Descriptive Epidemiology of IDDM in Hokkaido, Japan

The Childhood IDDM Hokkaido Registry

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OBJECTIVE — To identify the incidence of IDDM with regard to sex, age, family history of diabetes, season, and 5-year period of childhood IDDM among children ages 0–14 years from a population-based epidemiological study in Hokkaido, Japan, from 1973 to 1992.

RESEARCH DESIGN AND METHODS — Registration of all new IDDM cases in Hokkaido was conducted by the Childhood IDDM Hokkaido Registry Study Group from 1973 to 1992. The cases were selected from among *1*) patients who were admitted to the member hospitals of the study group, 2) patients who answered a questionnaire distributed to hospitals and diabetic clinics throughout Hokkaido, and 3) patients whose cases were recorded in free-treatment medical records of urban and rural districts. The case ascertainment rate was estimated to be 100%. Differences in incidence with regard to sex, age, family history of diabetes, season, and year period were analyzed by the Poisson regression analysis by GENMOD.

RESULTS — During the 20-year period studied, 396 cases (181 boys, 215 girls) of abrupt-onset IDDM were registered. Statistically significant differences in annual incidence were found according to sex (female), age (8–14 years), history (having no diabetes in family), season (spring), and 5-year period.

CONCLUSIONS — This is the first population-based, long-term epidemiological study of childhood IDDM from Japan. We observed a significantly higher annual incidence (per 100,000/year) of IDDM in female subjects (1.81), older age-groups (2.25 for 8–14 years), subjects with no family history of diabetes (1.26), diabetes onset in the spring (2.20), and an increased trend over the 20 years. In addition, the heterogeneity of IDDM among Japanese children needs to be elucidated.

Diabetes Care 21:1632–1636, 1998

The etiology and pathogenesis of IDDM has not been fully elucidated. However, recent molecular, immunological, and epidemiological studies have revealed that some environmental factors may play an etiologic role in the development of diabetes in genetically predisposed individuals (1,2). A large difference in incidence has been reported in recent epidemiological studies from various countries throughout the world (3).

The incidence of childhood IDDM in Japanese and other Asian populations has been reported to be much lower than that of North American and European populations (3), and IDDM found among the Japanese population is heterogeneous; however, few accurate and long-term studies have been reported on IDDM in the Japanese population.

This study describes the incidence, age at onset, and seasonal variation in IDDM onset in the age-group (0–14 years) during the 20-year period from 1973 to 1992 in Hokkaido, Japan. Hokkaido, located in the northernmost part of Japan, covers 83,511 km^2 and has a population of 5.3 million (1.31 million in 1975 and 1.03 million in 1990 <15 years of age). Parts of this study were reported previously (4–7).

RESEARCH DESIGN AND METHODS

— The survey was limited to children with IDDM, and included all children age <15 years who were residents of Hokkaido at the time of diagnosis. Criteria for abrupt-onset and slow-onset IDDM have been previously reported (8). The first survey was performed in 1973, when a summer camp for diabetic children was started in Hokkaido. The survey has been repeated every January and February since 1977 up to the present time. The Childhood IDDM Hokkaido Registry Study Group was organized in January 1989 to extend this study. The subjects were selected from among *1*) patients who were admitted to the member hospitals of the study group, 2) patients who answered a questionnaire distributed to 41 pediatric clinics in general hospitals and 31 internal medicine clinics in Hokkaido, and 3) patients whose cases were recorded in free-treatment medical records of urban and rural districts that routinely kept records of the medical expenses incurred by IDDM patients (4). Data were collected using a standardized form previously described (4). The cases collected from the three sources noted above from 1973 to 1992 were the primary source of data. The membership files of the Hokkaido Childhood Diabetic Association were used as the secondary source, and the records of those IDDM children attending summer camp for diabetic children in Hokkaido from 1974 to 1992 comprised the tertiary source for estimating the degree of ascertainment. Case ascertainment rate was calculated by the

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Received for publication 26 August 1997 and accepted in revised form 11 May 1998.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Figure 1—*Age-specific incidence per 100,000 of abrupt-onset IDDM in patients ages 0–14 years in Hokkaido.*

equation modified by Chapman (9) and Cochi et al. (10).

Because of substantial year-to-year variation of incidence of IDDM by sex, age, family history, season, and year period in abrupt-onset cases, these cases were calculated and described per 100,000/year by sex, age-group (0–7 years, 8–14 years), family history of diabetes within second-degree relatives (yes, no), season (winter [December–February], spring [March–May], summer [June–August], and autumn [September– November]), and year period (1973–1977, 1978–1982, 1983–1987, and 1979–1992, based on the population reported in the National Census from 1975, 1980, 1985, 1990, respectively). We analyzed the data under the assumption that the denominators, i.e.,, the population at risk, were the same within each age-group, sex group, and year period. Differences of IDDM incidence with regard to sex, age-group, family history, season, and year period were analyzed based on abrupt-onset cases (thus excluding slow-onset cases) by the Poisson regression analysis by GENMOD, from the SAS Institute (11). A log-linear relationship is specified by the log-link function, and the log of the number of the population at risk is used as an offset. Statistical differences in IDDM incidence by term were described in terms of χ^2 value with its degree of freedom (df). Statistical significance was set at the 5% level; 95% CIs were calculated under the assumption of Poisson distribution.

RESULTS

Case ascertainment rate

A total of 450 cases (196 boys, 254 girls) of IDDM were registered in Hokkaido from 1973 to 1992. The number of cases collected through the primary, secondary, and tertiary sources was 450, 213, and 261, respectively. All patients collected through the secondary and tertiary sources were included with those patients collected through the primary source. Thus the case ascertainment rate was estimated to be 100%.

Incidence of IDDM by sex, age, family history, season, and year period

Among 450 cases, 54 (15 boys, 39 girls) were asymptomatic and showed no ketoacidosis at diagnosis, which was determined in most cases by urine glucose screening at school. Because the nature of this slow-onset form was not defined, the 54 slow-onset cases were excluded from statistical analysis.

The age-specific and annual incidence of 396 cases of abrupt-onset IDDM from 1973 to 1992 are shown in Figs. 1 and 2. The incidence by sex, age-group at diagnosis, and year period is shown in Fig. 3 and Table 1, and incidence by season is shown in Fig. 4. Poisson regression analysis for the 396 cases revealed that a model composed of these five terms and an interaction term of year period times sex most closely fitted the data (χ^2 = 88.79; df = 88) among the several possible models (i.e., models including higher order of interaction terms or those without any interaction terms).

Therefore, our data indicated that statistically significant differences existed in the annual incidence (per 100,000 per year) of IDDM with regard to *1*) sex (greater in girls [1.81] than in boys [1.45]; χ^2 = 4.74, df = 1); 2) age-group (greater in ages 8–14 years [2.25] than in ages 0–7 years [1.04]; χ^2 = 50.58, df = 1); 3) family history (greater with no family history than with a family history of diabetes; χ^2 = 126.95, df = 1); 4) season (winter [1.71]; spring [2.20]; summer [1.37]; autumn [1.23]; χ^2 = 20.47, df = 3); and 5) year period (1973–1977 [0.90]; 1978–1982 [1.57]; 1983–1987 [1.92]; 1988–1992 [2.28]; χ^2 = 40.85, df = 3). Although the rate was higher for girls than for boys for most years, those rates were reversed during the latest year period studied (1988–1992) (for year period × sex, χ^2 = 9.47, df = 3). Thus the incidence was significantly higher in girls than in boys, in the older age-group (8–14

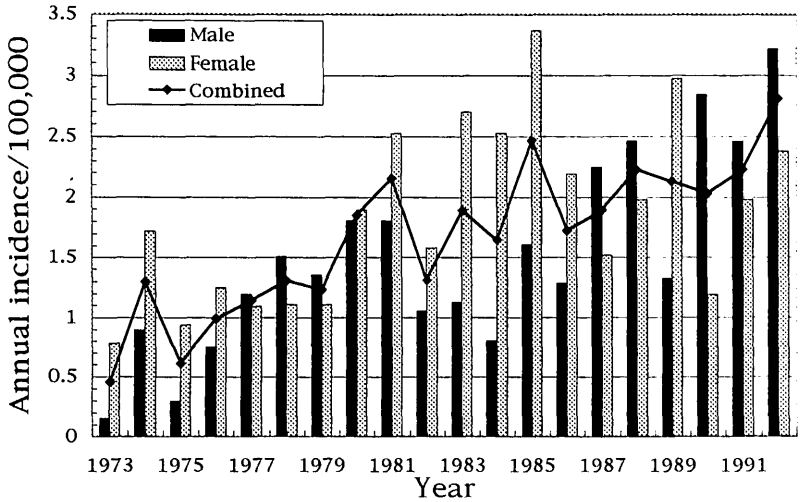

Figure 2—*Annual incidence per 100,000 of abrupt-onset IDDM in patients ages 0–14 years in Hokkaido, 1973–1992.*

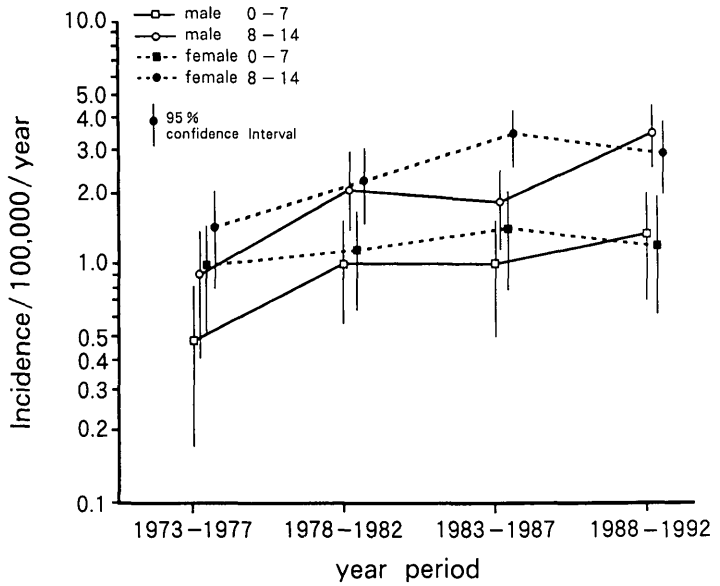

Figure 3—*Incidence per 100,000 by sex, age-group at diagnosis, and year period. The incidence is depicted as logarithmic scale.*

years) than in the younger age-group (0–7 years), and in those having no family history of diabetes than in those with a family history of diabetes. Furthermore, we did observe a seasonal variation in onset and found a clear annual trend of increasing incidence over the 20-year period.

A family history of abrupt-onset diabetes involving a first- or second-degree relative was seen in 24 (6.1%) and 65 cases (16.4%), respectively. Among the 24 first-degree relative cases, in 9 (37.5%) cases the father was diabetic and in 15 cases (62.5%) the mother was diabetic.

CONCLUSIONS — This is the first population-based, long-term epidemiological study of childhood IDDM from Japan. It has been reported that IDDM in Japanese children is not a uniform disease (8). There are at least two forms of IDDM, an abrupt-onset and a slow-onset form, with most of the latter cases being detected by an annual urine glucose screening in Japan. In this study, we excluded all slow-onset cases, because the nature of these cases has not been fully studied with regard to insulin secretory capacity, HLA genotypes, autoantibodies, and so on. The differences in incidence with regard to sex, age-group, family history, season, and year period were analyzed only in cases of abrupt-onset IDDM.

Age and sex

Bimodal distribution of age at the onset of IDDM was seen in both sexes, as was found in Hungary (12) and in Great Britain (13). Only monomodal distribution has been observed in Finland and Great Britain (14,15). The incidence in male subjects exceeded that in female subjects in most countries where the incidence of IDDM was high (14–20), but was lower than that in female subjects in countries with a lower incidence of IDDM, such as Hungary, Latvia, Lithuania, Poland (12, 21), and Japan in this study. No sex difference was observed in studies in Iceland, the state of Colorado, and Catalonia, Spain (22–24).

Seasons

Our study observed a significant seasonal variation in IDDM incidence, as has been reported for most countries (12,14–16, 23,24). Such seasonal variation was not observed in Sardinia (17), and was observed only in male subjects in Finland (25) and the older age-group in Yorkshire, U.K. (13).

Annual incidence

The mean annual incidence of abrupt-onset IDDM in Hokkaido during the 20-year study was 1.63 per 100,000/year. This figure is ~7% of the incidence in Scandinavian countries and 20% that of other Caucasian countries, as reported previously (3,26); however, the Hokkaido figure is higher than that reported for Korea (27). The annual trend obviously increased over the 20 years.

One might argue that the lower incidence we found during the 1973–1982 period was due to the low ascertainment rate of cases. Our registration system started in 1974, and repeated surveys were conducted every year since then. Moreover, a free medical system for IDDM patients was started in 1974, and medical records of this free treatment were kept in urban and rural districts. The number of IDDM patients was verified by checking these records every year. Therefore, it is unlikely that the low

Table 1—*Age-specific annual incidence (per 100,000) of IDDM by sex, age-group, and 5-year period in Hokkaido, 1973–1992*

	Age-group 0–7 years			Age-group 8–14 years		
Year period	Number at risk	Number of patients	Incidence (95% CI)	Number at risk	Number of patients	Incidence (95% CI)
Boys						
1973–1978	1,861,715	9	0.48 (0.17–0.80)	1,494,865	13	0.87 (0.40–1.34)
1979–1982	1,766,105	18	1.02 (0.55–1.49)	1,559,220	32	2.05 (1.34–2.76)
1983–1988	1,504,445	15	1.00 (0.49–1.50)	1,612,620	29	1.80 (1.14–2.45)
1989–1992	1,272,735	17	1.34 (0.70–1.97)	1,373,030	48	3.50 (2.51–4.49)
Girls						
1973–1978	1,771,150	17	0.96 (0.50–1.42)	1,435,325	20	1.39 (0.78–2.00)
1979–1982	1,680,510	19	1.13 (0.62–1.64)	1,488,545	33	2.22 (1.46–2.97)
1983–1988	1,436,820	20	1.39 (0.78–2.00)	1,535,925	53	3.45 (2.52–4.38)
1989–1992	1,211,430	15	1.24 (0.61–1.87)	1,314,060	38	2.89 (1.97–3.81)

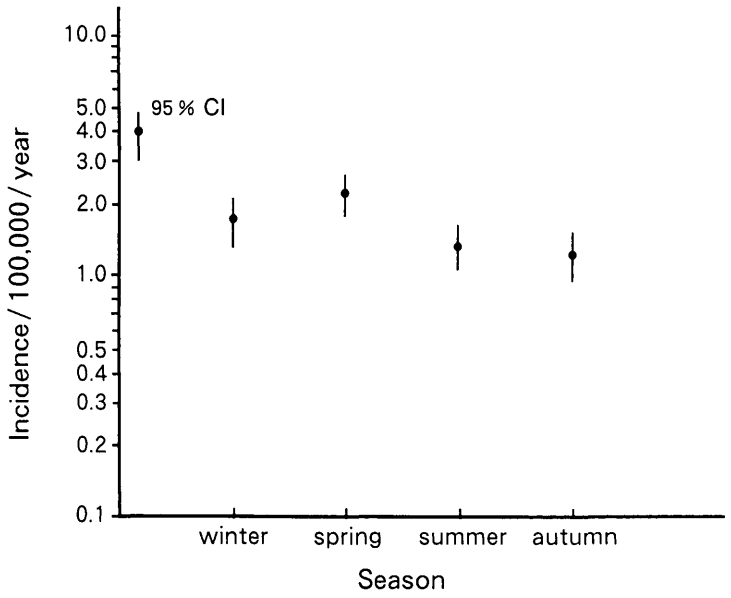

Figure 4—*The incidence per 100,000 by season. The incidence is depicted as logarithmic scale.*

incidence during the first 10 years was due to low ascertainment of cases.

To explain the low incidence among the Japanese population and change of incidence rate, we have to consider genetic and environmental factors. The most important genetic factor for development of IDDM is HLA genes, particularly class II genes (28). Among these, HLA-DQ-α,β genes and the DR-β gene are important for the development of IDDM (28). The frequency of HLA-DQ-β non-Asp 57, the highest susceptibility gene in Caucasians, is much lower among the Japanese population than among other ethnic groups, although the frequency of the DQ-α gene does not differ (28,29). By contrast, the frequency of DR-β non-Asp 57 is increased in the Japanese population (30). However, it is not clear at present whether the difference in susceptibility genes is responsible for the difference in IDDM incidence in Japanese (28–31).

Viral infection (32,33), intake of cow's milk (34), and other variables (35) are environmental factors thought to be responsible for the development of IDDM. Epidemiological studies from Norway and Sweden have shown that the incidence of IDDM increases with decreased duration of breast-feeding, and that the time-lag between the two factors is ~10 years (36). Great economic expansion took place in the 1970s in Japan. The rate of breast-feeding became lowest, and powdered milk production per newborn infant became highest by 1975. The incidence of IDDM was high in 1985, which would coincide with a 10-year time-lag from the lowest breast-feeding rate. It is too early to conclude that increased cow's milk intake was responsible for the increased incidence of IDDM during the 10 years from 1973 through 1982; the intake of other animal products and processed food, which also increased with economic expansion, and the simultaneous increased Westernization of Japanese lifestyle are other factors that must be considered. Analytical epidemiological studies are necessary to clarify the environmental factors responsible for change in incidence of IDDM in the Japanese population.

Family history

A history of diabetes involving a first- or second-degree relative was seen in 6.1 and 16.4% of patients, respectively. Most of these parents had NIDDM, and more often the mother was diabetic rather than the father. The rate of parental diabetes is much higher in Caucasians (37,38), and the incidence of diabetes in fathers is much higher than in mothers (37,38).

In conclusion, this comprehensive 20-year population-based study has shown for the first time that age at onset, sex, family history, and season correlate with the incidence and prevalence of IDDM in children ages 0–14 years in Japan. We found a marked difference in incidence as compared with Caucasians, and also a heterogeneity of IDDM among Japanese children, although further analytical epidemiological studies are necessary to clarify what genetic differences and environmental factors play roles in the etiology of IDDM.

Acknowledgments— This work was supported by a Grant-in Aid for Scientific Research (B) from the Ministry and Education, Science and Culture, Japan (07457182) and a Grant for Diabetes Research from the Ministry of Health and Welfare.

We wish to thank the pediatricians and physicians throughout Hokkaido for their excellent cooperation. We thank Mami Ofuji and Michiyo Kanda for preparation of manuscript and Kim Barrymore for proofreading the manuscript. We also thank Prof. R.E. LaPorte for his valuable comments and encouragement of this study.

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