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HLA -A, -B, -C and -DR Antigens in Individuals with Sensitivity to Cobalt

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In a skin investigation of 853 individuals working with hard metal manufacturing 39 cases of cobalt allergy were found. Thirty-five of the individuals with cobalt sensitivity and 102 matched controls were HLA-A, -B, -C and -DR typed. No significantly deviating HLA antigen frequencies were observed when the two groups were compared. Thus, there are no signs that a certain HLA antigen would dispose to cobalt allergy. In the cobalt sensitive group the B7 positive individuals showed particularly often simultaneous reactions to other contact allergens ($p=<0.025$). The B12 positive individuals had low reactivity ($p=<0.0001$) while the A28 positive showed high reactivity ($p=<0.015$). *Key words: Cobalt sensitivity; Hard metal manufacturing; HLA-typing.* (Received June 10, 1983.)

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Previous HLA typing of individuals with contact sensitivity (1–5) have with one exception (5) not given any evidence of an association between contact dermatitis and HLA class 1 antigens. Only one incomplete study concerning HLA-D has been performed (2).

The Langerhans' cells play an important role in the contact dermatitis reaction (6). They carry class 2 (HLA-DR) structures which present foreign antigens to unstimulated helper T cells. The main lymphocytes which appear in contact eczema reactions are the helper T cells (7), which are supposed to have a regulatory function in the type IV allergic reaction. A smaller part of the inflammatory lymphocyte infiltration consists of suppressor cells which are considered to co-react with the helper cells in the immune response. Human Langerhans' cells have been shown to present antigens of PPD (7) and nickel (8) to purified autologous lymphocytes in vitro thereby inducing a proliferative response. For this reason HLA antigens of both classes 1 and 2 have been included in this study in an attempt to correlate certain HLA antigens to cobalt sensitivity.

MATERIALS AND METHODS

Thirty-five out of 39 hard metal workers with sensitivity to cobalt (9) were HLA typed. Eleven of them showed +++ reactions, 22 ++ reactions and 2 + reactions. Twenty-three of them showed isolated cobalt sensitivity, 7 concomitant sensitivity to cobalt and nickel, 2 to cobalt and chromium, one to cobalt, nickel and chromium, one to cobalt and tetramethylthiuram disulphide and finally one to cobalt and balsam of Peru. The diagnosis of contact sensitivity was verified with positive patch tests according to the European standard method. Each cobalt sensitive individual, except a Lebanese woman, was matched with three controls, altogether 102 individuals. The matching was performed according to sex, ethnic group, type of hard metal work, family atopy and/or own atopy. Individuals with metal allergy were excluded from this group.

HLA -A, -B and -C typing

Lymphocytes were prepared from defibrinated blood by Ficoll-Isopaque centrifugation. The typing was performed with the microlymphocytotoxicity technique described by Kissmeyer—Nielsen & Kjerbye. The following specificities were included in the study:

HLA -A 1, 2, 3, 9, 10, 11, 28, W19
HLA -B 5, 7, 8, 12, 13, 14, 15, 17, 18, 27, 37, 40, W16, W21, W22, W35, W41
HLA -C W1, W2, W3, W4

HLA -DR typing

The HLA-DR tests were performed with a technique previously described (10). Well defined HLA -DR antisera, employed in international HLA workshops, were used. With these sera HLA -DR 1, 2, 3, 4, 7 and W8 could be detected. At least two sera defining the specificity were used.

Statistics

Relative risk (RR) values were calculated according to Svejgaard et al. (11). Corrected p-values were calculated after multiplication by the number of HLA specificities tested (in this study 35). The chi-square (X^2) test or Fisher's exact test were used to evaluate differences between subgroups in the material.

RESULTS

The phenotype frequencies and relative risk (RR) values of the HLA -A, -B, -C and -DR antigens are shown in Table I.

Among class I antigens (HLA -A, -B and -C) the highest RR values concern BW22 (RR=4, 7), BW21, A11, B5 and B18 (RR=2, 3) in decreasing order. The RR-values do not significantly deviate from 1.

The frequencies of the class 2 (HLA -DR) antigens do not deviate from those among the matched controls.

Two different DR antigens were identified in 37% of the patients and in 43% of the matched controls. One DR antigen was found in 54% and 47% and no DR antigen was found in 9% and 10% for the patient- and control groups, respectively.

When the 23 patients with isolated cobalt sensitivity (66%) were compared to those 12 with simultaneous reactions to other contact allergens (34%) it was observed that five out of 7 B7 positive individuals belonged to the group with multiple reactions, $p=<0.025$. One out of 4 DR7 positive patients (25%) and all 4 DRW8 positive belonged to the isolated cobalt sensitivity group, $p=<0.08$ and 0.17 respectively.

Eleven patients showed very strong (+++) patch test reactions to cobalt. Four out of 5 A28 positive individuals belonged to the group with +++ reactions, $p=<0.015$. The great majority 10/11 (91%) of the B12 positive and all 4 DRW8 positive individuals ($p=<0.0001$ and 0.20 respectively) belonged to the groups with ++ and + reactions.

DISCUSSION

Previous HLA studies in contact dermatitis have not included HLA -DR antigens. HLA-DR antigens are present on the surface of Langerhans' cells, and can present foreign antigens to unstimulated T helper cells thereby initiating the immune response. Therefore they should be of greater interest as genetic markers in contact dermatitis than the class I (HLA -A, -B and -C) gene products.

The previous negative reports (1-4) of HLA antigens as genetic markers in patient groups with nickel and/or chromium sensitivity do not exclude a connection between contact sensitivity and HLA antigens. In the HLA system there is a linkage disequilibrium which, however, is not so strong that lack of association with any HLA-B antigen can eliminate the possibility of an association with HLA-DR antigens.

Hard metal manufacturing involves heavy exposure to cobalt. If genes within the major histocompatibility system determine the ability to react against cobalt, the possible association between HLA antigens and contact sensitivity to cobalt would be ideal to study among hard metal workers. The careful testing and classification of the workers made it possible to perform a careful matching and thus to increase the possibility to discover a possible association.

However, no significantly deviating HLA pattern was found when the patient and control groups were compared and thus no signs that a certain HLA antigen would dispose to cobalt sensitivity.

The summation of gene frequencies for the DR specificities tested are among Scandinavians, 0.75 which means that there is a blank of 0.25. In this study the blank is of equal size in both groups. Thus, we do not have to suspect that we have missed a more pronounced

Table 1. *HLA -A, -B, -C and -DR phenotype frequencies in patients with contact sensitivity to cobalt and their matched controls with calculated relative risk (RR) values*

HLA	Patients $n=35$	RR	Controls $n=102$	Significance level
A1	0.26	1.01	0.25	
A2	0.63	0.94	0.64	
A3	0.26	0.72	0.32	
A9	0.14	1.05	0.14	
A10	0.17	1.90	0.10	
A11	0.17	2.81	0.07	$X^2=3.01$ NS
A28	0.14	1.96	0.08	
AW19	0.11	0.81	0.14	
B5	0.14	2.67	0.06	$X^2=2.35$ NS
B7	0.20	0.69	0.26	
B8	0.17	0.55	0.27	$X^2=1.43$ NS
B12	0.31	1.88	0.20	
B13	0.03	0.35	0.08	$X^2=0.95$ NS
B14	0.03	1.47	0.02	
B15	0.26	0.66	0.34	
B17	–		0.07	
B18	0.09	2.30	0.04	$X^2=1.11$ NS
B27	0.20	1.88	0.12	
B37	0.06	2.00	0.03	
B40	0.17	0.80	0.21	
BW16	0.03	1.47	0.02	
BW21	0.03	2.97	0.01	$X^2=0.58$ NS
BW22	0.09	4.69	0.02	$X^2=2.73$ NS
BW35	0.11	0.97	0.12	
BW41	–		0.01	
CW1	0.11	1.19	0.10	
CW2	0.14	1.72	0.09	
CW3	0.40	0.78	0.46	
CW4	0.03	0.40	0.07	$X^2=0.71$ NS
DR1	0.14	0.73	0.19	
DR2	0.29	1.30	0.24	
DR3	0.23	0.78	0.27	
DR4	0.40	1.12	0.37	
DR7	0.11	0.69	0.16	
DRW8	0.11	1.07	0.11	

association concerning DR antigens at present impossible to identify due to lack of antisera.

Lidén et al. (4) reported a trend that B7 positive individuals had an increased tendency to contact sensitization in general. The same trend is found in this study where 5 out of 7 B7 positive individuals were among those 12 with concomitant reactions.

The interesting fact that individuals with strong and weak test reactions dissociate regarding HLA-specificities has not been reported previously, and may indicate HLA associated differences in immune reactivity and/or inflammatory response.

The BW21 antigen found in increased frequency among individuals sensitive to nickel (5) was found in only one of our patients and she was nickel sensitive.

In a Finnish study of HLA and nickel contact sensitivity (2) the lowest, but statistically insignificant, p values concerned the BW22 and DW4 antigens. In our study none of the 3 BW22 positive cobolt sensitive patients showed concomitant reactions to nickel and the DR4 frequency was equal to that of the controls.

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