Brief Notes and Comments

Histocompatibility Antigens and Diabetic Retinopathy

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SUMMARY

Of 160 patients with onset of diabetes at or after 30 years of age, the 84 with no evidence of diabetic retinopathy were found to have significantly increased prevalences of HLA-A1 and B8 when compared with the 76 with retinal complications or with the 282 healthy blood donors. In addition, in 90 patients with onset of diabetes before age 30 years, we could confirm the reported significant increase of HLA-B8 and decrease of B7, but no differences were noted between those juvenile-onset diabetics with and those without retinopathy. DIABETES *26*:997-99, October, 1977.

The prevalences of HLA-A1, B8, B18, Bw15, and Cw3 are reported to be increased and that of B7 to be decreased in patients with juvenile-onset diabetes mellitus.[1-5] Increased HLA-A1 and B8 are also noted in the juvenile-onset diabetics with severe nephropathy and microangiopathy.[6] The present study compares HLA frequencies in juvenile- and adult-onset diabetics with and without retinopathy.

MATERIALS AND METHODS

Two hundred and fifty Caucasian patients with diabetes mellitus were recruited for HLA typing. There were 90 patients with onset of diabetes before age 30 years and 160 with onset at or after age 30. HLA typing for 28 specificities was carried out by the Missouri-Illinois Regional Red Cross Blood Program with lymphocyte microcytotoxicity methods.[7] Two hundred and eighty-two healthy blood donors, typed concurrently, served as controls. Retinopathy with or without proliferative changes was diagnosed by direct and indirect ophthalmoscopy through dilated pupils.

RESULTS

When compared with controls, increased frequencies of HLA-A1, B8, and the combination of A1 and B8, as well as a decrease of B7, were noted in juvenile-onset diabetics (table 1). The 60 per cent prevalence of HLA-B8 in diabetics with onset before age 30 years was significantly greater than the 20 per cent of controls ($P = 2.0 \times 10^{-9}$) and the 31 per cent of patients whose diabetes began at 30 years of age or older ($P = 9.6 \times 10^{-6}$). No significant differences from the control group were found in the juvenile diabetics for prevalences of B18 or Bw15. The HLA antigen frequencies of 57 juvenile-onset diabetics with retinopathy did not differ from those of the 33 without retinopathy (table 1).

In the 160 patients whose diabetes began at 30 years of age or older, altered HLA frequencies were found only in those without retinopathy (table 2). Frequencies in the 76 patients with adult-onset diabetes who presented with retinopathy did not differ from those of controls. However, the 84 diabetics with no retinopathy demonstrated significantly increased prevalences of HLA-A1, B8, and the combination of both A1 and B8 when compared with either the retinopathy group or the controls (table 2).

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TABLE 1

Prevalence of HLA antigens in juvenile-onset diabetes mellitus
(age onset below 30 yr.)

Diabetic	No. pts.	A1 no. (%)	B8 no. (%)	A1+B8 no. (%)	B7 no. (%)	B18 no. (%)	Bw15 no. (%)
No retinopathy	33	13 (39%)	19 (58%)	13 (39%)	3 (9%)	4 (12%)	4 (12%)
Retinopathy	57	23 (40%)	35 (61%)	22 (39%)	6 (11%)	5 (9%)	10 (18%)
Total	90	36 (40%)	54 (60%)	35 (39%)	9 (10%)	9 (10%)	14 (16%)
Control	282	80 (28%)	56 (20%)	44 (15%)	87 (31%)	21 (8%)	33 (12%)
P* (Total vs. Control)		0.038	2.0×10^{-9}	2.6×10^{-6}	8.3×10^{-5}	0.44	0.34

*Chi-square analysis (not corrected for the 28 specificities tested).

TABLE 2

Prevalence of HLA antigens in adult-onset diabetes mellitus
(age onset 30 or more yr.)

Diabetic	No. pts.	A1 no. (%)	B8 no. (%)	A1+B8 no. (%)
No retinopathy	84	48 (57%)	36 (43%)	32 (38%)
Retinopathy	76	24 (32%)	14 (18%)	10 (13%)
Control	282	80 (28%)	56 (20%)	44 (15%)
P (No retinopathy vs. Retinopathy)		0.0012	0.00087	0.00034
P (No retinopathy vs. Control)		1.2×10^{-6}	2.0×10^{-5}	8.2×10^{-6}

DISCUSSION

The present report confirms the highly significant increased prevalence of HLA-B8 and the decrease of B7 in juvenile-onset diabetics compared with healthy blood donors.[1-6] No differences are noted, however, between juvenile-onset diabetics with and those without retinopathy. The increase of A1 in diabetics with onset before age 30 years is not significant when corrected for the 28 specificities tested. The increased A1 is probably secondary to the increased B8, since A1 and B8 are known to be in linkage disequilibrium in the Caucasian population.[8] In fact, of the 36 juvenile-onset diabetics with the A1 antigen, 35 (97 per cent) also had B8 (as against 55 per cent of controls and 58 per cent of adult-onset diabetics).

The significant increases of HLA-A1 and B8 in adult-onset diabetics without retinopathy above those of patients with retinopathy or the controls appear to be new findings with interesting implications. Here the increase in A1 may be a primary factor, and the increase in B8 may be due in part to linkage disequilibrium. Thus, of 36 adult-onset diabetics without retinopathy who have the HLA-B8 antigen, 32 (89 per cent) also have A1, while only 79 per cent of controls, 65 per cent of juvenile-onset diabetics, and 71 per cent of adult-onset diabetics with retinopathy have A1. One may postulate heterogeneity in diabetes with onset at or after age 30 years: one group with increased prevalences of HLA-A1 and B8 and less predilection to retinopathy and another group with no significant increases of A1 or B8 over those of nondiabetics, but with a greater chance of developing retinopathy. To test this hypothesis, prospective studies of newly discovered patients with adult-onset diabetes are planned to include HLA typing, sequential ophthalmoscopic examinations, fluorescein angiography, and quantitative vitreous fluorophotometry.[9] Also in progress are comparisons in adult-onset diabetics of the association of HLA-A1 and B8 with such factors as family history of diabetes, sex, insulin dependence, ease of diabetic control, concentration of hemoglobin A_{1c}, duration of diabetes, capillary basement membrane thickness, adrenocortical function, and corticosteroid responsiveness.[10]

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