12. HLA, Autoimmunity and Insulin-Dependent Diabetes Mellitus

J. NERUP, P. PLATZ, O. ORTVED ANDERSEN, M. CHRISTY, J. EGEBERG, J. LYNGSØE, J. E. POULSEN, L. P. RYDER, M. THOMSEN, and A. SVEJGAARD

The etiology and pathogenesis of juvenile diabetes mellitus (JDM), i.e., insulin-dependent diabetes in nonobese individuals, are still poorly understood.
None of the many hypotheses as yet proposed has been able to explain the essential pathologic finding in this disease: The functioning B-cell mass is reduced due to reduction of the total amount of islet tissue as well as a striking reduction of the number of B-cells (15, 19).
The purpose of this presentation is to propose a hypothesis concerning the etiology and pathogenesis of insulin-dependent diabetes based on a review of observations reported during recent years:

1. There is a well-known tendency to aggregation of diabetes in families, but no pattern of inheritance has been established (16,21). In monozygous twins a surprisingly low concordance rate, of about 50% of JDM, suggests that exogenous factors play an important part in the development of the disease (47).
Thus, what is inherited is not the disease JDM as such but rather a susceptibility to develop JDM under the influence of certain environmental factors.

2. Evidence that viral infections might be of importance has been reported. High titers of virus-neutralizing antibodies against Coxsackie B4 and other viruses have been demonstrated with unexpected high prevalences in JDM patients (10,17,18). In mice a diabetic state can be induced by Coxsackie B4 and EMC virus (3,4,8,10,12,26). Interestingly enough this susceptibility to diabetogenic viruses in mice is observed only in certain strains and might therefore be genetically determined (11).

3. Indirect evidence that autoimmunity is involved in the pathogenesis of JDM stems from the observation that clinical and chemical diabetes occurs in combination with organ-specific autoimmune endocrine disorders (Graves' disease, myxedema, Hashimoto's disease, idiopathic Addison's disease, hypergonadotropic hypogonadism and idiopathic hypoparathyroidism) more often than expected by chance alone (1,22,35,36). Furthermore, lymphocytic infiltration in and around the islets of Langerhans - insulitis - is a characteristic finding in JDM of short duration (19,24,27).

4. Direct experimental evidence that organ-specific autoimmune phenomena play a part in patients suffering from JDM has also been reported. Nerup *et al.* (38,40) found antipancreatic cell-mediated immunity (APCI) directed against antigenic determinants in the endocrine pancreas in patients with JDM of short duration. Other workers have confirmed this finding (30,43). Recently Botazzo *et al.*, Irvine *et al.*, and Lendrum *et al.* (2,28,29) have reported the occurrence of an IgG antibody di-

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rected against the pancreatic islet cells in patients with JDM. This islet cell antibody (ICA) was found with the highest frequency in patients with JDM of recent onset. By immunization of experimental animals with homogenates of isolated islets of Langerhans, a transient diabetes-like syndrome can be induced, that is characterized by reduced glucose tolerance, cell-mediated immunity against the endocrine pancreas, discrete lymphocytic inflammation in the islets of Langerhans, and B-cell degeneration and destruction (37).

The exact biochemical nature and characteristics of the antigenic determinant in the endocrine pancreas against which these autoimmune phenomena were directed is still unknown, but the antigen(s) is organ-specific, species nonspecific, and different from insulin. During the past few years several investigations have shown that different antigens of the major human histocompatibility system, the HLA-system, are found with increased frequency in patients suffering from different diseases showing aggregation in families and in which virus and autoimmunity seem to be involved (31,46).

It was of interest, therefore, to investigate the prevalence of different HLA antigens in diabetic patients (41). A total of 146 patients with diabetes mellitus were HLA-typed. In 85 patients diabetes was diagnosed before the age of 40 (juvenile diabetes) and in the remaining 61 patients age at onset was 41 years or more (maturity onset diabetes). All patients were unrelated Danish Caucasian out-patients. The number of obese (i.e. > 125% of normal weight) and of insulin-dependent patients is shown in Table 3.

For the HLA-typing the microlymphocytotoxicity test was used (25). In all patients and in 1967 unrelated Danish Caucasian controls the presence or absence of 23 different HLA antigens of the A and B series were determined (see Table 1 for details about the antigens in question and the new and old nomenclature of HLA antigens. In this presentation the new nomenclature will be used).

Table 1. HLA nomenclature - new and old (only antigens tested for in this study are included)

A-series	(LA)	B-series	(Four)	D-series	(MLC)
New	Old	New	Old	New	Old
HLA-A1	HL-A1	HLA-B5	HL-A5	HLA-Dw2	7a
HLA-A2	HL-A2	HLA-B7	HL-A7	HLA-Dw3	8a
HLA-A3	HL-A3	HLA-B8	HL-A8	HLA-Dw4	W15a
HLA-A9	HL-A9	HLA-B12	HL-A12		
HLA-A10	HL-A10	HLA-B13	HL-A13		
HLA-A11	HL-A11	HLA-B14	W 14		
HLA-A28	W28	HLA-B18	W 18		
HLA-Aw19	W19	HLA-B27	W 27		
		HLA-Bw15	W 15		
		HLA-Bw16	W 16		
		HLA-Bw17	W 17		
		HLA-Bw21	W 21		
		HLA-Bw22	W 22		
		HLA-Bw35	W 5		

Ref: IUIS Nomenclature Report. In: Kissmeyer-Nielsen (ed.) Histocompatibility Testing. Copenhagen: Munksgaard, 1975.

The relative risk was calculated as described by Svejgaard *et al.* (45). The only antigens appearing with increased frequencies were HLA-B 8 and HLA-Bw15. As shown in Table 2 the increased frequency of B 8 was restricted to the group of juvenile diabetics, whereas Bw15 was found with increased frequency in juvenile diabetics as well as in maturity onset diabetics, although not significantly so in the latter. Table 3 shows that the group of insulin-dependent, nonobese diabetics (i.e., juvenile diabetics irrespective of age) was responsible for the increase in HLA-B 8. The so-called relative risk indicates the calculated risk of healthy carriers of a certain HLA antigen for developing the disease in question.

Table 2. Some HLA frequencies in patients with diabetes mellitus and in normal individuals

	Control	Diabetics total	Juvenile diabetics	Maturity onset diabetics
	N = 1967	N = 146	N = 85	N = 61
HLA-B 8	23.7%	37.7%[a]	44.7%[b]	27.9%
HLA-Bw15	17.9%	31.5%[b]	32.9%[b]	29.5%
HLA-B 7	26.8%	15.8%	10.6%[c]	23.0%

Statistics: Fisher's exact test. P-values corrected for one-sidedness of the test (x2) and for the number of antigens investigated (x23).
[a] $p < 0.01$.
[b] $p < 0.001$.
[c] $p < 0.05$.

Table 3. HLA-B 8 and Bw15 in diabetes mellitus: correlation with obesity and insulin dependency

	Obesity		Insulin dependency		Controls
	No (N = 112)	Yes (N = 31)	Yes (N = 109)	No (N = 37)	(N = 1967)
HLA-B 8	46 (41.1%)	8 (25.5%)	46 (42.4%)	9 (24.3%)	(23.7%)
HLA-Bw15	36 (32.1%)	9 (29.0%)	38 (34.9%)	8 (21.6%)	(17.9%)
HLA-B 8 and/or Bw15	70 (62.5%)	14 (45.2%)	70 (64.2%)	16 (43.2%)	(39.2%)

In Table 4 it is shown that HLA-B 8- or Bw15-positive individuals carry a risk of about 2.5 times that of HLA-B 8- or Bw15-negative individuals of developing juvenile diabetes (i.e., insulin-dependent diabetes in the nonobese patient). In contrast they carry no increased risk as far as maturity onset diabetes was concerned. It is noteworthing, (1) that persons positive for HLA-B 8 and Bw15 carry a risk that is the sum of the calculated relative risk of each of the individual, (2) that hetero- and homozygous carriers of HLA-B 8 or Bw15 have identical relative risks (46).

Table 4. Relative risk of insulin-dependent and non insulin-dependent diabetes in HLA-B 8- and Bw15-positive subjects

	Insulin-dependent diabetes mellitus	Non insulin-dependent diabetes mellitus
	Relative risk	Relative risk
HLA-B 8	2.4 ($p = 1.9 \times 10^{-5}$)	1.0 (N.S.)
HLA-Bw15	2.5 ($p = 3.2 \times 10^{-5}$)	1.3 (N.S.)

Statistics: Fisher's exact test.

These findings have to be interpreted in the following way: (1) HLA-B 8 and Bw15 seem to predispose to different diabetes-provoking factors. (2) No gene-dose effect of HLA-B 8 and Bw15 exists. Thus, the highest prevalence of diabetes mellitus should be expected amongst siblings of JDM patients positive for both HLA-B 8 Bw15. The results shown in Table 5 confirm this expectation. The significantly increased frequency of HLA-B 8 and Bw15 in patients with JDM has now been confirmed by others (5,13,23).

Table 5. Prevalence of diabetes in siblings of juvenile diabetics with different HLA types

Patient HLA type	Diabetic siblings	
	No.	%
HLA-B 8	10/99	10.1
HLA-Bw15	9/79	11.4
HLA-B 8 and Bw15	7/34	20.6
Other HLA types	7/127	5.5

HLA-B 8 and Bw15 thus seem to be genetic markers of insulin-dependent diabetes mellitus. This type of diabetes is further characterized by an early age of onset, normal weight, lymphocytic infiltration in and around the islets of Langerhans, reduction of the functioning B-cell mass, antipancreatic cellular immunity (APCI), and high titers of islet cell antibodies (ICA). Therefore these findings support the concept that juvenile, insulin-dependent diabetes in nonobese patients is a disease entity of its own different from non insulin-dependent diabetes with respect to etiology and pathogenesis (41).

Figure 1 demonstrates a family including several cases of insulin-dependent diabetes. It is seen that the phenotype diabetes follows the HLA-haplotype. The significance of the occurrence of this HLA-haplotype in the nondiabetic family members is discussed briefly below. Cudworth and Woodrow also found that aggregation of diabetes in families is closely connected to the HLA region on chromosome No. 6 and especially to the HLA types B 8 and Bw15 (14). HLA-B 8 and/or Bw15 can be demonstrated in 65% of patients suffering from JDM as compared to only 39%

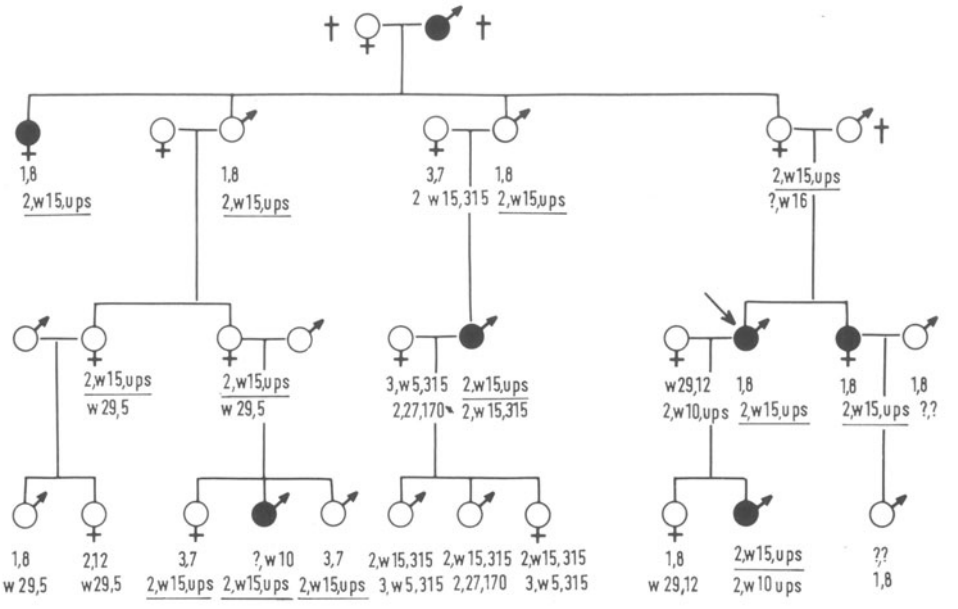

Fig. 1. HLA genotypes in a family including 7 cases of diabetes (black). Propositus is marked by an arrow. The HLA-A2, Bw15, CW3 haplotype shared by all diabetic members of the family (and some nondiabetics) is underlined
? = haplotypes that could not be definitely established

Table 6. D-Types (MLC types) in insulin-dependent (juvenile) diabetes mellitus

	Diabetics	Controls N = 35	Relative risk
Dw3	29/50 (58%)	16%	6.4
Dw4	33/75 (42%)	16%	3.7

in the background population. An even stronger association was demonstrated between insulin-dependent diabetes mellitus and the HLA-Dw3 and Dw4 antigens of the D-series of the HLA system (previously known as LD or MLC types) (Table 6).
The antigens of this fourth locus of the major human histocompatibility region on chromosome No. 6 can at present only be typed by means of unidirectional mixed lymphocyte cultures and thus, they differ from other histocompatibility antigens (for further details see Thomsen *et al.* (48)).
Dw3 and/or Dw4 was found to occur in 80% of patients compared to 24% of the control population. In other words: a genetic marker for insulin-dependent diabetes mellitus could be demonstrated in 80% of the juvenile diabetics.

It is still unknown how the HLA factors confer the susceptibility to develop insulin-dependent diabetes. As mentioned above, diabetes is often seen together with other endocrine disorders. For this reason it is worth noting that HLA-B 8 and Dw3 also occur with increased fre-

quency in patients suffering from Addison's disease (20), Graves' disease (20,33), and certain cases of hypergonadotropic hypogonadism (7). Thus Dw3 or possibly one or more immune response gene(s) linked to Dw3 could be involved as a common denominator of organ-specific autoimmune endocrinopathy. Some preliminary observations suggest future lines of research in this field. It has been demonstrated (Table 7) that islet cell antibodies (ICA) in juvenile diabetics were found predominantly in the sera of the HLA-B 8-positive patients in small series (6).

Table 7. Islet cell antibody (ICA) and juvenile diabetes mellitus

	HLA-B 8	Other HLA types	Total
ICA	13/18 (72%)[a]	8/20 (40%)[a]	21/38 (55%)

[a]P = 0.05 (Fisher's exact test).
Mean duration of diabetes: 3.2 years, range (1-20 years).

No correlation was found between the occurrence of ICA and APCI. This is, however, in accordance with the findings in other autoimmune endocrinopathies, e.g., idiopathic Addison's disease (34). Autoimmunity (ICA and/or APCI) was present in 73% of the juvenile diabetics (Table 8) and it is worth noting that autoimmunity against the endocrine pancreas was found to be statistically significant more often in the HLA-B 8-positive patients (89%), when compared to HLA-B 8-negative diabetics. However, the mean duration of disease in this small series was 3.2 years. Since ICA as well as APCI seems to fade away with increased duration of disease, we anticipate autoimmunity to be present with an even higher prevalence in juvenile diabetics when examined at time of diagnosis or, perhaps, of even greater significance in the months preceding clinical manifestation.

Table 8. Autoimmunity (ICA and/or APCI) in juvenile diabetes mellitus

	HLA-8 positive	Other HLA types	Total (N = 37)
ICA and/or APCI	16/18 (89%)[a]	11/19 (58%)[a]	27/37 (73%)

[a]P = 0.04 (Fisher's exact test).

Similarly, a tendency toward a correlation between HLA-B 8 and high titers of neutralizing antibodies against Coxsackie B4 virus was demonstrated, but the correlation was not statistically significant in this small retrospective study. Further evidence in support of an association between HLA and viral infections was provided by the observation that more than 70% of the children with congenital rubella who developed diabetes were HLA-B 8-positive (22). Furthermore, the seasonal variation in the incidence of JDM was reported to be accounted for by the HLA-B 8-positive cases (44). Thus evidence is accumulating to suggest that immune response genes associated with HLA-B 8 predispose to the development of JDM through the susceptibility to isletotrophic viruses leading to B-cell destruction directly or through the triggering of autoimmune reactions.

As previously mentioned, B 8 and Bw15 seem to predispose to the development of JDM through different mechanisms. Data to elucidate the possible action of Bw15 are sparse. However, studies of the early insulin response as estimated by the method of Thorell (49) suggest that in the Bw15-positive nondiabetic members of the family shown in Figure 1 the insulin response to intravenous glucose is lower than in the non-Bw15 nondiabetic members. This might implicate the presence of an inherited insensitivity to glucose, an inherited reduced B-cell mass, or an impaired regeneration capacity to subclinical islet damage.

In conclusion: A statistically significant correlation between HLA-B 8 and Bw15 and insulin-dependent diabetes mellitus (juvenile diabetes) has been found. In addition, some preliminary - as yet incomclusive - findings suggest the existence of more specific connections between HLA-B 8 and viral infections, between HLA-Bw15 and low insulin response, and between both these HLA factors and antipancreatic autoimmune reactions. With this background the following hypothesis for the etiology and pathogenesis of insulin-dependent diabetes mellitus is proposed:

1. The inherited susceptibility in certain individuals to develop juvenile diabetes mellitus when exposed to some environmental factors (virus? chemical agents?) is at least in part conferred by HLA-Dw3- and Dw4-associated immune response genes (Ir-genes).

2. In susceptible individuals these Ir-genes cause a defective T cell response (T-B lymphocyte cooperation) against environmental factors, leading to B-cell destruction directly or through autoimmune mechanisms.

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