We thank Mr Colin Rees and the staff at Management Services, South Glamorgan Health Authority, for their help in collecting data.

References

- ¹ Registrar General. *Review of Registrar General on death in England and Wales 1975*. Mortality Statistics in Childhood DH3. London: Office of Population Censuses and Surveys, 1975.
- ² Illingworth C M. Paediatric accident and emergency: medical or surgical? *Public Health* 1977; **91**: 147-9.
- ³ Maddocks G B, Sibert J R, Brown B M. A four-week study of accidents to children in South Glamorgan. *Public Health* 1978; **92**: 171-6.
- ⁴ Court S D M, chairman. *Fit for the future*. Report of the Committee on Child Health Services. London: HMSO, 1976.
- ⁵ Sibert J R. Stress in families of children who have ingested poison. *Br Med J* 1975; **iii**: 87-9.

- ⁶ Brown G W, Davidson S. Social class, psychiatric disorder of mother, and accidents to children. *Lancet* 1978; **i**: 378-80.
- ⁷ Jackson R H, Wilkinson A W. Why don't we prevent childhood accidents? *Br Med J* 1976; **i**: 1258-62.
- ⁸ Craft A J, Shaw P A, Cartledge N E F. Bicycle injuries in children. *Br Med J* 1973; **iv**: 146-7.
- ⁹ Sibert J R, Newcombe R. Bicycle injuries in children. *Br Med J* 1977; **i**: 613-4.
- ¹⁰ Lillington A W, Ross M S. Letter: Dog bites in children. *Lancet* 1976; **ii**: 984.
- ¹¹ Hervey E. Incidence of bites due to dogs and other animals in Leeds. *Br Med J* 1977; **ii**: 53-4.

Correspondence to Dr J R Sibert, Department of Child Health, Welsh National School of Medicine, Llandough Hospital, Penarth, South Glamorgan CF6 1XX.

Received 7 November 1979

HLA-DR antigens in insulin-dependent diabetes

E SCHOBER, G SCHERNTHANER, AND W R MAYR

Paediatric Department, Department of Medicine II and Institute of Blood Group Serology, University of Vienna, and Ludwig Boltzmann Institute for Clinical Endocrinology, Vienna, Austria

SUMMARY HLA-A, B, C, and DR-typing was performed in 51 children with insulin-dependent diabetes. A close association between childhood diabetes and HLA-DR3 and DR4 was established. DR3 was found in 55% and DR4 in 75% of the diabetic children, compared with 20% and 26% respectively in healthy controls. The combination of DR3 and DR4 was present in 37% of the diabetic children compared with only 4% of the controls. This investigation provides strong evidence that the susceptibility genes for insulin-dependent diabetes are in close linkage disequilibrium with the HLA-DR locus. In diabetic children DR4 seems to be a more important susceptibility factor than in patients with manifestation of insulin-dependent diabetes after 15 years.

investigation was to determine the frequencies of the HLA-antigens of the A, B, C, and DR locus in diabetic children who had manifestations of the disease before age 15.

Subjects and methods

HLA-A, B, C, and DR antigens were determined in 51 (17 girls and 34 boys) insulin-dependent diabetic children. Mean chronological age 12.1 (range 4.3-18), mean age at onset 7.9 (range 1.75-14.5) years.

HLA-antigens of the A, B, C locus were evaluated in 3000, and HLA-DR antigens in 160 healthy controls. HLA-A, B, and C typing was performed by means of the standard NIH-microlymphotoxicity technique, DR-locus typing by the 2-colour fluorescence technique.² The relative risk was calculated by the formula of Woolf.³

Results

Table 1 shows the distribution of HLA-DR antigens of the diabetic children compared with controls. Children positive for DR3 showed a 4.9-fold and children positive for DR4 an 8.2-fold risk of developing insulin-dependent diabetes compared with individuals who were negative for these antigens. 37% of the diabetic children presented both DR3 and DR4, and in them the risk of developing juvenile

In recent years it has been accepted that diabetes mellitus is made up of a heterogeneous group of diseases, which can be distinguished by clinical, biochemical, and pathogenetic factors. There are at least two main entities: the insulin-dependent juvenile onset (type 1), and the insulin-independent adult onset (type 2) form of diabetes.

During the last few years the inherited susceptibility to develop type 1 diabetes has been linked with particular genetic markers of the HLA system (B8, B15, B18; Cw3, DR3, DR4).¹ The intention of our

Table 1 HLA-DR frequencies in diabetic children and controls

HLA-DR antigen	Diabetic children (n=51)		Controls (n=160)		χ^2	P	Risk
	No	(%)	No	(%)			
DR1	12	(23)	32	(20)	0.3	NS	1.2
DR2	5	(10)	35	(22)	3.7	<0.1	0.4
DR3	28	(55)	32	(20)	23	<0.001	4.9
DR4	38	(75)	42	(26)	38	<0.001	8.2
DR5	1	(2)	37	(23)	10	<0.01	0.1
DR7	5	(10)	45	(25)	7	<0.01	0.3
DR3/DR4	19	(37)	6	(4)	42	<0.001	15.0

Table 2 Frequencies of HLA-B and C antigens

HLA-antigen	Diabetic children (n=50)		Controls (n=3000)		χ^2	P	Risk
	No	(%)	No	(%)			
B8	16	(32)	543	(18)	6.35	<0.05	2.1
B15	13	(26)	355	(12)	3.20	<0.1	1.8
B18	5	(10)	330	(11)	0.05	NS	0.9
Cw3	17	(34)	645	(21)	4.52	<0.05	1.9
B8/B15	4	(8)	40	(1.3)	11.04	<0.001	6.4

diabetes was 15. DR2, DR5, and DR7 were found less often in the diabetic children compared with the controls. Individuals positive for DR2, DR5, and DR7 have a reduced risk for developing juvenile diabetes.

HLA-B8 and Cw3 were greatly increased in the diabetic children compared with controls, and showed a risk of 2.1 and 1.9 (Table 2). The combination of B8 and B15 was observed in 4 patients; in them the relative risk of developing insulin-dependent diabetes rose to 6.4. A strong linkage disequilibrium exists between DR3 and B8, and between DR4 and B15. All (n = 16) the B8-positive patients were also DR3-positive, while 28 (43%) of the DR3-positive diabetic children did not present B8. All (n = 13) the B15-positive diabetics also showed DR4, but 37 (65%) of the DR4-positive diabetics were B15-negative.

Discussion

Our results show an increased frequency of DR3 and DR4 in diabetic children compared with healthy controls. This is in accordance with recently published data found in insulin-dependent diabetics irrespective of the age of onset of diabetes.^{1,4} The combination DR3/DR4 appears to act in an additive manner by increasing the relative risk of developing insulin-dependent diabetes. The distribution of

DR5 and DR7 in diabetic children showed a significant difference from controls. The decrease of DR2 in our patients was not significant. We also found increased frequencies of B8, Cw3, and B8/B15 in the diabetic children. The present data confirm that the association of insulin-dependent diabetes to antigens of the HLA-B and C locus is only secondarily due to linkage disequilibrium with antigens of the DR locus.⁴

Recent studies provide some evidence for heterogeneity in type 1 diabetes. DR3 (B8) as one genetic risk factor, and DR4 (B15) as another, increase the risk of developing type 1 diabetes, DR2 (B7) associated gene-products may act as protective factors.

In childhood diabetes DR4 is the more important susceptibility antigen and 75% of the children were DR4-positive. This is in accordance with recently published data,⁴ which show that the incidence of DR4 is significantly higher in childhood diabetes than in type 1 diabetes with manifestation after age 15. In individuals who developed insulin-dependent diabetes after age 15 the prevalence of DR4 was only 55%.⁴

There seems to be heterogeneity in type 1 diabetes between DR3- and DR4-positive patients not only in age of manifestation but also in immunogenetic mechanisms. Diabetic individuals positive for DR3 show a higher frequency of persisting islet cell antibodies in long-standing diabetes.⁴ They have an increased risk of developing other autoimmune disorders,⁵ they tend to produce circulating immune complexes,⁴ and they show a lower IgG-antibody response to exogenous insulin. DR4-positive diabetic patients have a greater ability to produce antibodies against heterologous insulin,⁶ even after mono-component insulin administration.⁴ There is also some evidence that in DR4-positive diabetics beta-cell-residual function is diminished during the early years of the disease.⁴

There are some conflicting observations about late diabetic complications.⁷⁻⁸ Möller *et al.* did not find a correlation between the risk of developing diabetic microangiopathy and HLA-antigens.⁷ Recent investigations⁸ suggest that DR4-(B15) positive diabetics develop more severe retinopathy, whereas DR3-(B8) positive patients have milder microvascular retinal changes.

References

- 1 Nerup J, Platz P, Andersen O O, *et al.* HLA-antigens and diabetes mellitus. *Lancet* 1974; ii: 864-6.
- 2 van Rood J I, Leeuwen A, Ploem J S. Simultaneous detection of two cell populations by two-colour fluorescence and application to the recognition of B-cell determinants. *Nature* 1976; 262: 795-7.

- ³ Woolf B. On estimating the relation between blood group and disease. *Ann Hum Genet* 1954-55; 19: 251-3.
- ⁴ Scherthaner G. New aspects in the pathogenesis and in the course of type I diabetes. *Wien Klin Wochenschr* 1980; 92: Supplement 114, 1-35.
- ⁵ Cudworth A G. The HLA-system, autoimmune endocrinopathy, and diabetes mellitus. *Eur J Clin Invest* 1978; 8: 355-7.
- ⁶ Ludwig H, Scherthaner G, Mayr W R. Ia-type allo-antigens and humoral autoimmune responsiveness in insulin-dependent diabetes mellitus. *Metabolism* 1979; 28: 797-800.
- ⁷ Möller E, Persson B, Sterky G. HLA-phenotypes and diabetic retinopathy. *Diabetologia* 1978; 14: 155-8.
- ⁸ Bertrams J, Dewald G, Spitznas M, Rittner Ch. HLA-A, B, C, DR, Bf, C² alleles in insulin dependent diabetes mellitus with proliferative retinopathy. *Immunobiology* 1981; in press.

Correspondence to Dr Edith Schober, Department of Paediatrics, University of Vienna, Währinger Gürtel 74-76, A-1090 Vienna IX, Austria.

Received 14 October 1980

Successful use of danazol for hereditary angio-oedema

C RAJAGOPAL AND J R HARPER

General Hospital, Northampton

SUMMARY A 10-year-old boy with severe hereditary angio-oedema was given danazol, 200 mg each day. There was a pronounced reduction in the frequency and severity of oedema.

Danazol (17 α -Pregna-2,4-dien-20-yno[2,3-*d*]isoxazol-17-ol) is an orally active pituitary gonadotrophin inhibitory agent, without oestrogenic or progestational activity. It does not appear to affect other pituitary endocrine axes and its effect on gonadotrophins is reversible. Since its introduction to the UK in 1974 it has been used in adults for endometriosis and breast disorders.¹ It has been successfully used in children with precocious puberty.²

We report here the successful use of danazol for the prevention of hereditary angio-oedema.

Case history

The boy's parents came from St Helena. He was first admitted at age 3 years with painless oedema of one hand. Examination showed no other abnormality. A diagnosis of hereditary angio-oedema was confirmed on estimation of C1 esterase inhibitor levels, which were not detectable. His father also suffers from hereditary angio-oedema, with episodes of oedema and, occasionally, airways obstruction.

Since his original presentation he has been admitted with episodes of varying severity ranging from oedema of limbs or face to obstruction of the upper airways. Acute symptoms on these occasions were treated with fresh frozen plasma and aminocaproic acid. To try to quantitate the effects of

prophylactic treatment, his symptoms were graded according to severity: grade 1, swelling of the extremities or scrotal swelling; grade 2, facial swelling, abdominal pain with or without vomiting, swollen tongue; grade 3, upper airways obstruction manifesting as stridor or dyspnoea.

During the last four years he has been admitted to hospital about 6 times a year with symptoms of grade 1 severity. In addition to this, he has had four episodes of grade 3 severity. He has been treated with aminocaproic acid during this time, but his frequent absences from school and his frequent hospital admissions have been causing concern. At age 9 years 10 months it was decided to start him on danazol 100 mg twice daily. Before starting the drug, basal studies on puberty, growth, estimates of complement activity and testosterone levels were carried out, and were normal.

During 10 months of treatment with 100 mg danazol twice daily, he has had only two episodes of grade 1 symptoms and none of grades 2 or 3. He has

Figure Facial swelling during a bout of angio-oedema.