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Originals

The Swedish childhood diabetes study - Results from a nine year case register and a one year case-referent study indicating that Type 1 (insulin-dependent) diabetes mellitus is associated with both Type 2 (non-insulin-dependent) diabetes mellitus and autoimmune disorders

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Summary. From July 1, 1977 to July 1, 1986, 3,503 incident cases of Type 1 (insulin-dependent) diabetes mellitus were registered in the Swedish childhood diabetes study. Using data from this register and from a case-referent study, including all incident Type 1 diabetic children in Sweden during one year and, for each patient, two referent children matched according to age, sex and county, we have studied the associations between Type 1 diabetes and familial Type 1 and Type 2 (non-insulin-dependent) diabetes, thyroid, adrenal, allergic, rheumatic, heart and bowel disease. The mean annual incidence per 100,000 during the nine year period was 25.1 for boys and 23.5 for girls. In 8.5% of the patients, one parent had Type 1 diabetes, 73% of whom were fathers. Fifty-six of the patients (1.7%) had a parent with Type 2 diabetes. The prevalence of parental Type 1 diabetes tended to be higher in patients with younger age at onset; whereas, the opposite was found for patients with parental Type 2 diabetes. In the case-referent study, the age-adjusted odds ratio for Type 1 diabetes when a first and/or second degree relative had Type 1 diabetes was 5.5 (95% confidence limits 4.0-7.7), and in accordance with the findings of the case register, the odds ratio tended to be highest in patients with the youngest age at onset. Season at onset of the patients was not associated with parental Type 1 diabetes. The odds ratio for Type 1 diabetes was significantly increased 3.3 (95% confidence limits: 2.3-4.6) when Type 2 diabetes was reported in relatives (three generations). Odds ratios were also significantly increased ($p < 0.05$) when thyroid or rheumatic diseases were reported among relatives.

It is concluded that although the majority of incident Type 1 diabetic children lack family history, parental Type 1 diabetes may influence the age at onset of the disease but has no effect on sex distribution of these children. An increased risk for Type 1 diabetes in children is also indicated when Type 2 diabetes, (non-insulin-treated) thyroid or rheumatic disease is reported in relatives.

Key words: Type 1 (insulin-dependent) diabetes, heredity, epidemiology.

To study the genetic and environmental connections in the aetiology and pathogenesis of a disease, large population-based epidemiological studies are necessary. Therefore, from July 1, 1977, all incident cases of Type 1 (insulin-dependent) diabetes 0-14 years of age in Sweden are prospectively recorded. Analyses based on this registration have shown a high and increasing incidence of Type 1 diabetes in Swedish children, a significant geographic variation within Scandinavia, as well as within Sweden and significant age- and season-related variations [1-3].

To further analyse the combined effects of genetic, environmental and immunological factors of possible importance for the risk of Type 1 diabetes, we have performed a nationwide case-referent study including all incident patients with Type 1 diabetes during one year and with two referent children matched according to age, sex and county using the combined information from a mailed questionnaire and serum-sampling. We here report the analysis of the familial disease pattern from this study.

Based on the finding that the HLA-DR3 and HLA-DR4 specificities coded for in chromosome 6 are strongly associated with Type 1 diabetes but not with Type 2 (non-insulin-dependent) diabetes [4, 5] and also the difference in twin concordance between Type 1 and Type 2 diabetes [6, 7], these two types of diabetes have been suggested to have different genetic backgrounds. On the other hand, a genetic link between Type 1 and Type 2 diabetes was indicated by the increased risk for Type 1 diabetes that was reported for siblings of Type 1 diabetics when one parent had Type 2 diabetes [8]. Dif-

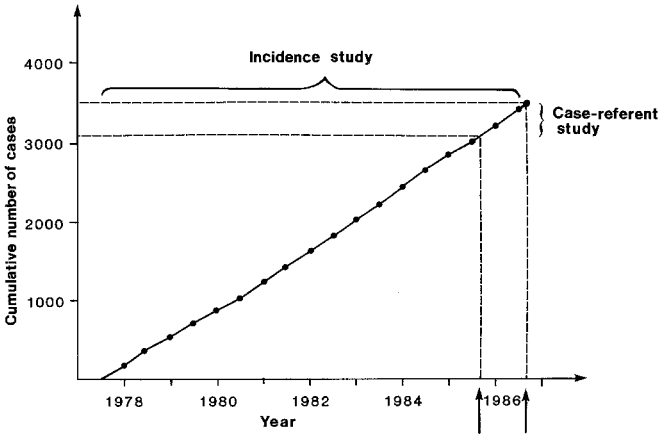

Fig. 1. The cumulative number of cases in the Swedish childhood diabetes register and in the case-referent study

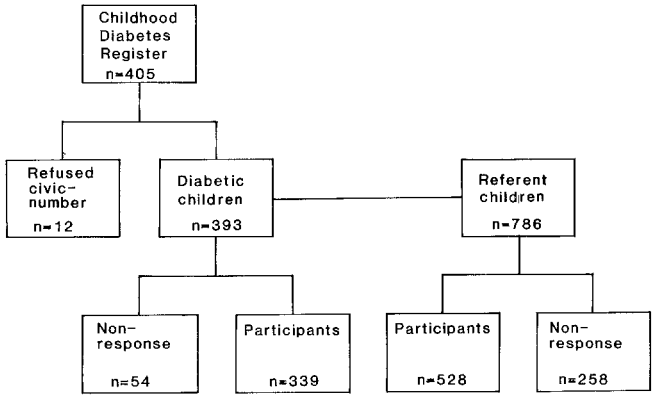

Fig. 2. The design of the case-referent study

Table 1. Patients and referents who returned the questionnaire by age and sex

Age group (years)	Boys		Girls	
	Number of patients	Number of referent children	Number of patients	Number of referent children
0- 4	32	46	40	72
5- 9	51	72	64	96
10-14	80	128	72	114
0-14	163	246	176	282

ferences in the distribution of HLA-DR3 and HLA-DR4 in Type 1 diabetes with different age at onset [9–11], season at onset [12] and residual B-cell function [13] have pointed at a possibility of different types of Type 1 diabetes with possible different aetiologies. An association between Type 1 diabetes and other diseases which are associated to determinants coded for in the major histocompatibility complex has also been indicated in numerous studies [14–20]. Against this background, we have used the data both from the case register and the case-referent study to analyse the following questions: (1) Is the occurrence of Type 1 diabetes in first degree relatives of children with Type 1 diabetes related to sex or age at onset of the case? (2) Will the presence of Type 2 diabetes in relatives influence the risk to develop Type 1 diabetes? (3) Will the presence of other diseases, such as thyroid, adrenal, rheumatic, allergic, heart or coeliac disease in relatives increase the risk to develop Type 1 diabetes in childhood?

Subjects and methods

The study was approved by the Ethics Committee at the Karolinska Institute, as well as by the Swedish Data Inspection Board. In the Swedish health care system, all children aged 0–14 years with suspected diabetes are referred to paediatric departments. In the present study, all 44 paediatric departments in the 24 counties of Sweden collaborated. A standardised form is used to record the civic number, sex, county, reporting hospital, date of diagnosis (i.e. the day when the first insulin injection was given), number of siblings and the presence of insulin-*treated* diabetes and/or non-insulin-*treated* diabetes in first degree relatives. To ensure a high level of ascertainment, our contact person at each department of paediatrics received, once a month, a list of patients reported from his/her department during the preceding months. This list is checked with the hospital admission/discharge register. Missing or inaccurate data are corrected by telephone interview with the contact person. The ascertainment has recently been further validated for a part of this nation-wide registry by using an independent source. Thus, recorded members of the Swedish Diabetes Association born after December 31, 1977, and resident in Stockholm metropolitan area (a low incidence area) and in Jönköping (a high incidence area) were individually matched with the nation-wide register data set. All 119 listed members of the Swedish Diabetes Association in these age groups were recorded in the nation-wide register. Given these data, as well as the knowledge regarding hospitalisation pattern of diabetic children in our country, we estimate the completeness of our registration to be close to 100%.

From July 1, 1977 to July 1, 1986, a total of 1,839 boys and 1,664 girls were registered to yield a mean annual incidence of 25.1 per 100,000 boys and 23.5 per 100,000 girls in Sweden. From September 1, 1985 to August 31, 1986, we performed a case-referent study based on the incidence register (Fig. 1), and when the registration form from the patient was received (approximately 4–10 days after admission to the hospital), we matched them with two referent children according to age, sex and county using the official Swedish population register (SPAR-DAFA). Approximately four weeks after diagnosis, the patient and the two referent children received a mailed questionnaire. In the introduction letter, the stated purpose of the study was to analyse relations between childhood disease, heredity and environmental factors. Diabetes was not specifically mentioned. If the questionnaire was not returned within two weeks, the families were first reminded by post card during the following 2–6 weeks; those who had still not responded, were reminded by telephone. Questionnaires that were incompletely or inaccurately completed were corrected by a telephone interview.

From September 1, 1985 to August 31, 1986, a total of 405 cases were registered (Fig. 2). Twelve of them refused to give the civic number; thus, questionnaires were sent to 393 diabetic and to 786 referent children. The questionnaire was returned by 86% of the diabetic children and by 67% of the referent children (Table 1). There were no significant differences in diabetic or referent children who returned and who did not return the questionnaire as to age, sex and county.

Statistical analysis

When comparing proportions of children with Type 1 diabetes among parents or siblings to those without Type 1 diabetes among first degree relatives, the proportions were compared using the 2×2 contin-

gency table method. When analysing data in the case-referent study, the matching was dissolved, since the ratio between the odds ratios from matched and unmatched data were close to one [21]. The relative risk was estimated by an odds ratio and a 95% confidence interval was calculated according to Miettinen [22]. When the lower confidence limit of the odds ratio is >1.0, the relative risk is considered to be significant. As the incidence of Type 1 diabetes in age-dependent, the odds ratios given are age-adjusted according to the direct method.

Results

Familial Type 1 diabetes and age, sex and season at onset for the child

Results from the case register. One parent with Type 1 diabetes was present in 8.5% of the diabetic children; and 73% of them were fathers. Four percent of the children (151/3,503) had a sibling with Type 1 diabetes. In families with more than one diabetic child, the proportion of children with parental Type 1 diabetes tended to be higher compared to families with more tha one child but only one of them with Type 1 diabetes (10.6% versus 7.2%), but the difference was statistically not significant ($p>0.05$). The percentage of children with reported insulin-treated diabetes among parents tended to be highest in the younger age groups (Fig. 3). Paternal diabetes was found among 6.6% of the boys and 5.7% of the girls (non-significant difference), whereas maternal Type 1 diabetes was found among 2.3% of the boys and 2.3% of the girls. The proportion of children with reported Type 1 diabetes among parents was similar in patients with clinical onset during winter, spring, summer and autumn.

Results from the case-referent study. Twenty-eight out of the 339 (8.3%) diabetic children had a first degree relative with Type 1 diabetes compared to 6 among the 528 (1.1%) referent children. The age-adjusted odds ratio for Type 1 diabetes when a first degree relative had Type 1 diabetes was 7.8 (95% confidence limits were 3.6–16.8). When analysing three generations (specified as grandparents, parents and parental siblings, cousins and siblings in the questionnaire), 41% of the diabetic children had relatives with insulin-treated diabetes compared to 11% of the referents. The odds ratio for Type 1 diabetes when a relative also had Type 1 diabetes was therefore 5.5 (Fig. 4). There was a clear tendency to increased odds ratios for Type 1 diabetes in younger age groups when a relative had Type 1 diabetes (Table 2). The odds ratio for Type 1 diabetes when a relative had Type 1 diabetes was similar for boys and girls (5.4 and 5.6 respectively).

Familial Type 2 diabetes and the risk for Type 1 diabetes

Results from the case register. Parental non-insulin-treated diabetes was reported in 56 (1.7%) of children with Type 1 diabetes. The prevalence of reported

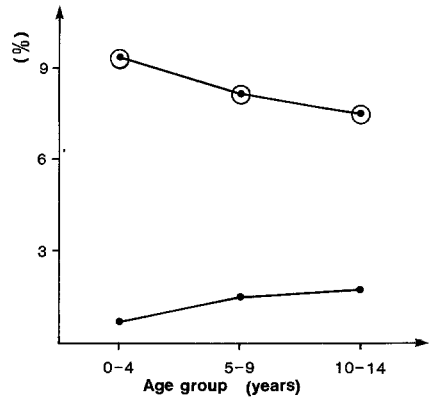

Fig. 3. The percentage of children with reported Type 1 (insulin-dependent) (-⊙-) or Type 2 (non-insulin-dependent) (-●-) diabetes respectively among parents by age at onset of diabetes in the child. Results from the case register

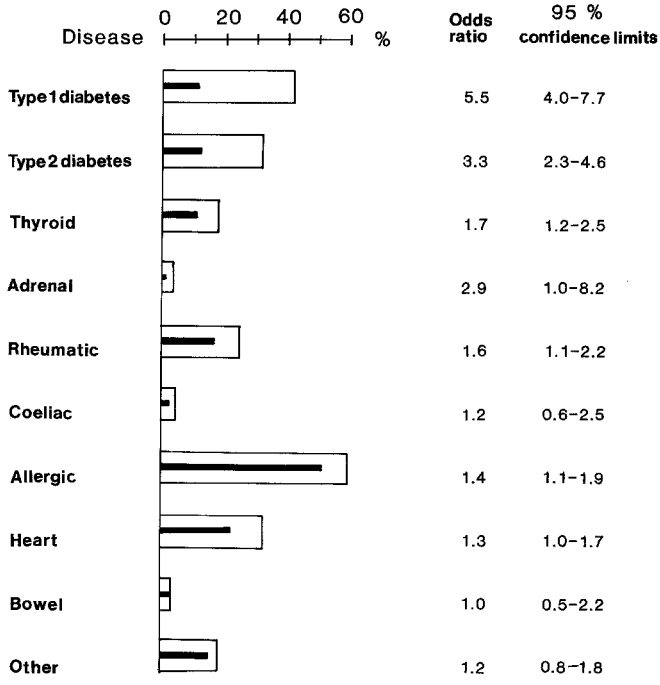

Fig. 4. The frequency of positive family history of different diseases in three generations of relatives of patients □ and referent children ■. Odds ratios for Type 1 diabetes and the 95% confidence limits are indicated. When the lower confidence limit is >1.0, the odds ratio is significantly increased

Table 2. Age-specific and age-adjusted odds ratios for Type 1 (insulin-dependent) diabetes in diabetic children with reported Type 1 diabetes in three generations of relatives

Age group (years)	Family history of Type 1 diabetes		No Type 1 diabetes reported		Odds ratio
	Patients	Referent children	Patients	Referent children	
0- 4	25	9	47	109	6.44
5- 9	53	21	62	147	5.98
10-14	61	29	91	213	4.92
0-14	139	59	200	469	5.52

Type 2 diabetes in parents tended to be higher in children with older age at onset (Fig. 3).

Results from the case-referent study. Type 2 diabetes was reported in *first* degree relatives of 4/339 Type 1 diabetic children and in the relatives of 3/528 referent children. When including *three* generations 31.8% of the Type 1 diabetic children reported Type 2 diabetes in relatives compared to 12.5% in the referent families (Fig. 4) to give the odds ratio for Type 1 diabetes when Type 2 diabetes was reported among relatives (three generations) of 3.3 (95% confidence limits 2.3–4.6).

Familial occurrence of other diseases and the risk for Type 1 diabetes

Results from the case-referent study. Odds ratios for Type 1 diabetes were significantly increased when thyroid, allergic or rheumatic disease was reported in relatives of Type 1 diabetic children (Fig. 4). No significant increase in odds ratio was found when coeliac or heart disease was reported among relatives. The odds ratio was 2.9 for adrenal disease but the lower 95% confidence limit was 1.0. A total of 68% of Type 1 diabetic children had a relative with either Type 1 or Type 2 diabetes, thyroid or rheumatic disease, compared to 39% of referent children. Fourteen percent of Type 1 diabetic children had one or more of these diseases in first degree relatives compared to 6% in first degree relatives of referent children.

Discussion

Similar to the previous reports from this register [1, 2], we find that the prevalence of Type 1 diabetes in parents of Type 1 diabetic children is only around 10%. When the disease occurs in parents, the prevalence in fathers is twice the prevalence in mothers of Type 1 diabetic children. This finding cannot only be explained by a lower number of pregnancies among diabetic mothers, since Warram et al. [24] reported a 6.1% prevalence of Type 1 diabetes in children of Type 1 diabetic fathers compared to only 1.3% in the children of Type 1 diabetic mothers. A genetic background for these findings was suggested in 1979 by Cudworth et al. [25], who reported that the incidence of the HLA A1–B8 haplotype inherited from fathers was found in 64% of the offspring of both diabetic and healthy families, i. e. significantly higher than the expected prevalence of 50%. This finding could, however, be explained by the fact that the analysis was confined to heterozygous parents and their families. Cudworth et al. [25] also found that the HLA A1–B8 haplotype was not only inherited from fathers but also significantly increased in male children, thus indicating a father-to-son inheritance of these risk alleles. When analysing data from the incidence register, we found no significant difference in male-to-female sex ratio in children whose fathers had Type 1 diabetes compared to those with maternal Type 1 diabetes.

The data from the case-referent study shows an increased risk for childhood Type 1 diabetes when Type 2 (non-insulin-dependent) diabetes is reported in relatives. As in most case-referent studies, it could be assumed that the control group would be more forgetful about diseases, especially outside the primary family compared to the patients. Furthermore, in our study-like most other case-referent studies, there was a higher percentage of non-responders among the referent children. However, an extreme lack of awareness would have to be present as an increase of referent children with Type 2 diabetes among relatives, from the reported 66 to 138, would be necessary to decrease the lower 95% confidence limit of the odds ratio for Type 1 diabetes below 1.0. Furthermore, the increase in risk for Type 1 diabetes would become non-significant, only if as many as 47% (120/258) of non-responding referent children (compared to the 12% among those referent children who responded), but none of the non-responding patients would have reported Type 1 diabetes among relatives. The increased odds ratio for Type 1 diabetes in children with heredity for Type 2 diabetes is in accordance with the previously noted increased frequency of juvenile onset diabetes among offspring of maturity onset diabetes [26] and, also, the reported increased risk to siblings of Type 1 diabetic children when at least one parent had Type 2 diabetes [8]. Without disregarding the difficulties to translate juvenile onset/maturity onset diabetes or insulin-treated/non-insulin-treated diabetes into Type 1 and Type 2 diabetes, our findings may suggest a genetic association between the two diseases different from that expressed in the major histocompatibility complex. On the other hand, similar environmental risk determinants for Type 1 and Type 2 diabetes may also explain the association.

An increased risk for thyroid, as well as adrenal disease, is well documented in Type 1 diabetes. Thus, the finding of an increased odds ratio for Type 1 diabetes in children with thyroid and adrenal disease among relatives was not surprising. This finding also strongly accords with a known high prevalence of thyroid and adrenal autoantibodies found in both diabetic patients and their first degree relatives [14–16]. The increased risk for Type 1 diabetes when reported in the family is in accordance with the association between rheumatic disease and HLA-DR4 [27]. Furthermore, an excess of Type 1 diabetes has been reported in families with rheumatic arthritis [28].

In our study, we found no increased risk for Type 1 diabetes in patients with relatives reporting coeliac disease. This was somewhat unexpected in view of the known association between coeliac disease and Type 1 diabetes, which has been explained to be due to the increased frequency of HLA-B8 and DR3 found in both diseases [19, 20]. It should, however, be noted that

coeliac disease is a rather uncommon disease and was thus present in small numbers in our case-referent study, which may explain the lack of a statistically significant association. On the other hand, in both diabetic children and referent children, allergic diseases were very prevalent, and the biological significance of the slightly increased the odds ratio for Type 1 diabetes when relatives reported allergic disease may thus be questioned.

In conclusion, this study has shown that parental Type 1 diabetes may influence the age at onset of the disease in the proband; whereas, sex and season at onset was similar in cases with and without parental Type 1 diabetes. A definite relationship between Type 1 and Type 2 diabetes is indicated by the increased odds ratio found in the Type 1 diabetic children when Type 2 diabetes was reported in their relatives. The earlier suggested association between Type 1 diabetes and thyroid disease is confirmed in this case-referent study, and, furthermore, an association with rheumatic disease is indicated.

Even if as many as 68% of the patients had first or second degree relatives with Type 1 or Type 2 diabetes, thyroid or rheumatic disease, as many as 39% of the referent children reported these diseases among their relatives. Thus, the predictive value of the familial disease pattern as to Type 1 diabetes in childhood is low. Studies on environmental factors of possible aetiological importance are necessary and are proceeding in the Swedish childhood diabetes study.

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