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Diabetologia

HLA and Retinopathy in Type 1 (Insulin-Dependent) Diabetic Patients in Iceland

Dear Sir,

The association of certain HLA phenotypes and Type 1 (insulin-dependent) diabetes in various populations, including Iceland, is now well established [1–2]. A relationship between some of these HLA specificities and diabetic retinopathy has been claimed [3–5, 10] and refuted [6–9]. We have had an unique opportunity to study this question in the Icelandic diabetic population.

One hundred and sixty Type 1 diabetic patients have been HLA and Bf typed. This represents approximately 60% of all known insulin-dependent diabetic patients in Iceland. A large proportion of these (128) were genotyped. In addition, for comparison, 228 healthy subjects were also HLA and Bf genotyped. 212 (76% of the total) Type 1 diabetic patients have been carefully screened by fundus photography for the presence of retinopathy by an experienced ophthalmic surgeon with a special interest in diabetes who did not have detailed clinical information about the individual patients. From this material the following groups were compiled for the present analysis: – (1) patients with duration of diabetes of 15 years or more with an age of onset of diabetes of less than 30 years. These patients were divided into those with proliferative retinopathy and those with no retinopathy. (2) patients were also assorted into those with duration of diabetes of 10 years or more irrespective of the age at diagnosis; again these patients were divided into two groups according to the presence or absence of retinopathy.

Table 1. HLA-types and proliferative retinopathy in Icelandic insulin-dependent diabetic patients with a duration of disease ⩾ 15 years

HLA-type	Normal population (n = 456)	Proliferative retinopathy (n = 22)		Retinopathy absent (n = 20)		Risk ratio for retinopathy
	Frequency	Frequency	Relative risk	Frequency	Relative risk	
B8	0.081	0.227	3.33	0.200	2.84	1.2 increased
B15	0.074	0.227	3.68	0.300	5.36	1.5 decreased

Duration of diabetes: 24.2 ± 7.6 years (range: 15–38 years) versus 20.1 ± 4.2 years (range: 15–30 years) (t = 1.55, NS)
Age at diagnosis: 12.8 ± 7.4 years (range 2–27 years) versus 15.5 ± 10.1 years (range: 6 months – 29 years) (t = 0.69, NS)
(n = haplotypes; NS = not significant)

Table 2. All degrees of retinopathy in relation to HLA-types in insulin-dependent diabetic patients in Iceland with duration of diabetes ⩾ 10 years

HLA-type	Normal population (n = 456) Frequency	Retinopathy present (n = 44)		Retinopathy absent (n = 54)		Risk ratio for retinopathy	p[a]
		Frequency	Relative risk	Frequency	Relative risk		
A2	0.280	0.318	1.20	0.463	2.22	1.9 decreased	0.116
B8	0.081	0.205	2.93	0.204	2.91	1.0 –	0.397
B15	0.074	0.136	1.97	0.315	5.76	2.9 decreased	0.045
Bfs-B15-A2 ∅	0.022	0.000	0.80	0.130	6.83	8.5 decreased	0.120

Duration of diabetes: 16.7 ± 4.0 versus 15.3 ± 5.2 years (t = 1.5, NS) (mean ± SD)
Age at diagnosis: 19.9 ± 13.6 versus 17.6 ± 12.6 years (t = 0.6, NS)
(n = number of haplotypes; NS = not significant)
∅ Calculations based on 26 haplotypes for retinopathy present, 46 for retinopathy absent (Haldane's method). Mean duration of diabetes: 16.7 ± 4.0 versus 15.6 ± 5.4 years (t = 0.9). Mean age at diagnosis: 19.5 ± 16.7 versus 18.2 ± 12.7 years (t = 0.3) for present versus absent retinopathy
[a] Two-tailed Fisher's exact test

The frequencies and relative risks of HLA-B8 and B15 in relation to the presence of proliferative retinopathy or the absence of retinopathy in patients with duration of diabetes of 15 or more years are shown in Table 1. HLA-B8 is similarly distributed in both groups. In contrast, HLA-B15 shows a reduced frequency and relative risk in the group with proliferative retinopathy. Table 2 shows the results in those subjects with a duration of diabetes of 10 years or more. A similar pattern of results can be observed. Thus there is a significantly reduced risk ratio for retinopathy of 2.9 (p = 0.045). The same conclusions emanate from the Bfs-B15-A2 haplotype results, giving a decreased risk ratio of 8.5 for retinopathy (p = 0.12).

These findings are in contrast to previous reports which have found an increased frequency of B15 and of DR4 in patients with proliferative retinopathy [3, 10]. HLA-B8 has also been reported to be increased in patients with proliferative retinopathy [4, 5], but again we were unable to confirm this.

These discrepancies may indicate a variability of HLA associations with Type 1 diabetic patients in different populations. In Iceland both HLA-B8 and B15 are associated with the disease. The haplotype Bfs-B8-A2 represents the strongest association with diabetes but, unlike the likewise diabetes-associated Bfs-B15-A2 haplotype, it was not found to be related with retinopathy.

Yours sincerely,

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Criteria for Patient Selection for Pancreatic Transplantation

Dear Sir,

Although the techniques of pancreatic transplantation have changed since the first clinical transplant performed in 1966 [1], the indications for using this potential modality of treatment in insulin-dependent diabetic patients have not been properly established. The various criteria for patient selection for pancreatic transplantation could be grouped as follows: (1) early pancreatic transplantation in patients with Type 1 (insulin-dependent) diabetes, who have not shown signs of renal involvement (serum creatinine less than 265 μmol/l), but have shown definite progression of other complications, such as neuropathy, retinopathy and other signs of microangiopathy; (2) synchronous pancreatic and renal transplantation in Type 1 diabetic patients with advanced secondary complications [2, 4], and (3) asynchronous renal first and then pancreatic transplantation in patients with diabetic end-stage renal disease [5, 6].

Since the inception of our programme in January 1980 (until May 1981), we have seen 40 patients with Type 1 diabetes who have sought pancreatic tranplantation. Nineteen patients (48%) were rejected after the initial medical assessment. Of these 19 patients, 15 had Type 1 diabetes of 6–10 years' duration with no evidence of secondary complications, and four patients had too advanced nephropathy and were referred directly for kidney transplantation. The remaining 21 patients were carefully assessed. Seventeen patients (42% of those initially presenting) were accepted as transplant candidates. Four patients (10%) were rejected, three because of psychiatric unsuitability and the fourth did not have secondary manifestations of the disease.

Since rejection episodes appear to be more frequent in preuraemic diabetics than in uraemic diabetic patients receiving synchronous pancreatic and renal transplants [7], we have recently uti-

Table 1. Results of segmental pancreatic transplantation in six patients with Type 1 diabetes

Patient	Age (years)	Sex	Characteristics of donor pancreas	Pancreas – with or without kidney transplant	Duration of pancreas transplant	Cause of pancreas removal	Survival
1	37	M	Cold storage – 3 h Hypothermic pulsatile perfusion – 13 h Warm ischaemia – 30 min	Pancreas alone	None Pancreas removed 2 days	Ischaemic necrosis due to ischaemic injury and poor perfusion	Alive on insulin
2	20	F	Hypothermic storage – 4 h 29 min	Pancreas alone	60 days Pancreas removed 75 days	Rejection	Alive on insulin
3	28	M	Hypothermic storage – 7 h 34 min	Pancreas alone	36 days Pancreas removed 48 days	Rejection	Alive on insulin
4	30	M	Hypothermic storage – 7 h 7 min	Pancreas alone	48 days Pancreas removed 56 days	Rejection	Alive on insulin
5	33	F	Hypothermic storage – 3 h 48 min	Pancreas alone	40 days Pancreas removed 46 days	Rejection	Alive on insulin
6	29	M	Hypothermic storage – 18 h	Simultaneous pancreas and kidney transplant	> 2 months Pancreas functioning	Functioning	Alive without insulin