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 ≥ 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.

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Transition of Distinctive Symptoms of Semantic Dementia during Longitudinal Clinical Observation

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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

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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.

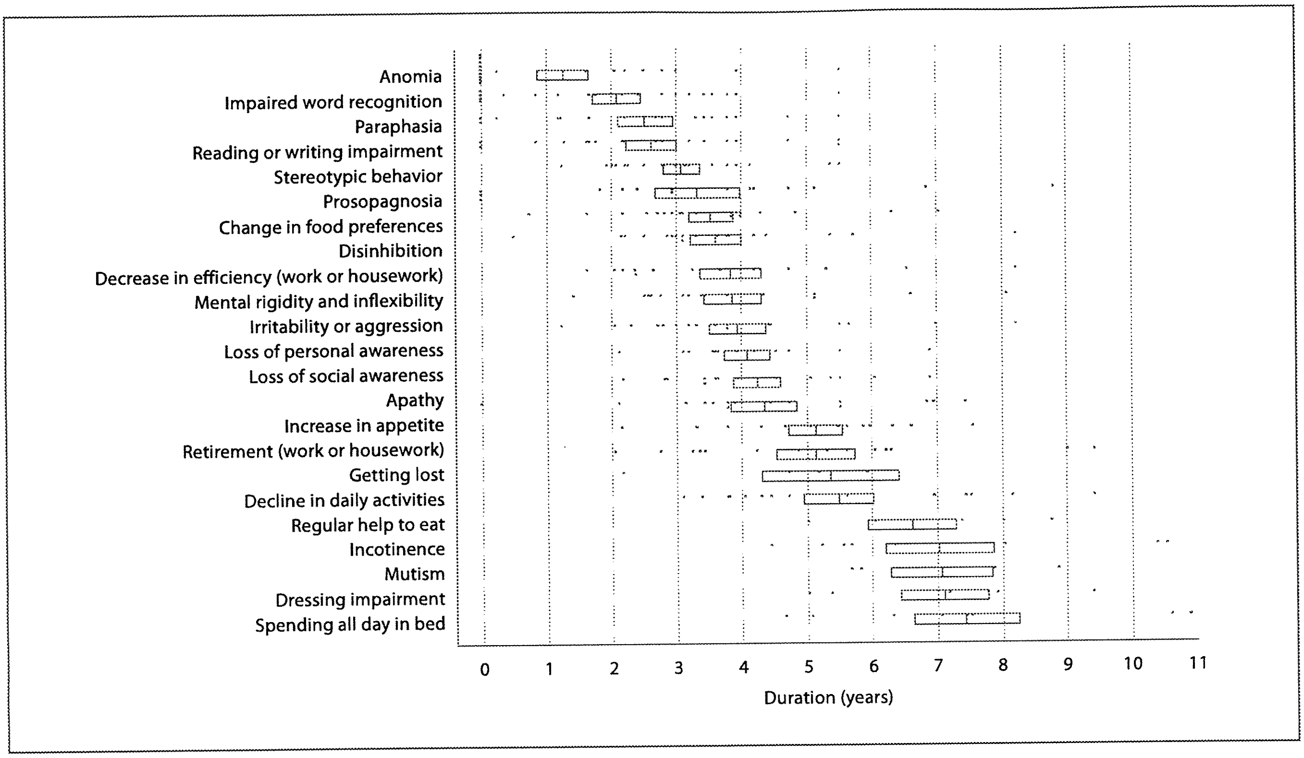

Fig. 1. The duration from disease onset to the occurrence of each clinical symptom in SD. The bars indicate the mean ± SE of the duration from disease onset to the occurrence of each symptom. Each dot shows the onset point of each symptom.

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 effective, 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.

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syndromes with known serum antibodies, such as relapsing polychondritis and Sjögrens, have been subsequently diagnosed in patients presenting with subacute encephalopathy.

The aetiology of a humourally mediated central nervous system condition may require initial compromise of the blood–brain barrier. This could expose the brain to serum factors, such as antibodies, resulting in central nervous system damage after the development of serum antibodies. Such serum antibodies could have been initially raised against skin tissue in our patient, and subsequently cross-react with neurons to mediate cognitive deterioration.

The autoantigens BP180 and BP230 are structural components of dermal hemi-desmosomes and are known to be targeted by antibodies in BP. Recent work has shown that BP230 also exists in human CNS neurons, with prominent expression within hippocampal neuronal somae and axons, providing a theoretical common antigen binding site.[5] Furthermore, IgG from our patient bound to hippocampal somae and axons during the peak of the illness, at a time when the skin biopsy demonstrated features consistent with basement zone IgG deposition. This suggests the concomitant presence of skin and neural antibodies during disease onset. However, serum analysis for BP180 and BP230 was negative in our patient. Hence, our patient may have antibodies to an antigenic target which is common to both skin and brain but is not BP180 or BP230.

This is the first study to directly link the clinical entities of encephalitis and BP through an antibody-based mechanism. It also emphasises the importance of recognising autoimmune encephalopathies and the benefits of prompt immunotherapy.

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Characteristics of abnormal eating behaviours in frontotemporal lobar degeneration: a cross-cultural survey

Frontotemporal lobar degeneration (FTLD) is characterised by behavioural changes, including loss of insight, disinhibition, apathy, mood changes, stereotypic behaviour and abnormal eating behaviour.[1 2] Although many studies have highlighted the high prevalence of alterations in food preference and eating habits in FTLD and described loss of appetite in dementia represented by Alzheimer disease (AD),[3] there have been few systematic studies comparing FTLD subgroups, or contrasting AD and FTLD.[1 2 4] Eating behaviours are modulated by many factors including personal habits, ethnic culture and climate, such that alteration in eating behaviour in dementias may be confounded by ethnic or cultural factors. Food culture, meal styles and customs differ substantially between Western countries and Japan. People in the UK consume considerably more sweets, and total daily calorific intakes are higher than they are for the Japanese. (Data derived from the Food and Agriculture Organization of the United Nations; http://faostat.fao.org/.) Therefore, it is unclear whether altered eating behaviours of FTLD in Western cohorts are an entirely disease-specific effect or whether they are modulated by ethnic–cultural factors. The aims of this study were to investigate changes in eating behaviours in Japanese FTLD and AD patients and to compare the profile of abnormal eating behaviours in Japanese and Western patients using the same instruments.

A total of 163 patients were involved: 72 from Ehime, Japan (18 frontotemporal dementia (FTD), 11 semantic dementia (SD) and 43 AD), and 91 from Cambridge, UK (23 FTD, 25 SD, 43 AD) (fig 1). A detailed description of British patients has been reported previously;[5] all were of white European ethnicity. All patients were living at home. Patients in the FTD and SD groups fulfilled consensus criteria for FTLD. FTD with motor neuron disease patients were excluded. The diagnosis of probable AD was made according to the NINCDS-ADRDA criteria. All underwent comprehensive investigation including MRI and/or HMPAO-SPECT, a battery of screening blood tests, neuropsychological and psychiatric evaluations, mini-mental state examination (MMSE) and clinical dementia rating (CDR).

The care-giver-based questionnaire consisted of 36 items investigating five domains: swallowing, appetite, food preference (including sweet food preference and food fads), eating habits (including stereotypic eating behaviours and decline in table manners) and other oral behaviours (including food cramming and indiscriminate eating). It was emphasised that a "symptom" should reflect a substantive change from a patient's premorbid state. If care givers endorsed a particular item, they were asked to rate the frequency and severity, to derive a frequency×severity score.[5] Patients' present weights were measured, and patients' premobid weights were ascertained from their previous check-up to estimate the amount of weight change.

As demographic variables, there were no significant differences between patients in Japan and in the UK in age, education and CDR grade. There were significantly more females in the Japanese cohort, and the mean MMSE score of Japanese patients was significantly lower. Figure 1 shows the total scores (frequency×severity) for each domain in the three patient groups in Japan and UK. For all five domains, two-way ANOVAs showed a significant main effect of diagnosis only, no significant main effect of patients' nationality and no interaction between diagnosis and nationalities. In all instances, FTD patients scored significantly higher than AD patients. For appetite change, food preference and eating habits, SD patients also scored significantly higher than AD patients. A weight gain of more than 7.5 kg was found in 30% of the FTD cases and 36% of SD cases in UK, compared with 5.6% of FTD cases and 9.1% of SD cases in Japan.

Patients with FTD and SD presented similar abnormal eating behaviours both in Japan and in the UK. Changes in eating behaviours in Japanese patients with both of the FTLD subtypes were significantly more common than AD patients, as was the case in the UK. Therefore, it is clear that patients with FTD and SD exhibit similar abnormal eating behaviours, as is the case with other behavioural and psychiatric symptoms.[1 2] Changes in eating behaviours in FTLD groups appear to be universal, and although ethnic-cultural factors might modulate these changes to some extent, they are likely to be a direct consequence of the pathology of FTLD. Changes in food preference and eating habits were the main alteration in SD. The FTD group also showed changes in appetite and oral behaviours. These findings are in keeping with prior reports.[2] The

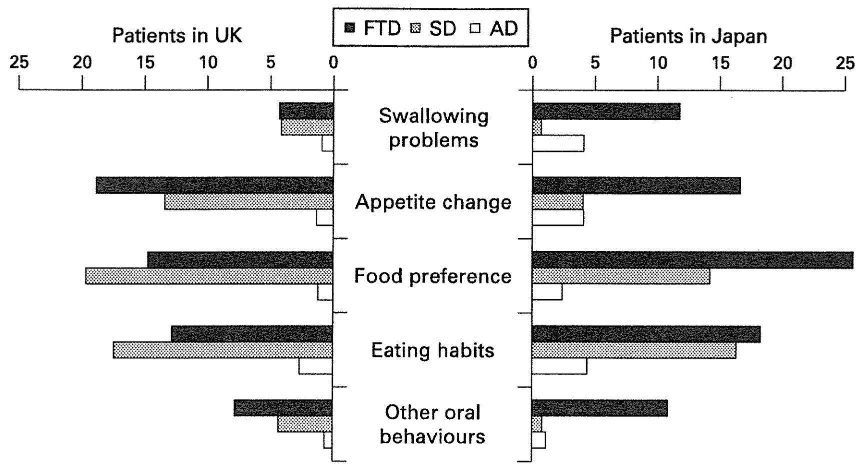

Figure 1 Score (frequency×severity) for each symptom domain in three patient groups in UK and Japan. Frequency: 1, occasionally, less than once per week; 2, often, about once per week; 3, frequently, several times per week but less than every day; 4, very frequently, once or more per day or continuously. Severity: 1, mild, easily controlled; 2, moderate, not easily controlled; 3, marked, embarrassing or otherwise disturb family. FTD, frontotemporal dementia (Japan: n = 18, age 65.5 (SD 7.0) years, F/M 9/9, mini-mental state examination (MMSE) 16.1 (9.4); UK: n = 23, age 61.1 (6.6), MMSE 22.9 (7.4)). SD, semantic dementia (Japan: n = 11, age 66.8 (7.6) years, F/M 7/4, MMSE 15.7 (10.8); UK: n = 25, age 65.1 (7.0), MMSE 17.2 (8.3)). AD, Alzheimer disease (Japan: n = 43, age 70.1 (9.8) years, F/M 30/13, MMSE 13.7 (7.9); UK: n = 43, age 68.3 (7.7), MMSE 20.6 (5.7)).

higher rate of appetite change in British SD may reflect the more advanced disease of the British: four out of 11 Japanese patients were moderate or severe demented cases (CDR≥2), whereas 16 out of 25 were moderate or severe in the UK cohort.

It appears that some abnormal eating behaviours such as appetite increase are modulated by cultural factors. A weight gain of more than 7.5 kg was found in 30% of FTD and 36% of SD cases in the UK, while it was found in less than 10% of FTD and SD cases in Japan. As described above, sugar intake and total calorie consumption differ significantly across Japan and the UK. We suggest that Japanese FTLD patients did not manifest such severe weight gain, because their eating behaviours are not amplified by cultural factors.

The current results highlight the stability of abnormal eating behaviours in FTLD across cultures with significantly different dietary habits and reinforce the view that changes in eating behaviour are diagnostically useful in detecting FTLD.[1 5]

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Posterior circulation strokes without systemic involvement as the presenting feature of Fabry disease

Fabry disease is a multisystem lysosomal storage disorder with serious effects including cardiomyopathy and renal failure. Although neurological involvement at presentation is unusual, it is increasingly recognised that Fabry disease may present with ischaemic strokes and may be responsible for up to 5% of cryptogenic strokes in young men.[1] Early recognition is vital to permit early therapeutic intervention and family screening, and could prevent clinical progression and recurrent stroke. We report a patient who presented with recurrent brainstem ischaemic strokes due to Fabry disease, with no evidence of systemic manifestations at presentation. Fabry disease should be considered in cases of cryptogenic stroke (especially young men with vertebrobasilar territory symptoms) even without multisystem involvement.

CASE REPORT

In January 2007, a 24-year-old man was admitted with sudden rotatory vertigo and nausea. He reported three previous similar episodes. In 2004, he had diplopia for 5 days; later that year, he experienced transient vertigo and gait ataxia. The third episode occurred in February 2005, when he suffered the abrupt onset of unsteadiness, nausea, slurred speech and right-sided weakness. An MRI scan of the brain at this time showed a lesion of high signal on T2-weighted images in the left pons; MR angiography, carotid duplex scan and transoesophageal echocardiogram (TOE) were normal. Demyelination was considered, but when a cerebrospinal fluid (CSF) examination failed to show oligoclonal bands, a diagnosis of probable cryptogenic stroke was made. He made a good recovery over several weeks and remained symptom-free on aspirin and simvastatin until the present admission.

His general and neurological examinations were unremarkable. His only known vascular risk factor was smoking; there was no history of drug abuse, family history of stroke or premature vascular disease. He did not report painful acroparaesthesias during childhood. Pulse and blood pressure were normal. Routine haematology, biochemistry and cholesterol levels were normal. Detailed thrombophilia and vasculitic screens were negative. T2-weighted MRI of the brain revealed the old lesion in the left pons and a new lesion in the right midbrain compatible with ischaemia (fig 1), but an extensive battery of investigations (including repeat MR angiography and TOE) failed to reveal any cause. There was no signal abnormality in the thalamic pulvinar on T1-weighted images. However, plasma and leucocyte alpha-galactosidase A activity were very

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Characteristics of eating and swallowing problems in patients who have dementia with Lewy bodies

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ABSTRACT

Background: Eating problems occur frequently in patients with dementia, and almost half of all patients with Parkinson's disease have such problems. It has therefore been assumed that eating problems are also common in patients with dementia with Lewy bodies (DLB). However, few systematic studies have investigated eating problems in DLB patients. The aim of this study was to clarify the frequency and characteristics of eating problems in patients with DLB.

Methods: We examined 29 consecutive patients with DLB and 33 with Alzheimer's disease (AD) in terms of age, sex, education, Mini-mental State Examination, clinical dementia rating (CDR), neuropsychiatric inventory (NPI), Unified Parkinson disease rating scale (UPDRS), fluctuations in cognition, and usage of neuroleptic drugs / antiparkinsonian drugs. We employed a comprehensive questionnaire comprising 40 items and compared the scores between the two groups.

Results: DLB patients showed significantly higher scores than AD patients for "difficulty in swallowing foods," "difficulty in swallowing liquids," "coughing or choking when swallowing," "taking a long time to swallow," "suffering from sputum," "loss of appetite," "need watching or help," and "constipation". Only the UPDRS score significantly affected the scores for "difficulty in swallowing foods," "taking a long time to swallow" and "needs watching or help" score, whereas only the NPI score affected the score for "loss of appetite." The scores for UPDRS, NPI and CDR significantly affected the scores for "difficulty in swallowing liquids." No significant independent variables affected the scores for "coughing or choking when swallowing," "suffering from sputum" and "constipation."

Conclusion: Although DLB patients show many eating problems, the causes of each problem vary, and the severity of dementia or Parkinsonism is not the only determinant.

Key words: dementia with Lewy bodies, eating problems, swallowing problems, extrapyramidal signs, autonomic dysfunction

Introduction

It is well known that eating problems occur in association with cognitive dysfunction, psychiatric problems, and decline of daily activity in individuals with dementia (Frissoni *et al.*, 1998; Holm and Soderhamn, 2003). It is also known that eating/swallowing problems are associated with extrapyramidal signs (EPS) in Parkinson's disease (PD), almost half of all patients having some kind of eating problem (Liberman *et al.*, 1980). Dementia with Lewy bodies (DLB) is a dementing disorder clinically characterized by marked fluctuations in cognition, visual hallucinations, EPS, and sensitivity to typical neuroleptics (McKeith *et al.*, 1996; 2006). As DLB is clinically and pathologically related to PD, eating/swallowing problems have been considered common in DLB patients because of their EPS, autonomic dysfunction, fluctuations in cognition, and psychiatric problems. In a recent report from the DLB Consortium, "eating and swallowing difficulties" are described as a part of autonomic dysfunction in supportive diagnostic features (McKeith *et al.*, 2005). For DLB patients

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and their caregivers, it is important to evaluate the clinical background to eating / swallowing problems.

DLB is the second most common form of dementia after Alzheimer's disease (AD), accounting for 15–20% of dementia cases in pathological studies (McKeith *et al.*, 1996). However, to our knowledge, only a few systematic studies have investigated eating/swallowing problems in DLB patients (McKeith *et al.*, 2006). The aim of the present study was to clarify the frequency and characteristics of eating/swallowing problems in DLB patients, and their relationship to other symptoms.

Methods

Subjects

The study participants comprised 29 consecutive outpatients attending the Higher Brain Function Clinic of the Department of Neuropsychiatry, Ehime University Hospital, Japan, with a diagnosis of probable DLB according to the international working group criteria (McKeith *et al.*, 1996), between June 2005 and September 2005. Thirty-three patients with AD were also selected, matched for age and Mini-mental State Examination (MMSE) score (Folstein *et al.*, 1975), clinical dementia rating (CDR) score (Hughes *et al.*, 1982), and education. Patients with AD satisfied the criteria for probable AD developed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKhann *et al.*, 1984). All subjects with DLB and AD underwent magnetic resonance imaging (MRI) and HMPAO-SPECT. All subjects were evaluated by senior neuropsychiatrists and underwent both physical and neurological examinations, as well as standard psychiatric evaluation, to exclude major functional psychiatric disorders such as schizophrenia or mood disorders. We also employed the usual battery of screening blood tests including vitamin B_{12} and thyroid function assessment to exclude treatable causes of dementia. All of the subjects were living with reliable caregivers. After a complete description of the study was presented to all patients or their caregivers, written informed consent was obtained.

Patients were assessed using a comprehensive battery of neuropsychological and neuropsychiatric tests, including MMSE, digit span test, verbal fluency test, Raven's Coloured Progressive Matrices (Raven *et al.*, 1990), CDR, and neuropsychiatric inventory (NPI; Cummings *et al.* 1994). We used the Unified Parkinson Disease Rating Scale (UPDRS) Part 3 score (motor score) to evaluate the severity of extrapyramidal signs (Fahn *et al.*, 1987). Caregivers were also asked whether the patients had fluctuations in cognitive functioning, or used neuroleptic or antiparkinsonian drugs. Patients' present weights were also measured.

Assessment of eating problems

In order to assess the characteristics of eating/swallowing problems in DLB patients, we used a comprehensive questionnaire that had originally been designed to assess eating/swallowing problems in patients with frontotemporal dementia/AD (Ikeda *et al.*, 2002), and had been revised for DLB patients. The questionnaire comprised 40 items investigating the following five domains: swallowing problems, appetite change, food preferences, eating habits, and other oral behaviors. Revision of the eating/swallowing questionnaire was conducted by adding four new questions relating to DLB and deleting seven questions relating to frontotemporal dementia. For example, "Episodes of spontaneous vomiting" and "Episodes of self-induced vomiting" were unified into a single item, and items such as "Fluctuation in swallowing ability" were added. We confirmed the validity of the revised questionnaire items by piloting this version of the prototype with DLB and AD patients. Information was gathered from caregivers familiar with the patients' eating problems. It was emphasized that a "symptom" should reflect a substantive change from the patient's premorbid state and was not a longstanding eating habit. If caregivers endorsed a particular item, they were asked to rate the frequency (0 = never; 1 = occasionally, less than once per week; 2 = often, about once per week; 3 = frequently, several times per week but less than every day; 4 = very frequently, once or more per day or continuously); and severity (1 = mild, easily controlled; 2 = moderate, not easily controlled; 3 = marked, embarrassing or otherwise disturbing to the family). For each eating problem item, we derived a product score of frequency × severity analogous to the method applied in the NPI (Cummings *et al.* 1994). We compared the product scores (frequency × severity) for each item between the DLB and AD groups. The rater who administered the questionnaire was blind to the patients' diagnosis.

Statistical analyses

Data analyses were carried out using the SPSS-PC software package. The significance of differences in age and education between the two groups was analyzed using the t-test. The Mann-Whitney U test was used for the comparison of MMSE score, CDR