Psychological Stress and the Onset of IDDM in Children

A case-control study

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OBJECTIVE — The purpose of the study was to determine whether psychosocial stress during different life periods could be a risk factor in the etiology/pathogenesis of insulin-dependent diabetes mellitus (IDDM) in children.

RESEARCH DESIGN AND METHODS — In a population-based sample of 67 case patients 0–14 years of age and 61 matched healthy control subjects, life events during the entire lifespan before the onset of IDDM were recorded as well as measures of child behavior before onset, social support, and family function.

RESULTS — Negative life events occurring during the first 2 years of life, life events with difficult adaptation, child behavioral deviances, and a more chaotic family function were more common in the case group. A stepwise logistic regression indicated that negative life events in the first 2 years increased the risk of IDDM and that premorbid child behavior as well as dysfunctional hierarchical family pattern affect the risk.

CONCLUSIONS — Stress early in life may increase the risk for IDDM, presumably by affecting the autoimmune process. To confirm these results, it is necessary to make a truly prospective study.

The theory of the etiology of insulin-dependent diabetes mellitus (IDDM) proposed in recent years is that IDDM is caused by an autoimmune destruction of the β-cells in genetically predisposed individuals (1). The majority of IDDM patients carry specific human leukocyte antigen (HLA) haplotypes in the major histocompatability complex region of chromosome 6, whereas other HLA haplotypes are associated with a reduced risk for IDDM (2,3). Because the concordance rate of IDDM among monozygotic twins is only ~30% (4) and the risk of an HLA-identical sibling of an IDDM patient is also only 30% (5,6), environmental factors must play a crucial role. Researchers have proposed viruses (7), dietary habits (8–11), and toxic agents (12) as possible environmental factors.

The association between psychological stress and the onset of IDDM was suggested as early as 1679 by Willis (13), followed by several more recent studies (14–16). These findings have been both contradicted and criticized on methodological grounds (17,18). More recent studies, using standardized measures of life events with control groups, have shown an increased number of life events before the onset of IDDM in adults (19,20). Support for these results was given by animal studies (21,22). In a comparatively large and truly population-based incident case-control study, Häglöf et al. (23) found that the total number of life events was the same for diabetic and control children. When more qualitative aspects were included by separately analyzing severe events experienced by children, such as actual or threatened losses within the family, such events turned out to be significant risk determinants for IDDM with onset between 5 and 9 years of age. However, in this study, only life events occurring during the last year were recorded. Robinson and Fuller (24) have shown that patients with newly diagnosed diabetes had more severe life events than siblings and neighborhood control subjects during a 3-year period before onset. The same group also showed an association between islet cell antibodies and severe life events (25). A limitation of these studies was that they consisted of very small samples.

Three different time periods of importance in the etiology/pathogenesis of IDDM have been discussed: *1*) when the

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CRS, Clinical Rating Scale; HLA, human leukocyte antigen; IDDM, insulin-dependent diabetes mellitus; ISSI, Interview Schedule of Social Interaction.

Table 1—*Demographic characteristics of the studied populations*

Variable	Case group	Control group
n	67	61
Age (years)	8.37 ± 3.95	8.23 ± 4.00
Gender (%)		
Boys	49	46
Girls	51	54
Socioeconomic status (%)		
University education and/or higher white-collar occupation		
Mothers	18	24
Fathers	23	40
High school and/or lower white-collar occupation		
Mothers	38	44
Fathers	30	26
No further education after ordinary school and blue-collar occupation		
Mothers	44	33
Fathers	47	34

Age data are means ± SD.

body learns to distinguish its own proteins from foreign proteins, at ~0–24 months of age (26,27); 2) when the autoimmune reaction starts, often many years before manifest disease, indicating a period up to 8 years before clinical onset of IDDM depending also on the child's age (28); 3) the time close to the clinical onset of IDDM, when stress may be a triggering factor, indicating the period up to 12 months before the clinical onset of the disease (20). To date mainly the last hypothesis has been discussed.

Besides measurement of life events, stress can be implied in other ways, such as behavioral deviances in children, which can be seen as unspecified indications of stress. The effect of life stress can be moderated by several factors. The vast field of social support research emphasizes the protective aspects of being integrated in a supportive social network (29). The family is of the utmost importance, especially for children. A good social network and a good family function should therefore serve as a protection against negative influences of life stress. A lack of social support and a dysfunctional family, on the other hand, may also be possible sources of stress.

In the present study we compared a group of children who had recent onset of IDDM with an age-matched control group for psychosocial stress factors, such as life events, behavior symptoms, family factors, and parental social network. We offer the following hypotheses. *1*) In the case group, we should find more life stress during the first period of life, 0–24 months, if stress influenced the immunological development. 2) In the case group, we should find more life stress during the entire period of life, 0–14 years, if stress influenced the autoimmunological process. 3) In the case group, we should find more life stress during the last year before the clinical onset of the disease if stress acted as a triggering factor. 4) If a good social network and family function is protected against the negative aspects of life stress, we should find that these factors decrease the risk in a multivariate statistical model.

RESEARCH DESIGN AND METHODS

Subjects

Children <15 years old, in whom IDDM had been diagnosed during 1988 and 1989 at five pediatric clinics in different geographic areas in Sweden, were invited to take part in the study. The patients should represent the total population of IDDM in these areas because at the time of the study the pediatric clinics covered all cases occurring in the region. Of a total of 82 case patients, 2 were excluded because of mental retardation and another was excluded because of onset of IDDM when the patient was abroad on vacation. Of the remaining 79 subjects, 67 (85%) agreed to participate in the family interview. For each diabetic family who took part in the study, a control child of the same sex and nearest in age attending the proband's class or day care center was invited to participate as a crude match for social status. Of the assigned 67 control subjects, 61 (91%) agreed to participate. Demographic variables of the samples are presented in Table 1. All case patients and control subjects were Caucasians. There was no difference in age and sex distribution between the dropouts and those who participated in the study. The socioeconomic status could not be evaluated. The study was described in more detail by Hägglöf et al. (30).

Design

About 2 months after the diagnosis of IDDM, an interview was held with the family. The interviewers had been cotrained in the methods used. In each study center, the same interviewer was used for case patients and control subjects. The interview covered life events, parental and child social support, child behavior, and a videotaped family task. The researchers also had access to social and medical data. The study was approved by the local ethics committees, and informed consent was obtained from all parents and children of relevant ages.

Life events. The parents were interviewed about life events during the whole lifespan of the child. A form based on Coddington's original questionnaire (32,33) and translated into Swedish by Hurme was used (23,34). For each event, the date was measured as carefully as pos-

sible on a monthly basis by comparing it to other important events in the child's and family's life such as beginning nursery school or preschool, grade in school, etc. To measure the appraisal of the event, the interviewer asked whether the child had experienced it as positive or negative on a five-point scale. By scoring the ease or difficulty of the adjustment on a four-point scale, an estimation of adaptation difficulties was made. Negative events were supposed to measure the appraisal of the event, and events with difficult adjustment were supposed to measure how the child actually adapted to the event. Because many of the children were young and the questionnaire covered the entire lifespan, we had to rely on the parents' opinion of how the event had affected the child to maintain consistency in the method. If the parents disagreed about the impact of a special event, we accepted the mother's opinion. The items asked for are shown in Table 2.

The life event questionnaire was evaluated in a 6-year follow-up study of a normal population of 193 children by Höök et al. (35). It showed that both the total life event load and a measure of adjustment difficulty made significant contributions to the prediction of child disturbance at the follow-up investigation. As in the study of Höök et al., items measuring positive events and conflicts were omitted. The positive events were not considered to be operationally defined well enough and conflicts were excluded because items in the child behavior questionnaire covering peer conflicts and family conflicts were integrated in the measure of family function. Besides, the conflict items in the life event questionnaire were shown to have a low reliability.

Obviously, a disadvantage with using the parents as informants is that parental factors influence the assessment. In the study by Höök et al. (35), mothers regularly regarded it more negative if the fathers remarried than if they themselves did so. Thus, we thought it was important to add a more objective way to determine whether an event was negative. Therefore, 27 events covered by the questionnaire that were defined as negative by earlier researchers were regarded as always negative (35). To this number, all neutral events that the child had experienced as negative or very negative were added. The following variables were calculated: *1*) the total number of life events; 2) the number of negative events; and 3) the number of life events causing difficult or very difficult adjustment.

Table 2—*Items in the life-event questionnaire*

Family composition and living conditions
1. Birth of a brother or sister
2. Addition of a third adult to the family
3. Brother or sister leaving home
4. Separation of the parents*
5. Divorce of parents
6. The family changes apartment/house†
7. The family moves to another place†
8. Jail sentence of a parent*
9. Mother married to a stepparent*
10. Father married to a stepparent*
11. Discovery of being an adopted child*
Child care and occupation of parents
12. Beginning nursery school or family day care
13. Changing nursery school or family day care†
14. Beginning the preschool year
15. Mother beginning to work
16. Father beginning to work
17. Loss of job by a parent
18. Financial status of parents markedly reduced
19. Job of parent requiring more absence from home
Serious illness or injury
20. Serious illness or injury of the mother*
21. Hospitalization of the mother*
22. Serious illness or injury of the father*
23. Hospitalization of the father*
24. Serious illness or injury of the child*
25. Hospitalization of the child*
26. Hospitalization of a brother or sister*
Deaths
27. Death of the mother*
28. Death of the father*
29. Death of a brother or sister*
30. Death of a grandparent*
31. Death of a close friend to the child*
Schooling
32. Beginning first year of compulsory education
33. Change to a new school†
34. Failure of a year in school*
35. Beginning seventh grade of compulsory education
Sexuality
36. Breaking up with a girl- or boyfriend*
37. Menarche
38. Unmarried pregnancy*
39. Fathering an unmarried pregnancy*
40. Abortion*

*Negative event. †Negative when occurring more than twice.

Measures of child behavior. The parents were interviewed about the child's normal behavior according to a symptom list, which encompasses 51 operationally defined behaviors. This interview focused on the behavior during the last year and before any signs of IDDM symptoms. The questionnaire is shown to have good validity and reliability, with internal consistency ranging from 0.81 to 0.85 and an average score about four times as high ($P < 0.001$) in a clinical group as in a normal group (36). The interviews were audiotaped, and a sample was evaluated by all interviewers. The inter-rater reliability varied between 0.92 and 0.99. The youngest children in the study were excluded because the questionnaire did not fit them. Seven diabetic and eight control children are thus missing. The symptoms were summed up into four factors (inhibition, acting-out, asocial, and anxiety) and a total score (36). Internal consistency for the combined case and control group was 0.64.

Measures of family function. A videotaped family task was evaluated blindly by a group of trained raters (none was an interviewer): *1*) all family members individually were asked to answer four questions regarding the family and afterwards discuss these and agree upon one answer for the entire family; 2) each family member was asked to state one positive and one negative opinion about the family; 3) the whole family was asked to participate in laying a puzzle, which was very difficult. There were 6 diabetic families and 1 control family that refused to be videotaped, and 11 tapes had to be excluded for technical reasons (7 diabetic and 4

control families). All together, 54 diabetic families and 56 control families were evaluated. We found no differences regarding age and sex between those who were videotaped and the other subjects.

The rating scales used were the Clinical Rating Scale–Turbo (CRS), Family Competence, and Family Style. The CRS was developed by Olson (37,38), building on his circumplex model and then revised by Gustafsson et al. (39). It is composed of three scales called Adaptability, Cohesion, and Hierarchical Organization (40). Adaptability and Cohesion are curvilinear dimensions. Adaptability measures family function dimension with the extremes rigidity and chaos, and Cohesion has the extremes enmeshment and disengagement. Hierarchical Organization is linear; a high value is negative. The CRS has been shown to predict metabolic control in adolescents with IDDM (39). The validity of CRS was estimated by its ability to differentiate between normal families and families with an identified psychiatric patient (41).

All raters received extensive training in these scales. The raters worked in pairs and made one individual and one consensus rating for each family. The inter-rater reliability was 0.93 for Family Competence, 0.81 for Family Style, 0.83 for Adaptability, 0.79 for Cohesion, and 0.87 for Hierarchical Organization.

Socioeconomic status. The official Swedish classification was used regarding parents' occupation. The parents were divided into three groups: *1*) university education and/or higher white-collar occupation; 2) high school and/or lower white-collar occupation; and 3) no further education after ordinary school and blue-collar occupation.

Parental social support. The Interview Schedule of Social Interaction (ISSI) was chosen due to its good theoretical foundation. It measures both availability and adequacy of social integration and attachment. The ISSI was originally developed by Henderson et al. (42). The original studies with the ISSI showed good internal consistency and reliability and both main and buffering effects on the development of neurosis. It has been translated into Swedish and revised by Undén and Orth-Gomér (43) into a self-report questionnaire, which is shown to have a good correlation with the long version. The original version of the instrument is shown to have a good test-retest stability (42). Thernlund and Samuelsson (44) found a lower test-retest stability for the revised version in a group of parents compared with a group of professionals (0.45–0.87). We have used the total score. High scores are equal to good social support. The internal consistency of the ISSI, measured by Cronbach's α, in the combined case and control group was 0.87.

Statistical analysis

The Mann-Whitney *U* test and Student's *t* test were used to compare the variables in the case and control groups. A logistic regression analysis was performed with IDDM status (yes/no) as the dependent variable. The stress factors were divided into those thought to be of importance for *1*) the first 2 years of life (life event variables), 2) the intervening period (life event variables from year 2 up to the last year before the clinical diagnosis), and 3) the last year before the clinical onset of IDDM (life event variables and child behavior). Family function and network factors were also included as possible moderators of stress. All factors included in the model were used as continuous variables. The contribution of each variable was tested in stepwise modeling.

RESULTS — All psychosocial measures for case groups were compared with those of the control group. The mean values and SD for the different variables in the case and control groups are shown in Table 3. There were no significant differences in socioeconomic grouping or family composition between the case patients and control subjects, nor were there any differences in social support for parents. The ISSI values did not differ from those of other normal populations (44).

Life events. The control group in this study had life event scores similar to those of another Swedish normal group (35). When looking at the total number of life events and events defined as negative, a statistically significant difference between case patients and control subjects was seen only when negative events occurred during the child's first 2 years of life. When a qualitative aspect of the child's adaptation difficulty was introduced with an event, there were significant differences for the entire lifespan as well as for the first 2-year period (Table 3).

Child behavior. The child behavior scores were within the range of normal levels compared with other Swedish studies for both the case and control groups (36). However, there were significantly more behavioral problems in the case group compared with the control group (Table 3).

Family function. The family function scores in the control subjects did not differ from those of other control groups in Sweden (41). There was no difference in the proportions of high rigidity, enmeshment, disengagement, or hierarchical organization among the groups, but there were significantly more families classified as chaotic in the case group (Table 3).

Risk determinants for IDDM. The psychosocial measures, which were unevenly distributed between the case and control groups, might be risk determinants for IDDM. Negative life events during the first 2 years of life, life events with difficult adjustment during the first 2 years of life, life events with difficult adjustment during the whole life, a high score of behavior problems, and a high score of family chaos were more common in the case group; these factors might thus be risk determinants.

In a stepwise logistic regression of all life event variables together with child behavior as an unspecified indicator of stress, family function, and social support, which could be stressors or moderators of stress, three variables—negative life events during the first 2 years of life, behavior problems (acting-out), and dys-

Table 3—*Psychosocial variables*

Variable	Case group	Control group	*P* value
Life events—first 2 years			
All life events	2.28 ± 1.90	1.89 ± 1.59	0.265
Negative life events	0.75 ± 1.20	0.41 ± 0.92	0.039
Life events with difficult adaptation	0.25 ± 0.84	0.02 ± 0.13	0.022
Life events—intervening period			
All life events	10.90 ± 6.69	11.11 ± 5.90	0.565
Negative life events	5.15 ± 4.17	4.87 ± 3.42	0.983
Life events with difficult adaptation	1.81 ± 2.15	1.05 ± 1.37	0.018
Life events during the last year			
All life events	1.07 ± 1.45	1.00 ± 1.05	0.672
Negative life events	0.44 ± 0.84	0.34 ± 0.52	0.994
Life events with difficult adaptation	0.13 ± 0.52	0.00 ± 0.00	0.112
Child behavior			
Inhibition	6.67 ± 12.94	3.00 ± 5.82	0.021
Acting-out	11.08 ± 13.75	5.00 ± 8.28	0.004
Asocial	2.08 ± 6.26	1.27 ± 5.11	0.214
Anxiety	9.55 ± 10.64	13.25 ± 18.84	0.735
Total score	53.25 ± 44.71	35.27 ± 27.17	0.013
Family organization	1.31 ± 1.45	0.80 ± 1.10	0.076
Family cohesion	13.67 ± 3.69	14.38 ± 2.67	0.229
Family adaptability	15.63 ± 2.94	14.63 ± 2.39	0.027
ISSI			
Fathers	22.86 ± 5.64	22.38 ± 4.86	0.339
Mothers	23.02 ± 5.79	23.02 ± 6.10	0.923

Data are means ± SD.

functional hierarchical organization—stood out in a significant model (Table 4).

CONCLUSIONS — Most researchers have studied the influence of life stress as precipitating the onset of IDDM, suggested to be due to stress-induced increase in peripheral insulin need (19,20,23), whereas our study focused on life stress occurring during the entire life period. We found no increase in life events the year before onset, but negative and difficult life events occurring during the first 2 years of life differed significantly between case patients and control subjects. Life events with difficult adjustment during the entire life also differed significantly between the case group and the control group. We introduced other measures that may be signs of life stress. A high behavior score before onset of IDDM symptoms and high family chaos increased the risk for IDDM. Psychological stress may play a more etiological role, e.g., by affecting the immunopathogenetic β-cell destruction starting long before the clinical onset of the disease (1). Such an explanation is supported by the many indications of interaction between psychological stress and the immune system (45–47) and the results of studies on animal models of autoimmune diabetes (21,22). Robinson et al. (25), who examined a 3-year period before the onset of IDDM, have found associations between severe life events and islet cell antibodies.

Both quantitative and qualitative life events may be associated with the overall social status, family composition, and social support of parents and children. Because there were no significant differences regarding socioeconomic status, family composition, and social support between the groups, this could not explain the difference between the groups. The result of the logistic regression showed that of all potential risk factors, negative events the first 2 years of life increased the risk for IDDM almost twofold. The risk was also affected by the hierarchical organization of the family and by acting-out behavior at the time of onset of the disease. Whether family function was a moderator of stress or a stress factor cannot be differentiated by this study design.

The most obvious methodological problem with a case-control design is the risk of disease-dependent biases, i.e., that diseased children and their parents may recall and/or act differently after the onset of a disease than they did before, whereas the control subjects would act normally. The nature of the study also made it necessary to inform the participants of the aim of the research, i.e., study how psychosocial factors influence the course of the disease and how the disease affects the child and the family. It was impossible to keep the interviewers blind to the participants' IDDM or control status. Paykel (31) has discussed the reliability and falloff with different methods and found that an interview could give more reliable answers, especially if the event was thor-

Table 4—*Results of the stepwise logistic regression of life events and psychosocial factors with IDDM status as the dependent variable*

Psychosocial factors	Variable	*P* value	Odds ratio
Life event	Negative event the first 2 years	0.030	1.94
Child behavior	Acting-out	0.022	1.05
Family function	Hierarchical organization	0.026	1.52

Model χ^2 test 19.85; $P = 0.0002$.

oughly timed by comparing it with other family factors. Severe negative life events such as a divorce, an accident, a severe disease, or the death of a family member and the approximate timing in the child's life (the last year before onset of IDDM or before the age of 2 years) would most probably be recorded similarly among case and control families by a skilled interviewer, whereas less severe or positive events might be biased. The recollection of the adaptive behavior of the child at the time of the event might be subjectively overestimated by a parent of a newly diseased child. The fact that there was no difference in the recollection of events the year before onset may imply that recall bias did not play an important role. A limitation of the life event scale is that it does not take into consideration the context of the situation of the individual and the family when the life event occurred.

There is also a possibility that the behavior problems may be a correlate to prodromal symptoms of the disease. The fact that more case patients had a chaotic family function may be an effect of a crisis reaction, even though 2 months had passed and the metabolic control of the child was normalized. The onset of IDDM is associated with a steep rise in anxiety that for the majority of patients fades within a couple of weeks (30). Many parents had a high level of distress at the end of the 1st year (30), in accordance with the report of Kovacs et al. (48), who found that 25% of the mothers (but not the fathers) were depressed during the 1st year. Only a prospective population-based cohort study examining both potential case patients and control subjects in a healthy state would overcome the problems of possible disease-dependent biases.

In conclusion, the present study indicates that negative life events occurring during the first 2 years of life may be a risk determinant for childhood-onset IDDM and that premorbid child behavior as well as dysfunctional hierarchical family pattern affect the risk. We found no clear-cut evidence supporting the precipitating hypothesis.

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