pairment as an early indicator of dementia. *J Clin Exp Neuropsychol*, **15** : 805-821 (1993).
3) 数井裕光，綿森淑子，本多留実，時政昭次ほか：日本版リバーミード行動記憶検査（RBMT）の有用性の検討．神経進歩，**46**：307-318（2002）.
4) Kazui H, Matsuda A, Hirono N, Mori E, et al.: Everyday memory impairment of patients with mild cognitive impairment. *Dement Geriatr Cogn Disord*, **19** : 331-337 (2005).
5) 松田明美，数井裕光，博野信次，森　悦朗：軽症アルツハイマー病患者におけるリバーミード行動記憶検査の有用性．脳神経，**54**（8）：673-678（2002）.
6) McKitrick LA, Camp CJ, Black FW : Prospective memory intervention in Alzheimer's disease. *J Gerontol*, **47** : 337-343 (1992).
7) 仲秋秀太郎：prospective memory（展望記憶）．（浅井昌弘，鹿島晴雄編）臨床精神医学講座・S2；記憶の臨床，137-156，中山書店，東京（1999）.
8) Nakaaki S, Watanabe H, Nakamura H, Yoshida S, et al.: The Influence of the Stroop interference effect on an event-based prospective memory task in Alzheimer's disease patients. *Psychogeriatrics*, **2** : 120-126 (2002).
9) 仲秋秀太郎，三村　將：初期記憶障害の特徴とその評価法．老年精神医学雑誌，**20**（10）：1071-1081（2009）.
10) Petersen RC, Smith GE, Waring SC, Ivnik RJ, et al.: Mild cognitive impairment ; Clinical characterization and outcome. *Arch Neurol*, **56** : 303-308 (1999).
11) Petersen RC, Stevens JC, Ganguli M, Tangalos EG, et al.: Practice parameter ; Early detection of dementia – Mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, **56** : 1133-1142 (2001).
12) Troyer AK, Murphy KJ : Memory for intentions in amnestic mild cognitive impairment ; Time- and event-based prospective memory. *J Int Neuropsychol Soc*, **13** : 365-369 (2007).

International Psychogeriatrics: page 1 of 8 © International Psychogeriatric Association 2010
doi:10.1017/S104161021000222X

Risk of progression from mild memory impairment to clinically diagnosable Alzheimer's disease in a Japanese community (from the Nakayama Study)

Naomi Sonobe,[1] Ryuji Hata,[1,2] Tomohisa Ishikawa,[1] Kantaro Sonobe,[1] Teruhisa Matsumoto,[1] Yasutaka Toyota,[1] Takaaki Mori,[1] Ryuji Fukuhara,[1] Kenjiro Komori,[1] Shu-ichi Ueno,[1] Satoshi Tanimukai[1] and Manabu Ikeda[3]

[1] *Department of Neuropsychiatry, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime, Japan*
[2] *Department of Functional Histology, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime, Japan*
[3] *Department of Psychiatry and Neuropathobiology, Faculty of Medical and Pharmaceutical Sciences, Kumamoto University, Honjo, Kumamoto, Japan*

ABSTRACT

Background: Memory impairment has been proposed as the most common early sign of Alzheimer's disease (AD). The aims of this work were to evaluate the risk of progression from mild memory impairment / no dementia (MMI/ND) to clinically diagnosable AD in a community-based prospective cohort and to establish the risk factors for progression from MMI/ND to AD in the elderly.

Methods: Elderly subjects aged over 65 years were selected from the participants in the first Nakayama study. MMI/ND was defined as memory deficit on objective memory assessment, without dementia, impairment of general cognitive function, or disability in activities of daily living. A total of 104 MMI/ND subjects selected from 1242 community-dwellers were followed longitudinally for five years.

Results: During the five-year follow-up, 11 (10.6%) subjects were diagnosed with AD, five (4.8%) with vascular dementia (VaD), and six (5.8%) with dementia of other etiology. Logistic regression analysis revealed that diabetes mellitus (DM) and a family history of dementia (within third-degree relatives) were positively associated with progression to AD, while no factor was significantly associated with progression to VaD or all types of dementia.

Conclusions: DM and a family history of dementia were significant risk factors for progression from MMI/ND to clinically diagnosable AD in the elderly in a Japanese community.

Key words: dementia, vascular dementia, mild cognitive impairment

Introduction

Alzheimer's disease (AD) is one of the most common causes of dementia in the elderly. There is increasing evidence that medical, behavioral and social interventions can delay the cognitive and functional decline associated with AD (Burns and O'Brien, 2006). Even though several treatment options are available, treatment is often started too late, i.e. when considerable neuropathological changes have already occurred (Hulette *et al.*, 1998). For early intervention, it is essential to identify subjects who will later develop AD (Heun *et al.*, 2006). This evaluation could be improved by a better knowledge of the early signs of AD, and the presence of mild cognitive impairment (MCI) could be an early sign of AD. MCI was first defined as an isolated memory disorder that can precede dementia, characterized by subjective memory complaints and objective memory impairment on neuropsychological testing in non-demented individuals (Petersen *et al.*, 1999). A substantial number of subjects with MCI progress to dementia. However, not all MCI subjects develop AD, as subjects may remain stable for a long period, revert to a normal state, or progress to another type of dementia (Petersen *et al.*, 2001). Moreover, the clinical diagnosis per se is often uncertain in MCI. To increase the accuracy of detection of MCI and its subtypes, a great

Correspondence should be addressed to: Ryuji Hata, MD, PhD, Department of Functional Histology, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime 791-0295, Japan. Phone: + 81 89960 5236; Fax: + 81 89960 5239. Email: hata@m.ehime-u.ac.jp. Received 28 Aug 2010; revision requested 22 Sep 2010; revised version received 19 Oct 2010; accepted 21 Oct 2010.

number of neuropsychological assessments have been proposed because several studies have shown that elderly individuals with MCI constitute a high-risk population for developing dementia (Luck *et al.*, 2010). Clinic-based cohort studies provide the opportunity to characterize MCI extensively and carefully. However, in community-based cohort studies, the burden of strict memory examinations or complicated neuropsychological assessments is too heavy for subjects and examiners. In clinical practice, it is quite beneficial to identify high-risk groups for developing dementia by using simple cognitive tests and additional evaluation of the risk of progression to clinically diagnosable AD or dementia.

Previously, we proposed criteria for mild memory impairment/no dementia (MMI/ND) using only the Mini-mental State Examination (MMSE) in a community-based prospective cohort study, because memory impairment was proposed to be the most common early sign of AD (Petersen *et al.*, 1999). We followed the subjects with MMI/ND for five years and demonstrated that MMI/ND was almost the same as MCI (Ishikawa *et al.*, 2006). In the present study, we assessed whether or not progression from MMI/ND to dementia is affected by several established and emerging risk factors.

Methods

This study was approved by the Ethics Committee of the Ehime University Graduate School of Medicine and conducted after obtaining informed consent from all subjects or their responsible relatives.

The Nakayama study

Nakayama is a Japanese rural community adjacent to Matsuyama City, a metropolis on Shikoku Island. We selected this town because of its population size (5038 total residents, of whom 1438 were over 65 years of age), population stability (only 3.1% of people aged over 65 had moved elsewhere, including those in institutions, in the three years preceding the first survey), and the active collaboration offered by family doctors. The first Nakayama study included all residents aged over 65 years living at home in the rural community of Nakayama between January 1997 and March 1998 by means of a door-to-door survey. Of 1438 inhabitants, 1162 (80.8%) completed the protocol. A more detailed description of the methods has been reported previously (Ikeda *et al.*, 2001). In brief, the screening interview consisted of a semi-structured questionnaire containing questions on education, occupation, daily life activities (Physical Self-Maintenance Scale (PSMS) and Instrumental Activities of Daily Living Scale (IADL)), alcohol consumption, exposure and risk factor profile, previous disease, Geriatric Depression Scale (GDS; Yesavage, 1988), medication, sleep, and appetite, followed by the MMSE for participants and the short memory questionnaire (SMQ) for a family member of each participant. All subjects were examined by senior neuropsychiatrists, and cranial CT was conducted on all subjects with any sign of dementia.

Subjects

Subjects were selected from the participants in the first Nakayama study (Ikeda *et al.*, 2001). Subjects in a community-based elderly cohort of MMI/ND were followed longitudinally. MMI/ND was defined according to the following criteria:

(i) normal general cognitive function, with MMSE $\geq$24;
(ii) objective memory impairment, assessed by three-word recall in MMSE (delayed recall 0/3 or 1/3);
(iii) neuropsychiatric examination: absence of dementia or depression, diagnosed by a senior neuropsychiatrist according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IIIR; American Psychiatric Association, 1987); and
(iv) no ADL impairment.

Follow-up assessment and diagnosis

Five-year follow-up was conducted on all these individuals between April and December 2003. A senior neuropsychiatrist administered MMSE to subjects, while a public health nurse conducted PSMS and IADL interviews with a family member of each subject. Subjects who had been hospitalized or were living in institutions were included. Cranial CT was conducted on all subjects whose MMSE score had declined by 2 or more points from baseline (Mohs *et al.*, 2001) or who had any sign of dementia. The diagnosis of dementia was established according to the DSM-IIIR criteria. Finally, subjects with dementia were classified into subgroups by the cause of dementia. AD was defined according to the NINCDS-ADRDA criteria for probable AD (McKhann *et al.*, 1984), while VaD was defined according to the NINDS-AIREN criteria (Román *et al.*, 1993).

Statistics

Student's two-tailed t-test and χ^2 test were used to compare cohorts in terms of continuous and categorical variables, respectively. Univariate and multivariate logistic regression analysis based on the maximum likelihood method were used to

estimate associations between putative risk factors and the progression from MMI/ND to AD, VaD or dementia. Odds ratios (OR) with the corresponding 95% confidence intervals (CI) were calculated. Statistical significance was indicated if p values <0.05. Variables shown to be significant in univariate analysis were entered in the model by means of a forward stepwise logistic regression procedure until no variable not in the model made a significant ($P < 0.05$) contribution. Before being entered into the logistic regression model, factors were tested for multicollinearity. If a factor was strongly correlated ($r > 0.5$) with another, the factor with the stronger association with the progression was included. All analyses were performed using the Statistical Package for the Social Sciences (SPSS), release 16 (SPSS Inc., Chicago, IL).

Table 1. Final diagnoses for 104 cases of MMI/ND

	NUMBER OF CASES
Died	14
Moved to other community	13
Refused	6
AD	11
VaD	5
Other types of dementia	6
MMI/ND	9
Normal	40
Total	**104**

AD = Alzheimer's disease; VaD = vascular dementia; MMI/ND = mild memory impairment/ no dementia

Results

Of the 1242 inhabitants who participated in the first Nakayama study, 104 subjects were diagnosed with MMI/ND (45 men, 59 women), all of whom consented to participate in the study. During the five-year follow-up period, 14 subjects died, 13 moved to other communities (mainly due to institutionalization), 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%) with VaD (three men, two women), two (1.9%) with dementia with Lewy bodies (one man, one woman), one (1.0%) with alcohol-related dementia (one man), and three (2.9%) with unclassified dementia (one man, two women). Nine (8.7%) subjects remained in a state of MMI/ND. Furthermore, 40 (38.5%) subjects showed restored three-words recall in MMSE (delayed recall 3/3 or 2/3) and were assessed as having normal general cognitive function (MMSE $\geq$ 24) (Table 1). The socialdemographic and clinical characteristics at baseline of these four groups are given in Table 2. Table 3 shows the baseline characteristics of MMI/ND participants who progressed to develop AD compared with those who did not. Those who converted to dementia had a significantly higher prevalence of diabetes mellitus (DM) ($p = 0.020$) and family history of dementia ($p = 0.019$).

To investigate the association of risk factors with the progression from MMI/ND to clinically diagnosable AD, VaD or all types dementia, univariate and forward logistic regression analyses based on the maximum likelihood method were used. Univariate logistic regression analysis revealed that DM (OR = 5.437; 95% CI 1.138–25.971, $p = 0.034$) and a family history of dementia (OR = 4.743; 95% CI 1.178–19.093, $p = 0.028$) were positively associated with progression from MMI/ND to AD, while sex, age, body mass index (BMI), education period, GDS score, hypertension, hypercholesterolemia, current smoking, current drinking, use of hypnotics, history of cerebrovascular disease and history of head trauma were not. On the other hand, univariate logistic regression analysis revealed that no factor was significantly associated with progression from MMI/ND to VaD or all types of dementia (data not shown). In addition, forward stepwise logistic regression analysis revealed that factors independently associated with progression from MMI/ND to AD were DM (OR = 6.626; 95% CI 1.216–36.091; $p = 0.029$) and a family history of dementia (OR = 6.071; 95% CI 1.351–27.282; $p = 0.019$) (Table 4), while no factor was significantly associated with progression from MMI/ND to VaD or all types of dementia (data not shown).

Discussion

MCI defines a transitional state along a continuous spectrum that ranges from normal aging to fully developed dementia (Petersen *et al.*, 2001). MCI is classified as four clinical subtypes: single domain amnestic MCI, multiple domain amnestic MCI, single domain non-amnestic MCI and multiple domain non-amnestic MCI. These four clinical subtypes are assumed to differ in etiology and outcome. Amnestic MCI is widely considered to be the condition most commonly associated with a high risk of progression to AD (Petersen, 2004), and is therefore regarded by most authors as a prodromal state of AD (Gauthier *et al.*, 2006). Previously, we estimated the rate of a shift to dementia in subjects with mild memory impairment/no dementia (MMI/ND) in a community-based cohort

Table 2. Baseline characteristics of study subjects

	MMI/ND N = 104	TO AD N = 11	TO VaD N = 5	TO DEMENTIA N = 22
Men/women	45/59	5/6	3/2	11/11
Age, years	74.4 ± 6.6	77.5 ± 3.3	74.4 ± 6.1	77.2 ± 5.3
Education, years	8.0 ± 2.0	8.5 ± 2.1	8.6 ± 1.9	8.1 ± 1.9
MMSE	26.2 ± 1.6	25.6 ± 1.2	26.2 ± 2.0	25.7 ± 1.5
BMI, kg/m^2	22.2 ± 2.7	21.6 ± 2.7	21.9 ± 2.6	22.1 ± 2.9
GDS	1.8 ± 2.3	1.6 ± 1.6	1.4 ± 1.1	1.6 ± 1.4
Current smoking	31 (29.8)	3 (27.3)	2 (40.0)	6 (27.3)
Current drinking	24 (23.1)	2 (18.2)	3 (60.0)	6 (27.3)
Hypnotic agent	9 (8.7)	2 (18.2)	0 (0.0)	2 (9.1)
Diabetes mellitus	9 (8.7)	3 (27.3)	0 (0.0)	3 (13.7)
Hypertension	44 (42.3)	5 (45.5)	3 (60.0)	11 (50.0)
Hypercholesterolemia	11 (10.6)	0 (0.0)	0 (0.0)	1 (4.5)
Previous CVD	11 (10.6)	1 (9.1)	1 (20.0)	2 (9.1)
Previous head trauma[a]	7 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
Family history of dementia[b]	13 (12.5)	4 (36.4)	0 (0.0)	4 (18.2)

Values are number or mean ± SD. Numbers in parentheses are percentages.
[a] with loss of consciousness.
[b] within 3rd-degree relatives.
BMI = body mass index; GDS = Geriatric Depression Scale; CVD = cerebrovascular disease.

Table 3. Characteristics of study subjects categorized by conversion to AD

	AD CONVERTED N = 11	NON AD CONVERTED N = 93	STATISTICS	P-VALUE
Men/women	5/6	40/53	$\chi^2 = 0.024$	0.877 (n.s.)
Age, years	77.5 ± 3.3	74.0 ± 6.8	F = 4.439, t = 1.662	0.100 (n.s.)
Education period, years	8.5 ± 2.1	8.0 ± 2.0	F = 0.775, t = 0.726	0.469 (n.s.)
MMSE	25.6 ± 1.2	26.3 ± 1.6	F = 4.987. t = 1.487	0.140 (n.s.)
BMI, kg/m^2	21.6 ± 2.7	22.2 ± 2.8	F = 0.451, t = 0.764	0.447 (n.s.)
GDS	1.6 ± 1.6	1.8 ± 2.4	F = 0.092, t = 0.170	0.865 (n.s.)
Current smoking	3 (27.3)	28 (30.1)	$\chi^2 = 0.038$	0.846 (n.s.)
Current drinking	2 (18.2)	22 (23.7)	$\chi^2 = 0.166$	0.684 (n.s.)
Hypnotic agent	2 (18.2)	7 (7.5)	$\chi^2 = 1.413$	0.235 (n.s.)
Diabetes mellitus	3 (27.3)	6 (6.5)	$\chi^2 = 5.394$	0.020 ($p < 0.05$)
Hypertension	5 (45.5)	39 (41.9)	$\chi^2 = 0.050$	0.823 (n.s.)
Hypercholesterolemia	0 (0.0)	11 (11.8)	$\chi^2 = 1.455$	0.228 (n.s.)
Previous CVD	1 (9.1)	10 (10.8)	$\chi^2 = 0.029$	0.865 (n.s.)
Previous head trauma[a]	0 (0.0)	7 (7.5)	$\chi^2 = 0.888$	0.346 (n.s.)
Family history of dementia[b]	4 (36.4)	10 (10.8)	$\chi^2 = 5.538$	0.019 ($p < 0.05$)

Values are number or mean ± SD. Numbers in parentheses are percentages.
[a] with loss of consciousness.
[b] within third-degree relatives.
BMI = body mass index; GDS = Geriatric Depression Scale; CVD = cerebrovascular disease; n.s.: not significant.

study (Ishikawa *et al.*, 2006). In our study, MMI/ND was not strictly defined as MCI because we did not use standardized memory tests except for MMSE to detect prodromal dementia subjects. Of the 1242 eligible inhabitants aged over 65 years, we selected 104 subjects with MMI/ND. The prevalence of MMI/ND was 8.95%, consistent with that in previous community- based studies ranging from 7.3% to 13.3% (Luck *et al.*, 2010). We followed these 104 elderly subjects with MMI/ND for five years and showed that the annual conversion rates from MMI/ND to AD and dementia were 3.1% and 6.2% per year, respectively. These annual conversion rates from MMI/ND to AD and dementia were also almost the same as those in the previous community-based cohorts with strict memory examinations, ranging from 1.1 to 9.0% per year and 1.6 to 10.3% per year, respectively (Mitchell and Shiri-Feshki, 2009). Hence MMI/ND is considered to be almost the

Table 4. Association of risk factors and other characteristics with conversion from MMI/ND to AD in multivariate logistic regression analysis in all study subjects (n = 104)

	FULLY ADJUSTED MODEL 1[A]		MODEL 2[B]	
RISK FACTORS	OR (95%CI)	P-VALUE	OR (95%CI)	P-VALUE
Sex	0.705 (0.50–9.872)	0.795 (n.s.)	n.a.	
Age	1.086 (0.960–1.227)	0.189 (n.s.)	1.082 (0.985–1.189)	0.102 (n.s.)
Education period	1.384 (0.851–2.253)	0.191 (n.s.)	n.a.	
MMSE score	0.802 (0.475–1.355)	0.410 (n.s.)	n.a.	
BMI	0.816 (0.594–1.122)	0.211 (n.s.)	n.a.	
GDS score	0.867 (0.560–1.344)	0.524 (n.s.)	n.a.	
Current smoking	0.422 (0.030–5.927)	0.522 (n.s.)	n.a.	
Current drinking	0.727 (0.049–10.682)	0.816 (n.s.)	n.a.	
Hypnotic agent	3.721 (0.397–34.858)	0.250 (n.s.)	n.a.	
Diabetes mellitus	20.795 (1.953–221.391)	0.012 ($p < 0.02$)	6.626 (1.216–36.092)	0.029 ($p < 0.05$)
Hypertension	1.135 (0.185–6.948)	0.891 (n.s.)	n.a.	
Hypercholesterolemia	0.000	0.998 (n.s.)	n.a.	
Past history of CVD	0.479 (0.024–9.513)	0.629 (n.s.)	n.a.	
Past history of head trauma	0.000	0.999 (n.s.)	n.a.	
Family history of dementia	16.437 (2.017–133.932)	0.009 ($p < 0.01$)	6.071 (1.351–27.282)	0.019 ($p < 0.02$)

[a] Fully adjusted model 1: adjusted for all other variables in table.
[b] Model 2: included only significant variables (forward stepwise method).
OR = odds ratio; CI = confidence interval; BMI = body mass index; GDS = Geriatric Depression Scale; CVD = cerebrovascular disease; n.s. = not significant; n.a. = not applicable.

same as MCI (mainly amnestic MCI) (Ishikawa *et al.*, 2006).

Compared with community-based cohorts, annual conversion rates from MCI to AD and dementia are often substantially higher in clinic-based cohorts (4.4–19.6% per year and 4.4–17.6% per year, respectively) (Mitchell and Shiri-Feshki, 2009). There are several explanations for the differences in findings between clinic-based and community-based cohorts. Farias *et al.* (2009) reported that clinic-based cohorts rather than community-based cohorts may be vulnerable to selection bias. The composition of clinic samples is shaped by various factors (e.g. the demographics of the individuals studied, patterns of self-referral and provider referral, etc.) that make generalization impossible (Farias *et al.*, 2009). In general, community subjects are recruited after the age of 65 without dementia and develop dementia during the study, whereas clinic patients are typically recruited at baseline with a history of cognitive decline and this impairment worsens during the course of the study. Clinic patients may also have greater financial, social and personal resources, resulting in longer survival after diagnosis, more severe pathology at death and a higher conversion rate to dementia (Schneider *et al.*, 2009). In agreement with these reports, the annual conversion rates to AD and dementia in our community-based cohort were relatively lower than those in clinic-based cohorts.

The present study showed that DM significantly increased the risk of progression from MMI/ND to clinically diagnosable AD. Patients with diabetes, of both type 1 (T1DM) and type 2 (T2DM), have been found to have cognitive dysfunction that can be attributed to their disease (Kodl and Seaquist, 2008). The association of DM with impaired cognitive function suggests that DM may contribute to dementia and AD. In fact, several longitudinal population-based studies showed that the incidence of dementia was higher in individuals with diabetes than in those without diabetes, and several researchers reported that DM has been implicated as a risk factor for the development of dementia and AD (MacKnight *et al.*, 2002; Arvanitakis *et al.*, 2004). Our results are in good agreement with these previous reports. DM might accelerate cognitive decline and conversion to AD by a number of potential mechanisms. They may be attributable to vascular risk factors such as hypertension, dyslipidemia, and atherosclerosis. Other mechanisms, such as accelerated aging of the brain, have also been implicated. As it accelerates cerebral atrophy, DM may reduce cognitive reserve and the threshold for the development of AD symptoms (Biessels *et al.*, 2006). DM may regulate cerebral amyloid and tau metabolism. In the preclinical syndrome of T2DM, hyperinsulinemia precedes hyperglycemia by many years. Insulin increases the secretion of Aβ into the extracellular space and stimulates tau phosphorylation to form

neurofibrillary tangles (Gasparini and Xu, 2003). Insulin also affects APP processing in vivo, a critical molecular step in generating Aβ, to promote secretion of sAPP (Gasparini and Xu, 2003). Insulin degrading enzyme (IDE) has also been shown to play a major role in the degradation and clearance of insulin in vivo. Among all secreted proteases from cells, only IDE can degrade Aβ. When the insulin level increases in the brain, it can competitively inhibit IDE, which may cause Aβ neurotoxicity and then accelerate AD pathology (Qiu and Folstein, 2006). In addition, insulin resistance seems to accelerate biological aging by fostering the formation of advanced glycation end-products (AGE) and, consequently, ROS (reactive oxygen species) (Roriz-Filho *et al.*, 2009). All these mechanisms are thought to contribute to mild cognitive impairment and AD. Although we did not clarify its mechanism, we demonstrated that DM was a significant risk factor for a shift from prodromal cognitive impairment to fully developed AD.

We also showed that the presence of a family history of AD significantly increased the risk of progression from MMI/ND to clinically diagnosable AD. A positive family history of AD suggests the relevance of genetic risk factors. A Swedish twin study has reported that 60–80% of AD is attributable to genetic effects (Gatz *et al.*, 2005), and several genetic risk factors are known to increase the risk of AD (Bendlin *et al.*, 2010). For early-onset AD, the APP, presenilin (PS)-1, and PS-2 genes play an important role. For late-onset AD, variation in the apolipoprotein E (APOE) gene is the strongest genetic risk factor. As the number of APOE-ε4 alleles increases, the risk of late-onset AD increases from 20% to 90%, and the mean age at onset decreases from 84 to 68 years (Chen *et al.*, 2009). Because of this overwhelming effect of APOE on late-onset AD, we speculated that a positive family history of AD was related to the APOE genotype, although further genetic investigation is required to confirm this assumption. In addition, Mosconi *et al.* recently reported that normal subjects with a maternal family history of late-onset AD showed more amyloid β deposition in the cerebral cortex than normal subjects with a paternal family history (Mosconi *et al.*, 2010). In our study, four MMI/ND subjects (three maternal, one paternal) developed clinically diagnosable AD while ten MMI/ND subjects (six maternal, three parental, one unidentified) did not. Although we could not demonstrate a positive correlation between the incidence of AD and a maternal family history, further epidemiological investigation is required to confirm this notion.

Vascular dementia (VaD) is defined as loss of cognitive function sufficient to cause functional disability in everyday life, resulting from ischemic, hypoperfusive, or hemorrhagic brain lesions due to cerebrovascular or cardiovascular disease. VaD and AD are the most prevalent types of dementia in the elderly. VaD is considered to have an abrupt onset of dementia, followed by stepwise deterioration of cognitive performance associated with neurological signs and symptoms reflecting focal brain lesions (Román *et al.*, 1993). It has generally been accepted that cognitive function deteriorates rapidly from normal at the time of or shortly after stroke, which warrants the diagnosis of VaD (Román *et al.*, 1993). However, subcortical ischemic VaD often has a more insidious onset with gradual cognitive deterioration, and the temporal relation between cognitive impairment and evidence of cerebrovascular disease may not be clear (Meyer *et al.*, 2002). Recently, the concept of vascular cognitive impairment (VCI) has been introduced to describe the spectrum of cognitive change related to vascular causes, from early cognitive decline to dementia (O'Brien *et al.*, 2003). By analogy with the concept of amnestic MCI, vascular cognitive impairment with no dementia (VCIND) has been proposed as a preclinical state linked to a high risk of dementia progression and a prodromal state of VaD (Stephan *et al.*, 2009). Since vascular risk factors for stroke, such as hypertension, diabetes mellitus, hypercholesterolemia, and smoking, are also associated with a higher risk of AD as well as VaD (Kirshner, 2009; Viswanathan *et al.*, 2009), we speculated that some of these established vascular risk factors for VaD may be risk factors for progression from MMI/ND to VaD. However, we showed that no factor, including previous history of CVD, significantly increased the risk of progression from MMI/ND to VaD. Although we cannot exclude the possibility that the number of examined subjects was too small to detect significant risk factors, our negative result implies that amnestic MCI (or at least MMI/ND) is not a prodromal state of cognitive impairment for VaD.

The main limitation of this study was that we did not evaluate MCI strictly. This would certainly lead to an overestimate of the prevalence of MCI because of its high sensitivity and low specificity. Our finding of a relatively low conversion rate from MMI/ND to AD might reflect this overestimate. However, any such overestimate is unlikely to alter our conclusion substantially, and we at least showed that DM and a family history of dementia were significant risk factors of progression to AD in subjects with objective mild memory impairment/no dementia. Second, we did not perform genotyping for the apolipoprotein E (APOE) alleles, although APOE is the strongest genetic risk factor for late-onset AD. In this study, we showed that a family history of AD

was a significant risk factor for progression to AD in subjects with MMI/ND. As mentioned above, a positive family history of AD might reflect the effect of the APOE genotype. Furthermore, we identified a few patients with VaD, which could bias the results in some way. In fact, the latest community-based study demonstrated that DM was a significant risk factor for progression to VaD as well as AD in elderly subjects aged over 85 years (Ahtiluoto *et al.*, 2010).

Conflict of interest

None.

Description of authors' roles

Naomi Sonobe supervised the data collection and wrote the paper. Ryuji Hata and Manabu Ikeda contributed to the concept and design of the study. Tomohisa Ishikawa, Kantaro Sonobe, Teruhisa Matsumoto, Yasutaka Toyota, Takaaki Mori, Ryuji Fukuhara and Satoshi Tanimukai collected and analyzed the data. Kenjiro Komori and Shu-ichi Ueno were responsible for the statistical design of the study and for carrying out the statistical analysis. All authors commented critically on the draft and contributed important intellectual content. All authors approved the final version.

Acknowledgments

This project was supported, in part, by grants from the Ministry of Education, Science, Sports and Culture of Japan. The authors thank the late Professor H. Tanabe (Department of Neuropsychiatry, Ehime University Graduate School of Medicine, Ehime, Japan) for his encouragement and helpful suggestions on our research.

References

Ahtiluoto, S. *et al.* (2010). Diabetes, Alzheimer disease, and vascular dementia: a population-based neuropathologic study. *Neurology*, 75, 1195–1202.

American Psychiatric Association (1987). *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn, revised. Washington, DC: American Psychiatric Association.

Arvanitakis, Z., Wilson, R. S., Bienias, J. L., Evans, D. A. and Bennett, D. A. (2004). Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Archives of Neurology*, 61, 661–666.

Bendlin, B. B. *et al.* (2010). Midlife predictors of Alzheimer's disease. *Maturitas*, 65, 131–137.

Biessels, G. J., De Leeuw, F. E., Lindeboom, J., Barkhof, F. and Scheltens, P. (2006). Increased cortical atrophy in patients with Alzheimer's disease and type 2 diabetes mellitus. *Journal of Neurology, Neurosurgery and Psychiatry*, 77, 304–307.

Burns, A. and O'Brien, J. (2006). Clinical practice with anti-dementia drugs: a consensus statement from British Association for Psychopharmacology. *Journal of Psychopharmacology*, 20, 732–755.

Chen, J. H., Lin, K. P. and Chen, Y. C. (2009). Risk factors for dementia. *Journal of the Formosan Medical Association*, 108, 754–764.

Farias, S. T., Mungas, D., Reed, B. R., Harvey, D. and DeCarli, C. (2009). Progression of mild cognitive impairment to dementia in clinic- vs community-based cohorts. *Archives of Neurology*, 66, 1151–1157.

Gasparini, L. and Xu, H. (2003). Potential roles of insulin and IGF-1 in Alzheimer's disease. *Trends in Neurosciences*, 26, 404–406.

Gatz, M. *et al.* (2005). Complete ascertainment of dementia in the Swedish Twin Registry: the HARMONY study. *Neurobiology of Aging*, 26, 439–447.

Gauthier, S. *et al.* (2006). Mild cognitive impairment. *The Lancet*, 367, 1262–1270.

Heun, R., Kolsch, H. and Jessen, F. (2006). Risk factors and early signs of Alzheimer's disease in a family study sample: risk of AD. *European Archives of Psychiatry and Clinical Neuroscience*, 256, 28–36.

Hulette, C. M., Welsh-Bohmer, K. A., Murray, M. G., Saunders, A. M., Mash, D. C. and McIntyre, L. M. (1998). Neuropathological and neuropsychological changes in "normal" aging: evidence for preclinical Alzheimer disease in cognitively normal individuals. *Journal of Neuropathology and Experimental Neurology*, 57, 1168–1174.

Ikeda, M. *et al.* (2001). Increased prevalence of vascular dementia in Japan: a community-based epidemiological study. *Neurology*, 57, 839–844.

Ishikawa, T., Ikeda, M., Matsumoto, N., Shigenobu, K., Brayne, C. and Tanabe, H. (2006). A longitudinal study regarding conversion from mild memory impairment to dementia in a Japanese community. *International Journal of Geriatric Psychiatry*, 21, 134–139.

Kirshner, H. S. (2009). Vascular dementia: a review of recent evidence for prevention and treatment. *Current Neurology and Neuroscience Reports*, 9, 437–442.

Kodl, C. T. and Seaquist, E. R. (2008). Cognitive dysfunction and diabetes mellitus. *Endocrine Reviews*, 29, 494–511.

Luck, T., Luppa, M., Briel, S. and Riedel-Heller, S. G. (2010). Incidence of mild cognitive impairment: a systematic review. *Dementia and Geriatric Cognitive Disorders*, 29, 164–175.

MacKnight, C., Rockwood, K., Awalt, E. and McDowell, I. (2002). Diabetes mellitus and the risk of dementia, Alzheimer's disease and vascular cognitive impairment in the Canadian Study of Health and Aging. *Dementia and Geriatric Cognitive Disorders*, 14, 77–83.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. and Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of

Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, 34, 939–944.

Meyer, J. S., Xu, G., Thornby, J., Chowdhury, M. H. and Quach, M. (2002). Is mild cognitive impairment prodromal for vascular dementia like Alzheimer's disease? *Stroke*, 33, 1981–1985.

Mitchell, A. J. and Shiri-Feshki, M. (2009). Rate of progression of mild cognitive impairment to dementia: meta-analysis of 41 robust inception cohort studies. *Acta Psychiatrica Scandinavica*, 119, 252–265.

Mohs, R. C. *et al.* (2001). A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology*, 57, 481–488.

Mosconi, L. *et al.* (2010). Increased fibrillar amyloid-{beta} burden in normal individuals with a family history of late-onset Alzheimer's. *Proceedings of the National Academy of Sciences of the United States of America*, 107, 5949–5954.

O'Brien, J. T. *et al.* (2003). Vascular cognitive impairment. *The Lancet Neurology*, 2, 89–98.

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine*, 256, 183–194.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G. and Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Archives of Neurology*, 56, 303–308.

Petersen, R. C., Stevens, J. C., Ganguli, M., Tangalos, E. G., Cummings, J. L. and DeKosky, S. T. (2001). Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, 56, 1133–1142.

Qiu, W. Q. and Folstein, M. F. (2006). Insulin, insulin-degrading enzyme and amyloid-beta peptide in Alzheimer's disease: review and hypothesis. *Neurobiology of Aging*, 27, 190–198.

Román, G. C. *et al.* (1993). Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*, 43, 250–260.

Roriz-Filho, J. S. *et al.* (2009). (Pre)diabetes, brain aging, and cognition. *Biochimica et Biophysica Acta*, 5, 432–443.

Schneider, J. A., Aggarwal, N. T., Barnes, L., Boyle, P. and Bennett, D. A. (2009). The neuropathology of older persons with and without dementia from community versus clinic cohorts. *Journal of Alzheimer's Disease*, 18, 691–701.

Stephan, B. C., Matthews, F. E., Khaw, K. T., Dufouil, C. and Brayne, C. (2009). Beyond mild cognitive impairment: vascular cognitive impairment, no dementia (VCIND). *Alzheimer's Research and Therapy*, 1, 4.

Viswanathan, A., Rocca, W. A. and Tzourio, C. (2009). Vascular risk factors and dementia: how to move forward? *Neurology*, 72, 368–374.

Yesavage, J. A. (1988). Geriatric Depression Scale. *Psychopharmacology Bulletin*, 24, 709–711.

Original Research Article

Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord 2010;29:224–232
DOI: 10.1159/000269972

Accepted: November 17, 2009
Published online: April 6, 2010

Transition of Distinctive Symptoms of Semantic Dementia during Longitudinal Clinical Observation

Tetsuo Kashibayashi[a] Manabu Ikeda[b] Kenjiro Komori[a] Shunichiro Shinagawa[c] Hideaki Shimizu[a] Yasutaka Toyota[a] Takaaki Mori[a] Tomohisa Ishikawa[a] Ryuji Fukuhara[a] Shu-ichi Ueno[a] Satoshi Tanimukai[a]

[a]Department of Neuropsychiatry, Neuroscience, Ehime University Graduate School of Medicine, Toon, [b]Department of Psychiatry and Neuropathobiology, Faculty of Medical and Pharmaceutical Science, Kumamoto University, Kumamoto, and [c]Department of Psychiatry, Jikei University School of Medicine, Tokyo, Japan

Key Words
Behavioral symptoms · Cognitive decline · Frontotemporal lobar degeneration · Semantic dementia

Abstract
Background/Aims: The aim of this study is to examine the clinical symptoms in a number of semantic dementia (SD) patients and to reveal the longitudinal progression and clinical course of these distinctive symptoms of SD. ***Methods:*** 19 consecutive SD patients were examined. Symptoms were classified into 23 distinct categories: behavioral symptoms, language and cognitive symptoms and symptoms concerning the impairment of activities of daily living (ADL). We divided patients into two subgroups, left- and right-dominant SD, and compared the onset of each symptom. ***Results:*** Language impairments occurred as the initial symptom in 16 cases. At the first examination, all cases showed both anomia and impairment of word comprehension. By around 3 years after onset, almost all language impairments were observed. Approximately 3–5 years after onset, prosopagnosia and behavioral symptoms appeared. Around the period when the loss of the language faculty and apathy became remarkable, impairment of ADL appeared. Patients spent all day in bed at this stage. Moreover, prosopagnosia appeared significantly earlier in right-dominant SD. ***Conclusion:*** Our findings clarify the progression of distinctive symptoms of SD patients. It is necessary to create a treatment strategy for SD patients with such a disease-specific course of SD.

Introduction

Semantic dementia (SD) is a group of disorders included in a family of disorders called frontotemporal lobar degeneration (FTLD) [1]. Patients with SD present with selective and progressive loss of semantic memory associated with focal atrophy of the anterior temporal lobes [2–4]. Their most prominent feature is a profound breakdown in semantic memory, such as that associated with the naming and conceptual knowledge of objects. SD patients present with severe anomia, impairment in the production and recognition of single words, and surface dyslexia, a condition in which the patient has difficulty reading words with irregular pronunciations. These language

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1420–8008/10/0293–0224$26.00/0

Accessible online at:
www.karger.com/dem

Satoshi Tanimukai
Department of Neuropsychiatry, Neuroscience
Ehime University Graduate School of Medicine
Shitsukawa, Toon-City 791-0295 (Japan)
Tel. +81 89 960 5315, Fax +81 89 960 5317, E-Mail satanimu@m.ehime-u.ac.jp

symptoms are known more generally as 'Gogi (word meaning) aphasia' in Japan [5–8]. There also exist several case reports on patients presenting with prosopagnosia, i.e. deficits in recognizing faces of familiar persons [9–11]. Those patients demonstrated greater atrophy on the right temporal lobe, while language symptoms were typically observed in the cases with left temporal lobe atrophy.

In addition to these cognitive and language impairments, the decrease in the control exerted by the frontal lobe cortex and posterior cortical hyperactivity lead to marked changes in personality and behavior, such as disinhibition, stimulus-bound behavior and stereotypic behavior [12–14] similar to patients with frontotemporal dementia. Behavioral and psychological symptoms in dementia (BPSD) lead to early hospitalization and admittance into skilled nursing facilities; this adversely affects the quality of life of the patients and caregivers. Therefore, it is necessary to provide appropriate treatment and care for BPSD. A few pharmacological or nonpharmacological treatments aimed at reducing BPSD in FTLD [12, 15–17] have been attempted, but appropriate treatment for each stage of SD has not been developed yet.

Investigation into the unique clinical symptoms of SD over a period of several years provides an important way to determine the appropriate treatment and care for each stage of SD and to improve the prognosis for SD patients as much as possible.

Therefore, we examined the onset of these clinical symptoms in a number of SD patients based on longitudinal clinical observations. The aim of this study is to clarify the time points at which distinctive symptoms appear during the clinical course of SD, in order to create appropriate treatment strategies for each stage of SD.

Materials and Methods

Patients

Patients were recruited from a total of 1,045 consecutive patients in the Higher Brain Function Clinic of the Department of Neuropsychiatry at Ehime University Hospital between January 1997 and June 2007, and were examined by senior neuropsychiatrists. All patients underwent physical and neurological examinations, laboratory blood tests including those for vitamin B_1, B_{12}, folic acid and thyroid function, magnetic resonance imaging (MRI) or computed tomography (CT) of the brain, and HMPAO-SPECT. A standard psychiatric evaluation was used to exclude patients with major functional psychiatric disorders such as schizophrenia and mood disorders.

Patients were assessed with a comprehensive battery of neuropsychiatric and neuropsychological tests, including the Mini-Mental State Examination (MMSE) [18], the Short-Memory Questionnaire (SMQ) [19, 20], Raven's Colored Progressive Matrices (RCPM) [21] and the Neuropsychiatric Inventory (NPI) [22, 23]. Activities of daily living (ADL) were evaluated by the Physical Self-Maintenance Scale and the Instrumental Activities of Daily Living Scale [24]. Language function was evaluated by a semantic test battery [25]. The semantic test battery was comprised of the Japanese Standard Language Test of Aphasia consisting of 26 subtests, each assigned to 1 of 5 linguistic functions (listening, speaking, reading, writing, and calculating) [26], and Object Naming from 80 line drawings of common everyday objects and 10 colors, as well as Word-Picture Matching with spoken word targets and 10 line drawing choices: the target plus 9 within-category distracters using the same 90 items as in the naming test [27].

Among all of the patients, 64 patients were diagnosed with FTLD, and 23 patients were diagnosed with SD according to consensus criteria [1]. Four patients were excluded because we could not follow up on these cases for 1 year, so 19 patients remained. This study was conducted with the informed consent of all patients or their caregivers.

Selection of Clinical Symptoms

After reviewing the existing literature on the subject and identifying frequently cited symptoms, 9 behavioral symptoms and 6 cognitive symptoms were selected based on the clinical criteria for FTLD. In addition, 8 symptoms associated with ADL were selected on the basis of the subcategories of the Instrumental Activities of Daily Living Scale, Physical Self-Maintenance Scale and earlier studies [1, 3, 17, 28–30]. We evaluated clinical symptoms of SD using these 23 symptoms divided into 3 categories.

Language and Cognitive Symptoms

Language symptoms examined included anomia, impairment of word comprehension, reading or writing difficulties, paraphasia, and mutism. The first episode of each symptom was counted mainly based on patient history information obtained from the patients or their caregivers, and confirmed by the semantic test battery. Sometimes the semantic test battery disclosed certain symptoms for the first time. Late-stage symptoms, for example mutism, were scored on the basis of a direct examination or an interview with the caregivers. The cognitive symptom closely associated with semantic impairment in recognizing faces of familiar persons is treated as prosopagnosia (inability to recognize relatives' and acquaintances' faces). We conducted the test to identify photographs of relatives' faces if any information was obtained from the patient or informant concerning difficulty identifying a familiar person from his or her face. The patients were defined as having prosopagnosia when they could not identify themselves and/or their family from the photograph.

Behavioral Symptoms

The behavioral symptoms examined included loss of social awareness (lack of empathy, acting without regard for others' opinions), loss of personal awareness (difficulty applying makeup or washing one's own hair, no interest in one's own clothes), disinhibition (tendency to lick dishes, inability to wait one's turn, talking to others at inappropriate times), apathy or social withdrawal of spontaneity (ceasing to pursue hobbies), stereotypic behavior (tendency to always walk the same route or buy the same products), mental rigidity and inflexibility (lack of flexibility about time, money management or abdominal symptoms), irrita-

Table 1. Demographic variables of patients

Sex (M:F)	7:12
Age at consultation, years	65.5 ± 9.1 (53–83)
Untreated duration, years	2.8 ± 1.4 (0.3–6.4)
MMSE score (max. 30)	20.1 ± 7.7
NPI score (max. 120)	13.2 ± 15.3
RCPM score (max. 36)	30.5 ± 4.3
SMQ score (max. 46)	29.0 ± 7.8
Follow-up duration after consultation, years	4.3 ± 1.9 (1.5–7.4)

Data are given as the number of patients or mean ± SD. Figures in parentheses indicate ranges.

bility or aggression (tendency to become angry or complain when unable to communicate), changes in food preferences (tendency to prefer sweet foods) and increase in appetite. Most of these behavioral symptoms were revealed by an interview with caregivers at every examination reported as a troublesome event that occurred in daily life. Some of them were already found in the patient history information at the first examination. A few of them were disclosed at the time of administering the NPI and neurological examinations.

ADL and Other Symptoms

Impairments in ADL examined included incontinence, dressing disorder, need for regular help to eat, tendency to spend all day in bed, decrease in efficiency (work or housework), ceasing to perform work or housework, getting lost and decline in daily activities. Dressing disorder is a condition where patients need help changing their clothes. These ADL symptoms were all reported in an interview with caregivers.

Interview Methods

Disease onset was defined as the time of the appearance of each initial symptom among 23 symptoms. It was emphasized that the initial symptom should be the first change the caregiver noticed and should reflect a substantive change from the patient's premorbid state, rather than a longstanding character trait. The untreated duration was defined as the time period from the disease onset to the first examination. Symptoms that appeared during the untreated duration were reported by the caregiver and were carefully confirmed by a senior neuropsychiatrist. For example, if a caregiver mentioned that the patient had begun to say the same phrases repeatedly, further clarification was sought to ascertain whether this represented repetitive questioning in the context of a memory disorder versus stereotypic catch phrase usage. In addition, if a caregiver or patient complained of memory disturbances, the symptom was carefully scrutinized to determine whether or not it involved word finding difficulties. During the follow-up duration, the examinations and interviews were performed every month or every 2 weeks by a senior neuropsychiatrist, and the appearance of each of the 23 symptoms was described. In 1 case (case 17), however, the caregiver had visited our hospital alone every 2 months for the last 3 years because of her strong refusal to attend the clinic after deprivation of her driving opportunity.

We determined the duration from the disease onset to the time of the occurrence of each symptom and calculated the mean values and standard error of these durations. Observations for this study were performed over the period from January 1997 to May 2008. Nineteen patients were classified into two subgroups, left- or right-dominant cases, based on the predominance of temporal lobe atrophy observed on the CT or MRI and the predominance of temporal lobe cerebral blood flow (CBF) hypoperfusion on HMPAO-SPECT. We compared the mean intervals from disease onset for 14 language, cognitive, and behavioral symptoms between the predominant left temporal lobe atrophy (left-dominant) and the predominant right temporal lobe atrophy (right-dominant).

Statistical Analyses

SPSS version 15.0 was used for statistical calculations. Mann-Whitney U tests were employed to determine the significance of the differences between the mean values for the left-dominant and right-dominant subgroups of SD patients.

Results

Patient Profiles

The demographics of the 19 cases, including sex, age at consultation, the untreated duration, MMSE score, SMQ score, RCPM score and NPI score, are summarized in table 1. The mean follow-up duration was 4.7 years (min. 1.5, max. 7.4). The mean total follow-up period from the onset of initial symptoms to the last follow-up examination was 7.1 years (min. 1.8, max. 11.2). Table 2 shows the data obtained at the first examination of each patient including sex, age at consultation, the untreated duration, MMSE score, SMQ score, NPI score and RCPM score, in addition to the follow-up duration and the outcome of the last examination.

All cases showed focal atrophy of the anterior temporal lobe on a CT or MRI in addition to either predominantly left or right temporal lobe CBF hypoperfusion on HMPAO-SPECT. There was no case whose CBF hypoperfusion was restricted to one side only. Fourteen cases had left-dominant SD while 5 cases had right-dominant SD. The mean duration of the follow-up periods from the first examination and the total follow-up period for each case are shown in table 2.

Clinical Symptoms

Among the 19 cases, language impairments occurred as the initial symptom in 16 cases. By the time of the first examination, some language impairments including anomia, impaired word comprehension, reduction of speech and paraphasia had already appeared. Among language impairments, anomia was the earliest symptom and was observed an average of 1.3 years after disease on-

Table 2. Demographics, neuropsychological test results at first examination and follow-up duration

Case No.	Sex	Education years	Dominancy	Age years	MMSE total (max. 30)	RCPM (max. 36)	Picture naming (max. 90)	Picture matching (max. 90)	SMQ (max. 46)	NPI (max. 120)	Untreated duration years	Follow-up duration years	Total follow-up duration, years	Course
1	M	16	left	57.4	26	35	30	74	30	8	3.4	7.4	10.8	under course
2	M	12	left	57.6	28	34	49	78	42	4	1.6	6.7	8.3	under course
3	F	9	left	58.5	6	28	17	28	23	36	4.5	5.5	10.0	under course
4	F	8	left	81.4	16	29	27	37	28	1	6.4	4.8	11.2	under course
5	M	9	left	76.9	25	28	33	65	26	45	3.9	4.5	8.5	hospitalization
6	M	16	left	58.8	23	33	53	77	37	11	1.8	4.3	6.1	under course
7	F	12	left	67.6	28	33	43	64	32	49	3.6	3.7	7.2	under course
8	M	13	left	56.6	18	36	17	58	17		2.7	3.3	5.9	hospitalization
9	F	9	left	70.7	20	31	32	51	32	5	4.7	3.3	8.1	under course
10	F	9	left	56.0	8	27	36	64	34	0	1.4	3.1	4.5	under course
11	M	12	left	56.7	27	35	29	74	32	0	1.7	2.6	4.3	under course
12	F	9	left	65.2	5	30	10	27	20	8	3.8	2.5	6.3	nursing facility
13	M	15	left	78.2	28	30	64	80	35	0	2.2	2.0	4.3	under course
14	F	10	left	82.8	12	26	30	68	12	0	0.3	1.5	1.8	under course
15	M	9	right	52.5	21	34	39	64	19	6	2.0	7.4	9.4	death
16	F	12	right	64.4	28	34	67	82	35	15	1.2	6.8	8.0	under course
17	F	12	right	65.4	27	28	43	58	40	4	2.8	6.4	9.2	under course
18	F	9	right	63.9	23	17	52	60	31	19	2.2	3.1	5.3	under course
19	F	11	right	73.8	13	32	21	45	26	26	3.2	2.1	5.3	nursing facility

Individual data for patients with left-dominant atrophy (n = 14) and right-dominant atrophy (n = 5). CDR = Clinical dementia rating; untreated duration = the duration from onset to first consult; total follow-up duration = untreated duration + follow-up duration; F = female; M = male.

set. The next symptom to appear was impaired word comprehension which presented at an average of 2.1 years after disease onset. Afterwards, paraphasia and reading and writing difficulties appeared at an average of 2.5 and 2.6 years, respectively, after disease onset. In 15 of the 19 cases, prosopagnosia appeared at an average of 3.3 years after disease onset. At the first examination, 11 cases complained of memory disturbances. We confirmed that these symptoms were the results of difficulties in recall and recognition of words and deficits in face recognition. Four patients developed mutism at an average of 7.1 years after onset (min. 5.6, max. 8.9).

Approximately 3–5 years after onset, behavioral and psychiatric symptoms including stereotypic behavior, disinhibition, mental rigidity, inflexibility or aggression, loss of personal awareness, loss of social awareness and apathy appeared, and patients had difficulty with their work or housework. Among the behavioral symptoms, stereotypic behavior was the earliest symptom to appear. It appeared an average of 3.1 years (min. 1.2, max. 5.5) after disease onset and was present in 18 cases. The only patient who did not show stereotypic behavior had a total follow-up period of only 1.8 years. All patients presented with changes in food preferences and the mean duration from the occurrence of this symptom to disease onset was 3.5 years (min. 0.7, max. 7.0), followed by an appetite increase at an average of 5.1 years (min. 2.2, max. 7.5) after disease onset (table 3; fig. 1).

During clinical observation, 14 cases showed a decline in daily activities at an average of 5.4 years (min. 3.1, max. 9.4), 4 cases showed a tendency to get lost at an average of 5.6 years (min. 4.7, max. 8.0), and 4 cases began to need regular help to eat at an average of 6.6 years (min. 5.0, max. 8.0) after disease onset. Eight cases presented with incontinence at an average of 7.0 years (min. 4.5, max. 10.4) after onset and 6 cases presented with dressing disorder at an average of 7.1 years (min. 5.0, max. 9.4) after onset. Eight cases began to show a tendency to sleep all day in bed at an average of 7.4 years (min. 4.7, max. 10.9) after onset (table 3; fig. 1).

Among all of the patients, 6 cases have already finished the longitudinal follow-up program. One patient died of hepatocellular carcinoma 9.4 years after the onset of SD. Two patients were admitted to hospitals for physical diseases 8.5 and 5.9 years after the onset of SD. The other 2 patients were admitted to nursing facilities 6.3 and 5.3 years after disease onset. One case dropped out of the study as a result of the caregiver's decision 5.3 years after onset. The other 13 cases were followed to the end of this study (table 2).

Table 3. The number of patients and the duration from disease onset to the occurrence of each symptom

Symptom	n	Mean duration
Anomia	19	1.3 (0.4)
Impaired word recognition	19	2.1 (0.4)
Paraphasia	16	2.5 (0.4)
Reading or writing difficulties	18	2.6 (0.4)
Stereotypic behavior	18	3.1 (0.3)
Prosopagnosia	15	3.3 (0.6)
Changing food preferences	19	3.5 (0.3)
Disinhibition	18	3.6 (0.4)
Decrease in efficiency (work or housework)	15	3.8 (0.5)
Mental rigidity and inflexibility	15	3.9 (0.5)
Irritability or aggression	17	3.9 (0.4)
Loss of personal awareness	12	4.1 (0.4)
Loss of social awareness	14	4.2 (0.4)
Apathy	15	4.3 (0.5)
Increase in appetite	13	5.1 (0.4)
Retirement (work or housework)	14	5.1 (0.6)
Decline in daily activities	14	5.2 (0.6)
Getting lost	4	5.4 (1.1)
Regular help to eat	4	6.6 (0.7)
Incontinence	8	7.0 (0.8)
Mutism	4	7.1 (0.8)
Dressing impairment	6	7.1 (0.7)
Spends all day in bed	8	7.4 (0.8)

Observations are ranked according to the length of the mean duration in decreasing order. Figures in parentheses indicate SE.

Table 4 shows data comparing left-dominant SD and right-dominant SD. There were no significant differences between the two groups in age, untreated duration, MMSE scores, SMQ scores, NPI scores, RCPM scores and the length of time from disease onset to the occurrence of language symptoms. Prosopagnosia, irritability, or aggression appeared significantly earlier in right-dominant SD. Mutism and ADL symptoms were not compared because few patients revealed these symptoms.

Discussion

In this study, we revealed the onset period of each distinctive symptom of SD by analyzing longitudinal clinical observations. Cross-sectional studies have been able to confirm the prevalence of each symptom, but have not determined the onset period and development order of each symptom. We clarified the common course of SD in several patients. SD patients initially showed cognitive impairment manifested as characteristic language symptoms, followed by gradual but profound personality and behavioral changes. This accompanied the progression of severe semantic memory impairment, and finally impairment of the ADL with a loss of language function and a remarkable decrease in spontaneity. SD patients who present with cognitive impairment as an early symptom

Table 4. The duration from disease onset to the occurrence of each symptom in left- and right-dominant SD

	Left-dominant SD		Right-dominant SD	
	n	mean duration	n	mean duration
Anomia	14	1.4 (0.5)	5	1.0 (0.6)
Impaired word recognition	14	2.0 (0.5)	5	2.4 (0.3)
Paraphasia	13	2.5 (0.5)	3	2.4 (0.6)
Reading or writing difficulties	13	2.8 (0.5)	5	2.2 (0.4)
Stereotypic behavior	13	3.3 (0.4)	5	2.5 (0.2)
Prosopagnosia**	10	4.5 (0.6)	5	0.9 (0.4)
Changing food preferences	14	3.5 (0.4)	5	3.8 (0.6)
Disinhibition	13	3.8 (0.4)	5	3.0 (0.8)
Mental rigidity and inflexibility	10	4.1 (0.6)	5	3.3 (0.2)
Irritability or aggression*	12	4.4 (0.6)	5	2.9 (0.5)
Loss of personal awareness	8	4.6 (0.4)	4	3.1 (0.3)
Loss of social awareness	11	4.1 (0.4)	3	4.6 (0.6)
Apathy	11	4.4 (0.6)	4	4.2 (1.0)
Increase in appetite	11	5.2 (0.5)	3	4.8 (0.8)

* $p < 0.05$; ** $p < 0.01$. Figures in parentheses indicate SE.

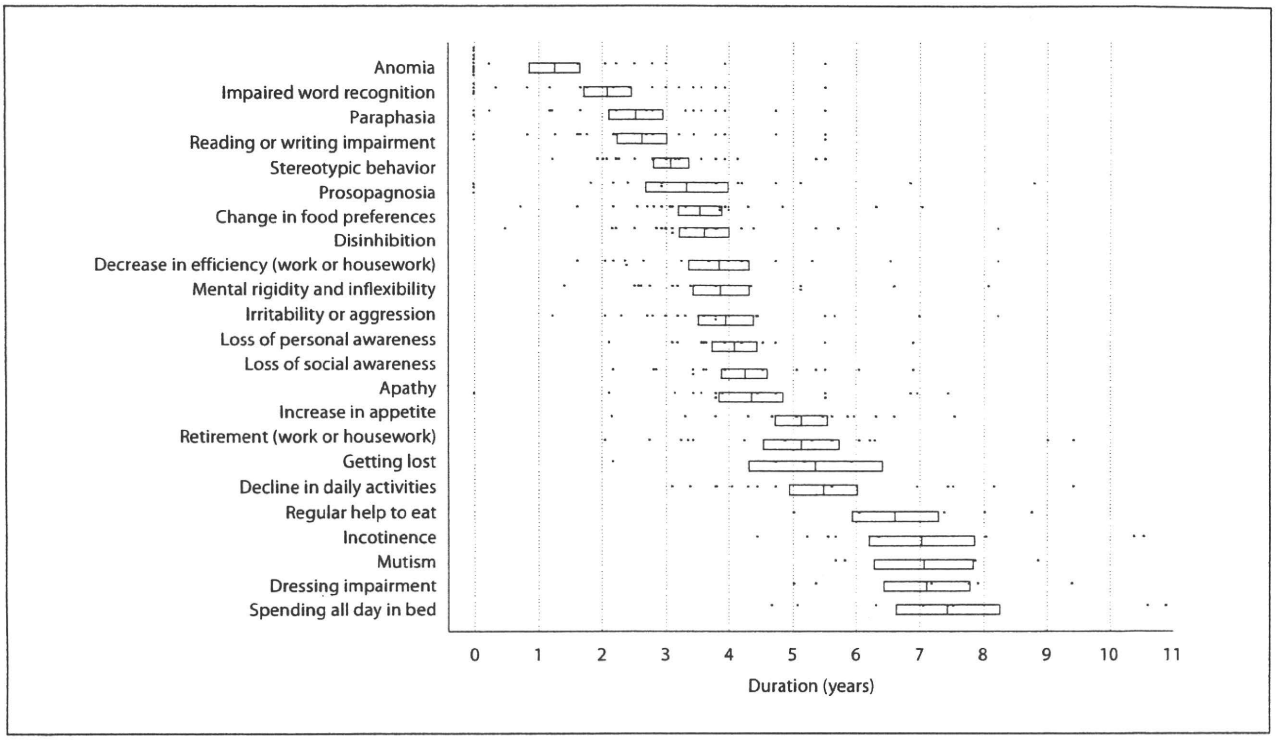

Fig. 1. The duration from disease onset to the occurrence of each clinical symptom in SD. The bars indicate the mean ± SE of the duration from disease onset to the occurrence of each symptom. Each dot shows the onset point of each symptom.

are often misdiagnosed with AD and given inappropriate treatment. For example, donepezil used in treating AD was actually found to worsen behavioral symptoms in patients with FTLD [31]. Consequently, they developed BPSD and their ADL were impaired, increasing the caregiver's burden. Information about the onset period of each symptom is important in enabling accurate diagnosis in the early stages of the disease and in determining appropriate treatment for behavioral problems in the later stages.

Language and cognitive symptoms appeared in all cases as manifestations of semantic memory impairment, and also appeared earlier than behavioral symptoms or ADL impairment. The initial symptoms of the SD patients were anomia, paraphasia and impairment of the ability to understand word meaning. Prosopagnosia seems to be a common symptom in SD patients. This symptom appeared at an average of 3.3 years after onset, later than language symptoms, and at a point when semantic memory impairment had progressed. Most cases presented with this symptom along with many behavioral symptoms. As we will describe later, it is important to note the time at which some symptoms appear because of differences in onset related to atrophic laterality.

Three to five years after onset, behavioral symptoms involving both increases and decreases in activity appeared. Symptoms involving increases in activity included disinhibition, stereotypic behavior, inflexibility, irritability and aggression. Symptoms involving decreases in activity included apathy and loss of personal awareness. Almost all cases presented with stereotypic behavior which was also the earliest behavioral symptom to appear. As a result of the progression of semantic memory impairment, the patients' range of interests narrowed and repetitive behavior became simpler and remarkable. Irritability or aggression seemed to develop when the repetitive behavior was prevented [32]. Some studies have reported that SD patients present with behavioral symptoms in the early stages [32, 33], but the precise time at which each symptom appeared was not described in detail. We revealed that behavioral symptoms appeared later than language symptoms.

In our study, we confirmed the hypothesis for abnormal eating behaviors in SD proposed in a cross-sectional study [34] reporting that first changes in food preferences occur, followed by increases in appetite. An increase in appetite and a decline in daily activities require appropriate treatment because these changes can lead to other health issues like an increase in body weight or diabetes. Of 4 cases who began to need regular help to eat, 3 patients were admitted to a hospital and 1 patient entered a group home. These 4 patients presented an increase in appetite at the early stage, and later became indifferent to eating, never to eat on their own initiatives.

In addition, a decrease in the efficiency of work or housework was noted during the period 3–5 years after onset. At more than 5 years after onset, many patients retired from their work. Among the 14 cases who retired from their work, 7 patients retired from their outside duty at an average of 3.8 years (min. 2.0, max. 6.1) after disease onset and 7 patients retired from their simple housekeeping at an average of 6.5 years (min. 3.4, max. 9.4). The occupation which could be continued considerably longer than other outside duty was simple agriculture (6.1 years after onset). Close support from their family might allow these patients a relatively long-term engagement with agriculture or housekeeping. In this advanced stage, semantic memory impairment progressed further, communication using language became difficult, and mutism appeared in 4 cases at an average of 7.1 years after onset. In this period, ADL disturbances such as requiring regular help to eat, incontinence, and dressing impairment appeared. Among 6 cases who presented with dressing impairment, 3 patients were admitted to a hospital, 2 patients entered a group home and 1 patient lived at home.

In our study, there were no significant differences in the time appearances of the language symptoms between left- and right-dominant cases at an early stage. However, prosopagnosia was observed significantly earlier in right-dominant cases than in left-dominant cases, and among 5 cases with right-dominant atrophy, 2 cases presented with prosopagnosia before language symptoms. Alternatively, among 14 cases with left-dominant atrophy, 10 cases presented with prosopagnosia at an average of 4.5 years after onset, around the time when behavioral symptoms appeared. As reported in a previous study, left-dominant cases did not present with behavioral symptoms in the early stage, while right-dominant cases presented with irritability or aggression significantly earlier than left-dominant cases [35]. These results suggest that the left and right temporal lobes might have different functions in semantic memory and that visual perception associated with semantics such as prosopagnosia, as well as mood instability are mainly associated with the right temporal lobe. However, we do not think that the left and right temporal lobes take completely independent roles and create completely different clinical concepts. Instead, we suggest that these differences between left- and right-dominant cases are the result of the gradual collapse of central semantic memory, which involves both the left and right temporal lobes, in the early stage of SD [36, 37]. In our longitudinal study, not only language impairment and prosopagnosia but also behavioral symptoms appeared in almost all cases regardless of whether atrophy occurred predominantly in the left or right temporal lobe. Previous studies emphasizing the difference between left- and right-dominant SD might probably have missed the opportunity for longitudinal observation of those patients. Statistical comparisons of the differences in impairment of ADL between left- and right-dominant cases were difficult to perform in this study. Few right-dominant cases were followed until the appearance of ADL impairment, so in further studies, it is necessary to observe more right-dominant cases.

Following selective cognitive impairments, SD patients presented with remarkable behavioral and personality changes such as stereotypic behavior, mental rigidity, apathy and social withdrawal of spontaneity. These symptoms also lead to tendencies to be persistent with some habits and reject other behaviors, tendencies which are difficult to modify. Since BPSD associated with these symptoms increase the caregivers' burden, some type of intervention is necessary. In a previous study, pharmacological treatment was attempted to treat the stereotypic behavior of SD patients in the early stage [16]. These treatments may contribute to the ease of long-term home care. It is also important to provide the patient's health care environment before the appearance of BPSD so that interventions can be carried out promptly if necessary. Therefore, we recommend a combination of pharmacotherapy using SSRIs and nonpharmacologic management such as behavior modification and environmental manipulation, which can enable caregivers to decrease their burden and maintain the long-term care at home [17, 38]. Moreover, the introduction of rehabilitation programs, which works with preserved cognitive functions and motivates the patient to continue treatment after the early stage, is an important way to ensure the quality of the treatment in the advanced stages [28, 39]. Continuing language rehabilitation exercises and jigsaw puzzle activities introduced in the early stage can decrease the burden of BPSD [12, 40–42]. For these interventions to be effec-

tive, early and accurate diagnosis is needed. At more than 5 years after onset, several patients require specialized care for ADL disturbances, including eating disturbances, dressing impairments and incontinence. In our study, patients were still capable of physical functions such as standing and walking in almost all cases in this advanced stage. Therefore, the ADL disturbances observed in SD patients might be caused by severe loss of semantic memory and decreasing spontaneity; appropriate treatment can enable caregivers to maintain the long-term care at home. In this study, 3 patients were followed for over 10 years. Their total follow-up periods were 11.2, 10.8 and 10.0 years. Among these 3 patients, 2 patients live at home and still visit our hospital regularly.

There are a few methodological issues that should be taken into consideration to fully appreciate our results. As this study is based on the retrospective recall of caregivers, it is possible that the informants' memories may be inaccurate [43]. For example, in some cases we could not confirm anomia during the early stage despite detailed accounts from the caregivers. In those cases, paraphasia or impairment in word comprehension was reported as an initial symptom. We believe that anomia is often an initial symptom of SD. However, a medical history obtained through a clinical interview is the common way of diagnosing dementia, so any possible bias introduced by the current methods is likely to be similar to that in routine clinical practice. Secondly, we investigated the symptoms of each case for as long as possible in our study, and as a result, the follow-up durations were different for each subject. We found the mean duration from the onset of SD to the occurrence of each symptom by only using data from the cases which presented with each symptom. To confirm the prevalence of each symptom, cross-sectional studies with larger cohorts are needed.

Our findings clarify the progression of distinctive symptoms that have previously been unclear and also suggest clinical characteristics of SD. In addition, our study can serve as a guide for establishing staging measures for SD and the longitudinal clinical observations performed in our study may support the recently reported FTLD clinical dementia rating (CDR) [44]. We think that because SD patients initially show language symptoms followed by gradual but remarkable personality and behavioral changes, the two new rating domains included in the FTLD CDR, language and behavior, and comportment and personality, reflect the severity of SD more precisely than the original CDR [45]. Because the various approaches to treatment for FTLD are rapidly evolving [17, 38, 46] and FTLD, including SD, is a progressive disease, understanding the clinical characteristics of SD is important to ensure appropriate treatment and care during each stage of SD. Moreover, by investigating the clinical course found in this study in combination with brain imaging, it may be possible to clarify the regions responsible for each symptom. Also, it may be useful to investigate the clinico-anatomical basis of each symptom of SD by correlating the results of this study with the functional imaging or the statistical image analysis of the brain.

Acknowledgements

We wish to thank the late Professor Hirotaka Tanabe for his instruction. Without it this study could not have been undertaken. The present study was undertaken with the support of grants provided by the Ministry of Education, Culture, Sports, Science and Technology for M.I. (Grant No. 20591414) and for K.K. (Grant No. 21500260) and the Ministry of Health, Labor and Welfare (research on dementia) for M.I. and R.F.

References

1 Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF: Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998;51:1546–1554.

2 Snowden JS, Goulding PJ, Neary D: Semantic dementia: a form of circumscribed cerebral atrophy. Behav Neurol 1989;2:167–182.

3 Hodges JR, Patterson K, Oxbury S, Funnell E: Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. Brain 1992;115:1783–1806.

4 Lladó A, Sánchez-Valle R, Rey MJ, Ezquerra M, Tolosa E, Ferrer I, Molinuevo JL: Clinicopathological and genetic correlates of frontotemporal lobar degeneration and corticobasal degeneration. J Neurol 2008;255:488–494.

5 Imura T: Aphasia: characteristic syndrome in Japanese language (in Japanese). Psychiatr Neurol Jpn 1943;47:196–218.

6 Sasanuma S, Monoi H: The syndrome of Gogi (word meaning). Selective impairment of kanji processing. Neurology 1975;25:627–632.

7 Tanabe H, Ikeda M, Nakagawa Y, Yamamoto H, Ikejiri Y, Kazui H, Hashikawa K, Harada K: Gogi (word meaning) aphasia and semantic memory for words (in Japanese). Higher Brain Function Res 1992;12:153–167.

8 Tanabe H, Nakagawa Y, Ikeda M, Hashimoto M, Yamada N, Kazui H, Nishikawa T, Okuda J: Selective loss of semantic memory for words; in Ishikawa K, McGaugh JL, Sakata H (eds): Brain Processes and Memory. Amsterdam, Elsevier Science, 1996, pp 141–152.

9 Tyrrell PJ, Warrington EK, Frackowiak RS, Rossor MN: Progressive degeneration of the right temporal lobe studied with positron emission tomography. J Neurol Neurosurg Psychiatry 1990;53:1046–1050.

10 Evans JJ, Heggs AJ, Antoun N, Hodges JR: Progressive prosopagnosia associated with selective right temporal lobe atrophy. A new syndrome? Brain 1995;118:1–13.
11 Gainotti G, Barbier A, Marra C: Slowly progressive defect in recognition of familiar people in a patient with right anterior temporal atrophy. Brain 2003;126:792–803.
12 Tanabe H, Ikeda M, Komori K: Behavioral symptomatology and care of patients with frontotemporal lobe degeneration – based on the aspects of the phylogenetic and ontogenetic processes. Dement Geriatr Cogn Disord 1999;10:50–54.
13 Shigenobu K, Ikeda M, Fukuhara R, Maki N, Hokoishi K, Nebu A, Yasuoka T, Komori K, Tanabe H: The Stereotypy Rating Inventory for frontotemporal lobar degeneration. Psychiatry Res 2002;110:175–187.
14 Rosen HJ, Allison SC, Ogar JM, Amici S, Rose K, Dronkers N, Miller BL, Gorno-Tempini ML: Behavioral features in semantic dementia vs other forms of progressive aphasias. Neurology 2006;67:1752–1756.
15 Swartz JR, Miller BL, Lesser IM, Darby AL: Frontotemporal dementia: treatment response to serotonin selective reuptake inhibitors. J Clin Psychiatry 1997;58:212–216.
16 Ikeda M, Shigenobu K, Fukuhara R, Hokoishi K, Maki N, Nebu A, Komori K, Tanabe H: Efficacy of fluvoxamine as a treatment for behavioral symptoms in frontotemporal lobar degeneration patients. Dement Geriatr Cogn Disord 2004;17:117–121.
17 Ikeda M: Frontotemporal dementia; in Ritchie CW, Ames D, Master CL, Cummings J (eds): Therapeutic Strategies in Dementia. Oxford, Oxford University Press, 2006, pp 287–299.
18 Folstein MF, Folstein SE, McHugh PR: 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr 1975;12:189–198.
19 Koss E, Patterson MB, Ownby R, Stuckey JC, Whitehouse PJ: Memory evaluation in Alzheimer's disease. Caregivers' appraisals and objective testing. Arch Neurol 1993;50:92–97.
20 Maki N, Ikeda M, Hokoishi K, Nomura M, Torikawa S, Fujimoto N, Komori K, Hirono N, Tanabe H: Interrater reliability of the short-memory questionnaire in a variety of health professional representatives. Int J Geriatr Psychiatry 2000;15:373–375.
21 Raven JC, Court JH, Raven J: Manual for Raven's Coloured Progressive Matrices. Oxford, Oxfords Psychologists Press, 1990.
22 Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J: The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–2314.
23 Hirono N, Mori E, Ikejiri Y, Imamura T, Shimomura T, Hashimoto M, Yamashita H, Ikeda M: Japanese version of the Neuropsychiatric Inventory – a scoring system for neuropsychiatric disturbance in dementia patients (in Japanese). No To Shinkei 1997; 49:266–271.
24 Lawton MP, Brody EM: Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969; 9:179–186.
25 Fushimi T, Komori K, Ikeda M, Patterson K, Ijuin M, Tanabe H: Surface dyslexia in a Japanese patient with semantic dementia: evidence for similarity-based orthography-to-phonology translation. Neuropsychologia 2003;41:1644–1658.
26 SLTA Committee: Standard Language Test of Aphasia Manual. Tokyo, Shinkou Igaku Shuppan-sha, 1997.
27 Ito K, Nakagawa Y, Ikeda M, Yamada N, Hashimoto M, Tanabe H: Category-specific word meaning impairment in Gogi aphasics (in Japanese). Higher Brain Function Res 1994;14:221–229.
28 Snowden JS, Neary D, Mann D: Frontotemporal Lobar Degeneration: Frontotemporal Dementia, Progressive Aphasia, Semantic Dementia. New York, Churchill Livingstone, 1996.
29 Shinagawa S, Ikeda M, Fukuhara R, Tanabe H: Initial symptoms in frontotemporal dementia compared with Alzheimer's disease. Dement Geriatr Cogn Disord 2006;21:74–80.
30 Mioshi E, Kipps CM, Dawson K, Mitchell J, Graham A, Hodges JR: Activities of daily living in frontotemporal dementia and Alzheimer disease. Neurology 2007;68:2077–2084.
31 Mendez MF, Shapira JS, McMurtray A, Licht E: Preliminary findings: behavioral worsening on donepezil in patients with frontotemporal dementia. Am J Geriatr Psychiatry 2007;15:84–87.
32 Snowden JS, Bathgate D, Varma A, Blackshaw A, Gibbons ZC, Neary D: Distinct behavioural profiles in frontotemporal dementia and semantic dementia. J Neurol Neurosurg Psychiatry 2001;70:323–332.
33 Bozeat S, Gregory CA, Ralph MA, Hodges JR: Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? J Neurol Neurosurg Psychiatry 2000;69:178–186.
34 Ikeda M, Brown J, Holland AJ, Fukuhara R, Hodges JR: Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. J Neurol Neurosurg Psychiatry 2002;73:371–376.
35 Chan D, Anderson V, Pijnenburg Y, Whitwell J Barnes J, Scahill R, Stevens JM, Barkhof F, Scheltens P, Rossor MN, Fox NC: The clinical profile of right temporal lobe atrophy. Brain 2009;132:1287–1298.
36 Patterson K, Hodges JR: Semantic dementia: one window on the structure and organization of semantic memory; in Cermak L (eds): Handbook of Neuropsychology (Memory and Its Disorders), ed 2. Amsterdam, Elsevier, 2000, pp 313–334.
37 Thompson SA, Patterson K, Hodges JR: Left/right asymmetry of atrophy in semantic dementia: behavioral-cognitive implications. Neurology 2003;61:1196–1203.
38 Ikeda M, Tanabe H: Reducing the burden of care in dementia through the amelioration of BPSD by drug therapy. Expert Rev Neurother 2004;4:921–922.
39 Graham KS, Simons JS, Pratt KH, Patterson K, Hodges JR: Insights from semantic dementia on the relationship between episodic and semantic memory. Neuropsychologia 2000;38; 313–324.
40 Graham KS, Patterson K, Pratt KH, Hodges JR: Relearning and subsequent forgetting of semantic category exemplars in a case of semantic dementia. Neuropsychology 1999;13: 359–380.
41 Snowden JS, Neary D: Relearning of verbal labels in semantic dementia. Neuropsychologia 2002;40:1715–1728.
42 Green HA, Patterson K: Jigsaws – a preserved ability in semantic dementia. Neuropsychologia 2009;47:569–576.
43 Oppenheim G: The earliest signs of Alzheimer's disease. J Geriatr Psychiatry Neurol 1994;7:116–120.
44 Knopman DS, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, Miller BL, Mercaldo N: Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. Brain 2008; 131:2957–2968.
45 Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL: A new clinical scale for the staging of dementia. Br J Psychiatry 1982; 140:566–572.
46 Vossel KA, Miller BL: New approaches to the treatment of frontotemporal lobar degeneration. Curr Opin Neurol 2008;21:708–716.

精神科，17(3)：295-301，2010

連載 Brain Science ㉛

認知症と自動車運転*
—医学的研究の最近の動向—

上村直人** 下寺信次**

Key Words：dementia, driving, medical guideline, fitness to drive

はじめに

現代社会において，自動車は便利な移動手段であるだけにとどまらず，生活の質を向上させる手段として欠かせないものになっている．近年，高齢の運転者数が急増しており，65歳以上の運転免許保有者は1,000万人を超えている[1]．そのことから認知症(痴呆)患者の自動車運転免許保有数は，免許保有者数と認知症の有病率から約30万人に上ると考えられ，認知症患者による事故をいかに防止するか各方面の対応が急がれている．そのような状況の中，2002年に道路交通法が改正され[2]，その103条で「公安委員会は痴呆症患者の運転免許証を停止，あるいは取り消すことができる」とされた．しかし，認知症の中にも症状・程度がさまざまあり，どのような基準で「認知症患者」を判定し，どういった評価で運転中止を決定するかといった具体的な指針は法律にも示されておらず，また，医療現場でも認知症者の運転中止の判断基準は存在していない[3][4]．

そのような背景を踏まえ，2003年に認知症と自動車運転に関する研究班(班長：池田　学)が立ち上がり，筆者も研究分担員として参加する機会を得た．本研究班は加速度的に増加が見込まれる認知症患者の運転実態を把握し，さらには認知症高齢ドライバーの運転が危険となる状態もしくは中断を勧告すべき要因について明らかにし，運転中止に伴う介護者の介護負担を軽減し，わが国における認知症患者の運転に対する医学的，行政的，福祉的問題に対するガイドラインづくりに資料を提供することを目的にわが国ではじめて立ち上げられたものである．

そこで本稿では，認知症の自動車運転に関する国内の研究について，筆者の所属していた「痴呆性高齢者の自動車運転と権利擁護に関する研究」研究班(班長：池田　学)および「認知症高齢者の自動車運転に対する社会支援のあり方に関する検討」研究班(班長：荒井由美子)において得られた研究成果の一部を紹介しながら，認知症と運転に関するわが国の医学的研究の動向と最近の話題について述べることとする．

研究班の目的と成果

研究班の検討から得られた成果の一部について以下に述べるが，詳細については前記研究班の報告書を参照いただきたい．

1．認知症と自動車運転の実態に関する調査報告

上村らは認知症患者30名の運転実態について，認知症患者の運転状況と医師および家族の対応について検討した[5]．その結果，多くの認知症患者が発症後も運転を継続していることが明らかとなった(30名中22名，73.3%)(図1)．特に軽度認知症患者の場合，運転の危険性が多いにもかかわらず運転中断に至っている例は少なく，家

* Brain Science㉛—Dementia and driving—Medical research in JAPAN—.

** Naoto KAMIMURA, M.D., Ph.D. & Shinji SHIMODERA, M.D., Ph.D.: 高知大学医学部神経精神科学教室〔〒785-8505 高知県南国市岡豊町小蓮〕; Department of Neuropsychiatry, Kochi University, Nankoku, Kochi 785-8505, Japan.

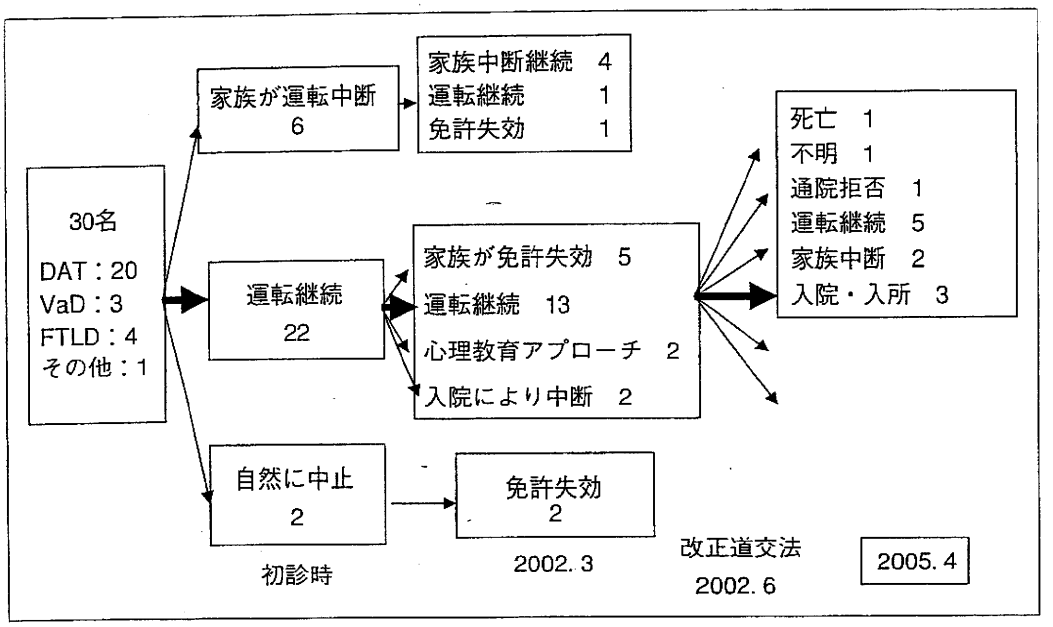

図1　痴呆患者の自動車運転の実態と医師対応
初診時評価は1995年9月から2001年9月までを含む．DAT：dementia of Alzheimer type, VaD：vascular dementia, FTLD：frontotemporal lobar degeneration　（文献[4]より）

族が対応に苦慮している実態が明らかとなった．その後も調査継続し，改正道交法施行直前では22名中13名(58.1%)は運転を継続していたが，改正道交法施行後も13名中5名(38.5%)が免許更新に成功し運転を継続していた．わが国で認知症の運転の実態についてはじめて大規模に行われた2008年の老年精神医学会の調査[6](2008年1～3月に診断された認知症患者7,329人分のデータ分析．全国各地の医師368人の参加)では，運転している認知症患者の6人に1人が交通事故を起こし，事故を起こした患者の約半数は75歳未満であった．また，患者の11%が運転を継続しており，そのうち16%に当たる134人が運転中に事故を起こしていた．このようにわが国でも認知症患者の自動車運転の問題は地方だけの稀な問題ではなく，すでに認知症診療においてどこでも遭遇する問題となっている．

2．認知症高齢者の運転中止に関するコンセンサスについての調査結果

これまで，わが国では認知症患者の自動車運転について十分な議論がなされていないだけでなく，高齢者や認知症患者の自動車運転についての意識に関する十分な資料もなかった．そこで豊田らは，地方都市での予備的研究[7]を踏まえ，公共交通機関の整備が進んでいる関西の都市在住の65歳以上の高齢者を対象に意識調査を実施した[8]．それらの結果から，改正道交法に関する情報では都市部(23.4%)，山間部(16.7%)とともに周知はされているとは言い難かった．また，「認知症患者は運転をやめるべきだと思うか？」という質問に対しては，「思う」と地方都市も含めて全地域の90%が認知症者は運転をやめるべきであると回答し，地域差はなかった．

また，筆者の所属する高知県の医師会会員1,551名を対象にした意識調査[9](有効回答441名；28.4%)では，認知症患者の運転の是非については絶対やめるべき：180名(41%)，やめるべき：185名(42%)で，8割以上の医師会会員が認知症患者は運転をやめるべきであると考えていた．こらのことから，わが国においても認知症患者は運転をやめるべきであるという社会的コンセンサスはほぼ得られていると考えられた．

3．認知症における運転免許制度の問題点に関する調査

改正道路交通法施行(2002年)と同時に免許更新者は，全員に自己の病状申告書の提出が義務化された．しかし，病識に乏しい認知症を有する患者においては実際の免許更新時に提出される申告書が十分に機能しているのか疑問な点も多い．そこで上村らは，運転免許を保持する認知症患者20名