Lack of Association between Allergic Contact Dermatitis and HLA Antigens of the A and B Series

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Abstract. A previous study of patients with allergic contact dermatitis yielded results which supported the hypothesis that the presence of certain HLA antigens led to a predisposition to allergen-specific reactions and others to multiple contact sensitivity. The present study was performed to test this hypothesis. 129 patients sensitive to one allergen only (either chromium, nickel, formalin or balsam of Peru) and 83 patients sensitive to two or more allergens were HLA typed regarding the A and B loci. A series of 368 persons matched with regard to sex, age and place of residence were used as controls. A tendency towards an association between HLA B7 and contact allergy was observed. No other data confirming the hypothesis mentioned above were obtained. Among 37 patients who also had atopic diathesis a decreased frequency of HLA B7 was found.

Key words: Allergic contact dermatitis; Contact sensitivity; HLA antigens; Delayed hypersensitivity

Sensitization to epicutaneous allergens was first shown to be genetically determined in guinea pigs. Corresponding data were presented for man in an early experimental study. Later clinical studies have given equivocal results. (For references see 7.) With the advent of new immunogenetic techniques the possibility of investigating immune responses was improved. Genetic control of immune responses of various types was shown to exist in several species. Paticularly relevant are the results of Schultz et al. (11) showing significant differences in levels of responses to the contact allergen picryl chloride among eleven mice strains. Their data revealed a clear association with the H-2 locus, the major histocompatibility locus in mice.

The aim of the present study was to test the hypothesis put forward in a preliminary study (7) that the presence of some HLA factors may create a predisposition to multiple contact sensitivity and others to allergen-specific reactions.

MATERIAL AND METHODS

The selection of the patients was based on the results of the previous study (7). From the six allergens dealt with in that work that showed statistically significant (uncorrected) associations with certain HLA factors, four were chosen as inclusion criteria for the group of 'single allergics', i.e. chromium, nickel, formalin and balsam of Peru. The term 'single allergics' means that only one positive reaction was observed when the patient was tested with a series of 25 standard allergens (Trolab, Copenhagen). This selection was made in order to test the hypothesis that an allergen-specific association occurs with certain HLA factors.

Another group of patients was selected to test the hypothesis that patients with HLA B7 have an increased tendency to contact sensitization in general. This group had positive test reactions to two or more of the allergens in the tray of standard tests. These were called 'double' and 'multiple' allergics respectively. 129 patients were assigned to the group of single allergics and 83 to the group of double or multiple allergics. No patient was included in more than one of these three groups. The patients were questioned and examined regarding the occurrence of psoriasis, dermatitis herpetiformis, diabetes mellitus, morbus Reiter and past or present atopy (atopic dermatitis, allergic rhinitis, allergic asthma). The material comprised 48 men with a mean age of 44.3 years (range 16–70) and 164 women with a mean age of 43.4 years (range 14–85).

The epicutaneous tests were carried out using Finn chambers® (9) on the patient's back for 48 hours. Only unequivocally positive tests were accepted (at least homogenous erythema with slight palpable infiltration) and they were all judged to be clinically relevant. The tests were read 48–96 hours after application on one or two occasions.

A control material was collected and matched as regards age ±5 years, sex and place of residence. The controls were mainly blood donors but in-patients from various wards were also included in order to satisfy the matching criteria, especially for the higher age groups. Of the entire control material of 368 persons, 288 were blood donors and 80 were in-patients. One control was selected for each patient for the most prevalent hypersensitivity—nickel allergy—and two controls for the other allergies. The patients resided in five different areas, four in the county of Västerbotten in northern Sweden and one in the Linköping area in the southeastern part of Sweden. In Västerbotten variations have been found to exist in the frequencies of various blood groups (1). The division of the county was made on the basis of these differences (as described in 16).

The HLA typings were performed using the microcytotoxicity test. At least two sera were used for each of the 21 specificities tested (A series, nos. 1, 2, 3, 9, 10, 11, 28; B series, nos. 5, 7, 8, 12–15, 17–18, 22, 27, 35, 40, 47). All typings were performed by the same laboratory.

Table I. *HLA antigen frequencies as percentages of the entire material (%)*

The material is subdivided into groups with contact sensitivity to one of four different allergens in a standard patch test tray ('single allergics') and groups sensitive to two ('double') or three or more different allergens ('multiple'). The values for the group of atopics are also shown. Cr = potassium bichromate, Ni = nickel, B Peru = balsam of Peru, *n* = number of individuals

	Single allergics								
	Cr	Ni	Formalin	B Peru	Total	Double	Multiple	Atopics	Controls
n...	22	56	27	24	129	39	44	37	368
A 1	5	23	48	25	26	21	30	24	20.1
2	68	63	56[b]	63	62	59	61	59	61.7
3	27[a]	23	33	21	26	33	23	24	31.3
9	14	27	15[a]	29	22	10	23	14	20.7
10	14	20	19	21	19	10	11	22	13.0
11	5	9	0	0	5	18	14	8	9.5
28	18	7	0	4	7	10	7	8	4.6
B 5	5	2	15	4	5	3	9	5	7.9
7	36[a]	32	37[a]	46[a]	36[a]	36[a]	36[a]	11	30.7
8	9	29[a]	41	21	26	13	23	30	23.1
12	36	25	26	50	32	26	27	32	27.4
13	0	4	0	4	2	0	0	0	0.3
14	5	2	0	0	2	0	0	5	1.1
15	23	29	7	13	20	23	23	19	22.8
17	0	2	0	0	1	3	2	0	4.3
18	9	4	4	8	5	3	9	0	5.2
22	0	4	0	4	2	3	2	0	3.5
27	23	18	7	8	15	23	20	19	17.9
35	0	13	7	13	9	18	9	22	12.8
40	23	14	19	17	17	23	18	22	21.2
47	0	2	0	0	1	0	2	0	3.5
A3+B7	14	13	15	8	12[a]	15[a]	7[a]	0	19.0

[a] Antigens statistically (uncorrected) increased and [b] decreased in the preliminary study (7).

Blood samples from some of the patients were also analysed regarding blood groups, serum proteins and red blood cell enzymes. This analysis and its results will be published in a separate paper (2).

RESULTS

In the previous study, five HLA antigens had a distribution suggesting an association with contact allergy. In the present study those five HLA antigens did not show any significant deviations in any patient group when compared with the matched controls. This was the case also when comparison was made with the entire control material, as seen in Table I. However, an increase in the frequency of HLA B7 was observed in all instances tested. Carriers of HLA B7 have a relative risk, calculated on the figures forming the basis of Table I, varying between 1.9 for contracting contact sensitivity to balsam of Peru and 1.3 for chromium sensitivity.

The regression of HLA B7 and the combination of A3+B7 on the number of allergies found in the previous study was not confirmed in the present material.

There were 37 patients with atopic diathesis. The HLA antigen frequencies are shown in Table I. The frequency of HLA B7 was only 11% amongst those patients with both allergic contact dermatitis and atopic diathesis, compared with 41% among patients with contact allergy only ($p<0.001$). No other significant differences between the atopics and the other patients were found. Of the other diseases registered there were 2 cases of psoriasis and 1 of dermatitis herpetiformis.

DISCUSSION

The most reliable way of clarifying the validity of results obtained in a complex multitest situation is to perform a new, repeat investigation (4). In the present repeat study, controls were collected who were matched not only with regard to age and sex but also to place of residence. This was done in an

attempt to compensate for the variations in exposure to the ubiquitous allergens dealt with and for possible ethnic differences in the population.

Animal experiments have given overwhelming evidence of a linkage of genes controlling immune responses to the animal counterpart of the HLA locus in man. This linkage may not exist for all immunologic functions and not in all species. For instance, the genes controlling the level of IgE production in man are not linked to the HLA locus, in contrast to the conditions in mice (3). Our results are consistent with this latter study, as HLA antigens of at least the A and B series do not reveal any statistically significant associations with the various contact allergens studied in our population. There are still some indications, however, that HLA B7 may be associated with contact allergy. The HLA B7 frequency was somewhat higher in the patient group than in the controls and there was a significant difference in HLA B7 frequency between atopic and non-atopic patients. As an isolated phenomenon the tendency towards an overrepresentation of HLA B7 among our patients is not strong enough to indicate a real biological significance. However, HLA B7 has been reported to have an allergen-specific association with ragweed allergen E (8) and ragweed hayfever (6). Taken together, this information indicates that the possibility of a relationship between HLA factors and certain allergens should not be completely rejected, even if the majority of the associations found in our previous study could not be verified. This finding is in agreement with those of Roupe et al. (10) who did not find any association between HLA antigens of the A, B and C series and sensitivity to chromium, and of Silvennoinen-Kassinen et al. (12) who also failed to find any association between contact sensitivity to nickel and HLA antigens of the A, B, C and D series.

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An Appraisal of Routine Direct Immunofluorescence in Vulvar Disorders

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Abstract. Sixty-four biopsies were obtained from patients with a variety of vulvar disorders for direct immuno-