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Family Histories of Diabetes Among Japanese Patients with Type 1 (Insulin-Dependent) and Type 2 (Non-Insulin-Dependent) Diabetes

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Summary. Family histories of diabetes mellitus in first-degree relatives were compared in Japanese patients with Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetes. The frequency of positive family histories for diabetes in first-degree relatives was 24% (13/55) in Type 1, 44% (281/631) in Type 2 ($p < 0.01$ versus Type 1) and 47% (16/34) when the type of diabetes could not be classified. The prevalence of diabetes in siblings of Type 2 patients was higher than in Type 1 diabetic patients ($p < 0.01$). Patients with Type 2 diabetes and definite obesity in the past had a lower frequency of a family history of diabetes ($p < 0.01$) and a lower prevalence of diabetes in their parents ($p < 0.01$) than did Type 2 patients without obesity. The highest rate of family history for diabetes was observed in non-obese Type 2 diabetic patients of early onset. Our data agree with the previously known higher frequency of familial diabetes in Type 2 compared with Type 1 diabetes, despite the fact that there are significant dissimilarities between Type 1 diabetes in Japanese and Caucasoid populations.

Key words: Family history of diabetes, Type 1 and Type 2 diabetes, obesity

The genetic factors involved in the pathogenesis of idiopathic diabetes mellitus appear to be different between Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetes [1]. It was reported that a family history of diabetes was significantly more prevalent in early-onset Type 2 diabetes than in Type 1 diabetes [2], and the concordance of diabetes in monozygotic twins was signficantly higher in Type 2 than in Type 1 diabetes [3]. These data were obtained mainly in Caucasoid diabetic patients.

Variations in the frequency of types of diabetes in different countries [4] suggest that the relative importance of genetic and possible environmental factors in the pathogenesis of diabetes differs between different ethnic groups. Here, we report on the analysis of family history of diabetes in Japanese patients with Type 1 and Type 2 diabetes.

Subjects and Methods

The subjects in this study were diabetic patients who visited the Endocrine and Metabolic Clinic at the Jichi Medical School Hospital and whose full family histories of first-degree relatives were recorded. Patients thought to have pancreatic disease, haemochromatosis, other endocrine diseases or who were being treated with corticosteroids were excluded. Patients were enrolled when their fasting blood glucose (venous plasma) exceeded 8 mmol/l on at least one occasion; or in cases whose fasting blood glucose ranged between 7 and 8 mmol/l, they were enrolled only if they had a clear history of diabetic symptoms or their 2-h blood glucose after a 100 g oral glucose load exceeded 13 mmol/l. (This corresponds approximately to a 2-h blood glucose level of 11 mmol/l after a 75-g glucose load, as proposed by the WHO Expert Committee [5]).

The family history was taken by questioning the patient at the first visit, and confirmed at subsequent interviews. The family history of diabetes was judged as positive when the patient reported that one of their first-degree relatives (parents, siblings and children) had diabetes. The record of changes in previous body weight was obtained from the patient's own history. Time of onset of diabetes was estimated from the first symptoms attributable to the disease. When symptoms were absent, the onset of diabetes was taken as the first detection of urine glucose. Weight percentages were calculated with reference to ideal body weight, i.e. (body height (cm) – 100) × 0.9 (kg).

In order to differentiate between Type 1 and Type 2 diabetes among insulin-treated patients, the mode of onset of the disease, tendency to ketosis, doses of insulin, lability of fasting blood glucose, and blood and urine C-peptide values [6] were taken into account. Only those patients judged to be almost devoid of endogenous insulin reserve were classified as Type 1. Cases in whom the differentiation of types was difficult were analyzed as 'type unclassified'. The significance of differences between frequencies in two groups was calculated by the Chi-squared test.

Results

Among 720 diabetic patients, 55 were classified as Type 1, 631 as Type 2 and 34 as type unclassified (Table 1). The mean ages of onset of diabetes in each

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Table 1. Frequency of positive family histories of diabetes, and the prevalence of diabetes in first-degree relatives, in patients classified by types of diabetes and age of onset

Estimated age of onset of diabetes (years)	Mean age at initial visit (years)	Frequency of positive family history of diabetes			Prevalence of diabetes among each class of first-degree relatives					
		Type 1	Type 2	Type unclassified	Type 1			Type 2		
					parents	siblings	children	parents	siblings	children
5–19	21.1	2/13 (15)	4/ 8 (50)	1/ 1 (100)	2/26 (8)	0/39 (0)	0/ 1 (0)	5/ 16 (31)[a]	0/ 12 (0)	0/ 1 (0)
20–29	30.6	3/14 (21)	15/ 32 (47)	7/10 (70)[a]	1/28 (4)	3/54 (6)	0/ 6 (0)	17/ 64 (27)[a]	4/ 99 (4)	0/ 24 (0)
30–39	41.8	5/14 (36)	59/117 (50)	6/11 (55)	5/28 (18)	0/48 (0)	0/26 (0)	38/234 (16)	44/482 (9)[a]	7/228 (3)
40–49	50.9	3/11 (27)	88/194 (45)	1/ 4 (25)	0/22 (0)	2/54 (4)	1/24 (4)	54/388 (14)	77/856 (9)	7/490 (1)
50–59	59.0	0/ 2 (0)	67/167 (40)	0/ 6 (0)	0/ 4 (0)	0/ 6 (0)	0/ 5 (0)	19/334 (6)	62/838 (7)	6/548 (1)
60–69	66.4	0/ 1 (0)	39/ 92 (42)	1/ 2 (50)	0/ 2 (0)	0/ 7 (0)	0/ 7 (0)	11/184 (6)	36/426 (9)	14/380 (4)
70–79	75.0		9/ 28 (32)					3/ 56 (5)	8/140 (6)	8/140 (6)
Total		13/55 (24)	281/631[b] (44)	16/34[a] (47)	8/110 (7)	5/208 (2)	1/69 (1)	147/1276 (12)	231/2853[b] (8)	42/1811 (2)
Age < 50 years		13/52 (25)	166/351[b] (47)	15/26[b] (58)	8/104 (8)	5/195 (3)	1/57 (2)	114/702[a] (16)	125/1449[b] (9)	14/743 (2)

Figures = observed frequencies; numbers in parentheses = percentages.
[a] $p < 0.05$; [b] $p < 0.01$: significantly different from the corresponding value of the Type 1 diabetic group

Table 2. Relationship between family histories of diabetes and previous maximal body weight index

Maximal previous weight index (%)	Frequency of positive family history of diabetes			Prevalence of diabetes in each class of first-degree relatives		
	Estimated age of onset of diabetes (years)			Parents	Siblings	Children
	< 30	⩾ 30	total			
< +20	12/18 (67)	84/174 (48)	96/192 (50)	60/384 (16)	72/849 (9)	13/515 (3)
+40 ⩽	2/ 9 (22)	44/134 (33)	46/143 (32)	17/286 (6)	37/635 (6)	8/393 (2)
p	< 0.05	< 0.01	< 0.01	< 0.01	NS	NS

Figures = observed frequencies; numbers in parentheses = percentages. NS = not significant

group were 29.9, 48.1 and 36.9 years, and median ages 30, 48 and 33 years, respectively. The frequency of patients who had first-degree relatives with diabetes was 43% for all, 24% for Type 1 diabetes, 44% for Type 2 ($p < 0.01$ versus Type 1) and 47% for 'type unclassified' ($p < 0.05$ versus Type 1). As Type 1 diabetes seldom occurred above the age of 50 years, patients with onset of their disease before the age of 50 years were studied. Among these patients, the frequency of positive family histories was 25% for Type 1 and 47% for Type 2 diabetes ($p < 0.01$).

The prevalence of known diabetes in each class of first-degree relatives is also shown in Table 1. There was a tendency for diabetes in the parents to be more frequent among the groups with younger-onset Type 2 diabetes, while patients with diabetic children were more often seen among those with older onset. The overall prevalences of known diabetes in parents, siblings and children were 7%, 2% and 1% for Type 1 and 12%, 8% and 2% for Type 2 diabetic patients. This difference was significant for siblings ($p < 0.01$). When patients with onset of diabetes before the age of 50 years were compared, the prevalences of affected parents and siblings were significantly higher in Type 2 than in Type 1 diabetes ($p < 0.05$ and $p < 0.01$ respectively).

Type 2 diabetic patients were subdivided by their previous maximal weight index. Family history of diabetes was compared between the non-obese group (past weight index < +20%) and the definitely obese group (past weight index ⩾ +40%; Table 2). The frequency of a positive family history was significantly less in patients who had been obese in the past ($p < 0.01$). When the patients were further classified by the estimated age of onset of diabetes, the frequency was highest in Type 2 diabetic patients who had never been obese and with onset of diabetes before the age of 30 years. The percentage of diabetes among parents was also significantly lower in Type 2 patients who had been obese in the past ($p < 0.01$).

Discussion

Some inaccuracy in assessing family histories is inevitable with the present method of simple questioning of patients. In order to minimize the bias due to differences in generations, we tried to compare family histories between groups with similar age of onset. We found that Japanese Type 1 diabetic patients had a lower frequency of positive family histories of diabetes and lower prevalence of diabetes among their parents and siblings than did Type 2 diabetic patients. This is in accord with a previous Japanese report which revealed a higher frequency of positive family histories for diabetes in Type 2 than in Type 1 diabetic patients when the onset of diabetes was before the age of 25 years [7]. Our data also agree with some reports from Western countries [2, 3], despite the fact that there are certain differences between Type 1 diabetes in Japanese and Caucasoid people. Typical juvenile-onset Type 1 diabetes is less frequent in Japan than in Western countries [8] and is associated with different HLA antigens from those seen in Caucasoid patients [9, 10]. Islet-cell antibodies are uncommonly demonstrated in Japanese patients with Type 1 diabetes [11]. The present data also indicate that the higher frequency of a positive family history in Type 2 diabetes compared with Type 1 is not confined to younger onset patients.

Among Type 2 diabetic patients, the frequency of a positive family history of diabetes and the prevalence of diabetes among parents were lower in patients who had been obese than in those who had never been so. Similar findings were reported by Köbberling who observed that the prevalence of diabetes in siblings was higher in non-obese than in obese diabetic subjects [12]. Baird compared the frequency of diabetes by a glucose tolerance test in siblings of Type 2 patients with and without obesity, and found that the frequency was highest in obese siblings of non-obese diabetics and lowest in non-obese siblings of obese diabetic patients [13]. These observations suggest that the diabetogenic effect of obesity is sufficiently strong for marked obesity to induce diabetes in subjects who have low genetic risks for diabetes. In our study, non-obese young-onset Type 2 diabetic subjects appear to be the population with the greatest hereditable tendency to diabetes. Although we were unable to trace the mode of inheritance in detail, this group of patients may be related to the type of young-onset Type 2 diabetes with dominant inheritance, first described by Tattersall [14].

The present study indicates that, in Japan, a positive family history of diabetes is more frequent among Type 2 than among Type 1 diabetic patients. It does not necessarily imply that heredity plays a more important role in the pathogenesis of Type 2 than of Type 1 diabetes: it is also possible that the environmental factors inducing Type 2 diabetes are of a more general nature than those for Type 1 diabetes. The data also suggest that obesity and heredity may play complementary roles in the pathogenesis of Type 2 diabetes.

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