

Atopy and systemic reactions to drugs

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To elucidate whether systemic reactions (SR) to drugs should be included in the atopic status in epidemiological studies, we compared the distribution of atopy in subjects with or without a history of SR to drugs. The studied population comprised 2067 adults, 20 to 60 years old, visiting a health care center for a check-up examination. The protocol included a questionnaire related to history of SR to drugs and a Phadiatop® test which evaluates on a blood sample the presence of specific IgE against common aeroallergens. Overall, 14.7 % of the study group, including 66 % women, reported reliable histories of SR to drugs. The cumulative prevalence of asthma, hay fever and childhood dermatitis was higher in the SR group. By contrast, the percentage of positive Phadiatop tests was similar in subjects with or without a history of SR. Thus atopy, defined by an objective criterion, i.e. the presence of specific IgE against common aero-allergens, is not associated with the occurrence of SR to drugs. Such a history should not be included as part of the atopic status.

Key words: atopic status.

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It is commonly stated that atopic status is a risk factor for the occurrence of systemic reactions (SR) to most drugs (14). More specifically, it has been suggested that reactions to anaesthetic drugs could be more frequent in atopics (9, 10, 11, 16, 21). The relevance of atopic status as a risk factor for SR to drugs has even been considered in IgE-mediated drug reactions, such as to penicillin (20) or muscle relaxants (12, 18). Thus, in epidemiological standardized questionnaires, drug allergy has sometimes been included as one of the possible signs of atopic status (19). However, in most of these studies, atopy was only defined on the basis of responses to questions related to the occurrence of asthma, seasonal or perennial rhinitis and childhood dermatitis, without measuring any laboratory parameter, such as specific IgE. In this survey, our goal was to find whether subjects reporting SR to drugs had a higher prevalence

of atopy, defined not only by clinical but also biological criteria.

MATERIAL AND METHODS

The study group comprised 2,067 adults, 20 to 60 years old, visiting a health care center for a check-up examination. There were 53 % men and 47 % women, mean ($\pm$ SD) age 39.4 ± 9.2 years. The study was performed from October 1986 to July 1987.

The protocol consisted of a standardized questionnaire and a Phadiatop® test. The questionnaire related to 1) demographic characteristics: sex, age, education, which could influence the prevalence of atopy (11, 12), 2) symptoms suggestive of atopy (i.e. asthma, hay fever, perennial rhinitis, history of childhood dermatitis), 3) drugs (which drug? which type of SR?). The Phadiatop test was performed on

a blood sample for detection of specific IgE against major aero-allergens. Phadiatop has been shown to be a much more reliable test than IgE level for identifying respiratory allergy. This serological test has a sensitivity comparable to 85 % of the sensitivity of skin tests and 94.5 % of RAST to common allergens (17). Its specificity was equal to 100 % in the former study and 96.9 % in the latter (5, 17). It provides a positive or negative response. The test could be performed in 2005 subjects, and a positive test was considered indicative of atopy.

Statistical analysis involved computation of the prevalence of symptoms suggestive of atopy, or positive Phadiatop tests in subjects complaining of SR to drugs and those without. In a second step, variables which appeared predictive of SR to drugs in a univariate analysis were evaluated in a linear logistic regression analysis (15) (BMDP software, University of Berkeley, USA) using SR to drugs as a dependent variable. This analysis provided a *P* value measuring the statistical association between each independent variable and the occurrence of SR to drugs, the value of the odds-ratio (OR) and its 95 % confidence interval (95 % CI). In this multivariate analysis the following variables were considered: symptoms of atopy, i.e. a positive response to questions related to a history of either asthma or hay fever or childhood dermatitis, age in four categories 20–29, 30–39, 40–49, 50–59, education graded in three groups: primary, secondary, higher, and Phadiatop test classified as positive or negative.

RESULTS

Overall, 303 subjects (i.e. 14.7 % of the study group) reported reliable histories of SR to

Table 2

Drug involved in systemic reactions

	<i>n</i>	%
Antibiotics	124	45
Aspirin or NSAID	48	17
Iodine	18	6
Others	86	31

drugs. The characteristics of subjects from the SR or no-SR groups are listed in Table 1. The age range was similar in both groups. In contrast, the percentage of women was almost double in the SR group (*P* < 0.001), whereas there were more men in the no-SR group.

The drug involved in these SR could not be identified in 27 instances. Among the remaining 276 cases (Table 2), antibiotics accounted for 45 % of the reactions, aspirin or non-steroidal anti-inflammatory drugs for 19 %, intra-vascular radiological contrast media for 6 % and miscellaneous other drugs for 32 %. Among the 124 subjects who reported antibiotics to be the responsible drug, 54 reported it to be “penicillin”, 13 a drug from the “ampicillin” subgroup, 10 a sulfamide, 8 a macrolide, 6 a cycline and the remaining 32 an “unspecified” antibiotic. Thirty-one subjects reported aspirin, 17 non-steroidal anti-inflammatory drugs, 5 glafenin and 3 other paracetamol. Nine subjects stated that the responsible drug was a corticosteroid. Five subjects reported an SR following anti-tetanus serotherapy.

The SR elicited were extensive urticaria in 129 subjects (63 %), angio-oedema in 99 (33 %), malaise in 71 (23 %), tightness of breath in 55 (18 %) and loss of consciousness in 25

Table 1

Characteristics of subjects from the SR or no-SR groups

	SR group	Control group
<i>n</i>	303 (14.7 %)	1764
Men	34 %	57 %
Women	66 %	43 %
Mean (±SD) age (years)	39.3±9.0	39.5±9.2

Table 3

Prevalence of symptoms suggestive of atopy in the SR or no-SR group

	SR group	No-SR group
Asthma (%)	9.2	5.2
Hay fever (%)	24.7	16.5
Childhood dermatitis (%)	12.2	5.1

(%). Many subjects reported several types of SR following drug intake.

The prevalence of any symptoms suggestive of atopy (Table 3) was significantly higher in the SR group ($P < 0.01$). This was especially true for asthma and childhood dermatitis, the prevalence of which was double in the SR group. In contrast, the percentage of positive Phadiatop in the SR group (17.6 %) and the no-SR group (19.5 %) was almost equal. Within the SR group, the prevalence of positive Phadiatop (Table 4) was similar regardless of the drug involved: e.g. penicillin (19 %), aspirin (17 %). The linear logistic regression analysis (Table 5) showed that, among the independent variables, several were significantly related to occurrence of drug reactions: sex ($P < 0.001$), symptoms of atopy ($P < 0.01$), and age. There was a significant trend ($P < 0.001$) towards a higher prevalence of SR in younger subjects. Taking the younger subjects as reference category (20 to 29 years old) those in the age range 40 to 49 and 50 to 59 had a lower risk of SR to drug. There was no obvious relationship between education and occurrence of SR, and a positive Phadiatop was not associated with SR to drugs.

DISCUSSION

This survey shows that the percentage of atopy, defined by a positive Phadiatop test, was not higher in subjects complaining of SR to drugs, even the penicillins which are expected to produce IgE-mediated reactions. By contrast, the prevalence of atopic symptoms was higher in the SR group, thus explaining why atopy was thought to be a risk factor for drug allergy in previous reports which relied only on a questionnaire to define atopy (9, 10, 11, 12, 16, 21,

22). In other studies, a biological criterion was considered, namely total IgE level. IgE levels have been found higher in patients reporting allergy to penicillin (1) or anaesthetics (6). However, an increased IgE level does not mean the presence of specific IgE. In a recent study (6), we compared skin tests to common aero-allergens, Phadiatop test and total IgE levels between 32 patients with a history of anaphylactic reactions to muscle relaxants and 128 control subjects. The percentage of positive skin test and positive Phadiatop was similar in both groups, whereas total IgE level was significantly higher in the case group. In a few studies apart from (6), skin tests to common aero-allergens have been used as markers of atopic status. In allergy to muscle relaxants, Moneret-Vautrin et al. (18) reported a higher prevalence of positive skin tests to common allergens in the case group. However, data collection was not concomitant for case and control series, and, further, the protocol for skin testing was not comparable. In a large in-patient population Ettlin et al. (8) demonstrated that there was no correlation between adverse drug reactions in general or allergic drug reactions, mainly to penicillin, and the number of positive skin tests to common aero-allergens. Recently, Astarita et al. (2), using skin prick tests as a marker of atopy, showed that atopy was not linked to drug intolerance in children. In the present study,

Table 4
Percentage of positive Phadiatop in the no-SR group, overall and according to the drug involved

No-SR group	SR group		
	Overall	Penicillin	Aspirin
19.5	17.6	19	17

Table 5 Linear logistic regression analysis			
Independent variables	P-value	OR	95 % CI
Sex (F/M)	< 0.001	1.24	1.11-1.40
Age	< 0.001		
2/1		1.10	0.91-1.32
3/1		0.81	0.67-0.98
4/1		0.75	0.60-0.95
Education			
2/1		0.80	0.70-0.94
3/1		1.09	0.93-1.27
Symptoms	< 0.01	1.32	1.15-1.52
Phadiatop®	0.75	1.02	0.87-1.21

For age range, category 1 refers to subjects 20 to 29 years old, category 2 to 30-39, category 3 to 40-49 and category 4 to 50-59. For education, category 1 refers to primary school, category 2 to secondary school and category 3 to university level.

among the reactors, the percentage of women was almost twice that of men. This striking predominance of women has also been noted in anaphylactic reactions to most anaesthetic drugs (16, 18). In our study the drugs involved in SR, were predominantly antibiotics followed by aspirin or non-steroidal anti-inflammatory drugs. This hierarchy is similar to the findings of De Weck (7) in a summing up of several studies from different countries about the main drugs involved in drug allergies.

Thus, in general, atopy is not a risk factor for the occurrence of drug allergy (a noticeable exception being chymopapain (21)). Consequently, drug allergy should not be included as part of the atopic status in epidemiological questionnaires.

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