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Extreme cutaneous histamine sensitivity with hay fever and increased IgE concentrations in an unselected population

CAMPBELL S WITT, MARTIN S STUCKEY, ROGER L DAWKINS

Abstract

Cutaneous sensitivity to histamine, responses to prick tests with allergens, and serum IgE concentrations were measured and hay fever assessed by questionnaire in an unselected population to determine whether increased sensitivity to histamine is an independent phenomenon contributing to allergic disorders or may be caused by allergic reactions. Increased cutaneous sensitivity to histamine was strongly associated with an increased number of positive responses to prick tests, high serum concentrations of IgE, and hay fever. This new test is simple, cheap, applicable to schoolchildren, and provides useful information.

Introduction

Subjects suffering from hay fever have an increased sensitivity of the nasal mucosa to histamine¹ and positive responses to allergens on cutaneous prick testing.² It is not known whether this increased sensitivity to histamine is restricted to nasal mucosa or whether skin is also affected. Furthermore, it is not known whether increased sensitivity to histamine and positive responses to prick test allergens are distributed independently in the population, with hay fever representing the coincidence of both traits, or are associated.

We and others have reported that there is a range of cutaneous histamine sensitivity in the population.^{3,4} In this study we measured cutaneous sensitivity to histamine, allergen prick test responses, and serum IgE concentrations and assessed hay fever in an unselected population.

Department of Clinical Immunology, Queen Elizabeth II Medical Centre, Nedlands, Western Australia

CAMPBELL S WITT, PHD, senior research officer
ROGER L DAWKINS, FRCPA, FRACP, associate professor and head

State Health Laboratory Services of Western Australia
MARTIN S STUCKEY, FRACP, FRCPA, immunologist

Correspondence to: Associate Professor R L Dawkins, Department of Clinical Immunology, Royal Perth Hospital, GPO Box X2213, Perth, Western Australia 6001.

Subjects and methods

Study population—The adults studied consisted of 3953 out of a total of roughly 7000 adults in the Busselton electorate who were asked to participate in the 1981 Busselton health survey. Their ages ranged from 18 to 88 (mean 49.6). Five consecutive adults out of each 15 attending for the survey (that is, 889 of 2670) were skin tested. All primary schools in the Busselton electoral area and one of the two high schools were surveyed in 1983. Over 95% of children attending school on the day of the visit completed a questionnaire. The children's ages ranged from 6 to 19 (mean 11.5). A total of 1307 children were skin tested. The first 400 were selected by testing every second child surveyed while the 907 others were selected by testing every child surveyed.

Measurement of histamine sensitivity—Each subject was prick tested by the method of Pepys⁵ with four dilutions of histamine phosphate dissolved in phosphate buffered saline and a control solution of the saline alone. Two diameters of any weals that resulted were recorded 15 minutes after application of the solution and the mean diameter recorded. The lowest concentration of histamine that produced a weal diameter of at least 2 mm was designated the histamine threshold concentration for that subject. The concentrations of histamine used were 1.0, 0.1, 0.01, and 0.001 mg/ml. Subjects not responding to 1.0 mg/ml were said to have a histamine threshold concentration of 10 mg/ml. Correction for responses to the control saline was not attempted; 83 (9.2%) adults and 14 (1.1%) children responded to the control saline.

Allergen prick testing—All subjects were prick tested by the method of Pepys⁵ with 14 allergens—namely, six local grass pollens, two weeds, one tree pollen, cattle, cat, and dog danders, and extracts of aspergillus and *Dermatophagoides farinae* in 50% glycerinated saline (Holister-Stier Laboratories, Spokane, Washington, United States).³ Allergen groups were defined on the basis of strong cross reactivity. Thus a positive response to any one of five grass extracts (in adults) or six grass extracts (in children) was considered a positive reaction to the grass group. Two weed and two house dust mite extracts were treated similarly. This resulted in eight different allergen groups for adults and seven for children. Weals with an average diameter of at least 2 mm were counted as a positive response.

Measurement of IgE concentration—Total serum IgE concentrations were measured in a subset of 400 adults by PRIST (Pharmacia Diagnostics, Uppsala, Sweden). Subjects were selected for one of three reasons. (1) They had previously given a positive result on bee venom radioallergosorbent testing (n=110). (2) They had been previously HLA typed (selection for typing was random) (n=220). (3) They were part of a family study on IgE (families were not selected for allergic symptoms or high IgE concentration) (n=70).

Definition of hay fever—The diagnosis of allergic rhinitis and hay fever was made by questionnaire. Subjects were asked to answer the following questions with a yes or no. Have you ever had longlasting or frequent: (a) blockage of the nose, nasal stuffiness? (b) watery discharge from the nose? and (c) sneezing or itching of the nose, roof of mouth, or throat? (d) are the symptoms still present? They were also asked to circle the month(s) of the year when the symptoms in questions (a), (b), and (c) were present and when

they were worse. Allergic rhinitis was diagnosed if the respondents answered yes to both questions (c) and (d) and yes to either question (a) or (b). This included subjects with perennial allergic rhinitis and seasonal allergic rhinitis ("hay fever"). Hay fever was diagnosed if allergic rhinitis was diagnosed and the symptoms were only present or were worse during the months of August through to March (the pollen season in the south west of Western Australia). Children were simply asked if they suffered from hay fever. Parents were asked to help complete their child's questionnaire.

concentration ($p < 0.01$). Figure 2 shows the relation between cutaneous histamine sensitivity and IgE concentration. Over the range of histamine threshold concentration of 10 mg/ml to 0.01 mg/ml there was no apparent relation (as previously reported).³ A histamine threshold concentration of 0.001 mg/ml, however, was associated with a higher IgE concentration than were all other histamine threshold concentrations ($p < 0.05$). To determine whether the high allergen reactivity of subjects with a histamine threshold concentration of 0.001 mg/ml could be accounted for purely by their high

Reaction of subjects to different allergen groups on prick testing. Figures are numbers (percentages) of subjects (14 subjects who responded to saline were excluded)

Histamine threshold concentration	No of different allergens giving positive reaction							
	0	1	2	3	4	5	6	7
Adults								
0.001 mg/ml	0	6 (18.2)	2 (6.1)	9 (27.3)	3 (9.1)	5 (15.2)	4 (12.1)	3 (9.1)
>0.001 mg/ml	426 (55.0)	98 (12.6)	81 (10.5)	53 (6.8)	50 (6.5)	32 (4.1)	20 (2.6)	11 (1.4)
Children								
0.001 mg/ml	0	0	1 (2.7)	13 (35.1)	11 (29.7)	5 (13.5)	4 (10.8)	3 (8.1)
>0.001 mg/ml	736 (58.6)	212 (16.9)	140 (11.1)	67 (5.3)	45 (3.6)	34 (2.7)	18 (1.4)	4 (0.3)

Statistical methods—Raw data were used to create a computer file that was analysed by the statistical package for the social sciences.⁶ The relation between the prevalence of hay fever and histamine threshold concentration was analysed with a multiple group χ^2 test. The relation between IgE concentration and histamine threshold concentration was analysed by analysis of variance after first taking the natural logarithm (ln) of the IgE concentration in IU/ml. IgE concentrations in subjects with a histamine threshold concentration of 0.001 mg/ml were compared with those in subjects not having a histamine threshold concentration of 0.001 mg/ml by the modified least significant difference procedure for a posteriori contrasts (statistical package for the social sciences). Multiple regression analysis was used to determine whether the prediction of allergen reactivity could be improved by using both IgE concentration and cutaneous histamine sensitivity. The natural logarithm of IgE concentration was used as one independent variable, and response to 0.001 mg histamine/ml was dichotomised (scored as 1 if the subject responded and 0 if not) as the second independent variable.

Results

Association between extreme cutaneous histamine sensitivity and hay fever—Figure 1 shows the prevalence of hay fever in adults and children with different cutaneous histamine sensitivities. Adults with extreme cutaneous histamine sensitivity (histamine threshold concentration of 0.001 mg/ml) had a higher prevalence of hay fever, as did those who responded to the control saline. The association of extreme cutaneous histamine sensitivity with hay fever was also apparent in the children. Thirty (81%) children with a histamine threshold concentration of 0.001 mg/ml claimed to have hay fever compared with 102 (24%) with a histamine threshold concentration of 10 mg/ml ($p < 0.0001$). In children histamine threshold concentrations of 0.1 and 0.01 mg/ml were also associated with a higher prevalence of hay fever. We have previously shown that the histamine sensitivity curve is shifted to the left in children compared with adults. The higher prevalence of hay fever in children who are insensitive to histamine compared with adults may have been due to the relatively simple questionnaire definition of hay fever used in children compared with the more stringent criteria used for adults.

Association between extreme cutaneous histamine sensitivity and positive response to prick test allergens—As hay fever was more prevalent in subjects with a histamine threshold concentration of 0.001 mg/ml the response of this group to prick test allergens was analysed. The table shows that both children and adults in this group invariably reacted to cutaneous prick test allergens. Most of these subjects reacted to three or more different allergens, whereas most subjects with a histamine threshold concentration greater than 0.001 mg/ml did not react to any allergens. (The four children with a histamine threshold concentration of 0.01 mg/ml were also highly reactive to prick test allergens.) Subjects responding to the control saline were omitted from this analysis because of the difficulty of measuring reactions to specific allergens in this group.

Influence of extreme cutaneous histamine sensitivity and raised serum IgE concentrations on allergen responses—Serum IgE concentrations were measured in 400 of the 889 adults skin tested. An analysis of variance indicated that IgE concentration was dependent on histamine threshold

FIG 1—Prevalence of hay fever in adults and children with different cutaneous histamine sensitivities. Numbers in parentheses are numbers of subjects with each histamine threshold concentration. (Data were missing for two adults and 54 children.)

IgE concentration a multiple regression of allergen reactivity (number of positive responses out of eight allergen groups) with ln IgE and extreme cutaneous histamine sensitivity (positive response to 0.001 mg/ml) was performed. After correction for IgE concentration sensitivity to 0.001 mg histamine/ml was still significantly correlated with allergen reactivity ($p < 0.001$). Similarly, after correction for histamine sensitivity IgE concentration was still significantly correlated with allergen reactivity ($p < 0.001$). (The multiple correlation coefficient when ln IgE was entered as the variable was 0.49, regression coefficient 1.27, and standard error of the regression coefficient 0.129; the corresponding values when a histamine threshold concentration of 0.001 mg/ml was entered were 0.54, 4.20, and

0.836, respectively.) Thus allergen reactivity could be predicted more accurately by both IgE concentration and histamine sensitivity than by either factor alone.

Positive response to cutaneous prick testing with saline—Subjects responding to prick testing with saline resembled subjects with a histamine threshold concentration of 0.001 mg/ml in that they had an increased prevalence of hay fever (fig 1) and increased mean serum IgE concentration (fig 2).

FIG 2—Mean ln IgE concentration (SEM) in subjects with different cutaneous histamine sensitivities.

Discussion

As shown in this and previous studies a subset of the population has extreme cutaneous histamine sensitivity: we define this as reactivity to 0.001 mg histamine/ml. In this study we showed that extreme cutaneous histamine sensitivity was associated with at least a fourfold increase in the prevalence of hay fever; cutaneous reactivity to at least one and generally many prick test allergens; and increased serum IgE concentrations.

Two major possibilities need to be considered in attempting to explain these associations. Firstly, and perhaps most simply, extreme cutaneous histamine sensitivity may be acquired after exposure to an allergen or some other factor that leads to hay fever, cutaneous allergy, and increased serum IgE concentrations. Cockcroft *et al* have shown that deliberate exposure of subjects with asthma to inhaled allergens can lead to an increase in bronchial reactivity to histamine.⁷ Cutaneous histamine sensitivity may perhaps reflect a similar phenomenon, but cutaneous and bronchial histamine sensitivity are only weakly associated. Furthermore, although lymphocyte histamine receptors may be concerned in regulating the production of IgE,⁸ the lymphocytes of atopic subjects seem to be fairly insensitive. We conclude that exposure to allergen is unlikely to account for all of the associations observed.

In mice Munoz *et al* found that injection of a single protein from *Bordetella pertussis* leads to increased histamine sensitivity within hours.⁹ Serum IgE concentrations also increase but over a longer period of time. These effects seem to be mediated by β adrenergic blockade.¹⁰⁻¹² It is relevant that increased β adrenergic responses

have been reported in hay fever.¹³ Further work is required to evaluate the possibility that a change in β adrenergic responsiveness is one factor leading to cutaneous histamine sensitivity, increased serum IgE concentrations, increased cutaneous allergen reactivity, and hay fever. Alternatively, extreme cutaneous histamine sensitivity may reflect a more fundamental characteristic of certain subjects who are inherently hyperreactive to histamine. For example, a particular concentration or quality of histamine receptor might explain at least some of the associations described in this study.

We were surprised to find that subjects who responded to saline alone also had a higher prevalence of hay fever and an increased serum IgE concentration. These subjects may have been responding to minute amounts of endogenous histamine released by the mechanical trauma of prick testing. This phenomenon may also represent a mild form of dermatographism, which may also be associated with high serum IgE concentrations.¹⁴

Irrespective of the importance of our findings, we propose that titrations of histamine be used at the time of prick testing with allergens. If extreme cutaneous histamine sensitivity can be shown the possibility of hay fever is increased. The test is simple, cheap, and applicable to school age children. We emphasise that the relation between extreme cutaneous histamine sensitivity and allergen reactivity is not absolute. Histamine testing will by no means replace allergen testing, but it can be standardised and does seem to provide useful information.

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