Genetic, Autoimmune, and Clinical Characteristics of Childhood- and Adult-Onset Type 1 Diabetes

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OBJECTIVE — To assess whether there are any differences in genetic, autoimmune, or clinical features between type 1 diabetes presenting in childhood and that diagnosed later.

RESEARCH DESIGN AND METHODS — We studied 352 individuals (252 children and adolescents <20 years of age and 100 adults ≥20 years of age) manifesting clinical signs of type 1 diabetes over a period of 7.5 years at a university hospital in northern Finland with a primary catchment area population of ~300,000. The patients were analyzed for susceptible and protective HLA-DQB1 alleles (*02, *0302, *0301, *0602, *0603, and *0604), islet cell antibodies (ICA), insulin autoantibodies, and antibodies to GAD and IA-2 (IA-2A). Their clinical symptoms and signs were recorded at diagnosis.

RESULTS — The adult patients carried the high-risk DQB1*02/0302 genotype less frequently than the children and more often had protective genotypes. They also had a decreased frequency of all 4 single autoantibody specificities and of multiple (≥3) autoantibodies. The proportion of patients testing negative for all autoantibodies was lower among the children than among the adults. IA-2A were associated with the DQB1*0302/x genotype in both the children and adults, and the same held true for ICA among the adults. The adults were characterized by a higher proportion of males, a longer duration of symptoms, and a lower frequency of infections during the preceding 3 months. In addition, they had a higher relative body weight on admission and milder signs of metabolic decompensation (higher pH, base excess, and bicarbonate concentrations) and a lower glycated hemoglobin level at diagnosis than the children.

CONCLUSIONS — Clinical manifestation of type 1 diabetes before the age of 20 years is associated with a strong HLA-defined genetic disease susceptibility, an intensive humoral immune response to various β-cell antigens, a higher frequency of preceding infections, and a shorter duration of symptoms and more severe metabolic decompensation at diagnosis. Taken together, these observations suggest that the age at clinical onset of type 1 diabetes is determined by the intensity of the β-cell–destructive process, which is modulated by both genetic and environmental factors.

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Abbreviations: GADA, GAD autoantibodies; IA-2A, autoantibodies to the protein tyrosine phosphatase–related IA-2 molecule; IAA, insulin autoantibodies; ICA, islet cell antibodies; JDF U, Juvenile Diabetes Foundation units; RU, relative units.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Type 1 diabetes is a chronic autoimmune disease resulting from progressive destruction of the pancreatic β-cells. There are indications that β-cell damage may be induced at any age (1) and that the timing of the clinical presentation is highly variable, with the youngest patients diagnosed in infancy and the oldest at a senior age. Epidemiological data suggest that 30–50% of cases may develop clinical signs of type 1 diabetes after the age of 20 years (2,3). Such patients have many features of classic type 1 diabetes, but previous studies indicate that subjects presenting with the disease in adulthood are characterized by a longer symptomatic period before diagnosis, better preserved β-cell function, a reduced frequency of insulin autoantibodies (IAA), and a decreased prevalence of HLA class II susceptibility alleles (4–6).

With the exception of IAA, there are conflicting results on the relation between diabetes-associated autoantibodies and age at clinical onset. In an extensive survey of children and adolescents with newly diagnosed type 1 diabetes, we observed that subjects testing positive for islet cell antibodies (ICA) were younger than those who were negative for ICA (7), whereas other studies have failed to show any association between age at diagnosis and ICA (8–10).

We set out to compare children and adolescents diagnosed with type 1 diabetes before the age of 20 years with adult-onset patients in terms of disease susceptibility markers at the HLA-DQ locus, the presence and levels of disease-associated autoantibodies, and clinical characteristics at the time of diagnosis to define similarities and differences between the disease manifested during childhood and during adulthood.

RESEARCH DESIGN AND METHODS

Study population

The study population comprised 352 patients (215 male subjects) with newly diagnosed type 1 diabetes admitted to the Departments of Pediatrics and Medicine, Oulu University Hospital, between 1 April 1988 and 30 September 1995. Their

Table 1—*Frequency of HLA-DQB1 genotypes in children and adults with newly diagnosed type 1 diabetes*

	n	Children	Adults	*P*
n		188	59	—
*02/0302	49	44 (23.4)	5 (8.5)	0.02
*0302/x†	136	101 (53.7)	35 (59.3)	NS
*02/y‡	43	33 (17.6)	10 (16.9)	NS
Other	19	10 (5.3)	9 (15.3)	0.03

Data are *n* or *n* (%). †x other than *02; ‡y other than *0302. $\chi^2_{df=3} = 11.07$; $P = 0.01$.

mean age was 16.8 years (range 0.6–61.9), and they included 252 children and adolescents <20 years of age with a mean age of 9.5 ± 4.7 years and 100 adults whose mean age was 35.3 ± 9.7 years. The inclusion criteria for the patients were *1*) that they had hyperglycemia at diagnosis, *2*) that they initially needed insulin treatment to achieve normoglycemia, and *3*) that they required continuous insulin therapy for at least the first 12 months of clinical disease. The hospital serves a total population of ~300,000, including ~90,000 <20 years of age. In the Finnish health care system, all children <16 years of age who are diagnosed with diabetes are admitted to the pediatric unit of their secondary care hospital, but not all older patients are necessarily admitted to the secondary care medical unit. The lower age limit for the group of adults was set at 20 years, considering the limit of somatic growth.

Study methods

The clinical features evaluated were the duration of symptoms before admission to the hospital and the history of infectious diseases over the preceding 3 months. Thirst, polyuria, weight loss, and general fatigue were recorded as symptoms of hyperglycemia. Clinical data were collected from the patients or their parents during interviews during the initial hospitalization. The height and weight of all subjects were measured on admission, the relative body weights of the children being assessed from Finnish growth charts (11) and those of the adults from Finnish reference values (12). The blood samples for the measurement of blood glucose, HbA_{1c}, serum C-peptide, capillary blood gases, bicarbonate, base excess, and autoantibodies were obtained before the initiation of insulin therapy.

Blood glucose concentrations were determined by a hexokinase method, and capillary blood gases, bicarbonate, and base excess were analyzed by routine laboratory methods. HbA_{1c} levels were determined by electrophoresis with a reference range of 4–6% in nondiabetic subjects. Serum C-peptide concentrations were measured with a commercial kit (Novo Nordisk, Bagsvaerd, Denmark).

ICA were determined by a standard immunofluorescence method using sections of frozen human group O pancreas (4). End-point dilution titers were examined for the positive samples, and the results were expressed in Juvenile Diabetes Foundation units (JDF U) relative to an international reference standard (13). The detection limit was 2.5 JDF U. Our laboratory has participated in the international workshops on standardization of the ICA assay, in which its sensitivity was 100%, specificity 98%, validity 98%, and consistency 98% in the most recent round.

Serum levels of IAA were quantified with a radiobinding assay modified from that described by Palmer et al. (14). Endogenous insulin was removed with acid charcoal before the assay, and free and bound insulin was separated after incubation with mono-(^{125}I-TyrA14)-human insulin (Novo Nordisk) for 20 h in the absence or presence of an excess of unlabeled insulin. The IAA levels were expressed in nanounits per milliliter, where 1 nU/ml corresponds to a specific binding of 0.01% of the total counts. The interassay coefficient of variation was <8%. A subject was considered to be positive for IAA when the specific binding exceeded 54 nU/ml (99th percentile in 105 nondiabetic subjects). The disease sensitivity of this assay was 26% and the specificity 97%, based on 140 samples derived from the 1995 Multiple Autoantibody Workshop (15).

Antibodies to the 65-kDa isoform of GAD were measured with a radioligand assay as described earlier (16). The results were expressed in relative units (RU) based on a standard curve run on each plate using a commercial software (MultiCalc; E.G.&G. Wallac, Turku, Finland). The cutoff limit for antibody positivity was set at the 99th percentile in 373 nondiabetic children and adolescents (i.e., 5.35 RU). This assay had a disease sensitivity of 69% and a specificity of 100% based on 140 samples included in the 1995 Multiple Autoantibody Workshop (15).

Autoantibodies to the protein tyrosine phosphatase–related IA-2 molecule (IA-2A) were analyzed with a radiobinding assay as described in detail elsewhere (17). The results were expressed in RU, based on a standard curve, as for GAD antibodies (GADA). The limit for IA-2A positivity (0.43 RU) was set at the 99th percentile in 374 nondiabetic Finnish children and adolescents. This assay had a disease sensitivity of 62% and a specificity of 97% based on 140 samples included in the 1995 Multiple Autoantibody Workshop (15).

HLA-DQB1 alleles associated with susceptibility to or protection against type 1 diabetes (*02, *0302, *0301, and *0602 or *0603) were analyzed as described in detail elsewhere (18). Samples positive for HLA-DQB1*02 were further assayed for the presence of either DQA1*05 (DR3, risk haplotype) or DQA1*0201 (DR7, neutral haplotype) (19). DNA samples for HLA analyses were available from 247 subjects (70%; 188 children [75%] and 59 adults [59%]).

Statistical analysis

The data were evaluated statistically by cross-tabulation and with χ^2 statistics, Student's *t* test (2-tailed), or parametric 1-way analysis of variance in the case of normal distribution and the Mann-Whitney *U* test or Kruskal-Wallis 1-way analysis of variance in the case of ordinal data. Logarithmic transformations were per-

Table 2—*Frequency of disease-associated autoantibodies in children and adults with newly diagnosed type 1 diabetes*

	Children	Adults	*P*
n	252	100	—
ICA	212 (84.1)	45 (45.0)	<0.001
IAA	137 (54.4)	20 (20.0)	<0.001
GADA	171 (67.9)	51 (51.0)	0.005
IA-2A	200 (79.4)	48 (48.0)	<0.001
MAA	176 (69.8)	34 (34.0)	<0.001

Data are *n* or *n* (%). MAA, multiple autoantibodies (≥3 antibodies).

formed to normalize skewly distributed continuous variables. All analyses were performed using the SPSS software package (SPSS, Chicago).

RESULTS

Genetic data

The high-risk HLA-DQB1*02/*0302 genotype was more common among the children than among the adults (Table 1), whereas DQB1non*02/non*0302 genotypes were seen more frequently in the adults. The frequency of the protective DQB1*0602–03 allele was higher among the adults (10.2 vs. 1.6%, $P = 0.008$), whereas that of the DQA1*05 allele was higher in the children carrying the DQB1*02 allele than in the DQB1*02-positive adults (93.5 vs. 73.3%, $P = 0.05$).

Diabetes-associated autoantibodies

The children had a higher frequency of all 4 autoantibody specificities analyzed, as shown in Table 2. ICA were the most common single autoantibodies in the children, whereas the adult patients most frequently tested positive for GADA. When the patients were divided into age-groups at 10-year intervals, there was an overall decreasing frequency of antibodies with increasing age up to 39 years (Fig. 1). The highest frequency of ICA, IAA, and IA-2A could be seen in the patients <10 years of age, whereas the children who were 10–19 years of age had the highest prevalence of GADA. Only 4% of the children had no detectable antibodies, whereas 30% of the adults tested negative for all 4 antibodies (Fig. 2). Close to 70% of the children but only one-third of the adults tested positive for multiple (≥3) antibodies.

The adult patients who were positive for GADA had higher antibody levels than the GADA$^+$ children (median 92.8 RU [interquartile range 34.1–166.2] vs. 31.2 RU [11.8–106.3], $P < 0.001$). No other significant differences in antibody levels could be observed between the children and adults.

Relationship between autoantibodies and HLA-defined genetic susceptibility

The subjects with the DQB1*02/y genotype had a lower frequency of IA-2A than those carrying the DQB1*02/0302 or *0302/x genotypes among the children (Table 3), and the prevalence of IA-2A was

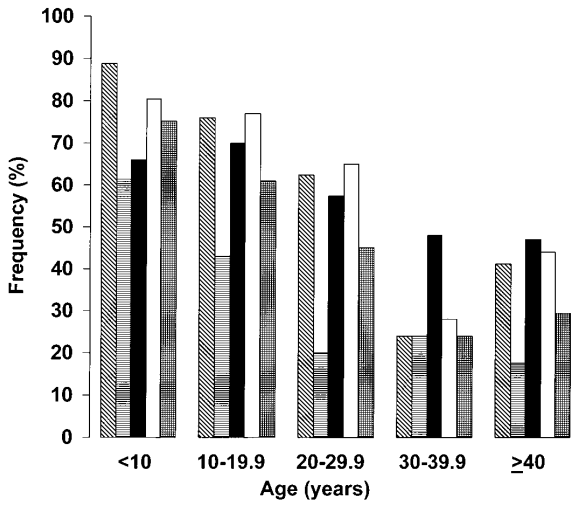

Figure 1—*Frequency of ICA (▧), IAA (▤), GADA (■), IA-2A (□), and multiple (≥3) antibodies (▦) in 352 subjects in relation to age at diagnosis of type 1 diabetes.*

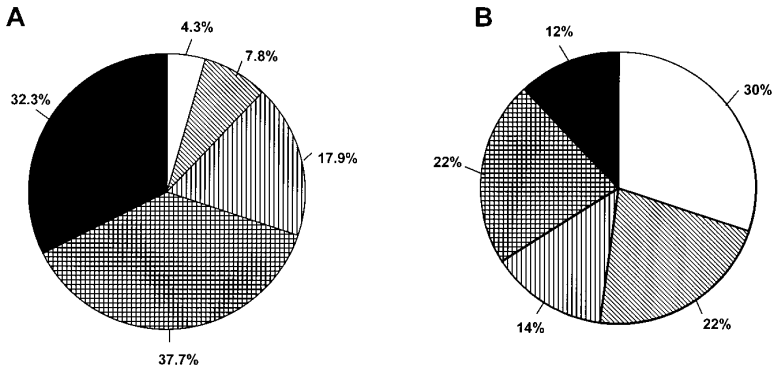

Figure 2—*Number of autoantibodies at clinical presentation of type 1 diabetes in 252 children and adolescents (A) and in 100 adults (B). No antibodies (■), 1 antibody (□), 2 antibodies (▧), 3 antibodies (▥), and 4 antibodies (▦).*

Table 3—*Frequencies of ICA, IAA, GADA, IA-2A, and multiple autoantibodies by DQB1 genotypes in subjects with newly diagnosed type 1 diabetes under and over the age of 20 years at diagnosis*

	DQB1*02/0302	DQB1*0302/x†	DQB1*02/y‡	Other DQ genotype
<20 years				
n	44	101	33	10
ICA	79.5	88.1	75.8	100
IAA	61.4	57.4	51.5	40.0
GADA	72.7	67.3	72.7	40.0
IA-2A	86.4§	89.1‖	60.6§‖	90.0
MAA	70.5	78.2	66.7	70.0
>20 years				
n	5	35	10	9
ICA	60.0	71.4§	30.0§	33.3§
IAA	0.0	31.4	20.0	22.2
GADA	80.0	68.6¶	60.0	44.4¶
IA-2A	60.0	71.4¶	20.0¶	33.3¶
MAA	60.0	57.0	30.0	22.2

Data % unless otherwise indicated. †x other than *02; ‡y other than *0302; §$P = 0.04$; ‖$P = 0.001$; ¶$P = 0.02$. MAA, multiple autoantibodies (≥3 antibodies).

Table 4—*Frequency (95% CI) of ICA, IAA, GADA, IA-2A, and multiple autoantibodies in subjects with newly diagnosed type 1 diabetes according to HLA-DQB1*0602 or *0603 protective alleles*

	Subjects with DQB1*0602 or *0603	Other subjects	*P*
n	9	238	—
ICA	55.6 (15.0–96.0)	79.0 (73.8–84.2)	NS
IAA	33.3 (5.1–72.0)	49.6 (43.1–56.0)	NS
GADA	33.3 (5.1–71.8)	68.5 (62.6–74.4)	NS
IA-2A	33.3 (5.1–71.8)	78.6 (73.3–83.8)	0.006
MAA	22.2 (8.9–56.7)	69.3 (63.7–75.6)	0.009

Data are *n* or % (range). MAA, multiple autoantibodies (≥3 antibodies).

also conspicuously low in the adults with the DQB1*02/y genotype—significantly lower than in the subjects carrying the DQB1*0302/x genotype. A similar difference in the frequency of ICA could be seen between these 2 genotypes also in the adult patients. The few individuals (9 in the total population) who carried the protective DQB1*0602–3 alleles had a decreased frequency of IA-2A and multiple antibodies (Table 4).

A lower level of IA-2A was seen among the children with the DQB1*02/y genotype (median 25.6 RU) than in those positive for DQB1*0302/x (median 105.5 RU, P = 0.002). There was also a significant difference in IA-2A levels between the children with *0302/x and those heterozygous for *02/0302 (median 43.8 RU, P = 0.04). Similar differences could be observed among the adults, with the highest IA-2A levels in the patients carrying DQB1*0302/x (median 109.8 RU) significantly higher than the IA-2 levels in the other patients (median 6.8 RU, P = 0.04). The few patients in the total population who carried the protective DQB1*0602–03 alleles had lower IAA levels than the other subjects (median 70 vs. 177.5 nU/ml, P = 0.01).

Clinical characteristics

The proportion of male patients was higher among the adults than among the children (Table 5), and the adults had a longer symptomatic period before diagnosis and had experienced fewer infections over the preceding 3 months before diagnosis. The relative weight of the children had declined more than that of the adults. There was no significant difference in blood glucose concentrations or serum C-peptide levels at diagnosis, but the children had a higher mean HbA_{1c} value than the adult patients, and the male patients had higher HbA_{1c} values than the female patients (median 11.3 vs. 10.0%, P = 0.04) among the adults. The adult patients had a higher pH concentration and higher bicarbonate and base excess concentrations than the children. Table 6 presents the clinical characteristics after dividing the children and adolescents into 3 age-groups.

CONCLUSIONS — In this evaluation of possible genetic, autoimmune, and clinical differences between childhood-onset and adult-onset type 1 diabetes, the critical issue is whether the adult patients really have type 1 diabetes. The arguments in favor of this in the present series are based on the observations that all of the adult patients had typical symptoms and signs of the disease before diagnosis; they had severely decreased endogenous insulin secretion, as reflected in serum C-peptide concentrations similar to those seen in the children and adolescents; they were not obese, with the exception of 20 subjects with a relative body weight ≥120%; and they remained insulin-dependent for at least 12 months after diagnosis.

Our results confirm that subjects presenting with type 1 diabetes during childhood have a stronger HLA-defined genetic susceptibility than those diagnosed during adulthood (4,5). This indicates that highly predisposing HLA genes not only increase the risk of type 1 diabetes but also have an effect on the rate of progression to clinical disease. The weaker HLA-conferred genetic risk in adults raises the issue of whether adult patients carry a stronger disease susceptibility as defined by non-HLA genes or whether they experience more exogenous factors predisposing them to type 1 diabetes in the preclinical period.

The children and adolescents in this survey definitely had a more frequent and stronger humoral immune response to various β-cell antigens than the adult patients, although the adults who were positive for GADA had higher antibody levels than the $GADA^+$ children. The higher prevalence of IAA in young patients is well documented (20–22), and in the present series, it was

Table 5—*Clinical characteristics of children and adults with newly diagnosed type 1 diabetes*

	Children	Adults	*P*
n	252	100	—
Male subjects (*n* [%])	145 (57.5)	70 (70.0)	0.04
Duration of symptoms (weeks)	2 (1 to 4)	5.5 (4 to 24)	<0.001
Relative body weight (%)	93.0 (87.0 to 100.5)	96.5 (87.5 to 110.0)	<0.001
Number of preceding infections	1 (0 to 2)	0 (0 to 1)	<0.001
n	195	99	
Blood glucose (mmol/l)	20.7 (14.9 to 25.7)	20.5 (17.8 to 25.8)	NS
n	251	100	
Glycated hemoglobin HbA_{1c} (%)	12.9 (10.8 to 15.5)	10.2 (9.0 to 12.7)	<0.001
n	219	225	
Serum C-peptide (nmol/l)	0.14 (0.10 to 0.21)	0.19 (0.11 to 0.27)	NS
n	74	47	
pH	7.37 (7.31 to 7.40)	7.41 (7.39 to 7.43)	0.02
n	250	93	
Bicarbonate (mmol/l)	22.0 (14.2 to 25.0)	24.5 (22.0 to 26.7)	0.002
n	243	91	
Base excess (mmol/l)	−2.7 (−10.1 to 0.6)	0.55 (−1.7 to 2.1)	<0.001
n	250	92	
Ketonuria (%)	168 (80.0)	78 (79.6)	NS
n	210	98	

Data are *n*, *n* (%), or medians (interquartile range).

Table 6—*Clinical characteristics of children and adults with newly diagnosed type 1 diabetes according to 4 age-groups*

	Group I (< 5 years)	Group II (5.0–9.99 years)	Group III (10.0–19.99 years)	Group IV (≥20 years)	Statistics	*P*
n	45	91	116	100		
Males (%)	23 (51.1)	49 (53.8)	73 (62.9)	70 (70.0)	$\chi^2_{df=3} = 7.40$	0.008
					I vs. IV	0.05
					II vs. IV	0.03
Duration of symptoms (weeks)	2 (1 to 3)	2 (1 to 4)	3 (1 to 4)	5.5 (4 to 24)	$H_{df=3} = 77.58$	<0.001
					I vs III	0.001
					I vs. IV	<0.001
					II vs. III	0.01
					II vs. IV	<0.001
					III vs. IV	<0.001
Relative body weight (%)	95 (89 to 99)	93 (88 to 103)	90 (84 to 98)	96.5 (87.5 to 110)	$F_{df=3} = 21.13$	<0.001
					I vs. IV	<0.001
					II vs. IV	0.002
					III vs. IV	<0.001
Number of preceding infections	1 (1 to 3)	1 (1 to 2)	1 (0 to 1)	0 (0 to 1)	$H_{df=3} = 69.72$	<0.001
n	39	66	90	99	I vs. III	<0.001
					I vs. IV	<0.001
					II vs. III	<0.001
					II vs. IV	<0.001
					III vs. IV	<0.001
Blood glucose (mmol/l)	20.5 (15.7 to 24.3)	19.2 (13.5 to 26.7)	21.9 (16.4 to 27.7)	20.5 (17.8 to 25.8)	$F_{df=3} = 8.78$	0.03
n	44	91	116	100	II vs. III	0.03
					II vs. IV	0.03
HbA_{1c} (%)	11.8 (8.6 to 14.8)	12.3 (10.2 to 15.1)	13.3 (11.3 to 15.8)	10.2 (9.0 to 12.7)	$F_{df=3} = 21.36$	<0.001
n	36	82	101	74	I vs. III	0.04
					II vs. III	0.04
					II vs. IV	0.02
					III vs. IV	<0.001
Serum C-peptide (nmol/l)	0.10 (0.06 to 0.15)	0.14 (0.10 to 0.21)	0.18 (0.13 to 0.25)	0.19 (0.11 to 0.27)	$F_{df=3} = 28.17$	<0.001
n	41	85	99	47	I vs. II	0.001
					I vs. III	<0.001
					I vs. IV	<0.001
					II vs. III	0.006
pH	7.37 (7.31 to 7.42)	7.39 (7.34 to 7.41)	7.37 (7.31 to 7.40)	7.41 (7.39 to 7.43)	$F_{df=3} = 9.80$	0.02
n	45	91	114	93	II vs. III	0.04
					III vs. IV	0.02
Bicarbonate (mmol/l)	20.0 (14.9 to 24.3)	22.0 (17.0 to 25.0)	22.0 (11.0 to 26.0)	24.5 (22.0 to 26.7)	$F_{df=3} = 16.10$	0.001
n	44	90	109	91	I vs. III	0.02
					I vs. IV	0.02
					II vs. IV	0.02
Base excess (mmol/l)	−4.0 (−9.9 to 1.2)	−1.5 (−7.1 to 1.3)	−1.6 (−13.1 to 1.2)	0.55 (−1.7 to 2.1)	$F_{df=3} = 14.74$	0.002
n	45	91	114	92	I vs. II	0.03
					I vs. IV	0.002
					II vs. IV	0.02
					III vs. IV	0.02
Ketonuria (%)	29 (80.6)	57 (76.0)	82 (82.8)	78 (79.6)	NS	
n	36	75	99	98		

Data are *n*, *n* (%), or medians (interquartile range). The *H* value is the result of Kruskal-Wallis nonparametric one-way analysis of variance. The *F* value is the result of the parametric one-way analysis of variance. Accordingly, these values are equal to the *t* value of Student's *t* test.

seen to drop from 62% among those <10 years of age to 20% in the adult patients. The latter group showed no further decrease in the prevalence of IAA with increasing age, however. There are conflicting results on the relationship between other disease-associated autoantibodies and age at diagnosis. We previously found the prevalence of ICA to be of the same magnitude in children and in adults (4), whereas ICA were significantly more often detectable in the children than in the adults in the present population. Accordingly, these data are in line with those reported in a German study with an ICA frequency of 83% among

patients diagnosed with type 1 diabetes before the age of 40 years and of only 46% among older patients (6).

Vandewalle et al. (22) observed a higher frequency of GADA in adult patients diagnosed before the age of 40 years than in children and adolescents, whereas we have previously reported a higher GADA prevalence in 10- to 14-year-old children with newly diagnosed type 1 diabetes than in younger patients (23). The patients in the present data set diagnosed between the ages of 10 and 19 years had the highest frequency of GADA, whereas the adult patients had the highest GADA levels. Taken together, these observations indicate that very young patients tend to mount a weak antibody response to GAD and that the intensity of the GAD response increases with age. IA-2A were the most prevalent antibodies in the age-group of 10–19 years and were still detectable in two-thirds of the young adult patients in the age-group of 20–29 years, whereafter less than half of the older adult patients tested positive for IA-2A.

The proportion of patients without any detectable autoantibodies at diagnosis was substantially higher among the adults. The question of whether there is a true autoantibody-negative nonautoimmune form of type 1 diabetes has remained unanswered. There are 2 other alternative explanations for the observation of antibody-negative patients at clinical presentation. One is that they have had detectable antibodies in the preclinical period but have turned negative before diagnosis, and the other is that the assays used are not sensitive enough to detect low antibody levels. The issue is further complicated by the finding that some antibody-negative patients do have antigen-specific T-cell responses (6), and an inverse correlation has been observed between the antibody and T-cell responses to GAD in individuals with an increased risk of type 1 diabetes (24) and responses to insulin when combining risk individuals and patients with newly diagnosed disease (25). In fact, Lohmann et al. (6) reported that all of their 23 subjects with diabetes diagnosed before the age of 40 years had disease-associated autoantibodies and/or T-cell reactivity to GAD, whereas the corresponding proportion among patients diagnosed with the phenotype of type 1 diabetes after 40 years of age was 83% (20 of 24). Accordingly, the lower frequency of autoantibodies in adult patients does not necessarily reflect a nonimmune form of type 1 diabetes.

Based on the observed dichotomy between antigen-specific humoral and cellular immune responses, one would expect to find enhanced T-cell responses to β-cell antigens in adult patients with newly diagnosed type 1 diabetes. This hypothesis has to be confirmed with actual data, however, because as far as we are aware, no such observations have been reported. Nevertheless, we interpret the finding of a higher frequency of various autoantibody specificities and of multiple antibodies in children and adolescents as an indicator of a more aggressive autoimmune attack against the β-cells in young patients, because it has been repeatedly confirmed that the risk of progression to clinical type 1 diabetes is directly related to the number of autoantibodies detectable in the preclinical period in individuals with an increased disease risk (26–28).

The fact that the patients with the DQB1*0302/x genotype had the highest prevalence of IA-2A among both children and adults confirms the previously reported association between IA-2A and the DR4/DQB1*0302 haplotype (17,29,30). Adult subjects carrying the DQB1non*02/non*0302 genotypes were characterized by a decreased frequency of ICA, GADA, and IA-2A, indicating a reduced humoral immune response in such individuals. This raises the possibility that this group of patients may comprise a few subjects having some form of maturity-onset diabetes of the young (31) rather than classic type 1 diabetes.

The strong male predominance among the adult patients is surprising from the point of view that most other autoimmune diseases are more common in female patients (32), whereas the fact that the adult patients indisputably had milder symptoms and signs at diagnosis than the children and adolescents is in line with the view that adult-onset type 1 diabetes represents a slowly progressive disease (4,33). The children and adults had blood glucose concentrations of the same magnitude at diagnosis, whereas the children had a significantly higher HbA_{1c} level, reflecting either a more severe or more prolonged period of hyperglycemia before diagnosis. The first alternative is supported by the finding that the young patients had a shorter symptomatic period before clinical presentation. The higher frequency of infections seen in children immediately before the diagnosis may also contribute to a more severe hyperglycemia in these patients. It may be possible that a few adult patients living in the catchment area and fulfilling our criteria of newly diagnosed type 1 diabetes but with mild symptoms were not admitted to the university hospital. In such circumstances, the actual differences between adults and children in clinical characteristics might be even more conspicuous than those observed in the present study population.

Our observations show that clinical manifestation of type 1 diabetes before the age of 20 years is characterized by a strong HLA-defined genetic disease susceptibility, a more frequent autoantibody response to various β-cell antigens, a higher frequency of preceding infections, and more severe metabolic decompensation at presentation than in patients diagnosed at an adult age. These results imply that β-cell destruction progresses more slowly in individuals presenting with the disease after the age of 20 years. Accordingly, the age at clinical onset of type 1 diabetes may be determined by the intensity of the β-cell destruction process, which may be modulated by both genetic and environmental factors.

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