Sex Differences in Secondary Attack Rate of IDDM to Siblings of Probands Through Older Ages

Pittsburgh Etiology of IDDM Study

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OBJECTIVE — To determine the descriptive epidemiological patterns of the secondary attack rate of insulin-dependent diabetes mellitus (IDDM) among siblings of probands through older ages.

RESEARCH DESIGN AND METHODS — A family history analysis was performed on 1774 IDDM probands who were diagnosed or seen within 1 yr of diagnosis at Children's Hospital of Pittsburgh from 1 January 1950 through 31 December 1981. The probands were discharged on insulin and were diagnosed at <17 yr of age. The time frame permitted the risk of IDDM for siblings of probands to be calculated over a broad spectrum of age.

RESULTS — Risk estimates for the 3966 full natural siblings through 10, 20, and 30 yr of age were 1.6, 4.1, and 6.3%, respectively. Secondary attack rates were equivalent for male and female siblings through 15 yr of age (3%); however, the risk to males increased an additional 4% between 16 and 30 yr of age compared with 2.5% for females ($P = 0.01$). There was no evidence of an excess sex concordance among affected sibling pairs.

CONCLUSIONS — Males have a greater secondary attack rate of IDDM at older ages than females. This may be due to an increased exposure to environmental agents among males or protective influences operating among females.

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The past decade of research in insulin-dependent diabetes mellitus (IDDM) has revealed the dual importance of environmental and genetic factors in the etiology of the disease (1). Population-based registries have documented a >35-fold difference in the incidence of IDDM worldwide (2). Investigators have indicated that the risk differences may be largely explained by differential distribution of a single polymorphism at position 57 of the HLA DQ β-chain (non–Asp57 homozygosity) (3). However, the 30–50% concordance rate for IDDM among identical twins stresses the importance of environmental factors (4). Family studies are useful for examining genetic-environmental interactions for IDDM, because first-degree relatives of cases are at highest risk for the disease (5–7).

The secondary attack rate of IDDM in siblings of probands is important from an epidemiological perspective. Although previous studies have examined such risk through younger ages (5,6,8–12), small sample sizes (9–11), or insufficient follow-up time (5,8,11, 12) have hindered the examination of the risk to siblings at older ages. Potentially unrepresentative populations have also been used in several studies (6,9,10). The purpose of this study was to ascertain the descriptive epidemiological patterns of the secondary attack rate of IDDM through older ages in a large, well-defined cohort of siblings in Allegheny County, Pennsylvania.

RESEARCH DESIGN AND METHODS

— The Children's Hospital of Pittsburgh (CHP) IDDM Registry has been previously described in several epidemiological investigations (5,13,14). Newly diagnosed IDDM cases who met the following eligibility criteria were included: *1*) diagnosis at <17 yr of age, *2*) on insulin therapy at time of hospital discharge, and 3) initial diagnosis made at CHP or seen at CHP within 1 yr of diagnosis. The CHP IDDM Registry is

Table 1—*Demographic information of insulin-dependent diabetes mellitus (IDDM) probands and their natural siblings identified from the Children's Hospital of Pittsburgh IDDM Registry, 1950–1981*

	IDDM PROBANDS		IDDM SIBLINGS*		NONDIABETIC SIBLINGS	
	%	*N*	%	*N*	%	*N*
SEX						
MALE	50.2	890	56.2	95	50.8	1928
FEMALE	49.8	884	43.8	74	49.1	1866
RACE						
WHITE	95.9	1701	97.6	165	94.9	3603
BLACK	4.1	73	2.4	4	5.1	194
LIVING STATUS						
ALIVE	92.1	1633	92.9	157	96.8	3677
DECEASED	7.9	141	7.1	12	3.1	116
AGE AT FOLLOW-UP (YR)						
0–9	9.0	159	4.1	7	8.2	310
10–19	35.6	632	23.7	40	26.7	1015
20–29	36.0	639	41.4	70	38.3	1454
30–39	18.2	323	23.7	40	18.8	712
≥40	1.1	20	7.1	12	6.4	243
AGE AT ONSET (MEAN ± SD)	8.0 ± 3.9		13.5 ± 7.6			

Sex was unknown for 3 nondiabetic siblings, and living status was unknown for 4 nondiabetic siblings. Age at follow-up was unable to be calculated for 63 nondiabetic siblings due to missing birthdate information. Age at follow-up was unable to be calculated for 1 proband, who had died during an unknown year.

*Continuous insulin therapy from onset with diagnosis at ≤30 yr of age.

representative of newly diagnosed cases within Allegheny County (5).

Family history of diabetes for probands diagnosed between 1 January 1950 and 31 December 1981 was evaluated in this study. The proband was defined as the first IDDM case in each family meeting the CHP eligibility criteria. Questionnaires to obtain the family history information were mailed during 1981–1982. Living status, age, and development of IDDM were assessed for all first-degree relatives as of 31 December 1981. A sibling was considered to have IDDM if he/she was on continuous insulin therapy from time of onset and was diagnosed at ≤30 yr of age. Information was obtained for 1774 of 1881 families (94.3%).

Secondary attack rates of IDDM for the 3966 full natural siblings of the probands were calculated with the BMDP life-table program (15). The degree of sex concordance between proband and sibling cases was analyzed with binomial and χ^2 tests.

RESULTS— Demographic characteristics of the study population and their natural siblings are presented by diabetic status in Table 1. Males and females were approximately equally represented in both probands and nondiabetic siblings; 95% of both groups were white. The mean age at time of follow-up was 25.4 ± 9.7 yr for the sibling cases and 23.3 ± 10.4 yr for the nondiabetic siblings.

The 169 IDDM siblings, 84 of whom were CHP registered, were represented in 156 families. Most families (145) had a single sibling case. Ten families had 2 affected siblings, and 1 family had 4 affected siblings. The mean duration between onset of first and second cases within families was 7.4 ± 5.2 yr.

The overall secondary attack rate estimates through 10, 20, and 30 yr of age were 1.6, 4.1, and 6.3%, respectively. The risks through 30 yr of age were 6.5% for whites and 2.8% for blacks ($P = 0.10$); the small number of black sibling cases ($n = 4$) limited further evaluation of potential race differences in risk. Male and female siblings had equivalent risks through 15 yr of age (3%; Fig. 1). However, a marked increase in risk for males began at age 16 yr and continued through age 30 yr, with an additional 4% increase in risk compared with 2.5% for females ($P = 0.01$). The overall secondary attack rates through 30 yr of age were 7% for males and 5.5% for females ($P = 0.17$).

There were 48 male proband–male sibling case pairs, 33 male proband–female sibling case pairs, 47 female proband–male sibling case pairs, and 41 female proband–female sibling case pairs. Probands and sibling cases thus did not display a significant overall sex concordance pattern. The mean duration between onset of the first and second cases within families was also similar for the four groups. There appeared to be an excess male concordance at older ages of onset, because 21 of the 30 IDDM siblings who were diagnosed between 16 and 30 yr of age of male probands were also male ($P = 0.02$). This pattern can at least be partly attributed to the high pro-

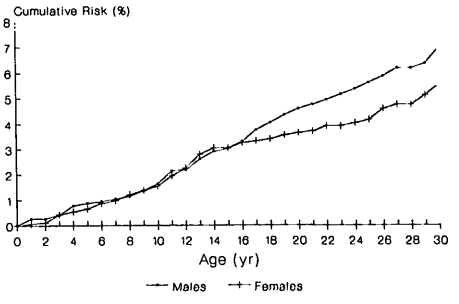

Figure 1—*Cumulative secondary attack rate to siblings through 30 yr of age by sex.*

portion of male siblings in such families (56 of 94, $P = 0.04$).

CONCLUSIONS— The use of the CHP IDDM Registry from 1950 to 1981 permits the risk of IDDM to siblings of probands to be ascertained over a broad spectrum of age. Families are identified through probands on the Registry who were diagnosed over several decades. The extended follow-up, large number of siblings (3966), and the relatively high number of IDDM sibling cases ($n = 169$, half of whom were CHP registered) ensure that accurate secondary attack rate patterns through older ages will be obtained. Such estimates have been lacking from any study.

The lack of a significant overall secondary attack rate pattern by sex indicates that the risk in families appears to follow the known population IDDM incidence patterns (16). Male and female siblings of probands have ~14 and 12 times the risk, respectively, of their general population groups. However, males appear to have higher secondary attack rates than females between 16 and 30 yr of age. This pattern may indicate an increased male exposure to particular environmental factors at that time of life or a protective effect, perhaps from hormonal influences, for females.

Excess sex concordance patterns seen in some HLA-related diseases, e.g., Hodgkin's disease, Behcet's disease, and multiple sclerosis, have been attributed to the interaction of genetic susceptibility with environmental factors that same-sex siblings are likely to share (17). However, there is no strong evidence from this study that environmental etiologic agents for IDDM include those which are likely to be shared by siblings of the same sex. The mean duration between onset of the first and second cases within families of 7.4 yr further supports the hypothesis that environmental factors beyond those shared by cases within a family contribute to the development of the disease.

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