Family Characteristics and Life Events Before the Onset of Autoimmune Type 1 Diabetes in Young Adults

A nationwide study

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OBJECTIVE — To elucidate whether family characteristics and stressful life events were associated with onset of autoimmune type 1 diabetes in young adults.

RESEARCH DESIGN AND METHODS — This investigation was based on a nationwide study (Diabetes Incidence Study in Sweden) of newly diagnosed patients aged 15–34 years. Patients clinically classified as type 1 diabetic with antibodies to islet cells and/or to GAD65 were compared with age- and sex-matched control subjects via questionnaire. The questionnaire covered diabetes heredity, social environment, educational level, and life events experienced during the 12 months before diagnosis.

RESULTS — The rate of response was 82% for the diabetic patients and 65% for the control subjects. Questionnaires from 349 diabetic patients and 979 control subjects were considered. Diabetes in relatives was more frequent in the patients (odds ratio [OR]2.6) who were born in Sweden and whose mothers were of Swedish origin. No major stress factors were detected in the diabetic patients; however, in comparison with the control subjects, the diabetic patients had experienced fewer conflicts with their parents and had less often broken contacts with friends.

CONCLUSIONS — Young adults with recent-onset type 1 diabetes were more exposed to heredity for diabetes, but no major prediabetic stress factors were detected. Our study does not directly support the concept that psychosocial stressful life events are involved in the development of autoimmune type 1 diabetes in young adults.

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Abbreviations: DISS, Diabetes Incidence Study in Sweden; GADA, GAD antibodies; ICA, islet cell antibodies; JDF, Juvenile Diabetes Foundation; LES, Life Event Scale; OR, odds ratio; W/H, waist-to-hip.

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

Both genetic and environmental factors are considered in the etiology of type 1 diabetes (1,2). An increased prevalence of diabetes among relatives, high maternal age, low education level of the mother, manual work by the father, and stressful life events within the family related to actual or threatened losses have been associated with onset of type 1 diabetes in children (3–5). The importance of stress for the development of autoimmune type 1 diabetes is in line with observations in other autoimmune diseases (6,7). The aim of the current study was to examine whether hereditary and environmental factors, including psychological stress, are associated with the onset of type 1 diabetes among young adults.

RESEARCH DESIGN AND METHODS

— The Diabetes Incidence Study in Sweden (DISS) (8,9), which began in 1983, is a population-based prospective registration of all newly diagnosed cases of diabetes in individuals aged 15–34 years in Sweden. The DISS records the age, sex, residence, blood glucose, symptoms (polyuria, weight loss, fatigue, or coma) of diabetes, duration of symptoms, height and body weight at diagnosis, initial maintenance treatment, and presence of ketonuria and acidosis among these individuals. Based on the clinical impression, diabetes is classified by the reporting physician as type 1, type 2, or unclassifiable diabetes. According to the current practice in Sweden, type 1 diabetic individuals are clinically defined as those with low or normal body weight, young age, severe hyperglycemia or ketoacidosis, and an immediate need for insulin therapy. The objective of DISS is to follow the trend in the incidence of diabetes in young adults and to find clues to the putative etiology and pathogenesis of diabetes and its complications.

This report includes individuals classified as type 1 diabetic and positive for islet-cell antibodies (ICA) and/or GAD 65

Table 1—*Characteristics of type 1 diabetic patients with islet antibodies (ICA and/or GADA) and control subjects in the DISS 1992-1993 patient-control study*

	Diabetic patients	Control subjects
n	349	979
Male/female	220/129 (64)	559/420 (57)
Age (years)	23.4 ± 5.5	24.4 ± 5.8
BMI (kg/m^2)	23.0 ± 3.4	22.7 ± 3.1
W/H ratio	0.84 ± 0.10	0.84 ± 0.10

Data are *n* (%) or means ± SD.

antibodies (GADA) registered in DISS during the years 1992 and 1993.

Methods

From 1992–1993, a patient-control study was performed. All incident cases of diabetes in Sweden of individuals 15–34 years of age were included. This study was designed to detect a 10% difference between the diabetic patients and the control subjects with a power of 95%. Accordingly, as in the Swedish Childhood Study (3,4), two control subjects were selected for each diabetic patient. The control subjects were taken from the official Swedish Population registry. The risk for autoimmune diabetes may be caused by socioeconomic factors. Therefore, diabetic patients and control subjects were matched for age (day of birth) and sex but not for socioeconomic factors, including educational levels of the parents. In Sweden, educational level is considered the major factor contributing to socioeconomic status. In the diabetic patients, a blood sample was taken at diagnosis for measurements of ICA and GADA.

At 4 weeks after the diagnosis of diabetes, diabetic patients and control subjects received a questionnaire covering the following items: heredity; social environment, including education level of both the parents and the respondent (grade school, college, or University); age of parents at the birth of the respondent; living conditions; health and disease; body characteristics, including height, weight, and waist-to-hip (W/H) ratio (waist and hip circumference measured in the standing position); and life-style habits and life events experienced during the previous 12 months. If the questionnaire was not returned within 2 weeks, the participant was reminded by postcard. Participants who did not report within 1 month were invited to participate by telephone call if the telephone number was available.

In the questionnaire, life experience was modified from Sarason's Life-Event Survey (10), and 26 questions of possible life events, such as marriage, pregnancy and delivery, bereavement, and educational and general successes or failures were listed. The questions reflected both desirable and undesirable life events. Each question was denoted a yes or no alternative. To quantify the degree of stress, a self-esteem analogue scale, the Life Event Scale (LES), was used. Ratings were conducted on a 7-cm scale ranging from extremely positive (+1) to extremely negative (+7), i.e., low values indicated a positive experience from the subjects point of view. The study was approved by the Karolinska Institute Ethics Committee and by the Swedish Data Inspection Board.

Analytical methods

Islet cell antibodies. A two-color immunofluorescence method previously described in detail (11) was used, and the values were expressed in Juvenile Diabetes Foundation (JDF) units, in accordance with a standard curve for the specific pancreas used (12). The interassay coefficient of variation was 26%, and the lower detection limit was 6 JDF units. In the International Diabetes Workshop (ICA proficiency workshop), the sensitivity and specificity were 100% for the pancreas used in the study.

Antibodies to GAD65

GADA was measured with a radioimmunoassay as previously described (13,14). A relative index was calculated according to the following formula:

GADA index = (mean cpm sample – mean cpm negative standard) / (mean cpm positive standard – mean cpm negative standard)

All samples were tested in duplicate, and a variation of 20% was accepted; otherwise, the samples were reanalyzed. The reference range was defined using 833 blood samples from age- and sex-matched control subjects. An index ≤0.07 (median and 95th percentile) was considered negative. The intra- and interassay variations for a positive control serum were 33% (n = 52) and 16% (n = 40), respectively. In the GADA proficiency test 3, sensitivity, specificity, validity, and consistensy were all 100% (15).

Statistical analysis

We used a patient-control technique to assess the risk associated with the characteristics of the diabetic patients and the control subjects before the onset of diabetes. The relative risk score was estimated by Mantel-Haenszel–adjusted odds ratio (OR) in a matched design and by multiple logistic regression. Data are presented as odds ± 95% CI or as means ± SD. Differences in LES and physical variables between the diabetic patients and control subjects were tested with analysis of variance (matched design). A P-value <5% was considered significant.

RESULTS — The mailed questionnaire was returned from 443 of 542 (82%) type 1 diabetic patients and from 979 of 1,498 (65%) control subjects. Among the diabetic patients, 349 of 443 (79%) were positive for ICA and/or GADA. There were no significant differences between responding and nonresponding participants with regard to age, sex, or the prevalence of ICA or GADA. The two groups were almost identical with regard to sex, age, BMI, and W/H ratio (Table 1).

Heredity

Among the first-degree relatives, diabetes was reported more frequently in patients than in control subjects; 52 of 295 (17.6%) vs. 32 of 426 (7.5%), respectively; OR 2.6 (CI 1.7–4.2). Indeed, the risk for diabetes increased significantly ($P < 0.001$) with the number of relatives with diabetes in the family. Among 295 diabetic patients, 99 had one relative with diabetes, 30 had two, 3 had three, and 1 had five compared with 98, 23, 2, and 0, respectively, among 426 control subjects.

Family characteristics

There were no significant differences regarding the mean age of parents in diabetic patients versus control subjects (fathers 31.3 ± 6.1 vs. 30.7 ± 6.2 years,

Table 2—*Family characteristics in type 1 diabetic patients with islet antibodies in the DISS 1992-1993 patient-control study with regard to heredity, parental age, number of siblings, and immigrants*

Family characteristics at diagnosis	Diabetic patients	Control subjects	*P*
Heredity			
First degree relatives with diabetes	17.6	7.5	0.001
Parental age (years)			
Father's age at birth	31.3 ± 6.1	30.7 ± 6.2	0.22
Mother's age at birth	28.2 ± 5.4	28.1 ± 5.2	0.90
Number of siblings			
0	10.3	7.9	0.18
1	52.8	50.5	0.35
≥2	47.2	49.5	0.35
Proportion of immigrants			
Subjects	2.7	8.0	0.003
Mothers	9.0	15.1	0.011
Fathers of mothers	9.4	16.0	0.007
Father of fathers	11.9	17.2	0.047

Data are % or means ± SD.

respectively, and mothers 28.2 ± 5.4 vs. 28.1 ± 5.2 years, respectively), and the number of siblings did not differ between diabetic patients and control subjects. However, compared with control subjects, a significantly higher proportion of the diabetic patients (284 of 292 [97.3%] vs. 391 of 425 [92%], $P = 0.003$), the mothers of the diabetic patients (264 of 290 [91%] vs. 360 of 424 [84.9%], $P = 0.011$), and the fathers of the mothers of the diabetic patients (259 of 286 [90.6%] vs. 352 of 419 [84%], $P = 0.007$) were born in Sweden (Table 2).

There were no significant differences between diabetic patients and control subjects for the frequency of maternal smoking during pregnancy (29 vs. 26%, $P = 0.199$) or during the first year of life (37 vs. 34%, $P = 0.495$) and for the duration of breast-feeding (duration >3 months) (54 vs. 59%, $P = 0.568$).

Education level

There was no difference in the frequency of education level (with regard to grade school, college, or university) between diabetic patients and control subjects (18, 64, and 17% vs. 20, 59, and 22%, respectively, $P = 0.538$); likewise, there was no difference in the frequency of maternal education level (49, 33, and 18% vs. 45, 35, and 20%, respectively, $P = 0.261$) or paternal education level (49, 35, and 16% vs. 43, 37, and 21%, respectively, $P = 0.57$).

Weight at diagnosis and self-reported weight during growth

Table 1 shows that there was no significant difference in mean BMI in the diabetic patients compared with the control subjects. In addition, with regard to the self-reported weight (under-, normal-, or overweight) during growth, there was no difference between diabetic patients and control subjects, $P = 0.528$.

Life events

Table 3 shows that diabetic patients had much higher rates for serious illness (questions 10 and 11) than control subjects. In addition, there were differences in the conflict pattern between diabetic patients and control subjects. During the last year before the diagnosis of diabetes, the diabetic patients had experienced fewer conflicts with their parents and had less often broken contacts with their friends than had the control subjects. On the other hand, in contrast to the control subjects, conflicts with spouses had not decreased among the diabetic patients. Moreover, the diabetic patients had experienced less success and had fallen in love less frequently than the control subjects. Noteworthy, the diabetic patients experienced changes of job more positively than did the control subjects (LES score 2.23 ± 2.36 vs. 3.69 ± 2.06, respectively, $P = 0.03$). Otherwise, there were no differences in the degree of stress as determined by the LES scores between diabetic patients and control subjects.

CONCLUSIONS — The onset of autoimmune type 1 diabetes is considered an interaction between hereditary and environmental factors (16). This study shows the importance of hereditary factors for the development of autoimmune type 1 diabetes in young adults. In keeping with the Sweden childhood diabetes study (3), an increased frequency of diabetes was reported in first-degree relatives. However, in contrast to findings in children (3), there were no differences in parental ages for young adults with recently diagnosed type 1 diabetes compared with control subjects. Moreover, other than a positive association to being born in Sweden, maternal smoking habits and breast-feeding habits did not differ between diabetic patients and control subjects.

Psychological stress factors may favor the onset of diabetes (17). However, this possibility was not directly supported by the observations in our study. There were no differences in major stress factors between diabetic patients and control subjects. Although, in our study, young adults diagnosed with autoimmune type 1 diabetes had a different conflict pattern than control subjects, ties to parents and old friends seemed to have deepened before diagnosis, whereas conflicts with spouses were unresolved. In addition, the diabetic patients had experienced fewer successes and had fallen in love less frequently than the control subjects. Hence, it appears that before the diagnosis of diabetes, diabetic patients had a tendency for isolation and regression combined with a low self-esteem and a fear of losing intimate friends and support. From this perspective, it is understandable why diabetic patients experienced a change of job as a more positive event than did control subjects. However, the possibility that fear of loss is as strong a stressor in teenagers and young adults as actual losses are in children (4) must be considered. An increased frequency of stressful events during the last year before the onset of autoimmune type 1 diabetes has previously been reported among young adults in France (18). Hence, stressful life events may precede a development to clinical type 1 diabetes in young adults. However, it is important keep in mind that the differences in life events between

Table 3—*Life events during the 12 months before diagnosis in 349 patients with recent- onset autoimmune type 1 diabetes compared with those of 979 age- and sex-matched control subjects according to data from a questionnaire used in the DISS (1992–1993) patient-control study*

Question no.		OR	95% CI
Family and living conditions			
1	You have had more conflicts with your partner	0.83	0.49–1.42
2	You have had less conflicts with your partner	0.50*	0.28–0.87
3	You have had conflicts with your parents	0.44*	0.26–0.73
4	A close friend has broken contact with you	0.50*	0.30–0.85
5	You have moved to another place	0.82	0.57–1.18
6	You have changed jobs	0.80	0.55–1.17
7	Your income has deteriorated	0.66	0.43–1.01
8	You have had difficulties financing your studies	0.80	0.45–1.44
9	You have been unemployed for >14 days	0.79	0.52–1.20
Serious illness or injury			
10	You have been seriously ill or injured	9.45*	6.34–14.07
11	You have been hospitalized for >1 week	12.17*	7.94–18.63
12	One or both of your parents has been seriously ill or injured	0.55	0.30–1.00
13	Someone in your family has been seriously ill or injured	1.16	0.64–2.07
14	Someone in your family has been hospitalized	0.95	0.59–1.51
Deaths			
15	One or both of your parents has died	0.60	0.24–1.49
16	One or both of your grandparents has died	0.65*	0.44–0.97
17	A close friend of yours has died	0.82	0.45–1.50
Sexuality			
18	You have fallen in love	0.65*	0.47–0.91
19	You have found a new partner	1.37	0.75–2.49
20	You have been pregnant (women)	0.88	0.40–1.93
21	Your partner has been pregnant (men)	0.51	0.24–1.08
22	You have had a baby	0.75	0.48–1.18
23	Your partner has had an abortion	0.64	0.12–3.44
24	You have been divorced or separated	0.62	0.34–1.12
Perceived competence			
25	You have experienced a great success/made an extraordinary achievement	0.58*	0.37–0.90
26	You have failed an important examination	0.59*	0.35–0.98

Analysis of relative risks score calculated as Mantel Haenszel–adjusted ORs and 95% CIs for patients compared with referents. *Significant.

diabetic patients and control subjects in the current study could be caused by events of independent illness or manifestations of early stages of diabetes. The institution of insulin treatment leading to improvement of glycemic control after the diagnosis may have induced an independent lifestyle in the diabetic patients (19,20), retrospectively explaining the differences found in social behavior between our diabetic patients and control subjects. Moreover, in keeping with our findings, major life stress and psychiatric disorders are not always found before the onset of childhood diabetes (21). Nevertheless, as in other studies (22,23), our diabetic patients with newly diagnosed diabetes tended to be socially isolated. Isolation in low people-density areas may increase the risk of developing diabetes (24). Hence, although the features of social isolation may be considered a consequence of the progression of diabetes, our diabetic patients may have personality traits favoring the development of diabetes. In conclusion, heredity factors but not psychosocial stressful life events were closely associated with the development of autoimmune type 1 diabetes in young adults.

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