Insulin dependent diabetes in Asians

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SUMMARY Type 1 diabetes is said to be extremely rare in children in India, where diabetes treated with insulin may be due to chronic pancreatic disease or malnutrition. To see whether typical type 1 diabetes occurred in Asian children in the United Kingdom, all known Asian children with diabetes in industrial West Yorkshire were ascertained. A total of 17 such children were studied; of these, seven were from three multiplex families and two fathers from these families had diabetes. All children were ketosis prone and developed diabetes while resident in the UK. There were significant increases in HLA-B8 and HLA-DR3 and increases in HLA-DR4 and HLA-DR3/DR4, while HLA-B15 was absent. Islet cell antibodies, either IgG or complement fixing, were present in four of 18 subjects tested, all of whom had disease of short duration. The prevalence of type 1 diabetes in Asian children aged 15 years or less in West Yorkshire was 36/100 000, assuming complete ascertainment.

It is concluded that typical type 1 diabetes may occur in Asian children and this condition may be more common in families who have migrated to the UK.

Diabetes is currently divided into two major forms.¹ Type 1 (insulin dependent) diabetes is characterised by an immune mediated slow destruction of the insulin secreting B cells of the pancreatic islets.² This form generally presents in childhood or early adult life, although it may occur at any age, even in the ninth decade. Plasma C peptide and insulin responses to stimulation are absent or blunted³ and patients are ketosis prone and insulin dependent. The immunological basis of type 1 diabetes is signified by the presence of circulating islet cell antibodies in most subjects at the time of diagnosis. Genetic susceptibility to type 1 diabetes is strongly linked with the human leucocyte antigen (HLA) system, encoded on the short arm of chromosome 6. In white patients with diabetes there is a high prevalence of HLA-DR3 and HLA-DR4 and the uncommon heterozygous state, HLA-DR3/DR4,⁴ which therefore increases the risk for the disease.

In contrast, type 2 diabetes increases in prevalence with age, although it may occasionally occur in childhood.⁵ Patients are often obese and have adequate insulin secretion. Its pathogenesis is poorly understood; it has a strong genetic basis, although this is not HLA linked, and may result from an abnormality in the peripheral insulin receptor.⁶

The concepts underlying this classification arise from studies mostly of white west European or American subjects.

The situation pertaining to diabetes in Asians, and Indian subjects in particular, is less clear. Insulin dependent diabetes presenting in childhood is said to be very rare in Asians⁷ whether resident in India⁸ or in the United Kingdom.⁹ Earlier studies of the HLA association with insulin dependent diabetes in Asians have not shown the usual B locus antigen associations seen in west Europeans, although HLA-DR has not yet been investigated.¹⁰

The aim of this study, therefore, was to investigate whether typical type 1 diabetes with its HLA associations and the presence of islet cell antibodies, as occurs in west European children, is found in Asian children.

Patients and methods

All consultant paediatricians in industrial West Yorkshire (Bradford, Leeds, Huddersfield, Halifax, and Dewsbury) were asked if they had any ketosis prone, insulin dependent Asian children with diabetes aged 16 years or less under their care. In addition, all relevant diabetes liaison health visitors were asked if any such children attended adult

diabetic clinics. All such known children were studied. Their place of birth, age at onset of diabetes, and family history were obtained. HLA typing for A, B, and DR antigens was performed by standard microlymphocytotoxicity techniques. Islet cell antibodies in serum were sought by immunofluorescent techniques, for both 'conventional' (IgG) and complement fixing antibodies.¹¹ In multiplex diabetic families samples were obtained from all available family members, whereas only the proband was studied in single affected cases. All subjects and parents gave informed consent to participation in the study.

Statistical analysis was by χ^2 with Yates's correction; p values were not corrected for the number of HLA determinants tested.

Results

Seventeen Asian children with diabetes (nine boys and eight girls) were ascertained. All were born in the UK. Their mean (SD, range) age at the onset of diabetes was 7 (4, 3–16) years and mean (SD, range) duration of diabetes was 2 (1, 0.5–6) years. Three multiplex families contained seven children with diabetes, while the remaining 10 children with diabetes were isolated cases. Two of the fathers of the multiplex families had insulin requiring diabetes, and one of these also had thyroiditis; the third died of unknown causes. The geographical origins of the families of the subjects studied were Pakistan (all three multiplex families and five single cases), Kenya, although previously from north west India (three single cases), and one single case each from Kashmir and Gujarat.

The prevalence of the human leucocyte antigens that are associated with type 1 diabetes in west European subjects in the children studied is shown in the Table. HLA-B8 was significantly more common in the diabetic probands (54%) than in a control Asian population (7%) from west India ($p<0.001$), while HLA-B15 was not present in any

of the subjects with diabetes, although it was present in 13% of the control population.¹² HLA-DR3 was significantly increased in the diabetic probands (85%) compared with the control population (16%) ($p<0.001$), while HLA-DR4 was also increased (38% v 16%), although not significantly. The heterozygous HLA-DR3/DR4 combination was present in 31% of the probands, and although figures are not available for this combination in an Asian control population, this prevalence is highly likely to be significantly increased.

Serum samples were available from 24 children (children with diabetes and their siblings) and four parents (with and without diabetes). Among the 18 subjects with diabetes tested (16 children and two fathers), four were positive for IgG islet cell antibodies and two for complement fixing islet cell antibodies. All those subjects positive for islet cell antibodies had a duration of diabetes of two years or less. One sibling without diabetes from a multiplex diabetic family, carrying HLA-DR4, was positive for both IgG and complement fixing islet cell antibodies.

The population of Asian children aged 15 or less in the area studied in 1981 was 46 977,¹⁵ and with 17 children with diabetes in this study, the population prevalence for Asian children with diabetes is 36/100 000, assuming complete ascertainment.

Discussion

This study confirms that insulin dependent diabetes with many of the characteristics of 'type 1' diabetes, as it occurs in white west European populations, can occur in Asians, who are also genetically white. The children studied had an onset of diabetes early in life and were ketosis prone. There was a familial aggregation of diabetes, in that three multiplex families contained seven children with diabetes, there was a disturbance in frequencies of human leucocyte antigens, and islet cell antibodies were present in subjects with disease of short duration.

Table Prevalence of human leucocyte antigens in the children studied compared with west European subjects

Antigens	Diabetic probands (n=13) (No (%))	Indian control population (%) [*]	English children with diabetes (%) [†]	English control children (%) [‡]
HLA-B8	7 (54)	7	54	32
HLA-B15	0	13	18	12
HLA-DR3	11 (85)	16	71	32
HLA-DR4	5 (38)	16	78	34
HLA-DR3/DR4	4 (31)	§	51	6

^{*}Ten single cases and three probands (eldest child with diabetes from three multiplex families, thus excluding all related cases).

[†]From the control population of van Eden (n=129).¹²

[‡]From Cudworth and Woodrow (n=15)¹³ and Wolf *et al* (n=122).¹⁴

[§]Figures not available.

Our subjects tended to originate from northern India. A previous study of subjects with diabetes from that area suggested that the usual classification of diabetes into types 1 and 2 did not apply there and that 'juvenile diabetes' was extremely rare.⁸

Most previous HLA studies in Asian subjects with diabetes have not examined DR antigens and have only presented results of A and B locus antigens. Only one recent study has examined HLA-DR frequencies.¹⁶ HLA-DR3, but not HLA-DR4, was significantly increased in a group of insulin dependent north Indian patients with diabetes with onset before 40 years, although none was said to have onset in childhood. Our results showed a significant increase in HLA-B8 and HLA-DR3 and increases in HLA-DR4 and the HLA-DR3/DR4 heterozygous state, all of which are increased in white west European subjects with diabetes.^{13 14} HLA-B15 (Bw62), which is also associated with type 1 diabetes in whites, was not present in any of the small number of subjects with diabetes tested. Previous studies of Asian patients with diabetes have found an increase in HLA-B8,^{17 18} while a study in north India could not confirm this and found instead increases of HLA-Bw21 and HLA-B7,¹⁹ antigens not associated with type 1 diabetes in western Europe. These latter increases may have been due to technical errors in HLA typing. Islet cell antibodies are present in almost all cases of type 1 diabetes at the time of diagnosis but disappear in subsequent months.²⁰ In accordance with this, the short duration cases of Asian children did have islet cell antigens, including the complement fixing type, which is the more important marker of recent onset diabetes. It is of interest that an HLA-DR4 positive sibling without diabetes also had both IgG and complement fixing islet cell antigens and was therefore at increased risk of developing type 1 diabetes.^{21 22} Islet cell antigens have previously been reported in north Indian subjects with diabetes when they were associated with coexistent autoimmunity in cases of long duration.²³

One study recently paid attention to the high prevalence of type 2 diabetes, often associated with obesity, seen in Asians in the UK.⁹ In that study, Asian children with diabetes were said to be few, although the prevalence was 63/100 000 children aged 14 years or less, which was almost double that found in Yorkshire. The prevalence of diabetes among Asian children under 15 years of age in Leicester was 54/100 000 and was lower than that in non-Asian children (99/100 000), although the difference was not significant.²⁴ Any differences between these estimates of prevalence may stem from both the small numbers involved and the degree of complete ascertainment.

It is concluded that type 1 diabetes occurs in Asian children and has the hallmarks of insulin dependence, ketosis proneness, disturbance of human leucocyte antigens, and the presence of islet cell antibodies. Whether type 1 diabetes is more common in Asian children living in the UK than it is in India is unclear, although previous reports suggest that this is the case. If so, such children may be exposed to an environmental agent in the West, which may be involved in the aetiology of diabetes that is less common in India.

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