Clinical Onset Characteristics of Familial Versus Nonfamilial Cases in a Large Population-Based Cohort of Childhood-Onset Diabetes Patients

GISELA G. DAHLQUIST, MD, PHD
LENA R. MUSTONEN

OBJECTIVE — To compare characteristics at clinical onset of childhood-onset diabetes patients with and without a first-degree relative with childhood-onset insulin-dependent diabetes mellitus (IDDM).

RESEARCH DESIGN AND METHODS — In a nationwide continuous incident diabetes register covering patients from 0 to 14 years of age with a high level of ascertainment, we compared 687 patients who at onset had at least one first-degree relative with insulin-treated diabetes with 5,137 patients without such relatives.

RESULTS — The pattern of change over the 15-year period was similar among familial- and sporadic-case patients. The seasonal pattern, with a lower incidence during the warmer period of the year, was similar in both groups. Age at clinical onset was also similar in both groups in either sex. When the proband had a sibling who already had the disease, the mean age at onset was significantly higher when compared with sporadic-case or other familial-case patients.

CONCLUSIONS — This analysis of a very large set of population-based cases of childhood diabetes showed that patients who had one first-degree relative with insulin-treated diabetes at onset shared the onset characteristics of those without such family members, including age at onset, sex ratio, seasonality, and secular trend. The findings may indicate that the complex interactions between genetic and nongenetic risk factors subsequently leading to IDDM are mainly shared by familial- and sporadic-case patients.

In ~10% of incident cases of childhood insulin-dependent diabetes mellitus (IDDM), the patient has a first-degree relative with the disease (1–4). It has been argued that familial-case patients may have specific onset characteristics. It has thus been indicated that in familial cases, the patients have an older age at onset (5), whereas another study indicated a younger age at onset (4). One study also showed that in familial cases, the patients were born to younger mothers (4), whereas in sporadic cases, the patients seem to have older mothers than nondiabetic individuals (6,7).

In the present large population-based study, we compared patients who at onset had a mother, father, or sibling with IDDM with patients who had no family member with IDDM at clinical onset with regard to secular trend, season at onset, age at onset, and sex.

RESEARCH DESIGN AND METHODS

— In Sweden, all childhood-onset diabetes patients 0–14 years of age are treated at the pediatric clinics. Contact persons at each pediatric clinic in Sweden report on a standardized form all incident cases of IDDM. The ascertainment of cases is checked regularly through hospital records (8), and comparisons with completely independent sources (9,10) have confirmed an ascertainment level of 96–99%. This study analyzes a total of 687 patients who at onset had a first-degree relative with IDDM and compared them with 5,137 patients without such relatives recorded from 1 January 1978 until 31 December 1992. Population data are obtained from the central bureau of statistics in Sweden. Comparisons between familial- and sporadic-case patients were performed using chi-squared analysis.

RESULTS

— In a recent Poisson regression analysis of the temporal variation of the incidence of all IDDM cases in Sweden over the 15-year period, a significant increase was shown over time when age and sex of the patients were taken into account (10). When comparing yearly the proportion of patients with and without family members with insulin-treated diabetes at onset of diabetes in the proband, the relative frequency of familial cases is similar ($P = 0.08$). The mean yearly per-

From the Department of Pediatrics (G.G.D.) and the Department of Epidemiology (G.G.D., L.R.M.), University of Umeå, Umeå, Sweden.

Address correspondence and reprint requests to Gisela Dahlquist, Department of Pediatrics, University Hospital, S-901 85 Umeå, Sweden.

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IDDM, insulin-dependent diabetes mellitus.

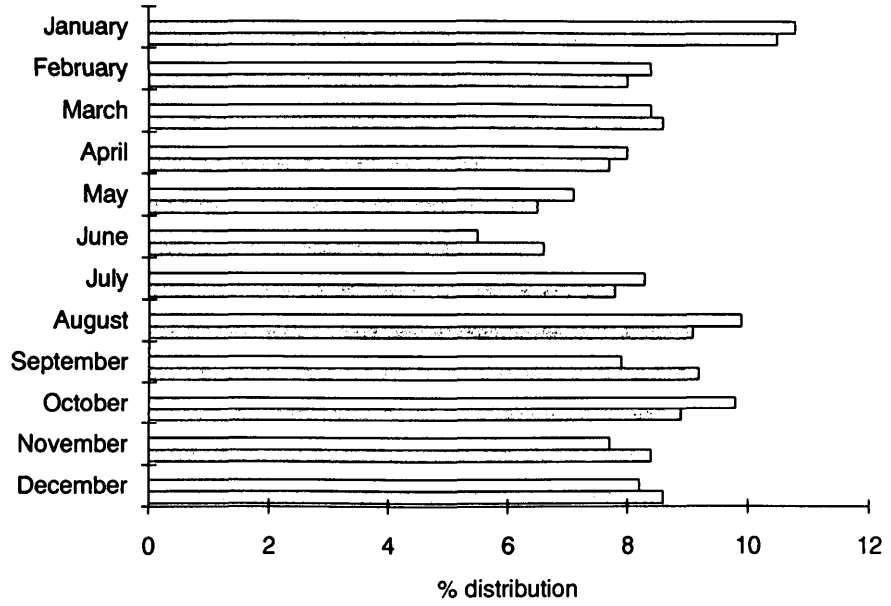

Figure 1—*Month at onset for children with (□) and without (■) a first-degree relative with insulin-treated diabetes.*

centage of all patients who had a first-degree relative with insulin-treated diabetes was 11.7 (range 9.2–16.7). The month at onset is shown in Fig. 1 for children with and without a first-degree relative with insulin-treated diabetes. Obviously, the seasonal pattern, with a lower incidence during the warmer period of the year in Sweden, is similar in both groups ($P = 0.90$). No significant difference is noted for age at onset in the groups (Fig. 2) in either sex ($P = 0.86$ and $P = 0.90$ for girls and boys, respectively). As can be seen from Table 1, a child who had a sibling with the disease had a significantly older age at onset compared with all other groups. The number of fathers with insulin-treated diabetes was more than 2.5 times the number of mothers. This was true even when standardizing for number of children. There was a statistically significant increase in male:female sex ratio in the whole study group when compared with the background population ($P < 0.05$). The sex ratio was similar when the mother, the father, or a sibling had insulin-treated diabetes. The frequencies of one-child families were similar in the two groups (familial cases 16.6% and nonfamilial cases 16.5%).

CONCLUSIONS — In this study, we show that the pattern of increase by time recorded in our population was similar among familial and nonfamilial cases.

The typical variability of monthly onset-time with the lowest incidence rates recorded during the warmest period of the year was also similar in familial- and sporadic-case patients, and we found no difference between the groups as to age at onset of diabetes in either sex. The last mentioned finding disagrees with a recent Danish study (4), which showed a younger age at onset among familial-case patients, and the Pittsburgh study showing an older age at onset among familial-case patients (5). It is possible that different societies have different lifestyle-related, nongenetic risk exposures that may operate at different age groups. In our study, we found that the age at onset of a child who had a sibling with diabetes was slightly but significantly older than that in sporadic-case or other familial-case patients. This is compatible with the findings of a higher mean age at onset for the second affected sibling than that for index patient (4). There was a slightly higher incidence of childhood-onset diabetes among males compared with females among sporadic as well as familial cases of IDDM. This increase in sex ratio was similar whether the mother, the father, or a sibling already had insulin-treated diabetes. Thus, our study does not give support to the idea that the risk of diabetes in offspring who are of the same

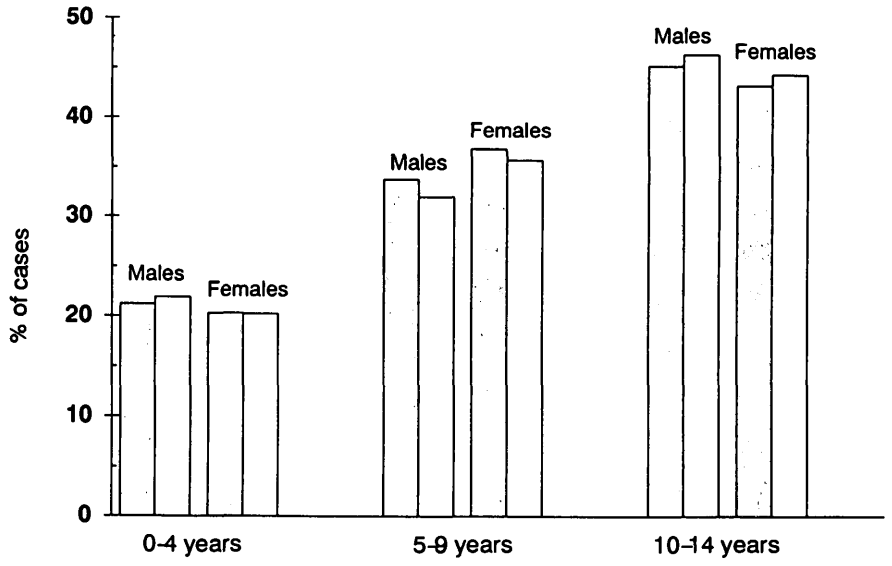

Figure 2—*Age at onset for children with IDDM with (□) and without (■) a first-degree relative with insulin-treated diabetes.*

Table 1—*Sex distribution of children with IDDM with a mother, father, or sibling with the disease, those with any relative with IDDM, and those without first-degree relatives with IDDM.*

	Boys	Girls	Boys + girls	Mean age at onset (95% confidence interval)	M:F ratio	Corrected chi-squared	*P* value
Mother with IDDM	80	58	138	8.3 (8.2–8.4)	1.38	1.19	NS
Father with IDDM	188	169	357	8.3 (8.2–8.4)	1.11	0.008	NS
Sibling with IDDM	123	104	227	9.00 (8.5–9.5)	1.18	0.915	NS
Any first-degree relative (one or more) with IDDM	370	317	687	8.25 (7.9–8.5)	1.17	0.174	NS
No first-degree relative with IDDM	2,719	2,418	—	8.3 (8.2–8.5)	1.12	—	—
All diabetic patients	3,093	2,738	—	8.3 (8.2–8.4)	1.13	13.68	<0.001
Background population	839,342	819,239	—	—	1.02	—	—

Means are for the years 1978–1992. Statistical comparisons were performed for mother with IDDM versus mother without IDDM, father with IDDM versus father without IDDM, sibling with IDDM versus no sibling with the disease, and any relative with IDDM versus no relative with the disease. The sex ratio for all diabetic patients was compared with that of the background population.

sex as a parent with IDDM is reduced (11).

This study compares IDDM patients who have a first-degree relative with diabetes at onset with those who do not, and certainly the proportion of multiplex families may increase with time. In a Danish study (12), during the follow-up of IDDM patients to at least 50 years of age no further parents got the disease, whereas the proportion of affected siblings increased from 8% at age 21 to 15.2% at age 50–60. If we only consider patients up to 15 years of age (assuming that the Swedish families are similar to the Danish) only a very small proportion of our sporadic cases would have been misclassified, whereas familial cases are correct up to this age. It is not very probable, taking into account the strong statistical power of the present study, that such changes in proportions would alter the findings of this study.

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