Mateer, 1986). This test assesses alternating attention, which refers to the capacity for mental flexibility that allows individuals to shift their focus of attention and move between tasks with different cognitive requirements, thus controlling which information will be selectively processed. In order to assess the memory ability, we used a Category Cued Recall test (Grober, et al, 1988). The Clock Drawing test, which requires subjects to draw the hands of a clock to depict the time at "ten after eleven" (Freedman, et al, 1994), was used to assess visuospatial function. We examined language ability using a category fluency test (Soloman and Pendlebury, 1998). The subjects were asked to generate as many examples as possible in 2 minutes from the semantic category 'animal'. The total number of animals named is the score for the test. To assess abstract reasoning ability, we employed the similarity subset of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler,1981).

This cognitive assessment was conducted in a group setting (maximum 50 participants) by an examiner with the use of a projector. All participants were asked to record their answer on the answer sheet. Each screening was supervised by approximately ten members of our research team. The mean length of the 5-Cog examination was 35 minutes. For participants who had difficulty in understanding the tasks or impaired hearing or vision, we conducted the examination using the individual version of the 5-Cog in a face-to-face setting.

During the interview and examinations, we estimated the visual acuity and hearing and speech ability of each subject. We also identified those who could not respond to our instructions and/or some of the scales because of obvious cognitive impairment.

Consensus Diagnosis

After each assessment, a group of psychiatrists and neuropsychologists reviewed the functional, medical, neurologic, psychiatric, and neuropsychological data and reached a consensus regarding the presence or absence of dementia by diagnosis of dementia according to the DSM-IV (American Psychiatric Association, 1994) criteria. Only those who were not diagnosed as having dementia were considered for a diagnosis of MCI.

MCI Diagnostic Criteria

Criteria for MCI were retrospectively applied among nondemented individuals after the consensus conference. Consistent with the standard criteria, for all subtypes of MCI described below, those considered for MCI were required to have: (1) objective impairment in at least 1 cognitive domain based on the average of the scores on the neuropsychological measures within that domain and 1 SD and 1.5 SD cut-off using normative corrections for age, years of education, and sex; (2) essentially preserved activities of daily living (defined above); (3) presence of the memory complaints (defined above); and (4) no diagnosis of dementia at the consensus diagnosis.

First, for our subtype of amnestic MCI single, memory impairment was defined as a score less than 1 or 1.5 SD below the demographically corrected mean on the category cued recall test, and performance on scores from all other cognitive domains (ie, attention, language, visuospatial,

and reasoning) was required to fall within normal limits (score must be more than 1 or 1.5 SD below the demographically corrected mean). Second, a diagnosis of amnestic MCI multiple was made if there was objective impairment on the memory domain score and if there was impairment on 1 or more cognitive domains. Third, a diagnosis of nonamnestic MCI single had a cognitive impairment in a single nonmemory domain and performance on scores in all other cognitive domains fell within normal limit. Finally, the diagnosis of non-amnestic MCI multiple was assigned if there was impairment in 2 or more of the 4 nonmemory domains, and if the memory domain score was within normal limits. The classification into the 4 MCI subtypes was mutually exclusive. Thus, we estimated the prevalence of the 8 types (2 cutoffs (1SD, 1.5SD)×4 subtypes) of MCI.

SECOND STUDY (Investigation of delayed-responders)

At the completion of the first study, we had identified a total of 1035 non-participants who were contacted but had refused to participate, excluding the above-defined uncontactable individuals. We attempted a door-to-door survey of those non-participants. This portion of the study was conducted with the aid of the general practitioners and local welfare commissioners of Tone town in the hope that their invitations would encourage the participation of new-comers from among non-participants. We asked them to contact and explain our project to individuals that appeared on the non-participants list. Subsequently, between April and June 2002, 225 of the non-participants agreed to participate. These 225 non-participants

are termed 'delayed-responders' hereafter. A psychiatrist (T. A.) and the psychologists visited each delayed-responder's home and conducted the same interview and tests that had been used on the first study. The individual version of the 5-Cog was used for cognitive assessment. After each assessment, we discussed the case on the basis of the consensus diagnosis described above.

STASTICAL ISSUES AND ANALYSIS

For the normative data, we excluded data from participants who did not complete the series of interview and examinations and had had a diagnosis of dementia. Test-retest reliability of the 5-Cog was confirmed (mean value of Pearson's correlation coefficient was 0.70, $p < 0.01$ for all of the five tests) using data from randomly selected 38 1st study participants collected at a mean interval of 64 (SD: 28) days.

The participants' characteristics and cognitive status were analyzed using a t-test and chi-square test for continuous and categorical variables, respectively. For analyses in which the expected frequency was less than 5, Fisher's exact probability test was used. The data were analyzed using SPSS 15.0J (SPSS Inc, Chicago, IL, USA). The results for continuous variables are given as mean ± SD. All analyses were conducted with significance established at the $p < 0.05$ level.

RESULTS

Basic issues

As Figure-1 shows, 132 of the 3083 potential candidates were excluded. Specifically, 87 had died and 45 had moved before the initial examination. Additionally, 253 residents were 'uncontactable individuals'. Thus, the remaining 2698 residents were considered the candidate at the baseline. Of the 1035 residents refused to participate (non-participants), 225 became 2nd study participants. Consequently, 1888 (1619 1st study and 225 2nd study participants, and 44 nursing home residents) (70%) of 2698 baseline candidates were enrolled.

Prevalence rate of MCI

As the results of the consensus diagnosis, we estimated 6.5 % prevalence for any types of dementia combined among 1888 participants. After excluding those who had been diagnosed as having dementia, 1433 subjects with complete data remained for the final analysis. The basic data for the subjects are shown in Table1, and the prevalence of the 8 subtypes of MCI among the subjects is shown in Table 2.

The main findings shown are as follows: 1) the prevalence of MCIs ranged from 1.7 to 16.5% depending on the diagnostic criteria applied, and the prevalence for the original MCI (amnestic MCI single 1.5SD) is lowest; 2) when cut-off of 1 SD and 1.5 SD were chosen, 19.5 to 39.3% of the study participants were operationally diagnosed as having any subtypes of MCI, respectively; 3) the prevalence of the MCI using 1SD cutoff is 1.5 to 3.5 times as high as that

using 1.5 SD for the 4 MCIs; 4) for amnestic MCI, the prevalence of the multiple is higher than that of the single, and highest prevalence is found in the MCI multiple 1SD (11.7%); 5) for non-amnestic MCI, the prevalence of the multiple is lower than that of the single.

Frequency of APOE4

The APOE genotyping revealed that 19.8% of the 1487 participants were APOE4 carriers (2/4, 3/4, 4/4). The frequency of APOE4 for each subtype of MCI is shown in Table 3. The frequency is higher for any types of MCI combined group than cognitively normal group. The APOE4 frequency of amnestic-MCI is higher than that of nonamnestic-MCI and normal groups. The frequncy is higher for 1.5 SD cutoff MCIs than that of 1 SD for all MCIs but the non-amnestic MCI multiple.

In the amnestic MCI group, the highest frequency of APOE4 (37.0%) is found in the multiple 1.5SD, whereas the lowest (23.3%) is found in the single 1SD. The frequency for the original MCI (amnestic MCI single 1.5SD) is 32.0%.

We compared the frequency among normal, amnestic MCI (single and multiple) and non-amnestic MCI (single and multiple) groups. For the purpose, we used chi-square analyses and Ryan's multiple comparison procedure as a post hoc analysis. As a whole, the highest frequency is found in the amnestic MCI group (single and multiple) (Fig 2)

DISCUSSION

General

The sample size of the present study seems to be comparable to the largest studies among previously reported population-based prevalence studies of pre-dementia syndromes including MCI from western countries (Panza et al., 2005). The reported prevalence of pre-dementia syndromes varies among the studies as a result of differences in diagnostic criteria, sampling and assessment procedure. About half of these studies used the amnestic MCI single as the diagnostic criteria, and most of these studies showed the prevalence rate of less than 6%. Thus our prevalence rate of 3.0 and 1.7% (1SD, 1.5SD) for the amnestic MCI single appears to be lower in comparison with the results of the previous studies. However, we believe the validity of our results on the following grounds. It has been reported that age, educational level, and gender are related to the prevalence of pre-dementia, however some of the previous studies estimating the prevalence did not control for the factors (Panza F et al., 2005). Our controlling for them might have contributed to the lower value.

To our knowledge, two previous studies have identified MCI subtypes using similar methods with ours (Busse et al., 2003, Jungwirth S, et al, 2005). General findings described in the results section bears resemblance to that of the two studies. Taking theses findings together, our estimated prevalence of MCIs including amnestic MCI single appear to be valid.

Regarding APOE4 frequency for Japanese, it is known that a little less than half of Japanese AD patients have at least one APOE4 allele and its value is about three times as much as that for

normal controls (Ueki A et al., 1993, Asada T et al., 1996). Thus distribution of 18.6% APOE4 for the non-MCI participants appears to be similar with that for Japanese healthy elderly, and the 37.0 % for amnestic MCI multiple 1.5SD subjects seems to be a little less than Japanese AD patients. The individuals with amnestic MCI are assumed to be likely to convert to AD, thus the latter value appears to be rational. To our knowledge, the only community-based study of MCI estimating the frequency of APOE4 carriers found the association between APOE4 and the original amnestic MCI (Lopez et al., 2003). In that study, the APOE4 frequency for amnestic MCI and healthy participants was 33% (12/40) and 20% (101/552), respectively. The results are very similar with ours. These findings together appear to support the validity of the results of the present study.

Differences in amnestic and non-amnestic MCIs

The frequency of APOE4 is higher for amnestic MCI group (single plus multiple) than non-amnestic group (single plus multiple) and normal elderly. Besides the pattern of cognitive impairment, amnestic MCI is different in APOE4 frequency from non-amnestic MCI.

Many of clinic based studies which examined the utility of APOE4 in the prediction of AD convert among patients with amnestic MCI have shown affirmative results (Tierney MC, et al. 1996, Fleisher A, et al. 2005, Devanand DP, et al. 2005). However, we must take notice of the finding that there is an increased frequency of APOE4 in Lewy body dementia (DLB) but that the effect is less prominent than in AD (Rapka, et al., 1998).

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.