HLA and Insulin-dependent Diabetes in South African Negroes

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Summary. The HLA antigens of 57 South African negroes with juvenile-onset, insulin-dependent diabetes were determined. The frequency of B8 was increased (29.8% vs 13.9%) as was the frequency of B14 (17.5% vs 6.1%). The frequency of patients with either one of these cross-reactive antigens was significantly increased after correction for the number of antigens tested (45.6% vs 19.2%, P (corrected) <0.005).

Key words: HLA, insulin-dependent diabetes, negroes.

Numerous studies of the HLA system in diabetes have shown clear associations between insulin-dependent diabetes mellitus (IDDM) and certain HLA antigens. Increased frequencies of HLA B8, B15, B18, Cw3, Dw3, Dw4, DRw3 and DRw4 have been found in white Caucasian populations with this disease [1]. An association between HLA B8 and IDDM has also been found in South Africa Indians [2] and in American Blacks [3, 4], but not in Japanese with IDDM [5, 6].

Materials and Methods

The diabetic patients attended the Diabetic Clinic of the King Edward VIII Hospital, Durban which is the main teaching hospital of the University of Natal Medical School. The patients were characterised by an acute onset of illness below 35 years old, and a dependence on insulin for control of symptoms and prevention of ketosis [7]. They were typed over a two year period for the HLA-A-B-C antigens and the frequencies were compared with those found in a healthy control population, many of whom were typed for International Workshops [8, 9]. The Negro population of Durban consists mainly of Zulus and the patients and controls studied by us were of pure descent. A total of 180 antisera were used in a two-stage microlymphocytotoxicity test [10] to determine the HLA

antigens of 57 Negroes with IDDM. Lymphocytes were isolated on a Ficoll-Hypaque density gradient [11]. Frequency differences were tested for significance with a χ^2 test (without Yates' correction) and the resulting probabilities corrected by multiplication by the number of antigens tested.

Results

Table 1 shows the antigen frequencies in the IDDM patients compared with the controls. The distribution of alleles at the A and B loci conform to Hardy-Weinberg equilibrium.

There were no significant differences between diabetics and control subjects at the A and C loci. The frequency of HLA B8 was increased in the diabetics (29.8%) compared to the controls (13.9%) but this was not significant after correction for the number of antigens tested. The frequency of HLA-B14, on the other hand, was significantly increased even after correction (17.5% vs 6.1%, P (corrected) <0.04). As HLA-B8 and B14 form part of a cross-reacting group, the number of patients and controls with either of these antigens were compared. The difference in the frequencies (45.6%) was highly significant ($P_c <0.004$). The relative risk (3.5) was about the same as for B14 alone (3.3) but greater than the relative risk for B8 alone (2.6).

There was a slightly stronger negative association between Bw42 and IDDM. The relative risk was 0.25 and the uncorrected $p <0.005$. This was no longer significant after correction for the number of antigens tested.

Discussion

Nerup et al. [12] discuss the possibility that there are two genes conferring increased risk of IDDM: one associated with B8 and the other with B15 or B18. In

Table 1. Percentage frequency of HLA antigens in Negroes with insulin-dependent diabetes mellitus (IDDM)

HLA	Control n = 756	IDDM n = 57	Control n = 756	IDDM n = 57
A1	5.8	7.0	B7	16.0
A2	20.1	14.0	B8	13.9
A3	13.5	10.5	B13	4.8
A11	0.1	0	B14	6.1
Aw23	19.2	26.3	B15	5.8
Aw24	3.3	3.5	B16	2.4
A25	13.9	5.3	B17	38.1
A26	7.5	7.0	B18	3.8
A28	20.0	24.6	Bw21	0.5
A29	16.7	12.3	Bw22	0
Aw30	39.6	36.8	B27	0.3
Aw31	12.6	10.5	Bw35	7.3
Aw32	1.4	8.8	B37	0
Aw33 ^d	2.7	3.5	Bw60	1.6
Only one antigen detected	23.6	29.8	Bw61	0
Cw1 ^d	0	1.8	Bw41 ^d	2.1
Cw2 ^d	18.5	21.1	Bw42	27.7
Cw3 ^d	9.6	17.5	Bw44	16.0
Cw4 ^d	15.8	17.5	Bw45	6.4
Cw5 ^d	4.1	3.5	Bw51	2.7
			Bw52	0
			Bw53	3.4
B8+B14	19.2	45.6 ^c	Only one antigen detected	41.1
				45.6

^a P < 0.005^b P < 0.001^c P < 0.0001^d N = 146 (Number of controls)

all the Caucasian populations studied to date the association with B8 has been a constant finding. The relationship with B15 and/or B18 has been confined to certain population groups. The association of these antigens appears to be secondary to the increased frequency of DRw3/Dw3 and DRw4/Dw4 [1, 13].

This study has demonstrated an increased frequency of B8 and of B14 in South African Negroes with IDDM. Since these antigens form a cross-reacting group it is probable that the same susceptibility gene is associated with either of these antigens in Negroes. Alternatively, it may be postulated that another susceptibility gene, associated with B15 or B18 in Caucasians, is linked to B14 in Negroes. This latter explanation seems less likely.

The Bw42 antigen has been detected only in Black populations. It is, however, one of the cross-reacting antigens associated with B7 which may be linked to some protective mechanism against IDDM [12]. The protective effect is not associated with HLA B7 in Negroes, indeed, the frequency of the

antigen is greater in the IDDM group than in the controls. The relatively low frequency of Bw42 in Negroes with IDDM may have a bearing on the low prevalence of IDDM in Negroes. Alternatively, it may be a reflection of the increased frequency of B8 and B14. The difficulties of establishing the significance of a negative association between HLA and disease have been discussed by Svejgaard et al. [13].

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