ORIGINAL CONTRIBUTION

Epidemiology in a Focus of Motor Neuron Disease on the Kii Peninsula of Japan : A Death Rate Survey

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In the Hohara area of Nansei-cho, one of the foci of motor neuron disease (MND) on the Kii peninsula, the death rates of MND and of leading causes of death were surveyed to obtain a clue to the etiology of MND in the Western Pacific. The crude annual death rate of MND in the Hohara area was 47.6 per 100,000 population (for 1961-1990), and the standardized mortality ratio of MND was 5403. The death rate survey showed that the mortality of nonischemic heart disease was higher and that of diabetes mellitus was lower in Hohara as compared with the whole Japanese population. The mortality of MND has a positive correlation with the mortality of cerebrovascular diseases, and also with that of nephritis and nephrotic syndrome in Nansei-cho. These death rate data may suggest that etiological factors of MND in this focus could also influence the mortality of some other diseases. *J Epidemiol*, 1994 ; 4 : 31-35.

motor neuron disease, Kii Peninsula, underlying cause of death

Three high incidence foci of motor neuron disease (MND) have been reported in the Western Pacific area, i.e., the Kii peninsula in Japan (the Hohara** and Kozagawa areas), Guam, and West New Guinea¹⁻³). Parkinsonism-dementia complex has been also reported to occur in high incidence in these areas^{2,3,5,7}). The etiology of MND in the foci is not yet established, but it has been suggested that environmental factors play an important role in the high incidence in the foci^{2,5,8}).

Whatever etiological factors exist in the foci, it may be expectable that these factors influence incidences of disease other than MND and parkinsonism-dementia complex. Death rates from MND and 15 leading causes in the Hohara area were surveyed in comparison with the rates in the neighboring population and also with the general Japanese population. The aim of this death rate survey is to ascertain whether the Hohara area is specific only for the high incidence of MND or whether other causes of death are also unusual. A possible association among the death rates may offer a clue to the etiology of MND.

MATERIALS AND METHODS*Description of study area*

Hohara is located on the Kii peninsula of Japan, facing the Western Pacific Ocean (Figure 1). The Hohara area is one of five administrative areas of Nansei-cho (109 km² in space) in the Mie prefecture (Figure 2). The population of the five areas, as of 1988, was 2731 in the Nankai area, 1662 in the Hohara area, 3793 in the Gokasho area, 949 in the Kamihara area, and 3337 in the Shukutaso area, and 12,472 for Nansei-cho as a whole.

Death rate analysis

The Ise Health Center is in charge of collecting abstracts of death certificates from Nansei-cho. Each of 3541 mortality cases in the five areas in Nansei-cho in 1961-90 was reviewed, and the underlying causes of death were re-coded according to the 9th revision of International Classification of Disease (ICD)⁹). The standardized mortal-

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*Former director ; retired. **has been reported as "Hohara" in other reports ^{6,7}). Local people however call this area "Hohara".

Figure 1. Map to show the location of the Hohara area in Japan. The Hohara area is located on the Kii peninsula of Honshu Island of Japan facing the Western Pacific Ocean.

Figure 2. The Hohara area in Nansei-cho. Nansei-cho is divided into 5 administrative areas as A) the Nankai area, B) the Hohara area, C) the Gokasho area, D) the Kamihara area, and E) the Shukutasa area.

ity ratios (SMRs) were calculated for the deaths in which underlying cause of death was MND or another 15 leading causes. A whole Japanese population of the same period (1961-1990) was taken as the standard population, and the mortality data were obtained from Vital Statistics of Japan 1961-1990¹⁰. The following ICD codes (9th revision) were used for classification of the causes of death; malignant neoplasms (140-208), ulcer of stomach and duodenum (531-533), gastroenteritis (008, 009, 535, 555, 556, 558, 562), tuberculosis (010-018), hypertensive disease (401-405), suicide (E950-E959), ischemic heart disease (410-414), non-ischemic heart disease (393-398, 415-429), nephritis and nephrotic syndrome (580-589), diabetes mellitus (250), cerebrovascular disease (430-438), pneumonia and bronchitis (480-486, 490, 491, 466.0), accidents and adverse effects (E800-E949), chronic liver disease and cirrhosis (571),

senility without mention of psychosis (797), and MND (335.2). The validity of death certificates for an epidemiological study of MND has been described in a previous study¹¹. For the period of 1961-1979, the codes of the 7th and 8th revisions which corresponds to those of 9th were used in the standard population. Although MND is coded as 335.2 in the 9th revision, data for code 335.2 was not available in the Vital Statistics of Japan. Accordingly, anterior horn cell disease (code 335) was taken to substitute MND in the standard population, because other anterior horn cell diseases are rare as compared with MND (e.g., the rate of deaths from total anterior horn cell disease to that from MND in 1978 was 53 to 51¹²).

Code 356 of 7th revision in 1961-67, and code 348 and 330.1 of 8th revision in 1968-78 were used in place of MND in the standard population. Population data in Nansei-cho were obtained from the Nansei Public Office. The populations in years 1965, 1975, 1985 were used for calculation of SMRs for 1961-1990. Data on the standard population were obtained from the Vital Statistics of Japan¹⁰. For any cause of death, the observed numbers were treated as a Poisson variable. Statistical analysis of SMRs was by the method of mathematical link between Poisson and the chi-squares distributions¹³.

RESULTS

The SMRs are shown in Table 1. There was no death certificate that described MND as other than underlying cause of death. The crude annual death rate of MND was 47.6 per 100,000 population in the Hohara area for 1961-1990. The SMR of MND in the Hohara area was 5403, and the probability of this SMR value was as small as less than 10^{-30} . The SMR of MND in the Gokasho area was 294, but the probability of this SMR value was insignificant ($p > 0.05$). Among leading causes of death, SMR for non-ischemic heart diseases (191) and diabetes mellitus (0) were significantly ($p < 0.05$) different in the Hohara area. The death rates for non-ischemic heart diseases were generally high and those for diabetes mellitus were generally low in Nansei-cho. The SMRs of some other causes, e.g. hypertensive disease, were also significant in the whole of Nansei-cho, but only the SMRs of these three diseases were significant ($p < 0.05$) in the Hohara area.

Correlation between SMRs of the 16 causes of death were examined in five areas in Nansei-cho. The coefficients of correlation between MND and the other 15 leading causes are shown in Table 2. At the 5% level, four correlations were significant, i.e., gastroenteritis *versus* pneumonia and bronchitis ($r = 0.96$, $p = 0.010$), ulcer of stomach and duodenum *versus* cerebrovascular disease ($r = 0.88$, $p = 0.047$), MND *versus* nephritis and nephrotic syndrome ($r = 0.90$, $p = 0.036$), and MND *versus* cerebrovascular disease ($r = 0.91$, $p = 0.033$).

Parkinsonism (code 332) was also surveyed in the abstracts of death certificates regardless of underlying cause of death. Two patients with parkinson disease and one patient with secondary parkinsonism were found in death certificates in the Hohara area for 1961-1990. No patient with parkinsonism-dementia complex or presenile dementia was found in the death certificates of the Hohara area. Thus, the annual incidence of parkinson disease was 3.7 per 100,000 population in the Hohara area.

DISCUSSION

MND occurs with high incidence in the Hohara area in Nansei-cho. The crude annual mortality rate was 47.6 per 100,000 population for 1961-1990, with a SMR of 5403. These values are comparable to values in other reports^{6-8,14}. At least four cases of parkinsonism with dementia were reported in the Hohara area in 1969⁷. Perusal of death certificate, however, showed only two cases of parkinson disease. Information on parkinsonism with dementia in Nansei-cho in a recent four year period (1987-1990) was obtained from two neurologists and one psychiatrist in two central hospitals in Ise. There was one case of parkinsonism with dementia in the Hohara area which was not detected in this survey of death certificates probably due to incomplete certificate description. One case of parkinsonism with dementia and one case of MND in the Hohara area were alive in 1990. Accordingly, there are at least six cases (four cases in Reference 7, one dead case and one live case by medical information) of parkinsonism with dementia in the Hohara area in the period 1969 to 1990.

The death rate survey showed that not only deaths from MND but also deaths from non-ischemic heart diseases and from diabetes mellitus were significantly higher and lower, respectively, in the Hohara area than in all Japan. It was also made clear that deaths from cerebrovascular disease, and nephritis/nephrotic syndrome correlate with deaths from MND in Nansei-cho (Tables 1 and 2).

It is possible that factors which increase the incidence of non-ischemic heart diseases have some etiological relations to the factors that increase MND in the Hohara area. If this is the case, a significant correlation between the SMR for non-ischemic heart diseases and that for MND should be observed in Nansei-cho. Although the SMR for non-ischemic heart diseases is highest in the Hohara area of Nansei-cho, the correlation with the SMR for MND is weak ($r=0.65$, $p=0.237$; Table 2). Thus, the factors which increase the SMR for non-ischemic heart diseases are not strong factors for MND in the Hohara area. They might be regarded as relatively weak factors, even if they had any etiological relation to MND. A similar consideration is possible for factors decreasing the SMR for diabetes mellitus. Although the SMR for diabetes mel-

litus is 0 and the lowest in the Hohara area, the correlation between the SMR for MND and that for diabetes mellitus is statistically insignificant ($r=-0.73$, $p=0.158$).

As the SMRs for cerebrovascular disease and nephritis/nephrotic syndrome correlate significantly ($p<0.05$) with the SMR for MND in Nansei-cho, the factors which increase deaths from cerebrovascular disease and/or nephritis/nephrotic syndrome should also increase deaths from MND in Nansei-cho. It is, however, possible that the analysis for correlations between pairs could be statistically significant just by chance. If a 5.0% significance level is employed, two or more significant correlations by chance should be observed with the possibility of 0.17 in the 15 pairs. Accordingly, the above two significant correlations might have resulted from statistical chance alone.

Some case-control studies suggest that MND is related to injuries¹⁵⁻¹⁷. The death rates from accidents and adverse effect were, however, not high in the Hohara area and were not related to those of MND in Nansei-cho in the present study (Tables 1 and 2).

In Guam, another MND focus in the Western Pacific, diabetes mellitus death rates in persons at ages of 45 years and over were two to three times greater than that in the corresponding population in the United States. Diabetes-associated deaths were highest in Chamorros who are a high-risk population of MND among the four ethnic groups in Guam¹⁸. A report¹⁹ on the comparison between Chamorros in Guam and whole Californian population described five points, i.e, 1) the rates for coronary heart disease were lower in Guam for both sexes, 2) the rates for cerebrovascular accidents were higher for Guam males, 3) the rates for hypertensive heart disease were higher in Guam for both sexes, 4) the rates for accidents and injuries were higher for Guam males, and 5) the rates for neoplastic diseases were lower in Guam for both sexes. In Guam, the incidence of MND varies depending on regions within the island¹. No report is available to show the correlation of MND with other causes of death in Guam. Thus, no obvious tendency of the causes of non-MND death common to the Hohara area and Guam can be deduced at present.

Although the relation of other diseases to MND is not close enough in Nansei-cho to reach a statistically significant level (Table 2), it might be possible to postulate that some of the risk factors for non-ischemic heart disease, cerebrovascular disease, and/or nephritis/nephrotic syndrome, as well as some factors which decrease the incidence of diabetes mellitus, are also the risk factors for MND in this focus. This hypothesis might be partly explained by the metal exposure theory which postulates that low calcium, low magnesium, and high aluminum in the water and soil are MND-inducing factors in the foci^{5,6,20}, because low calcium and low magnesium in the environment are related to higher incidence of circulatory disease²¹⁻²⁴. Up

Table 1. SMRs of motor neuron disease and 15 leading causes of death in Nansei-cho for 1961-1990.

Cause of death	Nankai			Hohara			Gokasho			Kamihara			Shukutazo			Nansei-cho, total			Age M $\pm$ SD ^a
	SMR	P	CI	SMR	P	CI	SMR	P	CI	SMR	P	CI	SMR	P	CI	SMR	P	CI	
Malign ^a	110	NS	95-127	97	NS	78-118	85	*	73-99	62	**	43-87	96	NS	82-112	94	NS	87-101	65 $\pm$ 14
Ulcer ^b	22	*	3-78	179	NS	82-339	58	NS	21-125	106	NS	22-311	113	NS	54-209	83	NS	56-115	66 $\pm$ 16
Gastritis ^c	97	NS	46-178	37	NS	4-133	88	NS	42-162	100	NS	21-293	41	NS	11-105	73	NS	49-102	75 $\pm$ 17
Tbc ^d	61	NS	29-113	79	NS	32-162	123	NS	78-184	64	NS	13-187	81	NS	43-138	87	NS	65-111	68 $\pm$ 14
HTD ^e	135	NS	92-189	122	NS	70-198	135	NS	95-187	219	**	127-350	261	***	198-338	170	***	144-197	80 $\pm$ 9
Suicide	61	NS	31-106	102	NS	51-182	81	NS	49-126	168	NS	81-309	43	*	20-82	76	*	58-96	55 $\pm$ 18
IHD ^f	84	NS	61-112	97	NS	65-139	86	NS	64-112	108	NS	65-169	71	*	50-99	85	*	73-99	73 $\pm$ 11
Non-IHD ^g	148	***	123-176	191	***	153-235	163	***	138-191	165	**	121-221	102	NS	81-127	149	***	136-163	75 $\pm$ 16
Nephritis ^h	112	NS	63-184	163	NS	84-284	130	NS	79-200	97	NS	26-248	100	NS	53-172	120	NS	92-151	64 $\pm$ 18
DM ⁱ	41	NS	11-106	0	*	0-67	80	NS	36-151	32	NS	1-176	85	NS	37-167	56	*	35-82	66 $\pm$ 16
CVD ^j	75	***	64-87	99	NS	82-118	80	*	70-92	85	NS	65-110	78	*	67-92	81	***	75-88	74 $\pm$ 11
Pneumonia ^k	97	NS	73-126	65	NS	40-101	84	NS	63-110	105	NS	63-163	60	*	41-85	81	*	69-93	71 $\pm$ 23
Accidents ^l	102	NS	73-139	92	NS	56-144	123	NS	93-160	126	NS	69-211	89	NS	62-125	105	NS	90-122	48 $\pm$ 24
Cirrhosis ^m	120	NS	73-185	53	NS	17-123	57	NS	28-102	59	NS	12-172	54	NS	25-102	71	*	52-93	65 $\pm$ 12
Senility ⁿ	60	*	41-84	121	NS	83-168	58	***	39-81	127	NS	78-193	220	***	180-267	110	NS	96-125	84 $\pm$ 7
MND	0	NS	0-426	5403	***	3562-7864	294	NS	61-858	0	NS	0-1411	0	NS	0-415	848	***	572-1177	57 $\pm$ 10
Pop ^o 1975	3564			1817			4266			1031			3903			14581			
TLC ^p deaths	756			493			352			255			736			3092			
MND deaths	0			27			3			0			0			30			

P: p-value. CI: 95% confidence interval. NS: not significant. *: p<0.05. **: p<0.01. ***: p<0.001.

^aMalignant neoplasms. ^bUlcer of stomach and duodenum. ^cGastroenteritis. ^dTuberculosis. ^eHypertensive disease. ^fIschemic heart disease. ^gNon-ischemic heart disease. ^hNephritis and nephrotic syndrome. ⁱDiabetes mellitus. ^jCerebrovascular disease. ^kPneumonia and bronchitis. ^lAccidents and adverse effects. ^mChronic liver disease and cirrhosis. ⁿSenility without mention of psychosis. ^oPopulation. ^pTotal leading causes. ^qMean $\pm$ standard deviation in years.

Table 2. Correlation between SMRs of MND and of other leading causes of death.

Cause of death	r	p-value
Malig ^a	0.21	0.730
Ulcer ^b	0.77	0.129
Gastritis ^c	-0.64	0.248
Tbc ^d	-0.01	0.983
HTD ^e	-0.50	0.394
Suicide	0.12	0.848
IHD ^f	0.31	0.616
Non-IHD ^g	0.65	0.237
Nephritis ^h	0.90	0.036
DM ⁱ	-0.73	0.158
CVD ^j	0.91	0.033
Pneumonia ^k	-0.49	0.405
Accidents ^l	-0.45	0.453
Cirrhosis ^m	-0.32	0.600
Senility ⁿ	0.00	0.997

^aMalignant neoplasms. ^bUlcer of stomach and duodenum. ^cGastroenteritis. ^dTuberculosis. ^eHypertensive disease. ^fIschemic heart disease. ^gNon-ischemic heart disease. ^hNephritis and nephrotic syndrome. ⁱDiabetes mellitus. ^jCerebrovascular disease. ^kPneumonia and bronchitis. ^lAccidents and adverse effects. ^mChronic liver disease and cirrhosis. ⁿSenility without mention of psychosis.

to now, however, there are no convincing data to show that the above metals are common to the environment in the three foci and that the people there are unusually exposed to these metals. The analysis of food and water in Nansei-cho for metals is in progress in this study group, and the results are to be published elsewhere.

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