Prevalence of Dementia and Dementing Diseases in Japan

The Tajiri Project

Kenichi Meguro, MD, PhD; Hiroshi Ishii, MD; Satoshi Yamaguchi, MD, PhD; Junichi Ishizaki, PhD; Masumi Shimada, PhD; Mari Sato, MSc; Ryusaku Hashimoto, MSc; Yoichi Shimada, MSc; Mitsue Meguro, BA; Atsushi Yamadori, MD, PhD; Yasuyoshi Sekita, PhD

Background: Vascular dementia (VaD) has been considered to be more prevalent than Alzheimer disease in Japan. However, this might be the result of overdiagnosis stemming from some problematic diagnosis of VaD or of the frequent use of magnetic resonance imaging to detect cerebrovascular disease in older adults.

Objectives: We investigated the prevalence of dementia and the ratios of dementing diseases. The effects of different criteria for VaD (DSM-IV, Alzheimer’s Disease Diagnostic and Treatment Centers [ADDTC], and National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences [NINDS-AIREN]) were considered. Hippocampal atrophy and vascular contribution to dementia were evaluated using magnetic resonance imaging findings.

Methods: We targeted all residents 65 years and older (n=3207) in Tajiri, Japan, and examined 1654 (participant group 1). Of these, 564 (participant group 2) were randomly selected, and 497 underwent magnetic resonance imaging and diagnosis of dementing diseases.

Results: We found the overall prevalence of dementia to be 8.5% (141/1654) in participant group 1. Of these, 21 (14.9%) had a history of stroke. Of the 113 participants who had a history of stroke independent of dementia, 18.6% (21/113) were demented. For participant group 2 (n=497), 32 were demented. The ratio among the dementia for probable VaD based on the NINDS-AIREN criteria was 18.8% (6/32), whereas that for ischemic vascular dementia was 31.3% (10/32) according to the ADDTC criteria.

Conclusion: We confirmed the overall prevalence of dementia in adults 65 years and older to be 8.5%. We found that VaD was not a common disorder according to the NINDS-AIREN criteria. Rather, the condition of possible Alzheimer disease with cerebrovascular disease was more common.

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For countries with large populations of older adults, knowledge of the prevalence of dementia is needed for health policy planning. Most studies reported the prevalence to be greater with older age.1,2 Vascular dementia (VaD), rather than Alzheimer disease (AD), has been believed to be the most common dementing condition in Japan.3 However, the diagnostic criteria for VaD are problematic. The DSM-IV4 requires “laboratory evidence indicative of cerebrovascular diseases that are judged to be etiologically related to the disturbance” for a diagnosis of VaD. Confirmation of etiologically related cerebrovascular disease (CVD) requires sophisticated neurological knowledge.

Also, the higher prevalence of suspected “vascular lesions,” which are frequently detected as high-signal intensity on T2-weighted magnetic resonance imaging (MRI) findings,3 might result in overdiagnosis. Because of the increasingly common practice of performing MRI, some patients might have received a diagnosis of VaD simply because they were demented and had CVD.

Other criteria were developed in an attempt to overcome this problem. The Alzheimer’s Disease Diagnostic and Treatment Centers (ADDTC) criteria5 require evidence of 2 or more strokes or a single stroke with a clear temporal relationship to the onset of dementia. The criteria of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN)7 state that a causal relationship between CVD and dementia is required for a diagnosis of VaD and propose that the conditions under which patients with dementia and concomitant CVD may be considered to have possible AD with CVD. We suspect that many
PARTICIPANTS AND METHODS

PARTICIPANT GROUP 1

Based on the Tajiri Project, a community-based study on stroke, dementia, and bed-confine ment prevention in Tajiri, a typical agricultural area in northern Japan,2-11 we targeted all residents 65 years and older (N=3207). We did not use a screening test design; the survey included Clinical Dementia Rating (CDR) assessments,12 dementia diagnosis, and results of a neuropsychological examination (not reported herein). The survey requested agreement for all components.

We included 1654 participants (51.6%) in the study. The participants/population for each age group were 404/1066 (65-69 years), 560/856 (70-74 years), 348/607 (75-79 years), 212/397 (80-84 years), and 130/281 (≥85 years). The reasons for refusal to participate were mainly psychological (25.6%) and physical (14.6%). Each age group satisfied the statistically sufficient number for the confidence interval to be 95%, provided that the prevalence of dementia was 10%.

Home interviews were performed for 87 participants. Fifteen participants were reported by families to be confined to bed; 8 of these participants, however, were able to maintain a sitting position without support. A medical history of stroke was present in 113 (6.8%) of the 1654 participants.

PARTICIPANT GROUP 2

From among the population of 1654, 564 adults were randomly selected to undergo MRI. The cost of all MRIs was officially paid for by the town government (about $300 per person). Finally, 497 participants agreed to undergo MRI. Figure 1 illustrates the study design. Written informed consent was obtained from all healthy participants and from the family members of patients with dementia.

MAGNETIC RESONANCE IMAGING

Using MRI (1.5 T; SIERA, GE-YMS, Japan), we evaluated hippocampal atrophy and CVD lesions, since both are important for the diagnosis of dementia.

For hippocampal assessment, the T1-weighted (repetition time/echo time, 400/14 ms) plane along the long axis of the hippocampus showing the measurement point described by Jobst et al13 was selected.14 Using the semiaxial plane, we measured the minimum width of the hippocampus13 and divided by the brain width on the same plane (defined here as the hippocampal width [HippW]).14 The HippW (given as a percentage) was measured by 2 board-certified neuroradiologists independent of this study. Each neurologist made 2 assessments. The interreader and intrareader reproducibilities were calculated as follows:

\[ 1 - \frac{(\text{HippW}_1 - \text{HippW}_2)/2}{(\text{HippW}_1 + \text{HippW}_2)/2} \]

For the interreader reproducibility, HippW1 and HippW2 were assessed by 2 neurologists. For the intrareader reproducibility, HippW1 and HippW2 were assessed by the same neurologist. Both results were better than 95%.

For the CVD evaluation, the combined axial T1-weighted and T2-weighted (repetition time/echo time, 3000/90 ms) images were used. Lesions were considered to be CVD when they showed low intensity on the T1-weighted MRI and high intensity on the T2-weighted MRI at the same location. We operationally classified CVD into the following 3 categories: (1) those smaller than 4 mm in size (defined here as etat crible), (2) those 4 to 8 mm (small CVD), and (3) those larger than 8 mm (large CVD).15 We counted the CVD numbers and assessed the moderate and large CVD distributions. After independent assessment by the 2 neurologists, the final evaluation was made by a third senior neurologist (K.M.).

ANALYSIS OF PARTICIPANT GROUP 1

We calculated the prevalence of dementia for both sexes in each age group. For the effect of educational level, participants were classified into the following 3 groups according to the old Japanese system: 6, 8, and 10 or more years of schooling. Dementia was diagnosed by means of the DSM-IV criteria. Severity of CDR was decided by a clinical team consisting of a psychiatrist, neurologists, and public health nurses. They assessed the subjects’ mental status by asking them about their daily lives and family situations. The patients with dementia exhibited a CDR rating of 1 or greater. Using the 113 participants who had a history of stroke, the prevalence of poststroke dementia was also calculated. For MRI measures, we evaluated the HippW of each CDR and age group and the prevalence of CVD.

ANALYSIS OF PARTICIPANT GROUP 2

For the patients with dementia (diagnosed by means of the DSM-IV criteria), we analyzed the dementing diseases using the following criteria: (1) DSM-IV for dementia of the Alzheimer type (DAT), (2) DSM-IV for VaD, (3) National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer’s Disease and Related Disorders Association16 for probable AD, (4) NINDS-AIREN for possible AD with CVD, (5) NINDS-AIREN for probable VaD, and (6) ADDTC for probable ischemic vascular dementia (IVD).

Based on a previous study,8 the presence of focal neurological signs for the diagnosis of VaD included at least 1 of the following: hemianopia, lower facial weakness, dysarthria, motor or sensory hemisindrome, hemiplegic gait, or a positive Babinski sign.

Since the poor interchangeability of the criteria for VaD was reported,8 we used only the probable criteria. Patients received a diagnosis of possible AD with CVD by means of the NINDS-AIREN criteria, provided that the vascular effect on dementia was considered to be too ambiguous to diagnose as VaD.

The Hachinski Ischemic Scale (HIS)17 was also used to evaluate the possible effect of differential diagnosis. For MRI measures, regional CVD distribution in dementia was also evaluated.
Since we suspected that the previously reported high prevalence of VaD in Japan was due to overdiagnosis, we sought to confirm this low interchangeability of the criteria by means of a community-based study. Therefore, we examined MRI findings in older adults in a community for the prevalence of dementia and the ratios of dementia diseases, with a focus on VaD.

RESULTS

PARTICIPANT GROUP 1

Figure 2 illustrates the prevalence of dementia. Overall, 64 (9.2%) of 694 male participants and 77 (8.0%) of 960 female participants received a diagnosis of dementia; 141 (8.5%) of 1654 participants had dementia.

For the effect of educational level, the prevalence of dementia was 15.5% (38/245), 7.7% (89/1157), and 5.6% (14/252) for the groups with 6, 8, and 10 or more years of schooling, respectively.

For the prevalence of VaD, the numbers were 0.4±0.1(CDR,0), 0.6±0.1(CDR,0.5), and 1.1±0.2(CDR, ≥1). We found a significant CDR effect (F = 15.635; P < .001).

For small CVD, the numbers were 0.5±0.3(CDR,0), 4.1±0.3(CDR,0.5), and 3.8±0.5(CDR,0.5), and 6.6±1.1(CDR, ≥1). Results of 1-way analysis of variance (ANOVA) showed no significant CDR effect (F=15.635; P=.002) without an interaction between CDR and age groups.

Data are expressed as mean ± SE. Two-way analysis of variance showed a significant Clinical Dementia Rating (CDR) group effect (F = 6.568; P = .001) without an interaction between CDR and age groups.

PARTICIPANT GROUP 2

Thirty-two participants received a diagnosis of dementia. Figure 3 shows the dementia diseases. The ratios of probable AD, possible AD with CVD, and probable VaD are shown. For these 3 diagnoses, the 2 neurologists were in perfect agreement. The prevalence of VaD was not as common as previously believed. The most common condition was possible AD with CVD. Other conditions included frontotemporal dementia,18 dementia with Lewy bodies,19 hypoxic encephalopathy, posttraumatic dementia, and alcoholic dementia.

Although the diagnoses by the 2 neurologists of the 3 conditions described in the previous paragraph were in agreement, the condition of possible AD with CVD was heterogeneous. As given in Table 2, this condition can be classified into 3 subgroups.

Subgroup 1

Patients in this subgroup had probable AD with concomitant, nonstrategic CVD. They met the DSM-VI criteria for DAT, but did not meet the ADDTC criteria for IVD. The 2 neurologists completely agreed.
Both possibilities existed (described as DAT/VaD).

CVD, 6 patients with a diagnosis of VaD (by means of NINDS-AIREN criteria) met the ADDTC criteria for IVD.

The mean±SE HIs values were 2.2±0.8, 4.1±0.5, and 6.7±0.8 for the groups with probable AD, possible AD with CVD, and probable VaD, respectively. Results of 1-way ANOVA disclosed a significant group effect (F = 7.664; P = .003), with the post hoc test showing a higher VaD score compared with the probable AD score (P = .004).

The HippWs (left-right mean±SE) were 8.4%±1.0%, 6.0%±0.6%, and 8.7%±1.0% for the groups with probable AD, possible AD with CVD, and probable VaD, respectively. Results of 1-way ANOVA disclosed a significant group effect (F = 3.782; P = .04) with no effect of age, with the post hoc test showing a smaller tendency of possible AD with CVD compared with that of probable VaD (P = .08).

As for the regional CVD distribution for dementia with CVD, 6 patients with a diagnosis of VaD (by means of NINDS-AIREN criteria) met the ADDTC criteria for IVD and the DSM-IV criteria for VaD. The 2 neurologists were in perfect accordance as to the VaD diagnosis for these patients. The patients tended to have CVD in bilateral basal ganglia regions, except for the putamen, or at least unilateral large cortical CVD. For the groups with AD and CVD, mostly nonstrategic areas were affected by CVD.

Subgroup 2

Patients in this group did not meet the ADDTC criteria for probable IVD, and the 2 neurologists did not completely agree on the DSM-IV-based diagnosis of DAT or VaD. Thus, both possibilities existed (described as DAT/VaD).

Subgroup 3

Patients in this group met the ADDTC criteria for probable IVD. There was complete agreement by the 2 neurologists, despite the fact that the NINDS-AIREN criteria for VaD were not satisfied. No complete agreement was obtained for the DSM-IV criteria, as with subgroup 2.

The increasing prevalence of dementia with age easily leads to the misconception that dementia is inevitable with aging.22 However, a meta-analysis of epidemiological studies23 concluded that dementia is better conceptualized as an “age-related” rather than an “aging-related” disorder. Results of neuropsychological investigations of healthy older adults31 and longitudinal25 studies on screening test performances during a 5-year period support that idea. However, further investigation is needed for the oldest old population or for the longitudinal incidence.

The prevalence of dementia was high in those with lower levels of education. Although the effect of education has not been fully analyzed compared with that of age, analysis of all such effects has disclosed the preva-
lence to be high in subjects with lower levels of education. Mortimer and Graves suggested that education could induce dendritic growth and that more highly educated people are protected to some degree against AD. However, Filley et al found no protective effect of education. Moreover, educational level may merely be a marker of other socioeconomic determinants such as nutrition. Further investigation is needed to clarify this point.

DEMENTING DISEASES IN JAPAN

Our results showed possible AD with CVD to be the most common dementing condition in Japan, contrary to the previous assumption that VaD is the most common dementing condition in Japan. As described earlier, the different criteria for VaD are not interchangeable. The biggest reason is the difficulty in identifying the type of CVD responsible for dementia. Participants with AD and CVD in subgroups 1 and 2 did not meet the ADDTC criteria for IVD, but met the DSM-IV criteria for DAT, since the vascular effect on dementia was considered to be too ambiguous to diagnose as IVD.

Confirmation of this etiologically related CVD requires sophisticated neurological knowledge. With recent developments of MRI technology, even small signal abnormalities can be easily detected. Some are apparently etat crible or perivascular space dilatation. A nonspecialist might easily misdiagnose this condition as VaD simply because the patient was demented and showed MRI abnormalities. The lower prevalence of VaD was supported by the analysis of poststroke dementia. These participants met the NINDS-AIREN criteria for possible VaD. However, we could not rule out the possibility that some residents who had refused to participate owing to physical reasons might be affected by VaD.

Another possibility is that the prevention of CVD has at least been partially successful in Japan, subsequently resulting in a lower prevalence of VaD compared with those of previous reports. Kiyohara et al compared 2 surveys of residents of Hisayama, Japan, conducted in 1985 and 1992. The overall prevalence of dementia was decreased from 5.4% to 3.3% for men and 7.5% to 6.3% for women. The prevalence of AD was the same for both sexes. A longitudinal incidence study is planned for participant group 1.

VASCULAR CONTRIBUTIONS TO DEMENTIA

The results indicate that etat crible was related to aging but not to dementia. Instead, the numbers of small or large CVD had some effect on dementia. The results of CVD distributions indicated that bilateral involvement of the basal ganglia region, except for the putamen, or at least unilateral cortical CVD, is associated with dementia. Global neural disconnection based on even subcortical vascular lesions might be associated with VaD, such as in AD as a disconnection syndrome. Global cortical glucose use was related to cognitive decline.

Although the number of patients with dementia was small, we found that the HIS and the HippW were effec-

### Table 2. Regional CVD in Patients With Possible AD With CVD and VaD

<table>
<thead>
<tr>
<th>Patient No./Age, y/Sex</th>
<th>NINCDS/NINDS (Subgroups)†</th>
<th>ADDTC‡</th>
<th>DSM-IV/Diagnosis</th>
<th>CVD Regions, Mild and Definite§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HIS Right</td>
</tr>
<tr>
<td>1/69/M</td>
<td>AD with CVD (1)</td>
<td>No</td>
<td>DAT</td>
<td>3</td>
</tr>
<tr>
<td>2/77/M</td>
<td>AD with CVD (1)</td>
<td>No</td>
<td>DAT</td>
<td>4</td>
</tr>
<tr>
<td>3/81/F</td>
<td>AD with CVD (1)</td>
<td>No</td>
<td>DAT</td>
<td>4</td>
</tr>
<tr>
<td>4/87/F</td>
<td>AD with CVD (1)</td>
<td>No</td>
<td>DAT</td>
<td>4</td>
</tr>
<tr>
<td>5/79/F</td>
<td>AD with CVD (2)</td>
<td>No</td>
<td>DAT/VaD</td>
<td>3</td>
</tr>
<tr>
<td>6/66/F</td>
<td>AD with CVD (2)</td>
<td>No</td>
<td>DAT/VaD</td>
<td>4</td>
</tr>
<tr>
<td>7/87/F</td>
<td>AD with CVD (2)</td>
<td>No</td>
<td>DAT/VaD</td>
<td>6</td>
</tr>
<tr>
<td>8/82/F</td>
<td>AD with CVD (2)</td>
<td>No</td>
<td>DAT/VaD</td>
<td>3</td>
</tr>
<tr>
<td>9/84/F</td>
<td>AD with CVD (2)</td>
<td>No</td>
<td>DAT/VaD</td>
<td>10</td>
</tr>
<tr>
<td>10/90/M</td>
<td>AD with CVD (2)</td>
<td>No</td>
<td>DAT/VaD</td>
<td>3</td>
</tr>
<tr>
<td>11/87/F</td>
<td>AD with CVD (3)</td>
<td>IVD</td>
<td>DAT/VaD</td>
<td>5</td>
</tr>
<tr>
<td>12/88/F</td>
<td>AD with CVD (3)</td>
<td>IVD</td>
<td>DAT/VaD</td>
<td>3</td>
</tr>
<tr>
<td>13/82/M</td>
<td>AD with CVD (3)</td>
<td>IVD</td>
<td>DAT/VaD</td>
<td>3</td>
</tr>
<tr>
<td>14/83/M</td>
<td>AD with CVD (3)</td>
<td>IVD</td>
<td>DAT/VaD</td>
<td>4</td>
</tr>
<tr>
<td>15/83/F</td>
<td>VaD</td>
<td>IVD</td>
<td>VaD</td>
<td>9</td>
</tr>
<tr>
<td>16/86/M</td>
<td>VaD</td>
<td>IVD</td>
<td>VaD</td>
<td>9</td>
</tr>
<tr>
<td>17/85/F</td>
<td>VaD</td>
<td>IVD</td>
<td>VaD</td>
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<tr>
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<td>IVD</td>
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</tr>
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<td>VaD</td>
<td>IVD</td>
<td>VaD</td>
<td>6</td>
</tr>
<tr>
<td>20/83/F</td>
<td>VaD</td>
<td>IVD</td>
<td>VaD</td>
<td>3</td>
</tr>
</tbody>
</table>

*Defined by the criteria of the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN). CVD indicates cerebrovascular disease; AD, Alzheimer disease; VaD, vascular dementia; NINCDS, National Institute of Neurological and Communicative Disorders and Stroke; ADDTC, Alzheimer’s Disease Diagnostic and Treatment Centers; HIS, Hachinski Ischemic Scale; HippW, hippocampal width; BG, basal ganglia; WM, white matter; Cx, cortex; DAT, dementia of the Alzheimer type; ellipses, no CVD; and IVD, ischemic vascular dementia.

†Subgroups are explained in the “Participant Group 2” subsection of the “Results” section.

‡The CVD numbers in the putamen are shown in parentheses; 1 (1) means 1 CVD in the BG area (except for the putamen) and 1 CVD in the putamen.
tive for distinguishing VaD or possible AD with CVD from other dementing conditions. The HIS was effective for separating VaD from probable AD. The HippW was smallest in the group with possible AD with CVD compared with probable VaD. This finding suggests that hippocampal atrophy was caused by AD traits and vascular lesions. The hippocampus is vulnerable to degenerative and general conditions.31

Two extreme concepts regarding CVD and dementia are possible. One is that there is no concept for VaD. As a matter of course, large infarctions can affect 2 or more cognitive domains, thus resulting in satisfaction of the criteria of VaD. However, small infarctions should not be considered as primary dementing conditions. What was previously considered as VaD is actually additional CVD in background AD pathologic characteristics resulting in the progression of dementia pathogenesis. Therefore, all VaD should be categorized as possible AD with CVD. The Nun study32 found that the vascular contribution to dementia was not primary but additive to the background AD pathologic traits.

An alternative is that the vascular factor should be considered as primary. The effectiveness of the HIS found in this study supports that concept. Central executive dysfunction could be the hallmark symptom of VaD,33 as memory impairment is of AD. Hachinski and Bowler34 proposed the concept of vascular cognitive impairment, whereas Erkinjuntti et al35 presented criteria for subcortical VaD. A further investigation based on extensive neuropsychological examination is needed to clarify this subject.

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Corresponding author and reprints: Kenichi Meguro, MD, PhD, Division of Neuropsychology, Department of Disability Medicine, Tohoku University Graduate School of Medicine, 2-1, Seiryō-machi, Aoba-ku, Sendai 980-8575, Japan (e-mail: meg@mail.cc.tohoku.ac.jp).

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