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The multiple drug allergy syndrome: A matched-control retrospective study in patients allergic to penicillin

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Several studies have previously reported an increased rate of allergic reactions to drugs in patients with a history of drug allergy. The earliest such report by Smith et al.¹ showed that in patients with penicillin reactions, some of whom had positive skin test reactions to penicillin derivatives, a history of a drug reaction was present in 29.1%, compared with 11.5% in patients without a penicillin reaction. Sullivan et al.² found that 21% of patients with a history of immediate hypersensitivity to penicillin experienced immunopathologic reactions to non- β -lactam antibiotics. In children with a history of multiple antibiotic sensitivity, Kamada et al.³ reported that 35% had positive skin test reactions to penicillin reagents. Importantly, Moseley and Sullivan⁴ screened 37 patients with a history of allergic reactions to antimicrobial drugs and found that 13.2% subsequently reacted to a course of antimicrobial drug therapy, compared with only 1.4% of 74 matched control patients. The relative risk of developing an allergic drug reaction with a history of drug allergy in that study was 9.4. These results have been interpreted as indicating that some individuals are at increased risk of reacting to drug haptens that are quite different

immunochemically, although the mechanism for such hyperreactivity is unclear.

Because it was difficult in the above-mentioned studies to determine whether skin test-proven immediate hypersensitivity to penicillin was a risk factor for multiple drug allergies and because control groups were sometimes absent or not clearly defined, we compared retrospectively the frequency of multiple drug allergies in matched groups of: (1) patients with skin test-proven immediate hypersensitivity to penicillins, (2) patients allergic to penicillin with negative skin test results but a positive history, and (3) patients with vasomotor rhinitis.

METHODS

A total of 44 consecutive patients (41 of whom were female) who had a history of penicillin allergy characterized by (1) urticaria or angioedema, (2) maculopapular eruption, or (3) anaphylaxis and were documented as having positive immediate hypersensitivity skin test responses to the major and minor determinants of benzylpenicillin or semi-synthetic penicillins (group A), diagnosed as described previously,⁵ were matched in terms of sex and age with 44 patients who had a similar positive history of penicillin allergy but negative skin test responses to penicillin reagents (group B). A third group of patients with a diagnosis of vasomotor rhinitis and negative skin test responses to common inhalant allergens were matched in terms of age and sex with the groups A and B (group C). The clinical reactions to β -lactam antibiotics that occurred before skin testing for penicillin allergy in group A and group B are shown in Table I. No significant differences were seen in the types of clinical reactions reported in the two groups. The frequency and types of allergic reactions caused by

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TABLE I. Frequency of clinical reactions induced by β -lactam antibiotics in patients with immediate positive and negative skin test results

Clinical reaction	Number of individuals reacting (%)	
	Skin test positive* (group A)	Skin test negative (group B)
Maculopapular rash	19/44 (43.2)	18/44 (40.1)
Hives/angioedema	15/44 (34.1)	15/44 (34.1)
Local reaction to injection	2/44 (4.5)	3/44 (6.8)
Anaphylaxis	2/44 (4.5)	0/44 (0)
Serum sickness	0/44 (0)	1/44 (2.3)
No history†	6/44 (13.6)	7/44 (15.9)

*A positive skin test response is a wheal with flare that is more than 3 mm larger than the diluent control.

†Patients in whom penicillin allergy was reported but who could not remember or did not know the details of the reaction.

non- β -lactam drugs were assessed in groups A, B, and C by chart review. Occasionally, these reactions predated the history of penicillin allergy. Drug reactions were classified as being due to either non- β -lactam antimicrobial drugs or nonantimicrobials to ensure that there were no differences in reporting patterns. The patient information was determined by (1) a questionnaire that the patient completed before attending the clinic and (2) questioning by the physician at the time of assessment in the clinic. The study had an 80% power to detect a difference of 20% between the two groups.

RESULTS

As shown in Table II, seven patients in group A reported reactions to non- β -lactam drugs (15.9%); three had maculopapular reactions, three had hives and angioedema, and one had bronchospasm. In group B, 10 patients had allergic reactions to non- β -lactam drugs (22.7%), seven with maculopapular eruptions and three with urticaria and angioedema. The drugs inducing these reactions were sulfonamides (3), erythromycin (1), acetylsalicylic acid (1), tetracycline (1), and nifedipine (1) in group A and sulfonamides (7), erythromycin (1), codeine (1), and norfloxacin (1) in group B. Surprisingly, eight (18.2%) patients with vasomotor rhinitis had had an allergic reaction to a non- β -lactam drug, and these reactions were caused by sulfonamides (5), erythromycin (1), acetylsalicylic acid (1), and prochlorperazine (1). Overall, the frequency of allergic reactions to non- β -lactam drugs did not differ among the three groups ($\chi^2 = 0.691$, $p = 0.708$). Neither was there evidence for a significant increase in the frequency

TABLE II. Frequency and type of allergic reactions to non- β -lactam drugs and to non- β -lactam antimicrobial drugs in groups A, B, and C

Clinical reaction	Number of individuals reacting (%)		
	Group A	Group B	Group C
Maculopapular rash	3/44 (6.8)	7/44 (15.9)	3/44 (6.8)
Hives/angioedema	3/44 (6.8)	3/44 (6.8)	5/44 (11.4)
Bronchospasm	1/44 (2.3)	0/44 (0)	0/44 (0)

of allergic reactions to non- β -lactam antimicrobials in patients with either skin test-positive penicillin allergy (11.4%; 95% confidence interval, 1.8%-21%), skin test-negative penicillin allergy (18.2%; 95% confidence interval, 6.6%-29.8%), or vasomotor rhinitis (13.6%; 95% confidence interval, 3.4%-24%) ($\chi^2 = 0.86$, $df = 2$, $p = 0.651$). In comparison with patients who had positive skin test responses to penicillin, the odds ratio for developing an allergic reaction to a non- β -lactam antibiotic was 1.73 in group B and 1.23 in group C. In each of the three groups, there were two allergic reactions to non- β -lactam nonantimicrobial drugs.

DISCUSSION

Earlier studies have demonstrated that patients with a history of penicillin allergy are more likely to have allergic reactions to other drugs.¹⁻⁴ Some of these studies lacked matched control groups. The presence of immediate penicillin allergy was not always documented by skin testing, and data from patients with positive and negative skin test responses were combined. We compared the frequency of reactions to non- β -lactam drugs in age- and sex-matched groups of 44 patients with (1) skin test-proven penicillin allergy, (2) negative skin test responses to penicillin and a positive history of penicillin allergy, and (3) vasomotor rhinitis (control group). Surprisingly, we found no significant differences among the three groups, although the risk of having a reaction to a non- β -lactam antimicrobial was least in patients with skin test-proven penicillin allergy. The frequency of reactions to non- β -lactam antimicrobials in our study varied from 15.9% in group A, 22.7% in group B, and 18.2% in group C, similar to the range reported in previous studies, which was 11.5% to 29.1%.^{1,2,4}

The numbers of patients in this survey were sufficient to detect a difference of 20% between patients allergic to penicillin and nonallergic subjects and compare favorably with those of earlier

controlled studies, in which the numbers of patients with a positive history ranged from 24 to 37. Although reactions occurred to both non- β -lactam antimicrobials and nonantimicrobial drugs, the frequency of these reactions was not greater in group A or B, compared with group C, which suggests that the existence of a history of penicillin allergy causing a change in prescribing habits was not a factor and that there was no significant difference in reporting patterns. Only one patient in the vasomotor rhinitis group gave a history of penicillin allergy, and this patient had no history of a reaction to non- β -lactam drugs.

Because patients with a history of penicillin allergy in this study have an incidence of reactions to non- β -lactam drugs that is equal to that found in the vasomotor rhinitis group, they do have multiple drug reactions, because they reacted to both β -lactam and non- β -lactam drugs. But the risk of reacting to non- β -lactams is not increased in either patients with a positive history of penicillin allergy or those with skin test-proven penicillin allergy, when compared

with the control rhinitis group. So although this survey is also subject to the deficiencies of retrospective evaluation and limited by the preponderance of female subjects and sample size, it does suggest, in contrast to previous studies, that the development of penicillin allergy and non- β -lactam allergy are not associated, but occur independently.

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Occupational asthma caused by roasted coffee: Immunologic evidence that roasted coffee contains the same antigens as green coffee, but at a lower concentration

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Occupational asthma in coffee production plant workers was described by Figley and Rawling,¹ who implicated the castor bean. Cross-reactivity between castor beans and green coffee beans was later suspected but could not be demonstrated.² Although green coffee beans contain allergens, it is not known whether roasted coffee beans contain allergenic proteins. Zuskin et al.³ found that 9% of

45 coffee workers had immediate skin reactivity in response to roasted coffee bean extracts, whereas the frequency was 12% in the case of green coffee bean extracts. However, Lehrer et al.² were unable to identify allergens in roasted coffee. In this study, we present the case of a subject who showed

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