	47	30	2.03 (1.08–3.79)	.026
Meals intake	12	10	1.24 (0.47–3.28)	NS
Wine & alcohols	12	17	0.64 (0.26–1.59)	NS
Passive smoking	70	49	2.40 (1.26–4.59)	.007
Occupation	23	21	1.12 (0.54–2.32)	NS
Air pollutants	51	34	1.98 (1.06–3.69)	.031
Climatic conditions	46	55	0.69 (0.38–1.27)	NS
Weather changes	42	29	1.71 (0.91–3.23)	NS
Cold weather	43	31	1.66 (0.89–3.10)	NS
Colds	46	36	1.54 (0.83–2.84)	NS
Menstruation periods ^a	10	17	0.48 (0.12–1.89)	NS
Aspirin intake ^b	21	2	10.30 (1.95–54.54)	.004

^aFor women only.

^bIn patients reporting aspirine intake.

($P = .012$), and cold air ($P = .018$) were more significantly acknowledged as triggers for asthma attacks.

Groups Defined According to a More Precise Phenotype

This group comprised asthmatic patients with negative skin tests and perennial rhinitis (lasting at least 3 consecutive months each year). There were 11 such asthmatic patients. Compared to the extrinsic group, no triggering factor was significantly demonstrated, apart from climatic changes (OR = 6.40; 95% confidence interval [CI] = 1.61–25.37) and strong smells (OR = 4.05; 95% CI = [1.13–14.61]).

Asthmatic patients with negative skin tests and a history of nasal polypectomy. There were 12 such patients. Compared to the extrinsic group, in the IA group, exposure to dust, feathers, and wool was significantly ($P = .04$) less often demonstrated (odds ratio [OR], 0.26; 95% CI = [0.08–0.86]). Asthma attacks after exposure to pollens was also significantly ($P = .004$) less often demonstrated (OR, 0.12; 95% CI, 0.03–0.58). Among nonallergenic triggers, climatic changes (OR, 7.20; 95% CI, 1.85–27.99) and colds (OR, 5.44; 95% CI, 1.40–21.05) were significantly more often encountered in the IA subjects with history of nasal polypectomy.

There were only 6 patients with negative skin tests and bronchial intolerance to aspirin. Extrinsic asthmatics were significantly more sensitive to exposure to dust, feathers, and wool (OR, 0) and to pollens (OR, 0.12; 95% CI, 0.01–1.08). Among nonallergenic triggers, emotional stress (OR, 10), climatic changes (OR, 12.00; 95% CI, 1.36–106.00) and cold weather (OR, 11.19; 95% CI, 1.27–98.76) were more often found to be triggers of asthma in the IA subjects with aspirin intolerance.

Bronchial Reactivity Levels in Intrinsic and Extrinsic Asthmatics

Using the slope of the dose–response curves as computed by the O'Connor method (9), we did not find any difference in the level of nonspecific bronchial reactivity in patients from both groups who performed the test. In addition, we computed the percentage of patients of both groups whose FEV₁ dropped by 20% or more after inhaling less than 1 mg of metacholine, less than 2 mg, and more than 2 mg. None of these differences were statistically significant.

DISCUSSION

IA patients had a higher sensitivity to some nonallergenic triggers, especially those which are airborne, than did EA, whereas extrinsic asthmatic patients are more sensitive, as expected, to allergenic triggers. The higher sensitivity to nonallergenic triggers reported by intrinsic asthmatic patients could be thought to be related to a lower baseline spirometric level because overall IA patients have lower baseline values; the latter are correlated with an increased level of nonspecific bronchial reactivity (8). However, our data demonstrate that, even in the subgroup of IA patients whose baseline spirometric values and slopes of the challenge test were in the same range of their extrinsic counterparts, there was still a higher rate of clinical responses to nonallergenic airborne triggers. Thus it may be hypothesized that in IA patients, sensitivity of airways irritant receptors might be increased, independently from bronchial response to the challenge test.

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