Prevalence and Etiology of Dementia in a Japanese Community

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Background and Purpose: We sought to determine the type-specific prevalence of dementia and its risk factors in elderly persons from the Japanese community of Hisayama.

Methods: We studied the prevalence of dementia in 887 Hisayama residents (353 men and 534 women) aged 65 years or older (screening rate, 94.6%) using various items of clinical information, neurological examination, and dementia scales. We also studied brain morphology in 50 of 59 determined to have dementia by computed tomography or autopsy during the subsequent 54-month period. Factors relevant to dementia were compared between 27 patients with vascular dementia and 789 control subjects without dementia in a retrospective fashion.

Results: The prevalence rate of dementia among Hisayama residents aged 65 or older was estimated at 6.7%, with a females to males ratio of 1:2. Among 50 cases of dementia in which brain morphology was examined, the frequency of vascular dementia was 56%; this rate was 2.2 times higher than that for senile dementia of the Alzheimer type. Aging, hypertension, electrocardiographic abnormalities, and high hematocrit were significantly (p<0.05) and independently associated with the occurrence of vascular dementia.

Conclusions: Prevalence of dementia among the Hisayama residents was relatively identical to that previously reported, but vascular dementia was more predominant. Risk factors for vascular dementia were similar to those for lacunar infarcts. Control of hypertension may be a key to reducing dementia among the Japanese population.

KEY WORDS • dementia • epidemiology • Japan • risk factors

The reported prevalence of severe dementia has varied from 1.3% to 6.2% in persons aged 65 years or older, with mild impairment in 4.3–15.4%. Variation in the estimated prevalence may partially be due to methodological differences, such as the differing diagnostic criteria and varying thoroughness of case findings. An additional important issue is the relative variation of diseases causing dementia in the elderly, particularly senile dementia of the Alzheimer type and vascular dementia. Many of the prevalence studies that attempted a clinical differentiation between these two have also demonstrated a discrepancy in the incidence of these two entities. This discrepancy may simply reflect the difficulty of accurate diagnosis.

At present, there are only a few reports that provide prevalence rates of dementia in Japan. It is expected that vascular dementia is more prevalent among the Japanese population than senile dementia of the Alzheimer type because, until the 1970s, cerebrovascular disease was the leading cause of death in Japan.

An epidemiological study of cerebral stroke has been carried out prospectively in a Japanese rural community, Hisayama, since 1961; its chief characteristic is that almost all study subjects have been autopsied at death. In addition, new cases of stroke have been examined by computed tomographic (CT) scan for the past 10 years. The design of this study provides a good opportunity to inquire into the prevalence of dementia by etiology in a Japanese community and, possibly, to analyze risk factors of dementia. Our survey differs from previous Japanese investigations in the following aspects: 1) the brain pathology of the identified cases of dementia was studied by CT scan or postmortem examination during the subsequent period of follow-up, which has enhanced diagnostic certainty, and 2) it was possible to analyze the risk factors of vascular dementia in the general population because previous medical or health data were available for many participants.

Subjects and Methods

Screening and Follow-up

Hisayama is a Japanese rural community adjacent to the city of Fukuoka, the metropolis of Kyushu Island; it has a population of approximately 7,000. In this town, a prospective population study was initiated in 1961 to explore the epidemiology of cerebrovascular disease in a general population sample aged 40 years or older. The
age, occupational, educational, economic, and social composition of the population had been almost identical to that of the whole of Japan according to a 1960 census. The details in characteristics of the town28 and the study design19-20 are given elsewhere. At the time of the national census in 1985, there were 938 Hisayama residents aged 65 years and older (378 men and 560 women). During the 8 months from May to December 1985, we examined a total of 887 subjects from this population (353 men and 534 women) to identify cases of dementia, with a screening rate of 94.6% (men, 93.3%; women, 95.4%). We screened 805 subjects at the regular examination for health checkup of the Hisayama study and examined the remaining 77 by a door-to-door, structured interview. A study physician with 3 years’ experience working in a psychological ward and two trained nurses worked as a team for screening under the direction or surveillance of a psychiatrist. Because five subjects had been admitted to hospitals or institutes, the study physician visited patients and conducted interviews and neurological examinations. Of 51 unexamined subjects, 26 died and 10 moved out of town during the screening period; only 15 refused the examination. According to the 1985 census, the age composition of the study population was almost identical to that of the whole of Japan.

The screening examination included an interview at which inquiries were made about chronic conditions diagnosed by physicians, drugs that had been prescribed, current fitness for work, and the history of limitations due to illness and invalidity. In addition, we obtained information about the subject’s normal daily life activity by asking 13 questions on a checklist. When neurological deficits were seen, we investigated a more detailed history of cerebral stroke and scrutinized various items of medical information, including hospital records, roentgenograms, and laboratory examinations. From Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III),21 we adopted the primary scale to determine dementia; we used Karasawa’s criteria for clinical evaluation of elderly dementia22 as supplementation. The latter has been widely used throughout Japan and divides cases with dementia into four grades of severity according to loss of intellectual abilities, severity of interference with social and occupational functioning, and inability to care for oneself. Psychological symptoms were estimated by checking 12 items such as memory impairment and delirium, and by checking 13 abnormal behaviors such as aggressiveness and dirtiness. Hasegawa’s dementia rating scale,23 comprising 11 questions to test memory, cognitive, and calculation capacities, was also used to define demented cases. Each question has an independent score, the sum of which ranges from 0 to 32.5. This procedure is similar to that in the Mini-Mental State test.24 We suspected that subjects had mild dementia if the sum of the scores was less than 20.0 and severe dementia if the sum was less than 10.0. An ischemic score by the method of Hachinski et al25 was applied to all cases with dementia to discriminate vascular dementia from senile dementia of the Alzheimer type. We suspected that patients had senile dementia of the Alzheimer type if Hachinski’s ischemic score was less than 4.0 and vascular dementia if it was greater than 8.0. The cases in which the ischemic score fell between 5.0 and 7.0 were classified as “mixed type” or “other.” The final diagnosis of dementia was made by the panel of study physicians, including a psychiatrist referring to collected data.

During the 8-month period from May to December 1985, we detected 59 cases of dementia out of 887 subjects aged 65 years or older among the Hisayama residents. All patients with dementia were followed up by the usual surveillance methods of the Hisayama study,26 and when patients died, autopsies were performed at the Department of Pathology of Kyushu University. Brain was cut at 1-cm intervals, and specimens were taken from 14 areas of the bilateral frontal, temporal, parietal, and occipital lobes; hippocampus; basal ganglia; and thalamus. Paraffin-embedded specimens were stained for neuropathology. Hematoxylin and eosin, periodic acid-Schiff, Mallory-Weismann, Bodian, and Congo red; the immunological method using amyloid antibodies was used to determine the presence of amyloid core. Neuropathologists determined the final diagnosis for the type of dementia, and we have discussed the accuracy of diagnosis in the clinical pathological conference. If new cerebral strokes occurred or patients were institutionalized during the follow-up, we gathered medical information concerning illness and referred to hospital records. A CT study was made at least once after the screening in almost all patients, mainly using CT (Toshiba) with 5-cm slices. Dementia was classified by its etiology into the following three types: vascular dementia, senile dementia of the Alzheimer type, and other (including mixed type). Moderate-to-severe brain atrophy with neither vascular lesions nor asymmetrical ventricular dilation and with or without periventricular lucency on CT scan was considered to indicate senile dementia of the Alzheimer type. A CT finding of diffuse periventricular lucency or leukoaraiosis27 only was not regarded as sufficient proof of vascular dementia. In pathology, senile dementia of the Alzheimer type was diagnosed by findings of both senile plaques and neurofibrillary tangles (paired helical filament) (at least found in each three microscopic areas in the half of specimens). This report presents the results obtained during the period of 4 years and 6 months from January 1986 to July 1990. A significant level for statistical difference was set at \( p < 0.05 \) based on the Mantel-Haenszel \( \chi^2 \) with two-tailed test after controlling for age.28

**Analysis of Risk Factors**

To elucidate the risk factors of vascular dementia or senile dementia of the Alzheimer type, we collected the following data on the screened population from the previous health checkup retrospectively: systolic and diastolic blood pressures, body mass index [weight/height\(^2\)], serum total cholesterol, hematocrit, electrocardiographic abnormalities (Minnesota code III, and/or IV-\(\alpha\)), glucose intolerance,29 drinking habits (consumed 34 g or more of ethanol a day), smoking habits (smoked 10 cigarettes or more a day), and history of hypertension. Because the date of the onset of clinical dementia could not necessarily be determined in all cases, we obtained such data from the records of the regular examinations in 1973-1974, or if data were lacking, in 1978, which were at a 12- or 7-year interval from the present screening, respectively. We made a comparison
of risk factors between nondemented cases (controls) and cases with vascular dementia or senile dementia of the Alzheimer type by analysis of covariance (Bonferroni), but because of the small number of cases with senile dementia of the Alzheimer type, analysis of risk ratio or multivariate analysis was performed only between controls and cases with vascular dementia.

Relative risks were expressed in odds ratios after controlling for age and sex by the Mantel-Haenszel \( \chi^2 \) test, in which continuous variables were categorized as follows: systolic blood pressure \( \geq 160 \) mm Hg and/or diastolic blood pressure \( \geq 95 \) mm Hg was defined as hypertension, serum total cholesterol \( \geq 180 \) mg/dl as hypercholesterolemia, body mass index \( \geq 25.4 \) as obesity, and hematocrit \( \geq 45\% \) as high hematocrit.

To evaluate an independent risk factor of vascular dementia, we used the multiple logistic regression model of Walker and Duncan, in which appropriately determined scores were assigned for ordinal variables (males, 1; females, 2; absence, 0; presence, 1), and continuous variables were entered directly into the equation. Two-tailed probability of <0.01 or <0.05 was judged as the significance level for statistics.

### Results

Table 1 presents the age- and sex-specific prevalence of dementia in Hisayama residents aged 65 years and older at the screening. Prevalence progressively increased with advancing age for both sexes and showed prominently high rates beyond the age of 80 years; more than one third of the surviving patients aged 85 years or older suffered from dementia. After the age composition of the study population was adjusted to that of the whole of Japan, the prevalence of dementia among the Hisayama residents aged 65 years and older was 57.4/1,000 for men and 70.0/1,000 for women, with the female: male ratio of 1:2 not significant in difference.

We examined the brain morphology of 50 cases with dementia out of 59 (85\%) by postmortem examination or CT scan during the 54-month period from January 1986 to July 1990 (Table 2). Thirty-four patients died, 32 of whom were autopsied; CT examination only was performed in the remaining 18 cases. Table 2 demonstrates coincidence rates of clinical diagnoses of diseases causing dementia at the screening compared with those determined by brain morphology. An agreement between the two was obtained in 19 of 21 patients with vascular dementia (90.5\%) and in five of eight with senile dementia of the Alzheimer type (62.5\%) but only in six of 21 (28.6\%) with dementia classified as other (including mixed type). Fifteen cases initially diagnosed as other were confined to the clinical diagnosis of mixed type because there was a lack of definite episodes of stroke or the degree of dementia was not severe enough for diagnosis as senile dementia of the Alzheimer type (Hasegawa's score >10.0). Eight cases of mixed type were classified into vascular dementia and seven into senile dementia of the Alzheimer type afterward on the basis of the morphological diagnosis. Vascular dementia accounted for 56\% of the morphologically diagnosed cases of dementia in both sexes, senile dementia of Alzheimer's type for 26\%, and other for 18\%, with a ratio of vascular dementia to senile dementia of the Alzheimer type of 2.2 for both sexes. Two patients with subdural hematoma, two with head injury, one with normal-pressure hydrocephalus, and one with Parkinson's disease were included in the category of other.

Of the 28 patients finally determined to have vascular dementia, 20 had clinical episodes that were considered cerebral stroke. Using clinical histories, CT scan, or

### Table 1. Prevalence of Dementia in Residents of Hisayama, Japan, Aged 65 Years and Older, 1985

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Subjects</th>
<th>Cases</th>
<th>Rate/1,000</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>65–69</td>
<td>118</td>
<td>2</td>
<td>16.9</td>
<td></td>
</tr>
<tr>
<td>70–74</td>
<td>108</td>
<td>4</td>
<td>37.0</td>
<td></td>
</tr>
<tr>
<td>75–79</td>
<td>68</td>
<td>1</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>80–84</td>
<td>47</td>
<td>7</td>
<td>148.9</td>
<td></td>
</tr>
<tr>
<td>85+</td>
<td>12</td>
<td>5</td>
<td>416.7</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>353</td>
<td>19</td>
<td>53.8</td>
<td></td>
</tr>
</tbody>
</table>

**Age composition was adjusted to that of the whole of Japan in 1985. CI, confidence interval.**

### Table 2. Coincidence Rates of Type Diagnosis for Dementia Between Clinical Scales and Brain Pathology in Hisayama, Japan, 1985–1990

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>No. cases examined</th>
<th>Final (morphological) diagnosis</th>
<th>Vascular dementia</th>
<th>SDAT</th>
<th>Other</th>
<th>Coincidence rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular dementia</td>
<td>21</td>
<td>19*</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>90.4</td>
</tr>
<tr>
<td>SDAT</td>
<td>8</td>
<td>2</td>
<td>5*</td>
<td>1</td>
<td>6*</td>
<td>62.5</td>
</tr>
<tr>
<td>Other</td>
<td>21</td>
<td>7</td>
<td>8</td>
<td>6*</td>
<td></td>
<td>28.6</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>28</td>
<td>13</td>
<td>9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Coincidence rates: asterisked numbers/examined cases. SDAT, senile dementia of the Alzheimer type.
autopsy findings, the type of cerebral infarction was determined (Table 3). Small multiple infarcts were present in 13 cases (46%), cerebral embolism in seven (25%), large infarcts in three, small solitary infarcts in two, Binwanger's disease in two, and intracerebral hemorrhage in one case. Binwanger's disease was diagnosed by findings of extensive periventricular lucency on CT scan, rapid deterioration of clinical course, and severe small intracerebral vascular lesions at autopsy. Small multiple infarcts were much more frequent in those aged 80 years or older, totaling 62 lesions. Their location on the brain was as follows, in order of frequency: 24 in the basal ganglia, nine in the temporal lobe, nine in the frontal lobe, seven in the occipital lobe, three on thalamus, and 10 in other regions.

Data obtained before the onset of dementia were available in 27 of 28 patients with vascular dementia and in 12 of 13 patients with senile dementia of the Alzheimer type. In addition, data at the regular examination in 1973–1974 or in 1978 were obtained in 789 of 828 control subjects (95%). Table 4 presents the average values and standard deviations of several parameters with continuous quantity for vascular dementia, senile dementia of the Alzheimer type, and control groups. The average age was significantly higher for patients with vascular dementia than for control subjects. Average blood pressures (including systolic, diastolic, and mean) were significantly greater in patients with vascular dementia than in control subjects.

Table 4 demonstrates risk ratio (odds ratio) and a 95% confidence interval for vascular dementia for each variable. In the case of systolic or diastolic pressure, mean blood pressure was selected as a variable. Age, electrocardiographic abnormalities, and high hematocrit were considered independent and significant risk factors for vascular dementia. The standardized coefficient of mean blood pressure was relatively large, and its probability value showed borderline significance.

### Discussion

The prevalence rate of dementia for those ≥65 years of age in our study was 6.7%, which included severe dementia in 2.4% and mild dementia in 4.3%. Our figures are relatively similar to those previously reported, except the study of Pfeffer et al., which reported a higher prevalence rate. This study was, however, designed for persons in the retirement community and was recently criticized for its acceptance of some cases on the basis of psychometric tests only, which artificially elevated the rates in that population.

Surveillance of dementia has been carried out in several municipalities in Japan since 1980, in which Karasawa's criteria for clinical evaluation of elderly dementia is commonly or widely used. With the
TABLE 6. Risk Factors for Vascular Dementia in Hisayama, Japan, Analyzed by Multiple Logistic Regression

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Standardized coefficients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.672</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex</td>
<td>0.176</td>
<td>0.605</td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td>0.452</td>
<td>0.051</td>
</tr>
<tr>
<td>ECG abnormalities</td>
<td>0.524</td>
<td>0.005</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.131</td>
<td>0.611</td>
</tr>
<tr>
<td>Serum total cholesterol</td>
<td>-0.231</td>
<td>0.361</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.706</td>
<td>0.013</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>0.090</td>
<td>0.766</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>-0.313</td>
<td>0.374</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>-0.166</td>
<td>0.548</td>
</tr>
</tbody>
</table>

ECG, electrocardiographic.

The relative importance of rates of vascular dementia and senile dementia of the Alzheimer type differed significantly from one study to another. Two Finnish studies showed rates of senile dementia of the Alzheimer type higher than those of vascular dementia. Jorm et al reported from the integration of the literature that the US studies showed no significant difference, whereas many studies from other western countries revealed a higher rate of senile dementia of the Alzheimer type than vascular dementia. The prevalence rates of dementia by etiology obtained from Japanese surveys were very similar, with those of vascular dementia higher than those of senile dementia of the Alzheimer type. It is uncertain whether the higher prevalence of vascular dementia derives from the specificity of the Japanese. In our study, approximately 50% of the cases initially diagnosed as other (including mixed type) fell into the categories of vascular dementia and senile dementia of the Alzheimer type, according to brain morphology. They were at first considered to be mixed type because of the lack of clear episodes of cerebral stroke, low grade on Hachinski's ischemic scores and greater number of aged subjects with moderately impaired dementia. More than 60% of those were found to have multiple infarcts at autopsy or on CT scan. It is doubtful whether multiple infarcts have contributed to the development of dementia, even though morphological evidence of senile dementia of the Alzheimer type, such as senile plaques or neurofibrillary tangles, was absent. Infarcts were localized in the cortex or subcortex in the frontal, temporal, and occipital lobes and in the thalamus and putamen, but there was no systematic or regulatory distribution. Tomlinson suggested that the loss of 50 ml or more of cerebral volume as a result of infarction could cause dementia. A clinical and autopsy study of dementia in Olmsted County, Minnesota, indicated that when cerebral infarction was suggested as the cause of dementia, in very few cases was there autopsy evidence of cerebral infarction large or extensive enough to cause dementia. Hachinski et al stressed the importance of the existence of leukoaraiosis on the CT scan as evidence of vascular dementia, which suggests demyelination in this area resulting from poor perfusion. It was originally and generally held that the combination of the severe penetrating vessel disease with hypoperfusion in the watershed area produced the pathological picture ofBinswanger's disease, which is associated with recurrent brief focal neurological deficits and features a progressive dementia. However, a recent report indicated that leukoaraiosis was observed in approximately 30% of patients identified as having senile dementia of the Alzheimer type. It is possible, therefore, that in one third or more of elderly patients identified as having senile dementia of the Alzheimer type, a vascular process is affecting the white matter and contributing to the recognition of the occurrence of dementia (mixed type). Intracerebral small vascular lesions, particularly on perforating arteries, are probably caused by angioneurotic (which is more closely related to hypertension) and by lipohyalinosis (probably induced by the arteriosclerotic process). However, pathological examination could not necessarily differentiate hypertensive lesions from arteriosclerotic processes because there is an overlapping of pathological findings between the two.

In the present study, aging, hypertension, electrocardiographic ST-T changes, and high hematocrit were perceived to be risk factors for vascular dementia. These factors can be associated with developments of both hypertensive and arteriosclerotic lesions. Risk factors for lacunar infarction of the autopsy series from Hisayama residents were aging, hypertension, high R or ST-T electrocardiographic changes, atrial fibrillation, and glucose intolerance. These are relatively similar to the risk factors for vascular dementia. High hematocrit possibly induces hypoperfusion because of increased viscosity of blood, and atrial fibrillation does so through decreased cardiac output. Long-term exposure to hypertension or diabetes mellitus results in not only the acceleration of atherosclerosis but also the enhancement of arteriolar lesions. From this aspect, the question of measures to prevent vascular dementia might come back to the question of how to prevent arteriosclerosis, a disorder for which no successful procedures have yet been discovered.

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