Prevalence and Causes of Early-Onset Dementia in Japan
A Population-Based Study

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Background and Purpose—Few studies are available that have addressed the prevalence of early-onset dementia (EOD), including early-onset Alzheimer disease and other forms of dementia in Japan.

Methods—A 2-step postal survey was sent to all of the 2475 institutions providing medical or care services for individuals with dementia in Japan’s Ibaraki prefecture (population, 2 966 000) requesting information on EOD cases. Data were then reviewed and collated.

Results—We identified 617 subjects with EOD. The estimated prevalence of EOD in the target population was 42.3 per 100 000 (95% CI, 39.4 to 45.4). Of the illnesses that cause EOD, vascular dementia was the most frequent (42.5%) followed by Alzheimer disease (25.6%), head trauma (7.1%), dementia with Lewy bodies/Parkinson disease with dementia (6.2%), frontotemporal lobar degeneration (2.6%), and other causes (16.0%).

Conclusions—The prevalence of EOD in Japan appeared to be similar to that in Western countries with the notable exception that vascular dementia was the most frequent cause of EOD in Japan. (Stroke. 2009;40:2709-2714.)

Key Words: early-onset dementia ■ prevalence ■ vascular dementia

Patients with onset of dementia before the age of 65 years, defined as early-onset dementia (EOD), endure significant personal psychological problems and are responsible for a considerable societal economic burden. Clinicians have been urged to improve their recognition of, familiarity with, and understanding of EOD.1

In Japan, previous studies of EOD have reported relatively small sample sizes due to inclusion of patients assessed only at hospitals and memory clinics.2–4 To more accurately estimate the prevalence of EOD as well as the individual diseases responsible, it is necessary to include all diagnosed cases in a region. Therefore, we aimed to estimate the prevalence of EOD in Japan by a 2-step survey capturing all known cases in a single large prefecture. This study was approved by the ethics committee of the University of Tsukuba and conducted with the aid of the Department of Health and Welfare of Ibaraki Prefecture.

Materials and Methods
The study was conducted in Ibaraki Prefecture, which is located 30 km north of the Tokyo metropolitan area, and has a population of approximately 2 966 000. This is the 11th largest of the 47 prefectures with an equal ratio of males and females and equivalent demographic composition to other prefectures in terms of proportion of working persons and socioeconomic status. EOD subjects were defined as those whose age at onset and age on April 1, 2006 (national census day) was <65 years.

Step 1
For the first step, a questionnaire was mailed to all kinds of medical institutions (including psychiatric and neurological outpatient departments), home-visit nursing services, long-term care insurance-related facilities, local branches of departments of prefectural health and welfare for the elderly, and local welfare commissioners. Each institution was asked, “How many EOD patients did you care for between April and October 2006?” A fact sheet detailing the diagnosis of dementia based on the Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised3 was also sent to each institution. It is worth noting that in Japan, all care services for community-dwelling elderly and individuals with EOD are provided by publicly funded long-term care insurance, which is separate from medical care insurance. Municipal long-term care insurance approval boards certify whether an applicant is eligible for long-term care insurance based on the results of screening for his or her mental and physical condition and the assessment report documented by a doctor in charge of him or her.

Step 2
For the second step of the postal survey, respondent institutions with one or more cases were asked to provide additional patient data, including initials, demographics, coexisting illnesses, duration and type of dementia (in the case of vascular dementia, specifying the subtype of cerebrovascular disease), severity of dementia, and functional status. Patients were then classified into subgroups according to the cause of their dementia. Alzheimer disease (AD), vascular dementia (VaD), and alcohol-related dementia were defined according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition6; dementia with Lewy bodies and Parkinson...
disease with dementia were diagnosed according to the revised criteria for the clinical diagnosis of dementia with Lewy bodies; and frontotemporal lobar degeneration was diagnosed according to Lund and Manchester criteria. Finally, patients fulfilling the Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised criteria for dementia, but not fulfilling criteria for any of the previously mentioned diagnostic categories, were assigned to the “other” category.

Answers for the additional information for cases reported from nonmedical institutions were made based on comments by the consulting physicians at these institutions. The age at onset of disease was defined as the age of the patient at which the earliest conclusive dementia symptom was noticed by caregivers or other close informants. During Steps 1 and 2, up to 3 reminder letters were sent to institutions that had failed to respond to maximize the size of the population.

Quality Control
For quality control purposes, we selected the 9 institutions with the highest number of reported EOD cases from those that had responded. Each of these institutions reported /H113505 cases and specialized in medical practice for dementia or stroke. For approximately half of the reported patients identified at Step 2, key psychiatrists and doctors of the selected institutions together reviewed their medical records and data, including the results of MRI, CT, and single photon emission CT.

Statistical Analysis
To reduce sampling bias due to failure to report cases, the prevalence was estimated for each institutional group adjusting for the reported response rates. For each category of institution: (1) the reciprocal of the product of the response rate for the first and second steps (sample weight) was calculated; and (2) the estimated number of patients in the category was calculated using the sample weight multiplied by the reported number of cases. The total number of patients across categories was then estimated by the sum of the estimated category totals. We calculated 95% CIs based on the Poisson distribution. The population denominators used were derived from census data of the target area on April 1, 2006. The significance of differences between rates was estimated by \( \chi^2 \) tests or Fisher exact tests. All analyses were carried out using SAS software, Version 9.1 (SAS Institute).

Table 1 shows the response rate for the postal surveys. In total, information from 717 patients was collected from 285 institutions. After careful review of the answer sheets, reported patients with the following diagnoses were excluded: schizophrenia (n=6), developmental disorder (n=11), depression (n=2), and other nondementia disorders (n=4). None of these

<table>
<thead>
<tr>
<th>Institutions</th>
<th>Target Populations</th>
<th>n*</th>
<th>Response Rate, %</th>
<th>Target Populations</th>
<th>n</th>
<th>Response Rate, %</th>
<th>Reported Cases</th>
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<tbody>
<tr>
<td>Hospitals with &gt;200 beds†</td>
<td>54</td>
<td>53</td>
<td>98.1</td>
<td>22</td>
<td>21</td>
<td>95.5</td>
<td>203</td>
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<tr>
<td>Hospitals with &lt;200 beds</td>
<td>113</td>
<td>106</td>
<td>93.8</td>
<td>21</td>
<td>16</td>
<td>76.2</td>
<td>186</td>
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<td>Clinics</td>
<td>1269</td>
<td>1111</td>
<td>87.5</td>
<td>46</td>
<td>37</td>
<td>80.4</td>
<td>53</td>
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<td>Health service facilities</td>
<td>103</td>
<td>91</td>
<td>88.3</td>
<td>31</td>
<td>28</td>
<td>90.3</td>
<td>66</td>
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<td>Special nursing homes</td>
<td>297</td>
<td>272</td>
<td>91.6</td>
<td>54</td>
<td>44</td>
<td>81.5</td>
<td>56</td>
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<td>Group homes</td>
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<td>198</td>
<td>81.8</td>
<td>45</td>
<td>41</td>
<td>91.1</td>
<td>52</td>
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<td>Home-visit nursing facilities</td>
<td>100</td>
<td>93</td>
<td>93.0</td>
<td>19</td>
<td>18</td>
<td>94.7</td>
<td>31</td>
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<td>Welfare living centers</td>
<td>156</td>
<td>145</td>
<td>92.9</td>
<td>25</td>
<td>22</td>
<td>88.0</td>
<td>29</td>
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<tr>
<td>Government services</td>
<td>69</td>
<td>66</td>
<td>95.7</td>
<td>9</td>
<td>8</td>
<td>88.9</td>
<td>23</td>
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<tr>
<td>Local welfare commissioners</td>
<td>47</td>
<td>46</td>
<td>97.9</td>
<td>10</td>
<td>8</td>
<td>80.0</td>
<td>17</td>
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<tr>
<td>Care managers</td>
<td>25</td>
<td>21</td>
<td>84.0</td>
<td>3</td>
<td>2</td>
<td>66.7</td>
<td>1</td>
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<tr>
<td>Total</td>
<td>2475</td>
<td>2202</td>
<td>89.0</td>
<td>285</td>
<td>245</td>
<td>86.0</td>
<td>717</td>
</tr>
</tbody>
</table>

*No. of respondent institutions.
†Hospitals with >200 beds include the University of Tsukuba.

**Results**

Figure 1. Flow chart indicating sources of identification for prevalent cases of presenile dementia in Ibaraki Prefecture. *Subjects who had dementia starting before the age of 65 years but who were >65 years at the time of the study.*
patients were considered to have had concomitant EOD. In addition, 29 patients were excluded because their age on the census day was >65 years, although their age at onset of dementia was <65 years. In some instances, 2 or more institutions contributed reports on the same individual cases: 36 individuals from 2 institutions, 2 individuals from 3 institutions, and one individual from 4 institutions. Five cases received different diagnoses: 4 with AD also classified as dementia with Lewy bodies (DLB) and one with AD also classified as alcohol-related dementia.

For the cases lacking diagnostic agreement, we accepted the final diagnosis of the most experienced clinical assessors according to the following order: diagnosis made by neurologists or psychiatrists of a general hospital, including university hospitals; psychiatrists of psychiatric hospitals; physicians of general hospitals; physicians of clinics; and physicians from other healthcare facilities. As a result, the final diagnosis for all of the former 4 cases was DLB and the latter case was AD. The final sample population was comprised of 617 patients (59.2% male). Of these, 286 patients received the study quality control evaluation (Figure 1). The mean age on the census day of this group was 56.9 years (SD, 7.3; range, 22 to 64 years) and the mean age at onset of dementia was 53.4 years (7.9; 18 to 64 years).

Table 2. Age-Specific Prevalence per 100,000 for the Causes of Dementia in Ibaraki Prefecture, Japan, April 1, 2006

<table>
<thead>
<tr>
<th>Age Range, Years</th>
<th>Population</th>
<th>n*</th>
<th>Prevalence</th>
<th>95% CI†</th>
<th>n</th>
<th>Prevalence</th>
<th>95% CI</th>
<th>n</th>
<th>Prevalence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–24</td>
<td>162,710</td>
<td>2</td>
<td>1.5</td>
<td>0.5–4.9</td>
<td>0</td>
<td>0.0</td>
<td>0.0–2.4</td>
<td>0</td>
<td>0.0</td>
<td>0.0–2.4</td>
</tr>
<tr>
<td>25–30</td>
<td>184,565</td>
<td>7</td>
<td>4.0</td>
<td>2.0–8.1</td>
<td>3</td>
<td>1.3</td>
<td>0.4–3.9</td>
<td>0</td>
<td>0.0</td>
<td>0.0–1.8</td>
</tr>
<tr>
<td>30–34</td>
<td>218,539</td>
<td>9</td>
<td>4.2</td>
<td>2.3–8.0</td>
<td>7</td>
<td>3.5</td>
<td>1.7–7.3</td>
<td>1</td>
<td>0.7</td>
<td>0.2–3.2</td>
</tr>
<tr>
<td>35–39</td>
<td>199,124</td>
<td>10</td>
<td>4.9</td>
<td>2.7–9.1</td>
<td>17</td>
<td>9.2</td>
<td>5.7–14.8</td>
<td>0</td>
<td>0.0</td>
<td>0.0–2.1</td>
</tr>
<tr>
<td>40–44</td>
<td>181,513</td>
<td>22</td>
<td>11.9</td>
<td>7.8–18.1</td>
<td>20</td>
<td>10.7</td>
<td>6.9–16.6</td>
<td>1</td>
<td>0.8</td>
<td>0.3–3.4</td>
</tr>
<tr>
<td>45–49</td>
<td>186,253</td>
<td>45</td>
<td>24.3</td>
<td>18.1–32.4</td>
<td>50</td>
<td>22.9</td>
<td>17.4–30.2</td>
<td>21</td>
<td>9.8</td>
<td>6.4–14.9</td>
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<td>50–54</td>
<td>218,713</td>
<td>109</td>
<td>50.0</td>
<td>41.5–60.3</td>
<td>107</td>
<td>42.2</td>
<td>34.9–50.9</td>
<td>71</td>
<td>28.0</td>
<td>22.2–35.3</td>
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<td>55–59</td>
<td>254,615</td>
<td>240</td>
<td>94.3</td>
<td>83.1–107.0</td>
<td>152</td>
<td>78.4</td>
<td>66.9–92.0</td>
<td>96</td>
<td>49.5</td>
<td>40.6–60.5</td>
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<tr>
<td>60–64</td>
<td>193,308</td>
<td>316</td>
<td>163.3</td>
<td>146.3–182.4</td>
<td>356</td>
<td>19.8</td>
<td>17.8–21.9</td>
<td>191</td>
<td>10.6</td>
<td>9.2–12.2</td>
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<tr>
<td>20–64</td>
<td>1,799,340</td>
<td>761</td>
<td>42.3</td>
<td>39.4–45.4</td>
<td>329</td>
<td>38.6</td>
<td>34.6–43.0</td>
<td>190</td>
<td>22.3</td>
<td>19.3–25.7</td>
</tr>
</tbody>
</table>

*Estimated no. of patients.
†95% CI for the prevalence.
Of the illnesses causing EOD, VaD was the most frequent (42.5%) followed by AD (25.6%), head trauma (7.1%), DLB/Parkinson disease with dementia (6.2%), frontotemporal lobar degeneration (2.8%), and others (16.0%; Figure 2). The frequency of the illnesses causing EOD was calculated from 2 subgroups; quality control detailed evaluation group (n=286) and clinical records only group (n=331; Figure 1). Subgroup analysis did not change the overall order of the 3 most frequent illnesses, namely VaD, AD, and DLB. However, there were significant differences in the frequencies for each illness (P<0.0001) with similar values for VaD (49.7%, 39.6%) and AD (25.1%, 31.3%) but higher frequencies for DLB (2.9%, 12.3%) and frontotemporal lobar degeneration (1.2%, 5.3%) for the selected subgroup under the quality control condition.

Subtypes of VaD were cerebral hemorrhage (37.5%), large cortical infarct (34.1%), subarachnoid hemorrhage (20.1%), multiple lacunar infarct (2.3%), mixed cerebrovascular disease (eg, cerebrovascular hemorrhage and large cortical infarct; 2.0%), other VaD (eg, moyamoya disease, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy; 2.0%), and unspecified VaD (2.7%; Figure 2). The “other” category included dementia secondary to alcohol-related dementia (2.8%), infection (2.3%), surgery for brain tumor (1.5%), and hypoxia (1.0%). The total estimated number of patients using the reciprocal of the response rate for both steps expected in the prefecture was calculated to be 761. The prevalence rate in those aged 20 to 64 years was 42.3 per 100 000 (95% CI, 39.4 to 45.4). From the age of 30 onward, the prevalence rate of dementia approximately doubled with each 5-year increase in age (Table 2).

Figure 3 shows the prevalence rate of AD and VaD by sex. The most frequent illness causing EOD was VaD in males and AD in females.

### Discussion

One of the key findings of the present study was the prominence of VaD as the most frequent underlying cause of EOD. Until recently, VaD had been considered to be the most frequent cause of late-onset dementia in Japan. However, a series of recent reports showed in fact a higher proportion of AD than VaD among the elderly population.10,11 Thus, the discrepancy in the causes of dementia between our EOD study and recent Japanese late-onset dementia studies requires explanation.

It is well known that aging is the most important risk factor for the development of AD, and in Japan, the average life expectancy has been rising with Japanese women now having...
the longest life expectancy in the world. The rise in life expectancy is likely to have contributed to the increase of AD. On the other hand, it has been said that the prevalence and incidence of stroke causing VaD has decreased in recent years. For example, the Hisayama study, which is the longest-duration longitudinal community-based stroke study in Japan, reported that the incidence of stroke had decreased in all age groups except the presenile group. This finding indicates that VaD as an illness causing dementia has likely decreased in the elderly but not in the presenile population. Furthermore, increases in life expectancy would not be expected to affect the incidence of early-onset AD. These observations could account in part for the discrepancy between causes of dementia in presenile and senile populations.

Another important issue is the difference in the pathogenesis of stroke between presenile and senile populations. The Japanese Standard Stroke Registry Study (JSSRS) used data from 16,630 patients with stroke from many centers. According to the JSSRS report, the peak age group for occurrence of subarachnoid hemorrhage is 50 to 59; for cerebral hemorrhage, it is 60 to 79; and for lacunar infarction, it is 70 to 79. This report indicated that cerebral and subarachnoid hemorrhage cause the majority of presenile strokes, whereas lacunar infarction is the main cause of senile stroke. It was also reported that among the various vascular illnesses causing VaD in the senile population, lacunar stroke had decreased in frequency, whereas no reduction in the proportion of cerebral and subarachnoid hemorrhage has yet been reported. Hence, hemorrhages have been assumed to be the most common causes of presenile VaD. Our study appears to support this with cerebral hemorrhage and subarachnoid hemorrhage accounting for 57.6% of conditions causing VaD. There is also a discrepancy between the predominant causes of EOD in the current study and those reported previously in Western countries. More than 2 decades ago, a Finnish study showed the incidence of stroke for Japanese presenile men as more than twice as high as that for the white presenile population of men and women combined. As described here, the incidence of stroke in the Japanese presenile group has probably not decreased. In addition, the results of the current study (Figure 3) show that the frequency of VaD for men was twice as high as for women, and this ratio is the same as that reported for all strokes in the Japanese general population for this age group. Thus, the prominence of VaD as an illness causing EOD appears to be attributable to the higher prevalence of stroke in presenile men.

Another key finding of this study is the higher frequency of DLB, which has recently been recognized as an illness and a common form of dementia in old age. Population-based studies investigating the prevalence of DLB are limited, particularly in younger populations. The number of patients with DLB was the third highest in our study, which is surprising considering the association of Parkinson disease and advancing age. A limitation of the current study is that the accuracy of these diagnoses was not able to be confirmed by neuropathological examination. In addition, although EOD is likely to come to medical attention, it remains possible that a proportion of individuals with EOD might not have been detected by the healthcare service.

To our knowledge, this is one of the largest studies estimating the prevalence of presenile dementia in a large community sample (Table 3). Case ascertainment was also more thorough, including both medical institutions and nonmedical (long-term care insurance) facilities. In addition, the study attained very high institutional response rates increasing the likely accuracy of the inferences about population prevalence.

Finally, it is clear that there is a sizable number of individuals with EOD in Japan who require support both by their caregivers and access to public services. The needs of these patients who, in comparison with elderly individuals, are more likely to have dependents and financial commitments are an area urgently requiring further evaluation. In addition, conventional services for individuals with dementia in Japan were designed for older people, which are likely to be suboptimal or inappropriate for the needs of younger individuals with EOD. This study may provide policymakers with basic data to estimate the budgets for evaluating and enabling optimal EOD healthcare policy.

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Disclosures
None.

References


