the proportion of "miscellaneous" between this and previous reports. The difference -- which may be explained by the selection bias -- makes it difficult to directly compare the results between this and previous studies.

In conclusion, the largest investigation on presenile dementia etiologies demonstrated that AD was the most common degenerative dementia. The findings showed that FTLD and DLB/PDD were the second and third most common degenerative dementia in presenile dementia. The prevalence of FTLD was higher, while that of DLB/PDD was lower in the presenile cases in comparison to the overall dementia cases. Contrary to some previous studies showing a high frequency of VaD in the presenile patients, the proportion in the present study was relatively small. This may reflect differences in the clinical sites where the study is conducted and in the pathogenesis of VaD between Western countries and Japan. This study may help to establish an accurate database regarding the prevalence of illnesses causing presenile dementia. This kind of knowledge may be useful for future planning and the establishment of health services for these patients.

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Table 1 Comparison of percentages of causes of presenile dementia of previous studies

				AD	FTLD	VD	DLB/ PDD	Miscella-neous
Woodburn et al. (1999) [2]	Scotland	(n=114)	Com	53	12	11	NR	24
Panegyres et al. (2000) [3]	Australia	(n=150)	Cli	21	24	5	NR	50*
Ratnavalli et al. (2002) [4]	England	(n=88)	Com	22	17	13	10	39
Harvey et al. (2003) [5]	England	(n=185)	Com	34	12	18	8	28
McMurtray et al. (2005) [6]	U.S.A	(n=278)	Cli	17	3	29	4	47
Total		(n=815)		27	12	18	4	39

AD, Alzheimer's disease; VaD, vascular dementia; FTLD, frontotemporal lober degeneration; DLB/PDD, Dementia with Lewy bodies/Parkinson's disease with dementia; NR, non reported. Com, Community-based study; Cli, Clinical-based study

*: Dementia due to psychiatric diseases was included

Table 2 Number of patients by diagnosis, gender, and age

Age at diagnosis	35-45	46-55	56-65	Total
AD				
Total	2	61	310	373
Women	2	35	147	184
Men	0	26	163	189
FTLD				
Total	0	16	58	74
Women	0	4	33	37
Men	0	12	25	37
VaD				
Total	1	4	25	30
Women	0	2	7	9
Men	1	2	18	21
DLB/PDD				
Total	0	5	19	24
Women	0	2	9	11
Men	0	3	10	13
All patients				
Total	3	86	412	501
Women	2	43	196	241
Men	1	43	216	260

AD, Alzheimer's disease; VaD, vascular dementia;
FTLD, frontotemporal lober degeneration;
DLB/PDD, Dementia with Lewy bodies/Parkinson's disease with dementia

Figure legends

Figure 1

Distribution of the causes of presenile dementia in each participating memory clinic (age <65 years; n=198 in Musashi Hospital of National Center of Neurology and Psychiatry; N=130 in Tsukuba University Hospital; n=110 in Fukuoka University Hospital; n=137 in Ehime University Hospital).

AD, Alzheimer's disease; VaD, vascular dementia; FTLD, frontotemporal lober degeneration; DLB/PDD, Dementia with Lewy bodies/Parkinson's disease with dementia.

Figure 2

Distribution of the causes of presenile dementia (age <65 years; n=575).

AD, Alzheimer's disease; VaD, vascular dementia; FTLD, frontotemporal lober degeneration; DLB/PDD, Dementia with Lewy bodies/Parkinson's disease with dementia

F i g. 1 F

Fig.1

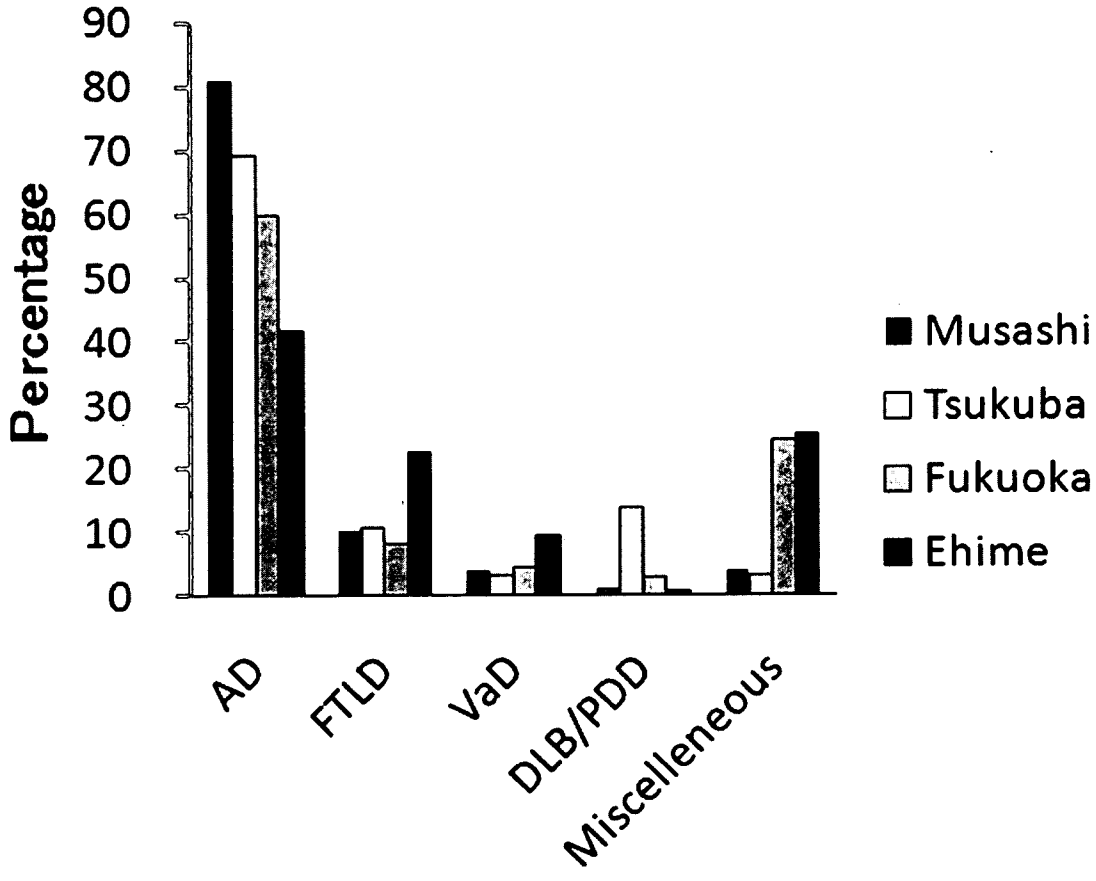
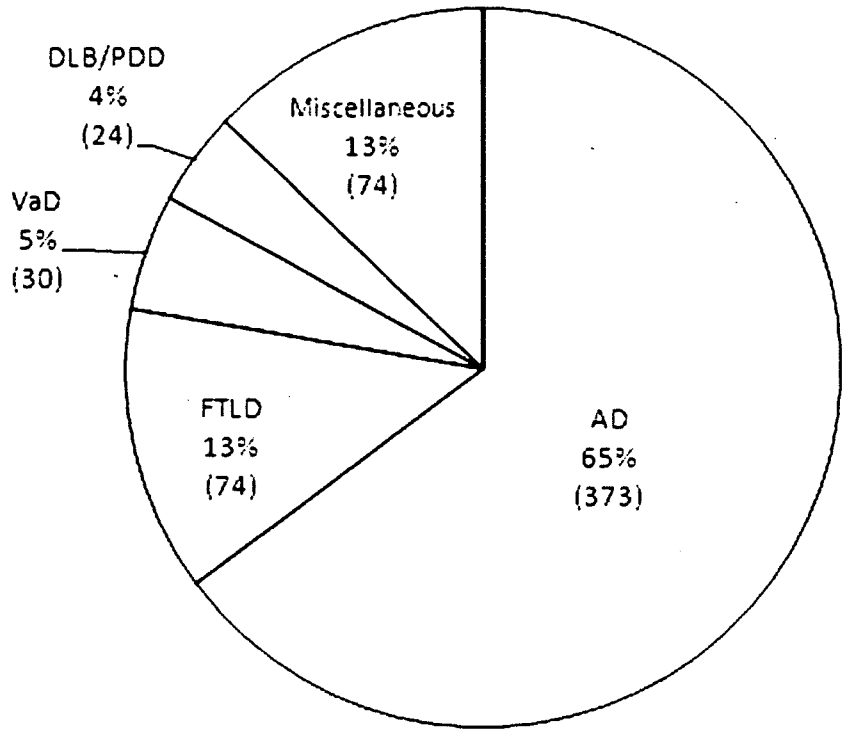

Percentage
90
80
70
60
50
40
30
20
10
0
AD
FTLD
VaD
DLB/PDD
Miscelleneous
Musashi
Tsukuba
Fukuoka
Ehime

Fig.2



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ORIGINAL ARTICLE

Mild cognitive impairment in a population-based epidemiological study

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Abstract

Background: It would be of considerable importance to be able to estimate the rate at which subjects with mild cognitive impairment (MCI) progress to dementia in a cohort of a population-based epidemiological study and to establish simple diagnostic methods for the identification of people at high-risk of dementia. Subjects in a community based elderly cohort of MCI were followed longitudinally.

Methods: Subjects were selected from participants in the first epidemiological study conducted on all persons aged 65 years and older residing at home in Nakayama, Japan, using the Mini-Mental State Examination (MMSE). Mild cognitive impairment was defined as memory deficit with objective memory assessment, without dementia, impairment of general cognitive function or disability in activities of daily living. The conversion rate was calculated using the person–year method.

Results: At baseline, the sample consisted of 104 subjects selected from 1162 community dwellers aged over 65 years of age. During the 5-year follow up, 11 subjects (10.6%) were diagnosed with Alzheimer's disease (AD), five (4.8%) were diagnosed with vascular dementia (VaD) and six (5.8%) were diagnosed with dementia of other etiology. In this survey, the annual conversion rate of MCI to AD was calculated as 8.5% per 100 person–years and shifted to dementia at a rate of 16.1% per 100 person–years. The proportion of subjects with MCI who progressed to develop dementia was the same as in previous reports. However, nearly 40% of subjects returned to normal.

Conclusion: The MCI concept, as currently defined, is an unstable and heterogeneous group.

Key words: *Alzheimer's disease, conversion rate, dementia, mild cognitive impairment, Mini-Mental State Examination (MMSE), Nakayama study.*

INTRODUCTION

Recently, the term 'mild cognitive impairment' (MCI) was proposed to describe the transitional state between normal cognition and Alzheimer's disease (AD).[1,2] Mild cognitive impairment is increasingly recognized as an important public health issue because it is common and is associated with significant morbidity, especially the development of clinically diagnosed AD.[3–5] As high-risk individuals for dementia, subjects with MCI could be a particularly suitable population for preventive intervention. Longitudinal studies of case series have revealed an increased risk of AD in MCI subjects, with a conversion rate ranging from 7 to 20% per year.[3,6–8]

Most studies investigating the natural history of MCI have been conducted on samples of subjects recruited in specialized outpatient clinics, such as memory clinics for AD. Such samples are highly selective and it is essential to identify subjects at high risk of dementia from community based surveys in order to carry out early intervention. To our knowledge, one community based prospective cohort study reported that the annual conversion rate to AD was 8.3% over 5 years.[9] The incidence and

outcomes of MCI in the general population are still largely unknown.

Standardized memory scales, such as the Wechsler Memory Scale Revised (WMS-R), can be used to identify subjects satisfying a strict definition of MCI.[1,2] However, it may be very difficult to undertake such time-consuming examinations in community based epidemiological surveys.

Nakayama study for MCI[10]

Nakayama is a Japanese rural community adjacent to Matsuyama City, a metropolis on Shikoku Island. We extracted a group of subjects with MCI using the Mini-Mental State Examination (MMSE),[11,12] based on the results of the first Nakayama study,[13] and tried to estimate the rate at which subjects with MCI shifted to dementia.

Subjects

The first Nakayama study included all residents over 65 years of age living in the rural community between January 1997 and March 1998 by means of a door-to-door survey with a three-phase design. Of 1438 inhabitants, 1162 (81%) completed the protocol. A more detailed description of the methods has been published elsewhere.[13,14]

In the present study, we selected subjects who were participants of the first Nakayama study and who satisfied the following criteria: (i) normal general cognitive function, with MMSE ≥24; (ii) objective memory impairment, assessed by three-word recall in MMSE (delayed recall 0/3 or 1/3); (iii) neuropsychiatric examination findings of an absence of dementia or depression, diagnosed by geriatric neuropsychiatrists according to DSM-IIIR[15] criteria; and (iv) no impairment of activities of daily living (ADL) evaluated using the physical self-maintenance scale (PSMS) and instrumental activities of daily living scale (IADL).

METHODS

A 5 year follow up was conducted on all subjects between April and December 2003. A senior neuropsychiatrist administered the MMSE to subjects, whereas a public health nurse interviewed one family member of each subject using the PSMS and IADL.[16] Subjects who were hospitalized or otherwise institutionalized were included in the study. Cranial computed tomography (CT) was conducted on all subjects whose MMSE score declined by more than 2 points from baseline.[17]

The diagnosis of dementia was established according to DSM-IIIR criteria. Subsequently, demented subjects were classified into subgroups based on the cause of dementia. Alzheimer's disease was defined according to the National Institute of Neurological and Communicative Disorders and Strokes-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD[18] and vascular dementia (VaD) was also defined according to NINDS-AIREN criteria.[19]

The conversion rate was calculated using the person–year method.[20]

RESULTS

The sample consisted of 104 subjects at baseline; 59 women and 45 men. The mean age of female and male subjects was 75.5 ± 6.7 years (range 65.1–90.2) and 73.6 ± 6.8 years (range 65.1–101.4), respectively.

Five years after the first Nakayama study, 14 subjects had died, 13 had moved to other communities (mainly due to their institutions) and six refused to participate in the follow-up investigation. Eleven (10.6%) subjects were diagnosed with AD (five men, six women), five (4.8%) were diagnosed with VaD (three men, two women) and six (5.8%) were diagnosed with dementia of other etiology. There were nine (8.7%) subjects who remained MCI (three men, six women). Furthermore, 40 (38.5%) subjects showed a restored MMSE score (Table 1). In our survey, the conversion rate from MCI to AD was 8.5% per 100 person–years and from MCI to dementia it was 16.1% per 100 person–years for 5 years.

The control group consisted of 74 participants (41 men, 33 women) at baseline. The mean age of female

Table 1 Outcomes for 104 subjects with mild cognitive impairment and 74 control subjects at the 5 year follow up

	MCI subjects (n = 104)	Control (n = 74)
Died (n)	14	9
Moved to another community (n)	13	2
Refused to participate in follow up (n)	6	0
Alzheimer's disease (n)	11	0
Vascular dementia (n)	5	2
Other type of dementia (n)	6	1
MCI (n)	9	1
Free of dementia and MCI (n)	40	59

MCI, mild cognitive impairment.

and male subjects was 75.4 ± 7.2 years (range 65.1–89.2 years) and 73.2 ± 6.7 years (range 65.1–92.4 years), respectively. There were no significant differences in age or in the gender ratio between the MCI and control groups. Of the 74 participants without dementia or MCI at baseline, nine subjects had died, two had moved to other communities, two were diagnosed with VaD (one man, one woman) and one was diagnosed with dementia of other etiology, one with MCI, and none developed AD (Table 1).

DISCUSSION

This is the first report of 5 year outcomes of MCI in a population-based study of dementia in Asia. Our survey differs from previous investigations in the following aspects. First, even in the screening interview, subjects were examined directly by a neuropsychiatrist and a cranial CT was performed on all subjects with any sign of dementia. Second, we have continued follow up over 5 years in the Nakayama community after the first Nakayama investigation with a definite examination at 5 years. Therefore, we were able to analyze the conversion rate using the person–year method.

Several studies have been undertaken to determine the natural course of MCI in attempt to estimate the 'conversion' rate to AD in this group.[21] As expected, most longitudinal studies of case series revealed a much increased risk of AD in MCI subjects.[1,22,23] Subjects with MCI may constitute a particularly suitable population for preventive interventions.

In previous clinic-based reports, MCI has been found to progress to AD at rates of 7–20% per year.[1,23,24] Standardized episodic memory examinations (e.g. WMS-R) with comprehensive neuropsychological tests have been suggested as a definitive means of identifying MCI. Therefore, measuring cognitive functions using MMSE, WMS-R, the Wechsler Adult Intelligence Scale Revised (WAIS-R) and the auditory verbal learning test were adopted in those studies. The differences in these rates are probably related to the different instruments and cut-off limits chosen to define MCI across the studies.

To our knowledge, there have been a number of community based prospective cohort studies following community dwelling MCI elderly people for several years.[9,25–27] In one of these studies,[9] comprehensive test batteries for the evaluation of global mental status (MMSE), visual memory (Benton's Visual Retention Test (BVRT)), verbal fluency (Isaacs Set Test), visuospatial attention (Zazzo's Cancellation Test) and simple logical reasoning and attention (Wechsler's Digit Symbol Test) were used. However, it may be difficult to administer comprehensive tasks in an ordinal epidemiological survey. Not only is it time consuming and expensive, but it is also a demanding task to ask of large numbers of participants, particularly the very old. Therefore, it is an unsuitable method for identifying those at high risk of AD among the general public.

There is an increasing need for fast and efficient cognitive screening instruments suitable for detecting MCI from normal aging individuals.[28,29] Such screening tests would lighten the burden on patients and physicians, economize medical resources and provide opportunities for dementia prevention and treatment when there is evidence that effective interventions exist.[30] In the present study, we used MMSE to select subjects who exhibit MCI. The total MMSE score was used to screen subjects and select them for neuropsychological evaluation/diagnosis; then, a subset of the MMSE (three-word recall) was used to further classify subjects as MCI. The MMSE is widely used as a screening instrument for cognitive decline or cognitive impairment in population-based studies, as well as in clinical practice, and is a well-validated instrument for assessing global cognitive function.[31] The MMSE is administered easily and quickly; thus, it is suitable for use in the community. The conversion rate of MCI in the present study was almost the same as in a previous community based MCI study with strict memory examinations.[9]

In the present study, we did not check for subjective memory complaints corroborated by the informant, which are considered characteristic of MCI based on strict criteria.[2] Observations by knowledgeable informants regarding an individual's cognitive abilities in everyday functioning have been shown to be sensitive and reliable for the detection of MCI.[5,32] However, it is difficult to use informant-based scales as screening tools because, in modern Japanese society and in many Western societies, considerable numbers of people live alone.

Conventionally defined MCI has reasonable predictive value and specificity for AD. Our finding supports the hypothesis that MCI is an intermediate stage before dementia or AD. However, the lack of stability was even greater in MCI, because approximately 40%

Table 2 Instability of subjects with mild cognitive impairment

Reference	Follow-up interval (years)	MCI still MCI, Stable (%)	MCI converted non-MCI, Improved, reverted to normal (%)
Larrieu *et al.* [9]	2 (total 5)	5.4–6.9	41.4–43.2
Ganguli *et al.* [26]	2 (total 10)	11.1–21.2	35.7–55.0
Ishikawa *et al.* [12]	5	8.7	38.5

MCI, mild cognitive impairment.

of our prevalent cases returned to normal. Mild cognitive impairment was very unstable across time in previous studies (Table 2).[9,12,26] Therefore, people displaying MCI, as currently defined, are an unstable and heterogeneous group. There is epidemiological evidence that many subjects labeled as having MCI do not worsen over time and may revert to normal cognitive abilities. A diagnosis of MCI as a predementia stage of AD in such individuals would be inaccurate and carry a heavy personal and societal burden. The heterogeneity within MCI has been noted and a new classification has been proposed, based predominantly on neuropsychological profiles, and includes amnestic or single-memory MCI, multiple-domain MCI and single non-memory MCI.[33] Conversely, concepts such as 'age-associated memory impairment' (AAMI) and 'age-associated cognitive decline' (AACD) consider such mild cognitive deficits to fall within the limits of normal aging in Europe.[34,35] Conceptually, these terms may include a broad range of cognitive impairments. Enlarging the definition of subjects with acquired cognitive impairment not qualifying as dementia would allow the screening of more subjects at risk of dementia and possibly yield more sensitivity in the prediction of the etiological subtypes.

Although MCI does not constitute a homogeneous clinical syndrome, the recognition that MCI is a risk state towards further cognitive decline is clinically relevant and the control of risk factors, such as systolic hypertension, hypercholesterolemia, diabetes mellitus and stroke, may delay progression to dementia. Therefore, MCI may be a promising therapeutic target and an important target for screening and possible early intervention.

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Original Research Article

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Frequency and Clinical Characteristics of Early-Onset Dementia in Consecutive Patients in a Memory Clinic

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Key Words
Early-onset dementia · Alzheimer's disease · Frontotemporal lobar degeneration · Dementia with Lewy bodies · Memory clinic

Abstract
Aims: To investigate the frequency, rate of causes of dementia, and clinical characteristics of early-onset dementia in consecutive patients of a memory clinic. ***Methods:*** A total of 668 consecutive demented patients were involved in this study. We examined the distribution of patients' diagnosis, differences in sex, education, dementia severity and cognitive function at the first visit, and the duration from onset to consultation. We also examined the changes in the proportion of subjects during the research period. ***Results:*** There were 185 early-onset patients, 28% of all demented patients. No significant differences were observed between the early-onset and late-onset dementia groups in Clinical Dementia Rating and Mini-Mental State Examination score at the first consultation, but the duration from onset to consultation was significantly longer in the early-onset group. In the early-onset group, the rates of patients with Alzheimer's disease and dementia with Lewy bodies were relatively low and the rate of patients with frontotemporal lobar degeneration was relatively high. There were no significant differences in the proportion between either demented subjects and nondemented subjects or early-onset dementia patients and late-onset dementia patients during the research period. ***Conclusion:*** We conclude that early-onset dementia is not rare and its clinical characteristics and causes are different from late-onset dementia.

Introduction

Early-onset dementia (EOD), with onset in those younger than 65 years, has a large psychological and economical impact on patients and caregivers because of their leading role in the society and family at the disease onset. However, EOD has been underrecognized until today and social support services for EOD patients are not enough compared with those for late-onset dementia (LOD) patients.

Although there are some studies about early-onset Alzheimer's disease (AD) [1–3], there are few systematic studies about cognitive function in and clinical features of EOD of the non-Alzheimer type [4, 5]. Further, epidemiologic data on relatively rare causes of dementia, in-

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Table 1. Clinical characteristics of EOD patients and LOD patients

	EOD patients (n = 185; 27.7%)	LOD patients (n = 483; 72.3%)	p
Age at consultation, years	58.3 ± 11.0	77.9 ± 5.6	
Sex ratio (M:F)	94:91	188:295	0.007
Education[1], years	11.4 ± 2.8	9.5 ± 2.5	0.000
MMSE score at first consultation[2]	18.4 ± 7.8	18.4 ± 6.4	0.978
CDR at first consultation (0.5:1:2:3)[3]	50:50:53:12	108:167:148:34	0.326
Duration from onset to consultation, months	59.6 ± 70.8	35.7 ± 25.9	0.000

Those who could not undergo MMSE or CDR at their first consultation or whose caregivers' information on patients' education was inaccurate were excluded.
[1] n = 628.
[2] n = 637.
[3] n = 622.

cluding dementia with Lewy bodies (DLB) and frontotemporal lobar degeneration (FTLD), are insufficient because pure cross-sectional or population studies are impractical for rare diseases [6]. Therefore, we aimed to clarify the frequency of EOD, rate of causes of dementia, and clinical characteristics of EOD in consecutive patients of our memory clinic.

Method

A total of 861 consecutive patients visiting the Higher Brain Function Clinic of the Department of Neuropsychiatry, Ehime University Hospital between January 1997 and September 2005 were examined. Of the 861 patients assessed, more than 80% resided in the Ehime prefecture, within a 100-km radius of the hospital, at their first consultation. The Ehime prefecture is a rural area of Japan with 1.5 million people, 21% of whom are over 65 years old. Our clinic is one of the few specialized clinics for demented people where we can evaluate patients with brain MRI and HMPAO-SPECT. More than 40% of all patients were referred from other doctors. Fifty percent of referrals were received from psychiatrists who are experts in demented patients to some degree, and the others were received from general physicians and geriatricians.

All patients were seen by senior neuropsychiatrists and underwent physical and neurological examinations. Thirty-three patients who came to our clinic only once or who could not undergo neuroimaging examination were excluded, as they could not complete enough evaluations for us to make a clear diagnosis. Patients were assessed with a comprehensive neuropsychological test battery, which included the Mini-Mental State Examination (MMSE) [7], Clinical Dementia Rating (CDR) [8], together with standard psychiatric evaluations to exclude major functional psychiatric disorders such as schizophrenia and mood disorders. All patients underwent brain MRI, except those with cardiac pacemakers who underwent brain CT instead. Almost all patients underwent HMPAO-SPECT except those who could not because of their behavioral symptoms. Patients were also assessed with screening blood tests including vitamin B_{12}, folic acid and thyroid function.

Dementia was diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition revised [9]. Patients with AD satisfied probable AD criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [10], and patients with vascular dementia (VaD) satisfied 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) [11]. DLB was defined according to the consensus guidelines for the clinical diagnosis of DLB [12]; FTLD was diagnosed according to the international consensus criteria [13]. Standard diagnostic criteria were also applied to dementia of other etiologies.

Information about onset of dementia was routinely and systematically queried from caregivers, and it was emphasized that 'onset' is the time when caregivers first noticed changes from the patients' premorbid state which should be substantive and not a long-standing character trait. One hundred and sixty patients were excluded as they did not fulfill the diagnostic criteria for dementia; 668 patients were included in this study. Among these nondemented patients, there were 31 patients with schizophrenia or delusional disorder, 19 patients with depression or anxiety disorder and 17 normal healthy subjects. The distribution of patients' diagnosis, differences in sex, educational level, severity of dementia according to CDR at the first visit, cognitive function according to MMSE at the first visit, and the duration from onset to consultation were compared between the EOD group (onset before the age of 65 years) and LOD group (onset after the age of 65 years). We examined the distribution of onset age and sex according to the causes of dementia in EOD patients. We also examined the changes in the proportion of subjects during the research period.

Data analyses were carried out using the SPSS-PC software package. Statistical differences between the EOD group and LOD group were assessed by the t test for age, education, duration from onset to consultation and MMSE score, and by the χ^2 test with post hoc Fisher's exact test for sex, CDR, distribution of diagnosis, and proportion of subjects. All examinations were conducted after obtaining informed consent from all subjects or their caregivers.

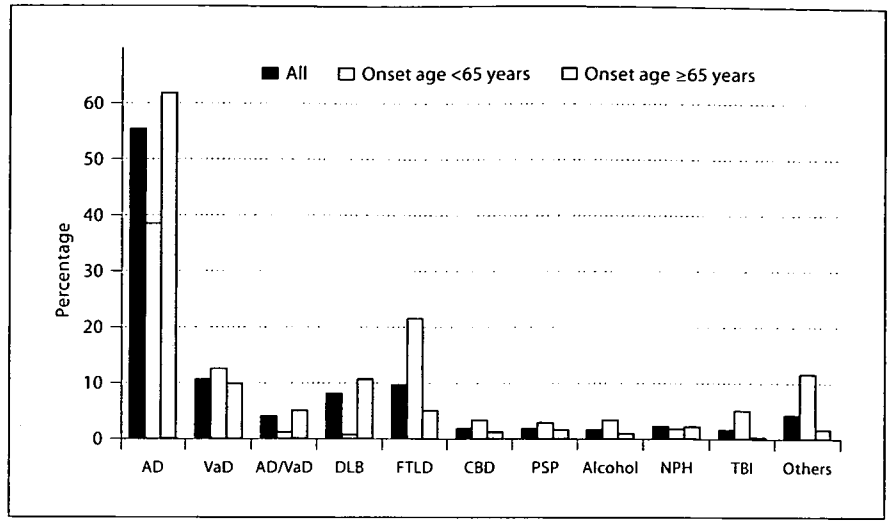

Fig. 1. Rate of causes of dementia in all patients, EOD patients and LOD patients. CBD = Corticobasal degeneration; PSP = progressive supranuclear palsy; alcohol = alcohol-related dementia; NPH = normal pressure hydrocephalus; others = dementia of other etiologies.

Result

Table 1 shows the clinical characteristics of the total 668 patients with dementia, comparing the EOD group and LOD group.

There were 185 EOD patients, 27.7% of all demented patients. In these EOD patients, mean age at consultation was 58.3 years and the sex ratio was almost equal (M:F = 94:91), meaning there were significantly fewer females than in the LOD group. Educational level was significantly higher than in LOD patients. There were no significant differences between the two groups in CDR and MMSE score at the first visit, but duration from disease onset to consultation was significantly longer in the EOD group compared to the LOD group.

Figure 1 shows the rate of causes of dementia in all patients, EOD and LOD groups.

Among all demented patients, AD was the most frequent cause of dementia (55.4%), followed by VaD (10.5%), FTLD (9.4%) and DLB (8.1%). Among EOD patients, AD was also the most frequent cause of dementia (38.5%). FTLD was the second most common cause of dementia (21.4%), followed by VaD (12.6%) and traumatic brain injury (TBI) (4.9%), and there were only a few DLB patients (0.5%). There were statistically significant differences between the EOD and LOD groups in the frequency of AD ($p = 0.000$), DLB ($p = 0.000$), FTLD ($p = 0.000$), alcohol-related dementia ($p = 0.031$), and TBI ($p = 0.000$). Neurosyphilis, carbon monoxide intoxication and post-encephalitis were relatively common in EOD patients with other etiologies.

Table 2. Changes in the proportion of subjects during the research period

	Demented		Nondemented	Total
	EOD	LOD		
1997–1999	39	146	56	241
2000–2002	69	164	63	296
2003–2005 (Sept.)	77	173	74	324
Total	185	483	193	861

Among all EOD patients and early-onset AD patients, the number of patients increased as the onset age got older, and there were no large differences in sex distribution in any generation. Among early-onset VaD patients, the number of patients increased with increasing onset age, and there were more males. Among early-onset FTLD patients, the number of patients increased after the age of 45 years, but no constant tendency was found in the sex ratio.

The changes in the proportion of subjects during the three sequential research periods are summarized in table 2.

Although the number of subjects increased with the passage of time in all groups, there were no significant differences in the proportion between either demented subjects and nondemented subjects or EOD patients and LOD patients. Among the demented patients, the severity of dementia according to CDR at the first consultation did not differ during the research period.

Discussion

This is a systematic study to reveal the clinical characteristics of EOD in consecutive patients over a period of 8 years at a memory clinic in Japan. It is worthy of notice that nearly 30% of the demented patients had an age of onset of less than 65 years.

Comparing with other studies in Japan, Miyanaga et al. [14] estimated that there are a total of 25,000 EOD patients (32 patients per 100,000 population) in Japan, only a few percent of more than 2 million demented patients. Yokota et al. [15] reported that only 34 patients (7.3%) had an age of onset of less than 65 years out of a total of 464 demented patients from their outpatients of psychiatric hospitals in Japan. Both studies showed a much fewer number of EOD patients than our study. Comparing with other countries, Harvey et al. [5] estimated that there are 54 EOD patients per 100,000 population in their epidemiological study in the UK, almost the same number as the one previously reported in Japan. An outpatient study in Denmark showed that a total of 314 patients per 1,000 demented patients were aged less than 60 years [4], an outpatient study in the USA reported that 29.3% of 948 demented patients were EOD patients [16], and a UK study showed that the proportion of EOD patients was 28.6% [17]. All these results are consistent with our result. An outpatient study in Brazil showed that 46.6% of all demented patients were EOD patients [18], a relatively high number compared to other studies. There may be more EOD patients in Japan than previously reported.

In our study, the sex ratio in the EOD group was almost equal, whereas there were more females in the LOD group. In fact, many epidemiological studies revealed that there were more female patients among the demented elderly [19–21], while there were more males among EOD patients [5, 14]. This may be because there are more male-related causes of dementia, such as VaD or alcohol-related dementia, in EOD groups. There is a possibility that the sex ratio of AD is affected by onset age, as some studies mentioned that there are more males in early-onset AD patients than in late-onset AD patients [3].

The education level was significantly higher in EOD groups. This may be due to changes in the educational system in Japan after World War II.

As there were no significant differences between the EOD and LOD groups in CDR and MMSE score at the first consultation, we performed this analysis with all causes of dementia together; however, cognitive function and severity of dementia could not be discussed for each cause of dementia. Therefore, further assessments are needed on cognitive function and psychiatric symptoms for all causes of dementia.

It is noteworthy that in EOD patients the duration from disease onset to consultation is longer than in LOD patients. Therefore, it seems that the progress of dementia in EOD patients is slow, even though the severity of dementia is equal between the two groups. However, in patients with AD, which is the major cause of dementia, early-onset groups are known to show a more rapid progression than late-onset groups [22, 23]. Therefore, we suppose that in EOD patients it takes longer to correctly diagnose the disease because early-onset patients are sometimes misdiagnosed as having psychiatric disorders such as schizophrenia or mood disorders. Furthermore, EOD groups consist of not only patients with neurodegenerative disorders or cerebrovascular diseases but also of patients with many heterogeneous causes of dementia, such as TBI or neurosyphilis. These pathologies sometimes require more time to be diagnosed by specialists in dementia. This misdiagnosis might have led to the underrecognition of EOD, and hence, to the underestimation of its prevalence. This issue is important from a socioeconomic point of view, and we need to inform people further about EOD.

There are also a few noteworthy findings in the classification of causes of dementia in our study. Among our patients, 12.6% of all EOD patients had VaD and there was no significant difference between that number and the number of LOD patients (9.7%). Although several epidemiological studies have reported that VaD was more common in patients aged less than 65 years compared with elderly patients [3, 18, 24], our result was not consistent with these findings. The distribution of the diagnoses of VaD is influenced by the specificity and sensitivity of the criteria used in each study, and the NINDS-AIREN criteria are known to be the strictest criteria, requesting onset of dementia within 3 months following a recognized stroke [25, 26]. This low prevalence of VaD in our study may be because we used the NINDS-AIREN criteria to diagnose VaD, and young patients may not have recognized their strokes. Furthermore, as our series of patients are outpatients of the neuropsychiatry department, there is a possibility that there might be few subjects with clear neurological symptoms due to cardiovascular disease.

Among our patients, DLB was the second most common cause of dementia (10.9%) in the LOD group while there were only a few DLB patients (0.5%) in the EOD group. Although there were little epidemiological data on clinically diagnosed DLB compared with research on au-