ORIGINAL CONTRIBUTION

An Epidemiological Study on Diabetes Mellitus in the Population Living in a Methyl Mercury Polluted Area

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The aim of this study was to determine the actual prevalence of diabetes mellitus and to investigate the contribution of various risk factors to the diabetes mellitus among the population in a methyl mercury polluted area. The study was a population based cross sectional mass screening survey. A case-control study was designed to estimate the role of various risk factors including methyl mercury exposure for diabetes mellitus. The study was confined to a small rural town 10km north of Minamata City; 1,087 persons older than 40 years were examined. Measurement of glucose metabolism was made on the basis of urine and haematological examinations. Data on risk factors were collected by questionnaire, and by measurement of body height and weight (obesity). The prevalence rate of the diabetes mellitus was 8.4% in males and 5.3% in females. The odds ratio of family history was significantly higher, 4.63. The odds ratio of residential history in a methyl mercury high polluted area was 0.58. The prevalence of the diabetes mellitus in this methyl mercury polluted area was not increased, contrary to what was expected based on the pathological findings. *J Epidemiol*, 1996 ; 6 : 204-208.

diabetes mellitus, methyl mercury, general population, case-control study, epidemiology

There are few well designed epidemiological studies of disturbance of glucose metabolism in the general population ^{1,2}. A mass health examination survey of disturbance of glucose metabolism was performed 1,139 subjects aged older than 40 years in 'A' Town of Kumamoto prefecture in the southeastern part of Japan. 'A' Town is located in a methyl mercury polluted area and there are 36.9 certified Minamata disease patients per 1,000 population. In this field survey the possible evidence of methyl mercury as a causative factor of disturbance of glucose metabolism was examined in the light of several previous studies. Takeuchi et al reported that disturbance of pancreatic islet cells was found in autopsy cases of fetal type and childhood Minamata disease, as well as in adult victims ³. They pointed out that in adult cases, complications arising from diabetes could be expected due to the many old people among the autopsy cases. In experiments using rats, Shigenaga found that β -cells of the islets of Langerhans were disturbed by methyl mercury and that a high level of blood sugar was induced by repeated administration of methyl mercury chloride ⁴.

The purpose of this study is to clarify the prevalence rate of the diabetes mellitus in 'A' Town and to investigate positive risk factors, including methyl mercury exposure, for the diabetes mellitus in a population cross sectional survey.

SUBJECTS AND METHODS

Mass multiple health examination for adult diseases including disturbance of glucose metabolism was performed in 1,139 subjects aged older than 40 years in 'A' Town near Minamata City in the summer of 1990 ⁵. Table 1 shows the subjects by sex, age and residential area. In the further analysis age group more than 80years was excluded because of a small number. 'A' Town is located in the southern part of Kumamoto prefecture, neighbouring Minamata City, and faces the Yatsushiro Sea. It extends back from the sea into a mountainous area leading to the Kyushu highlands. The authors analysed the geographical distribution of the subjects because 90% of the total verified Minamata disease patients in this locality have

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lived in fishing villages where much fish and shellfish were consumed, and also because it is easy to divide the locality into three areas, fishing villages, mountainous villages, and the middle areas as the authors previously reported detailed by using nutritional researches and blood mercury measurements ^{6,7)}.

In the first screening examination urine sugar positive of urine test paper and serum glucose level of 130mg/dl without fasting were selected. The following examination consisted of a 75 gram oral glucose tolerance test (OGTT) with measurement of serum glucose and serum insulin value. Table 2 shows the criteria of abnormalities of 75g OGTT, which is based on the criteria of the Japanese Diabetic Society ⁸⁾ applied to individuals who were screened by the first screening examination. Serum glucose levels after overnight fasting and at two hours after the oral glucose load were used to classify individuals into one of three groups, according to the criteria shown in Table 2. Blood analyses were performed using an SMA 12/60 autoanalyser.

A case-control study was carried out; 53 diabetes mellitus cases were selected based on the results of 75g OGTT, and 265 sex-age matched controls (5:1 within two years age matching) were selected from among subjects with no abnormal finding

in the first screening examination. We studied the following five related risk factors: obesity (Katsura's index $[(\text{weight}/(\text{height}-100) \times 0.9) \times 100]$ more than 115%), abnormal findings of fundus photogram (Sheie Classification), family history of diabetes mellitus (within a first or second degree relative), and the indirect risk factor of history of consumption of methyl mercury contaminated fish (fishing village residential history) ^{6,7)}. The odds ratio (approximate relative risk) was calculated from the results of case-control observations. From these results and the frequency of risk distribution, attributable risk percent, population attributable risk percent, and population relative risk were calculated to estimate the contribution of each risk factor for diabetes mellitus in 'A' Town. These analyses were performed on a personal computer using the ANALYST procedure of the Statistical Analysis System.

RESULTS

The urine sugar positive rate was 2.6% in males and 3.2% in females. The rate of increased serum glucose level was 46.0% in males and 31.3% in females. Three hundred twenty-six subjects (30.7 percent of the total subjects) were selected in this first screening examination and 233 subjects (71.5 percent of

Table 1. Numbers of subjects by sex, age, and residential area.

Age (years)	Male			Female			Total
	Fishing Villages	Mountainous Villages	Middle areas	Fishing Villages	Mountainous Villages	Middle areas	
40-49	35	12	15	46	22	24	154
50-59	49	26	26	81	40	65	287
60-69	72	43	53	108	69	77	422
70-79	34	35	26	39	34	30	198
80-	5	4	5	5	4	3	26
Total	195	120	125	279	169	199	1087

Table 2. Criteria for identification of diabetes mellitus.

75 g OGTT	Serum glucose level (mg/dr)			ΔIRI *
	fasting glucose level	30 minutes post glucose level load	2 hours post glucose level load	ΔBS
normal glucose Tolerance	< 110	< 160	< 120	$0.4 \leq$
impaired glucose Tolerance	110-139	160-169	120-199	< 0.4
diabetes mellitus	$140 \leq$	$170 \leq$	$200 \leq$	< 0.4

* $(\text{Serum insulin level 30 minutes post glucose load} - \text{fasting insulin level}) /$
 $(\text{Serum glucose level 30 minutes post glucose load} - \text{fasting glucose level})$.

the screened subjects) were examined for 75g OGTT. Table 3 shows the results of examination by sex and age. 74 patients with diabetes mellitus were detected, of which 53 patients were diagnosed according to the Table 2 criteria, furthermore, 21 patients showed more than 200mg/dl glucose level in fasting time, then diagnosed as diabetes mellitus without 75g OGTT. Totally the prevalence rate of diabetes mellitus was 8.9% in males and 5.7% in females. The prevalence rate of impaired glucose tolerance was 8.9% in males and 7.0% in females. There were no significant sex differences except in the 60 years of age group. Table 4 shows the results of 75g OGTT by the related risk factors, for example, family history of diabetes mellitus and obesity in the subjects who were examined 75g OGTT. The rate of family history was significantly higher ($P<0.05$) in the diabetes mellitus group. There were no significant differences among residential groups as shown in Table 4. Table 5 shows the frequency of risk factors in the cases with diabetes mellitus and controls. Table 6 shows the adjusted odds ratio for the four risk factors examined, based on the case-control study. The odds ratios were 0.41 for obesity, 1.07 for abnormal findings of fundus, 4.63 for family history of diabetes mellitus and 0.58 for history of residence in fishing villages near the Yatsushiro Sea. The odds ratio values for family history of diabetes mellitus were significantly increased. The attributable risk percent of diabetes mellitus was high (78.6%) in a population with family history of diabetes mellitus. Moreover, the contribution rate for diabetes mellitus (PAR and PAA) was higher for family history of diabetes mellitus in 'A' Town than for the other factors.

DISCUSSION

A mass screening survey of the disturbance of glucose metabolism was performed to detect the actual prevalence of diabetes mellitus and to investigate the contribution of various risk factors to the diabetes mellitus in the area studied. 'A' Town is a small rural community of approximately 6,100 inhabitants, 10km north of Minamata City. More than half of the residents are engaged in agriculture (mainly orange growing and rice cultivation), or fishing in the Yatsushiro Sea, and the rest are employed locally in small businesses located around Minamata City. One of the potent factors influencing the decision to locate the program in 'A' Town was the presence of a highly cooperative and informed medical organization and a reasonably stable population of adults. The other important factor was the fact that there is a high prevalence of Minamata disease in the area⁹. It is important to follow up the health state of inhabitants living in a methyl mercury polluted area, paying particular attention to diseases other than those of the central nervous system, which have been concentrically studied over a long period¹⁰.

Takeuchi et al. reported that disturbance of pancreatic islet cells was found in autopsy cases of fetal type and childhood Minamata disease as well as in adult victims³. In adult cases, complications arising from diabetes could be expected to be due to the many old people among the autopsy cases. However detailed studies on possible diabetes were not conducted in the clinical investigation. According to Tokuomi, of 11 confined patients, 3 had slightly high blood sugar values,

Table 3. Numbers and prevalence rate of diabetes mellitus.

Age	40—49	50—59	60—69	70—79	Total
Male	2(3.2)	11(10.5)	22(12.9)	3(3.4)	38(8.9)
Female	0	11(5.8)	17(6.7)	8(8.6)	36(5.7)

Table 4. Relationship between risk factors and diabetes mellitus.

Risk factor	Family history		Obesity		Residential area		
	Present	Absent	Present	Absent	Fishing villages	Mountainous villages	Middle areas
normal	8 (8.8)	110 (91.2)	13 (11.0)	105 (89.0)	47 (39.8)	40 (33.9)	31 (26.3)
impaired glucose tolerance	7 (11.9)	52 (88.1)	7 (11.9)	52 (88.1)	24 (40.7)	15 (25.4)	20 (33.9)
diabetes mellitus	12 (22.6)	41 (77.4)	8 (15.1)	45 (84.9)	17 (32.1)	17 (32.1)	19 (35.8)

Table 5. Frequency of risk factors in the cases with diabetes mellitus and controls.

	Obesity	Abnormal findings of fundus	Family history of diabetes mellitus	History of residence fishing villages
Cases with diabetes mellitus	8(15.1)	2(3.8)	12(22.6)	17(32.1)
Controls	21(8.2)	9(3.5)	15(5.9)	114(44.7)

Table 6. Odds ratios and the estimation of contribution to diabetes mellitus of the related risk factors.

	Obesity	Abnormal findings of fundus	Family history of diabetes mellitus	History of residence fishing villages
Odds ratio (95% confidence interval)	0.41 (0.20 ~ 1.33)	1.07 (0.16 ~ 5.55)	4.63** (1.89 ~ 11.54)	0.58 (0.30 ~ 1.14)
Attributable risk (%)	—	6.7	78.6	—
Population attributable risk (%)	—	0.14	20.9	—
Population relative risk (%)	—	1.00	1.26	—

**P<0.01

one with urine sugar, but no special attention was paid to them¹¹. According to an epidemiological report by Matsushita et al., 24(3.3%) of 725 residents of the contaminated area of Minamata showed a sugar reaction in urine test, and in Goshonoura, where the contamination was less severe, 21(2.1%) of 1,009 residents showed a positive reaction¹². However, these tests were simple and the blood sugar levels were not actually determined. Takeuchi et al. anticipated that the level of sugar would not be too high, based on observation of the islets of Langerhans in their autopsy cases, for even if the islets were destroyed, regeneration and hypertrophy should follow and their function would then be maintained. Nevertheless, size irregularities, atrophy, scar formation and reduction of the islets were definitely caused by the poisoning, and it is thought that islets unable to regenerate sufficiently might induce some increase in blood sugar, possibly leading to sugar in the urine³.

In experiments using rats, Shigenaga found that β -cells of the islets of Langerhans were disturbed by methyl mercury and that a high level of blood sugar was induced by repeated administration of methyl mercuric chloride. However, the damage was less severe than in the case of alloxan administration⁴.

The next step was to clarify the actual prevalence of diabetes mellitus or impaired glucose tolerance epidemiologically among inhabitants living in the methyl mercury polluted area. In this study, it was impossible to perform 75g. OGTT in all of the subjects for ethical reasons. However, this screening procedure has a somewhat problematic validity; in fact there was about a 50% rate of false positive results among the individuals screened by urine and sugar glucose measurement with no glucose loading. Terao et al. reported that the prevalence rate of diabetes mellitus was 8.7% in males and 4.9% in females in a urban area¹³. Nagai et al. reported that the prevalence rate of diabetes mellitus was 8.1% in males and 5.0% in females in a rural area. The results of this study agreed with these epidemiological prevalence studies in a general population.

A few case-control studies in Japanese populations were reported recently, but intensive epidemiologic studies for evaluating the quantitative magnitude of the risks in a Japanese population are rare^{13,14}. Yamamoto reported odds ratios of family history of diabetes to be 14.8 (CI=6.51-33.59) for getting diabetes mellitus. Nagai also reported odds ratios of diabetes mellitus history of father to be 10.94 (CI=1.18-101.14). The relative risk of maximum Body Mass Index for diabetes mellitus which was reported in a Japanese population study is

1.54; this model used the Body Mass Index as continuous variable as in the analysis of Nagai^{13,14}. These results seem to support the reliability of our study. According to the results of national health insurance surveys, the prevalence rate of diabetes mellitus was 1.0% in the fishing villages, 1.7% in the mountainous villages and 2.4% in the middle areas. In the risk analysis, history of residence in fishing villages shows no relationship to prevalence of diabetes mellitus.

In conclusion, the prevalence of diabetes mellitus in this methyl mercury polluted area was not increased, contrary to what was expected based on the pathological findings.

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