According to the consensus of the first Key conference of MCI, amnestic MCI single is presumably caused by prodromal AD, amnestic MCI multiple by AD or vascular dementia (Winblad et al., 2004). In fact, two recent community-based longitudinal studies showed that amnestic MCI is likely to convert to AD (Busse et al., 2006, Fischer et al, 2007). However none of the two studies showed the APOE4 frequency.

On the other hand, non-amnestic MCI single is presumably caused by DLB or VD, and non-amnestic MCI multiple by DLB or frontotemporal dementia. However, the course of non-amnestic MCI shown in the two studies is contradictory (Busse et al., 2006, Fischer et al, 2007). In the present study, the APOE4 frequency for these types of MCI is similar with that for the normal elderly. The clinical significance of non-amnestic MCIs is left open as yet, but it appears that amnestic- and non-amnestic MCI may differ in the course at least to some extent.

Clinical characteristics of amnestic MCIs

The prevalence of the MCI using 1SD cutoff is higher than that using 1.5 SD for single and multiple amnestic MCIs. For both analyses using 1 and 1.5 SD, the prevalence is higher for the multiple than the single. The highest prevalence (n=169, 11.7%) is found in the amnestic MCI multiple 1SD, and it is of note that prevalence of the original MCI (amnestic MCI single 1.5SD) (n=25, 1.7%) is the lowest. In view of APOE4 frequency, the highest value (37.0%) is found for amnestic MCI multiple 1.5 SD. This value seems to be not greatly different from that for Japanese AD patients. In addition, it appears to be difficult to clearly distinguish

amnestic MCI multiple which is operationally diagnosed from dementia that is clinically diagnosed according to the DSM-IV criteria. Thus some individuals having our operational diagnosis of amnestic MCI multiple 1.5 SD could reveal to be at the very early stage of AD. On the other hand, the multiple 1 SD which prevalence is highest among amnestic MCIs, shows relatively high APOE4 frequency (28.4%). Thus, theoretically estimated number of individuals who will develop AD in future for this type of MCI may be considerably larger than that of other MCI groups. It goes without saying that cognitive impairment of this type of MCI is milder than that of amnestic MCI multiple 1.5 SD. Taken together, it might be desirable to provide a preventive intervention for amnestic MCI multiple 1SD individuals, while individuals with amnestic MCI multiple 1.5 SD could be the best target for the early detection of AD.

Finally, this is a cross-sectional study of MCI, so we cannot evaluate sensitivity, specificity, and positive predictive power of each subtype of MCI. Taking this limitation into consideration, the present community-based study may provide workable information about MCI.

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Prevalence and causes of early-onset dementia in Japan: A population-based study

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Acknowledgements and Funding:

We thank all the institutions for their assistance with medical record abstraction; Jun Akanuma, MD, for his assistance with MRI reading; David Darby, MD and Shuzo Shintani, MD, for their helpful comments; and Hiroko Asada, Machiko Iijima, and Miho Kanda for their secretarial assistance.

This study was supported in part by a research grant from the Ministry of Health, Labor, and Welfare.

Full title:

Prevalence and causes of early-onset dementia in Japan:

A population-based study

Cover title:

Prevalence of early-onset dementia in Japan

Tables and figures:

・3 tables

・3 figures

Key words: early-onset dementia, vascular dementia, prevalence

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

Methods: A two-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 was 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, 39.4-45.4). Of the illnesses that cause EOD, vascular dementia (VaD) was the most frequent (42.5%), followed by AD (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, VaD was the most frequent cause of EOD in Japan.

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] In order 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 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 about 2,966,000. This is the 11th largest of the 47 Prefectures, with 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 less than 65 years.

Step 1

For the first step, a questionnaire was mailed to all kinds of medical institutions (including psychiatric and neurological out-patient departments), home-visit nursing services, long-term care insurance (LTCI) 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, revised (DSM-III-R)[5] 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 a publicly funded LTCI, which is separate from medical care insurance. Municipal LTCI approval boards certify whether an applicant is eligible for LTCI based on the results of screening for his/her mental and physical condition and the assessment report documented by a doctor in charge of him/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 edition (DSM-IV)[6]. 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[7], and frontotemporal lobar degeneration was diagnosed according to Lund and Manchester Criteria.[8] Finally, patients fulfilling the DSM-III-R criteria for dementia, but not fulfilling criteria for any of the above diagnostic categories, were assigned to the "other" category.

Answers for the additional information for cases reported from non-medical 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 step 1 and 2, up to three reminder letters were sent to institutions that had failed to respond in order 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 5 or more cases and specialized in medical practice for dementia or stroke. For about 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 magnetic resonance imaging (MRI), computed tomography (CT), and single photon emission computed tomography (SPECT).

Statistical analysis

In order 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: (i) the reciprocal of the product of the response rate for the first and

second steps (sample weight) was calculated, and (ii) 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% confidence intervals (CI) based upon the Poisson distribution. The population denominators used were derived from Census data of the target area on April 1, 2006.[9] The significance of differences between rates was estimated by chi-square tests or Fisher's exact tests. All analyses were carried out using SAS software, version 9.1 (SAS Institute).

RESULTS

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 non-dementia disorders (n = 4). None of these patients were considered to have had concomitant EOD. In addition, 29 patients were excluded because their age on the Census day was over 65, although their age at onset of dementia was less than 65. In some instances, two or more institutions contributed reports on the same individual cases: 36 individuals

from two institutions; 2 individuals from three institutions; and one individual from four institutions. Five cases received different diagnoses: 4 with AD also classified as DLB, and 1 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 health-care 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 Census day of this group was 56.9 years (SD, 7.3; range, 22-64 y) and the mean age at onset of dementia was 53.4 years (7.9; 18-64 y).

Of the illnesses causing EOD, vascular dementia (VaD) was the most frequent (42.5%), followed by Alzheimer Disease (AD) (25.6%), head trauma (7.1%), dementia with Lewy bodies (DLB)/Parkinson Disease with dementia (PDD)(6.2%), frontotemporal lobar degeneration (FTLD) (2.8%), and others (16.0%) (Figure 2). The frequency of the illnesses causing EOD was calculated

from two subgroups: Quality control detailed evaluation group (n=286); and Clinical records only group (n=331) (see fig.1). Subgroup analysis did not change the overall order of the three 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 FTLD (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 (e.g., cerebrovascular hemorrhage and large cortical infarct) (2.0%), other VaD (e.g., 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 was 42.3 per 100,000 (95% CI, 39.4-45.4). From the age of 30 onwards, 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 (LOD) 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 LOD 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,[12] 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

pre-senile group. This finding indicates that VaD as an illness causing dementia has likely decreased in the elderly but not in the pre-senile 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 pre-senile and senile populations.

Another important issue is the difference in the pathogenesis of stroke between pre-senile and senile populations. The Japanese Standard Stroke Registry Study (JSSRS) used data from 16,630 stroke patients from many centers.[13] According to the JSSRS report, the peak age group for occurrence of subarachnoid hemorrhage is 50-59, for cerebral hemorrhage it is 60-79, and for lacunar infarction it is 70-79. This report indicated that cerebral and subarachnoid hemorrhage cause the majority of pre-senile strokes, while lacunar infarction is the main cause of senile stroke. It was also reported that amongst the various vascular illnesses causing VaD in the senile population, lacunar stroke had decreased in frequency, whilst no reduction in the proportion of cerebral and subarachnoid hemorrhage has yet been reported.[14] Hence, haemorrhages have been assumed to be the most common causes of pre-senile 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[15-17]. More than two decades ago, a Finnish study[18] study showed the incidence of stroke for Japanese pre-senile men as more than twice as high as that for the Caucasian pre-senile population of men and women combined. As described above, the incidence of stroke in the Japanese pre-senile group has probably not decreased. In addition, the results of the current study (Figure 4) 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.[19] Thus the prominence of VaD as an illness causing EOD appears to be attributable to the higher prevalence of stroke in pre-senile 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.[20] The number of patients with DLB was the third highest in our study which is surprising considering the association of Parkinson's 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