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The Swedish childhood diabetes study: indications of severe psychological stress as a risk factor for Type 1 (insulin-dependent) diabetes mellitus in childhood

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Summary. This study is part of a nationwide case-referent study. All recent-onset Type 1 (insulin-dependent) diabetic children aged 0–14 years in Sweden were invited to participate. Referent subjects matched for age-, sex- and geographical distribution were selected. In all, 338 patients and 528 referent subjects took part. Life events during the last year prior to clinical onset of Type 1 diabetes were recorded on a questionnaire. The total frequency of life events did not differ between diabetic and referent children. However, qualitatively the life events reported by diabetic children revealed a tendency to increased severity. Events related specifically to actual or threatened losses within the family – events that may affect children differently in different age groups – were reported with a significantly higher frequency by diabetic patients than by referent subjects, aged 5–9 years. The relative risk that such events in fact comprise a risk factor for Type 1 diabetes was 1.82 (95% confidence limits 1.09, 3.03). The relative risk was significantly increased even when standardized for possible confounding factors such as age, sex and indices of social status of the family. We conclude that stressful life events, related to actual or threatened losses within the family, occurring in the vulnerable age group of 5–9 years, are associated with the onset of childhood Type 1 diabetes. Such stressful events may in fact be a risk factor for the disease.

Key words: Type 1 (insulin-dependent) diabetic children, psychological stress, disease onset.

Studies on the aetiology of Type 1 (insulin-dependent) diabetes suggest that certain immunogenic mechanisms predispose to an increased risk of developing Type 1 diabetes from environmental factors [1, 2]. Among environmental factors viral infections [3, 4], dietary habits [5–7], toxic agents [8, 9] and even emotional stress [10–12] have been proposed as possible triggering mechanisms.

Clinical and experimental studies have shown that psychosocial stress may affect immune function in a variety of ways [13, 14]. Furthermore, emotional stress increases the levels of the counter-regulatory hormones – catecholamines, growth hormones and cortisol – thus increasing the peripheral need for insulin [15].

Thus, it is of interest to examine whether epidemiological evidence also implicates psychosocial stress as a risk factor for Type 1 diabetes.

In a large population-based case-referent study we examined reported life events during a one-year period prior to the onset of Type 1 diabetes in childhood.

The following questions were analysed:

- Are the total number of life events a risk factor for Type 1 diabetes in childhood?
- Is there an association between the quality of life events and the risk for Type 1 diabetes in childhood?
- Will life events affect the risk for developing Type 1 diabetes differently in different age groups?

Subjects and methods

This study is part of a nationwide Swedish case-referent study focussing on different aetiological aspects of Type 1 diabetes. The study design and data collection procedure have been reported earlier in detail [16, 17]. During a one-year period all recent-onset Type 1 diabetic patients in Sweden age 0–14 years were invited to participate in the study. Two referent subjects, matched for age-, sex- and geographical distribution were selected for each patient, using the official Swedish population register (SPAR-DAFA). Of the patients 86% (338 of 393) and of the referent subjects 69% (528 of 786) entered the study. Analysis of the dropout subjects revealed no differences regarding age, sex and place of residence compared to the participants. Family characteristics such as marital status of parents, parental age, number of siblings, proportion of immigrants were similar in the diabetic families and in the referent families [17]. A questionnaire was submitted approximately 4 weeks after diagnosis of Type 1 diabetes to the patient's family at the same time as to the two referent families. To avoid primary recall bias, the specific focus on diabetes was not mentioned in the introductory letter.

The life events section of this questionnaire consisted of 45 events that might have occurred within the family during the past year (Table 1). The inventory was modified after a previous life

Table 1. Life event scores (LCU) by age group

Life events	Age (years)		
	0–4	5–9	10–14
1. Birth or adoption of a brother or sister	50	50	50
2.[a] Serious illness or injury of the mother	51	55	54
3. Loss of job by a parent	23	38	48
4.[a] Serious illness or injury of the father	51	55	54
5.[a] Death of the mother	89	91	94
6.[a] Marital separation of the parents	74	78	77
7.[a] Jail sentence of parent	50	55	63
8. Hospitalization of the child	59	62	59
9. Addition of a third adult to the family	39	41	34
10. Change in parents' financial status	21	29	40
11.[a] Death of the father	89	91	94
12.[a] Serious illness or injury of a sibling	37	41	44
13.[a] Brother or sister leaving home	39	36	33
14. Mother married to a step-parent	62	65	63
15. Father married to a step-parent	62	65	63
16. The family moves to another place	[b]	[b]	[b]
17. Discovery of being an adopted child	33	52	70
18.[a] Divorce of parents	78	84	84
19.[a] Death of a brother or sister	59	68	71
20.[a] Hospitalization of the father	51	55	54
21. Mother beginning to work	47	44	36
22.[a] Death of a grandparent	30	38	35
23. Death of a close friend to the child	38	53	65
24. The family changes apartment/house	[b]	[b]	[b]
25.[a] Hospitalization of the mother	51	55	54
26.[a] Hospitalization of a brother or sister	37	41	44
27. Beginning the pre-school year	42	–	–
28. Change pre- or nursery school	33	–	–
29. Change of "nursery-mother"	33	–	–
30. Beginning 1st year of compulsory education	42	–	–
31. Change to a different class or school	33	46	52
32. Father beginning to work	36	45	42
33. Decrease in arguments between parents	21	25	29
34. Increase in arguments between parents	44	51	48
35. Decrease in arguments with parents	22	27	29
36. Increase in arguments with parents	39	47	46
37. Outstanding personal achievement	23	39	45
38. Beginning 7th year of compulsory education	–	–	45
39. Failure of a year in school	–	57	62
40. Menarche	[b]	[b]	[b]
41. Unwed pregnancy	–	–	95
42. Fathering an unwed pregnancy	–	–	76
43.[a] Abortion	[b]	[b]	[b]
44. Breaking up with a boy- or girlfriend	–	–	47
45. Serious illness or injury of the child	59	62	59

[a] Life events including losses or threatened losses in the family.
[b] LCU not available. – Not relevant for the age group

event questionnaire developed and evaluated by Coddington [18, 19] and Hurme [20]. Items No. 8 and 45 were excluded in the analyses since the patients tended to regard the onset of diabetes itself as a "hospitalization" and "serious illness" event.

Three different methods were used for qualitative evaluation of the life events.

First the severity of life events was classified according to the life change values (LCU) defined by Coddington [19]. Coddington's values were based on the judgements of paediatricians, teachers and child psychologists. Later studies by Hurme [20] and by Monaghan et al. [21] confirmed the general applicability of the LCU scale for evaluating the severity of life events.

Second, each family evaluated "how upsetting" the occurred life event was to the child on a self-esteem analogue scale (SE) (range 0–100), previously used by Cederblad and Höök [22]. "Severe life events" were defined either as LCU level > 50 or SE level > 50 respectively.

Third, losses within the family have previously been reported as being associated with the onset of diabetes in both children and adults [23–25]. Therefore, we analysed separately those life events involving actual or threatened losses within the family (items No. 2, 4, 5, 6, 7, 11, 12, 13, 18, 19, 20, 22, 25, 26 and 43 of Table 1).

As life events may affect children in different ways in different age groups, all analyses were performed separately in children 0–4, 5–9 and 10–14 years.

The study was approved by the Ethics Committee at the Karolinska Institute as well as by the Swedish Data Inspection Board. Informed consent was received from all families.

Statistical analysis

Matching proved unnecessary since the ratio between the relative risk from matched and unmatched data for important associations was close to one [26]. The Chi-squared test was used when comparing frequencies. Relative risks were calculated as odds ratios and 95% confidence intervals according to Miettinen [27]. To control for possible confounding factors standardized risk ratios (SRR) and 95% confidence intervals were calculated. The analyses were performed using the Quest Software developed by L. Gustavsson, University of Umeå, Sweden.

Results

Quantitative estimates of life events

The relative frequency of the number of experienced life events during the last year for diabetic and referent children respectively are given in Figure 1. Nearly half of the children had experienced more than one event. No differences existed between the two groups. The mean number of life events was 1.9 for both diabetic and referent children. Furthermore, breakdown analysis into three age groups (0–4, 5–9, 10–14) failed to reveal any significant differences between diabetic and referent subjects (Table 2).

Table 2. Mean frequencies of life events in diabetic and referent children in different age groups, figures within brackets denote the number of life events

	0–4 years	5–9 years	10–14 years	Total
Diabetic children ($n = 338$)	$n = 70$ 1.7 (121)	$n = 116$ 2.1 (248)	$n = 152$ 1.7 (259)	$n = 338$ 1.9 (628)
Referent children ($n = 528$)	$n = 118$ 1.8 (212)	$n = 165$ 1.9 (313)	$n = 245$ 1.9 (456)	$n = 528$ 1.9 (981)

Table 3. Mean levels of life change estimation by use of SE[a] and LCU[b]

	Diabetic children $n = 338$	Referent children $n = 528$
SE[a]	x SD Range 56 (95, 0–800)	x SD Range 54 (82, 0–530)
LCU[b]	69 (86, 0–665)	66 (74, 0–481)

[a] Self esteem scores [22]; [b] LCU according to Coddington [18, 19] and Hurme [20]

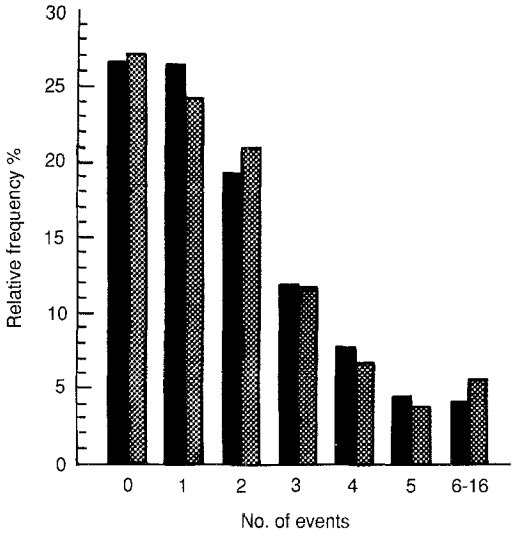

Fig. 1. Relative frequency of all life events among diabetic and referent children 0–14 years. ■ Diabetic children; ▨ Referent children

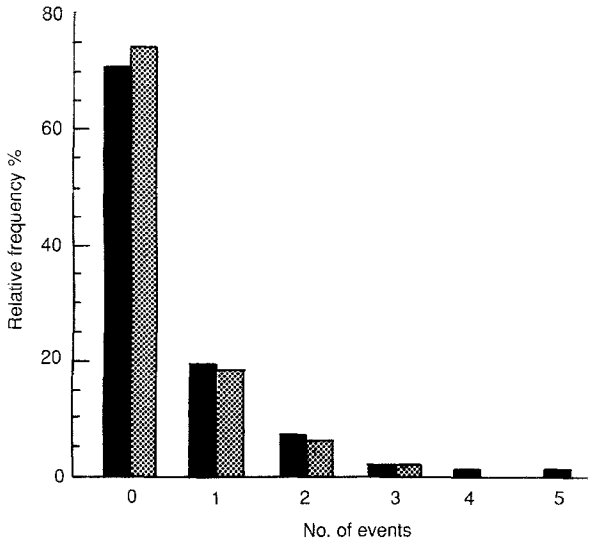

Fig. 2. Relative frequency of actual or threatened losses among diabetic and referent children 0–14 years. ■ Diabetic children; ▨ Referent children

Qualitative estimates of life events

Table 3 shows the means, standard deviations and ranges of the life events classified according to the self esteem (SE) and life change units (LCU) systems, respectively. No significant differences were seen between the diabetic and referent subjects. The number of severe life events as determined on the SE scale (SE > 50) tended to be higher among the diabetic children, but the difference was not statistically significant. The mean frequency of life events related to actual or threatened losses also tended to be higher in the diabetic compared to the referent children (0.45 vs 0.36, $p = 0.08$) as illustrated in Figure 2.

Table 4. Relative risk estimated as odds ratio of developing Type 1 (insulin-dependent) diabetes when exposed to life events including losses within the family

Age group (years)	OR estimate	95% confidence limits	
0– 4	1.05	0.51	2.17
5– 9	1.82	1.09	3.03
10–14	0.94	0.59	1.50
0–14	1.19	0.88	1.62

Table 5. Relative risk of developing Type 1 (insulin-dependent) diabetes in 5–9 year-old children when exposed to life events including severe losses within the family. Crude values and values standardized for different confounding factors. Mantel-Haenszel rate ratio is given

	Odds ratio	95% confidence limits	
Crude	1.82	1.09	3.03
Standardized for			
age	1.81	1.08	3.05
sex	1.82	1.09	3.03
maternal age	1.75	1.05	2.92
maternal education	1.85	1.11	3.09
Type 1 diabetes among 1st degree relatives	1.84	1.12	3.11

Qualitative estimates of life events in different age groups

Life events related to losses within the family differed among the different age groups. In the 5–9 year age group the frequency of such events was higher among Type 1 diabetic than among referent children, as illustrated in Figure 3. Likewise the odds ratio that such events comprise a risk factor for Type 1 diabetes was significantly higher among children of 5–9 years (Table 4). This increased risk was still significant when standardized for possible confounding factors such as age, sex, maternal age and education, and the existence of Type 1 diabetes among first-degree relatives (Table 5).

A similar discrepancy in odds ratios regarding the SE qualitative measure was found among the three different age groups, i.e. 0–4 years OR = 0.88, 5–9 years OR = 1.48 and 10–14 years OR = 1.17. However, confidence limits for the age group 5–9 years, included 1.0. The Coddington LCU index revealed no such age differences.

Discussion

In this large population-based case-referent study, recent-onset Type 1 diabetic children were compared with healthy referent children. No differences were found between the two groups in the total frequency of experienced life events during the year prior to the onset of diabetes. However, the frequency of life events that included actual or threatened losses within the family – events assumed to be very stressful for children – was significantly higher among diabetic than among referent children in the age group 5–9 years.

This age group could be especially vulnerable to the influence of stressful life events due to the discrepancy between cognitive skills and actual emotional development [28]. According to recent epidemiological studies, certain child psychiatric symptoms also show peak incidences in

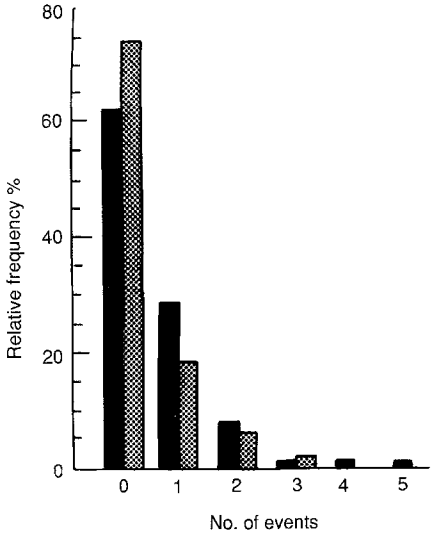

Fig. 3. Relative frequency of actual or threatened losses among diabetic and referent children 5–9 years. ■ Diabetic children; ▒ Referent children

this age group [29, 30]. Alternatively, it may simply be that some separation traumas, e.g. parental divorce, are more common for children at this age [31].

Another interpretation of the lack of significant association between psychological stress and Type 1 diabetes in the youngest and oldest age groups studied might just be explained by the possibility that other risk factors are prevailing in those age groups, to mask the role of stress.

The frequency of severe life events, as determined by the self esteem (SE) scale, was also higher, though not statistically significant among diabetic children, especially in the age group 5–9 years. On the other hand, severe life events as measured on the LCU scale did not differ between the two groups. This discrepancy could be due to the low rating scores (< 50) that certain items connected with family losses receive on Coddington's LCU scale [18, 19].

The present study suggests that severe psychological stress may be a risk factor for childhood Type 1 diabetes. The pathophysiological mechanism behind this finding is speculative. An increase in peripheral insulin requirements due to stress-induced increases in counter-regulatory hormones (i.e. catecholamines, growth hormone and glucagon) could be one possible mechanism. Stressful events would serve as a promoting factor, turning a prediabetic state into overt Type 1 diabetes. This hypothesis is in agreement with two recent animal studies [11, 12]. Alternatively, severe stress could influence the autoimmune destruction of the Beta cells. The adrenocortropic hormone-stimulated cortisol effect on immunologic processes could be of importance in this process [13]. The immune function is modulated by psychological stress in various ways [14].

As early as 1684 Thomas Willis stated that diabetes was related to "prolonged sorrow" [32]. Some decades later a "diabetic personality", at increased risk of developing Type 1 diabetes, was suggested [33, 34]. During the last decades, research has focussed on the occurrence of stressful life events prior to the clinical onset of Type 1 diabetes [23–25, 35–41]. Results of these life event studies, however, are contradictory.

A host of methodological problems complicates any serious evaluation of previous life event studies. Very divergent study designs have been employed. Likewise, different methods have been used for assessing both the types and the qualities of life stress. Furthermore, patients have been very heterogeneous with regard to ages and to selection methods. As a rule the samples have been small, i.e. ranging from 3 to 38 cases. In some of the studies no referent groups were used at all, in others referent subjects were not selected at random from the general population. Given these overwhelming methodological differences it is not surprising that the results from these studies are strongly divergent. Several studies, such as our own, fail to show an overall increase in the frequency of life events prior to the onset of Type 1 diabetes. At the same time, a number of previous studies (and even our own) indicate that severe life events – specifically events including losses in the family – are associated with Type 1 diabetes in childhood [23–25]. In three recent studies other qualitative measurements likewise revealed increased life stress in children prior to the onset of Type 1 diabetes [36–38].

Finally, a number of potential methodological biases in our own study must be critically examined. As in all case-referent studies it could be suspected that patients respond differently than non-patients. Specifically, that parents of a diabetic child, seeking an explanation for their child's illness, might tend to remember a greater number of life events than parents of a healthy child. The results, however, showed no differences in the number of reported events. On the other hand, severe life events, such as actual or threatened loss within the family, are less likely to be forgotten even in families with a healthy child. Thus, the reported differences are very likely real.

There was a higher number of dropouts among the referent families compared to the diabetic families. The age, sex and geographical distribution, however, was similar between both dropouts and participants.

It could be suspected that families with either low or with high social status might be over-represented among dropouts. However, the increased relative risk for Type 1 diabetes was similar when standardized for maternal education, an important social determinant for child health.

The present study indicates that severe emotional stress, induced by actual or threatened loss within the family, is associated with the onset of childhood diabetes, in the age group 5–9 years.

Further evaluation is required to determine whether severe psychosocial stress several years prior to clinical onset of Type 1 diabetes may also play a pathophysiological role. Likewise, further experimental studies are needed to determine the exact pathophysiological mechanisms behind severe stress as a risk factor for Type 1 diabetes in children.

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