

notification of the probability of dementia could lead to negative psychosocial consequences. Thus, it makes sense to value specificity more than sensitivity, especially in community settings.

The SED-11Q should not be used to detect MCI (CDR 0.5), as the screening of asymptomatic stages should be conducted carefully. The results of the present study showed a wide distribution of scores in CDR 0.5, and considering the negative psychosocial consequences which result from a false-positive judgment, a diagnosis of MCI should be carefully made.

Self-Rating Scales

Self-rating scales are not appropriate to detect dementia, because subjective cognitive impairment and memory complaints are common in elderly individuals [33–36]. It is controversial whether subjective complaints are associated with cognitive decline [37, 38], and it has been reported that such complaints are correlated with depressive symptoms or personality traits, rather than cognitive decline [39, 40]. In addition, those who are already demented tend to overestimate their functions, and their self-awareness of cognitive impairments diminishes as disease progresses, especially in memory [9, 10].

Other Informant-Based Questionnaires

Other informant-based questionnaires have been developed. In 1989, the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; available in 26- and 16-item formats) [41] was proposed. It requires an intrapersonal comparison between the present states and those of 10 years ago. However, memories of 10 years ago are vague, and normally aging individuals experience cognitive declines. Thus, the IQCODE can result in false-positive diagnoses, and age-related changes are often misdiagnosed as symptoms of dementia. Furthermore, the IQCODE includes questions on symptoms associated with rather advanced stages, e.g., not recognizing the faces of family members, not remembering the names of family members, not remembering things that happened to him/her when he/she was young, and not remembering things he/she learned when he/she was young.

Another example is the Observation List of Possible Early Signs of Dementia (OLD) [42]. This test focuses on cognitive decline, and questions about daily functioning are not included. Combined questionnaires that ask about cognitive function and daily functioning are desirable [43], as daily functioning requires multifaceted cognitive abilities, and deficits in functional integrity represent a key feature of dementia.

A brief scale combining a single-item informant report of memory problems and a 4-item IADL scale has also been proposed [44]. Although the test itself is easy and brief, the scoring system is complicated and arbitrary, and the test has not been validated with a large cohort.

Another scale that combines questions on cognitive abilities and daily functioning is the 8-item questionnaire, AD8 [43]. AD8 consists of questions about the patient's memory, orientation, and functional abilities by placing emphasis on intraindividual, rather than interindividual comparisons. However, the time frame for change is set as the last several years (an exact time frame is not required). Most of the informants whom we meet in daily practice tend to overlook longitudinal change. It would be more practical to ask about the patient's state during a short period, such as the last month. The validity and reliability were confirmed in early dementia; a score of 2 or more points suggested that cognitive impairment is likely present with a sensitivity over 84% and a specificity over 80%. The negative predictive value was around 70%, and thus there is a risk of overdiagnosis. AD8 was also recommended for detection of MCI, but screening of MCI using such brief tests could result in unnecessary false-positive judgment, as stated above. In the absence of informants, the authors recommend AD8 as a self-completion questionnaire, as they reported that self-rating of AD8 differentiated nondemented from demented individuals with the same specificity as informant ratings [45].

However, the results have not been validated in other cohorts. As stated above in the ‘Self-rating scales’ section, it is debatable whether self-ratings should be considered as reliable as informants’ reports.

Limitations

Reliable informants are not always available. In cases with no reliable informants, a detailed medical interview and examination should be conducted. It is inadvisable to rely on data derived from the SED-11Q when it has been used for self-rating for the reasons stated above. Moreover, it should be noted that scores can be biased by informant depression, care burden, and the relationship with the patient. False positivity is possible for those with depression, as depression, even without comorbid dementia, causes cognitive deficits. It might be necessary to rule out depression at the initial screening using the SED-11Q. Differentiation of dementia from depression requires careful examination, and depression itself is an important risk factor for dementia [46–48]. Another limitation is that this study included few cases of dementias other than AD, and samples should be collected to confirm the reliability of this test in other dementias.

The questionnaire should be validated in a multisite study in both practical and community settings.

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Intensive rehabilitation for dementia improved cognitive function and reduced behavioral disturbance in geriatric health service facilities in Japan

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Aim: To examine the efficacy of rehabilitation for elderly individuals with dementia at intermediate facilities between hospitals and home, based on the policies for elderly individuals to promote community-based care at home and dehospitalization.

Methods: Participants were older adults with dementia newly admitted to intermediate facilities. A total of 158 in the intervention group who claimed Long-Term Care Insurance for three consecutive months, and 54 in the control group were included in the analysis. The interventions were carried out in a tailor-made manner to meet individual needs. The personal sessions were carried out three times a week for 3 months after admission by physical, occupational or speech therapists. Outcome measures were cognitive tests (Hasegawa Dementia Scale revised [HDS-R] and Mini-Mental State Examination), and observational assessments of dementia severity, activities of daily living (ADL), social activities, behavioral and psychological symptoms of dementia (BPSD) using a short version of the Dementia Disturbance Scale (DBD13), depressive mood, and vitality.

Results: Significant improvement in the intervention group was shown in cognitive function measured by HDS-R (interaction $F[1, 196] = 5.190, P = 0.024$), observational evaluation of dementia severity ($F[1,198] = 9.550, P = 0.002$) and BPSD (DBD13; $F[1,197] = 4.506, P = 0.035$). Vitality, social activities, depressive mood and ADL were significantly improved only in the intervention group, although interaction was not significant.

Conclusions: Significant improvement by intervention was shown in multiple domains including cognitive function and BPSD. Cognitive decline and worsening of BPSD are predictors of care burden and hospitalization, thus intensive rehabilitation for dementia was beneficial for both individuals with dementia and their caregivers. *Geriatr Gerontol Int* 2013; ••: ••–••.

Keywords: behavioral and psychological symptoms of dementia, clinical medicine, Dementia Disturbance Scale short version, dementia, geriatric medicine, rehabilitation, tailor-made.

Introduction

Promoting community-based care at home and dehospitalization is one of the main policies for elderly individuals. In order to reduce the length of hospital stay, it is recommended to establish a rehabilitation and care system for the elderly just after leaving hospital. Thus, the Japanese government established the “Geriatric

Health Service Facility” in 1986 (Long-Term Care Health Facility after 2000; Roken), which is a transitional facility between hospital and home or nursing home to provide medical treatment, nursing care, and rehabilitation. Elderly individuals are admitted to Roken after their condition has become stable in hospital, and stay until they are ready to return home. After returning home, Roken offers community-based rehabilitation and various care services to support home-based care, and facilitates networks for intraregional exchanges among municipalities, local healthcare and social welfare services.

Since Roken was launched, the number of inpatients with dementia has markedly increased. Hospitalization

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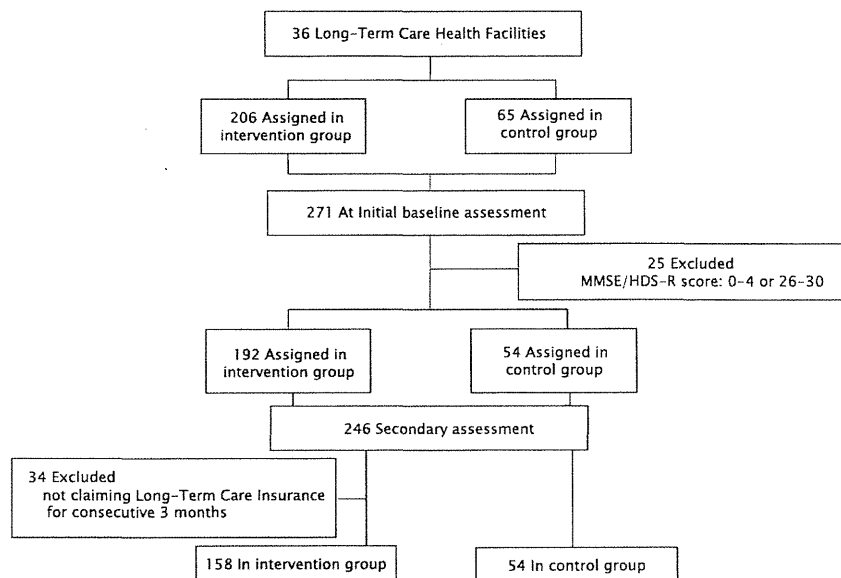


Figure 1 Flow of participants in the intervention and control groups. HDS-R, Hasegawa Dementia Scale revised. MMSE, Mini-Mental State Examination.

itself can cause cognitive deterioration, even during a hospital stay for diseases other than dementia, and patients are often not expected to recover to their pre-hospitalization level.¹ Other predictors of hospitalization are caregivers' burden and the interrelationship with caregivers.² Behavioral and psychological symptoms of dementia (BPSD) are a source of distress for caregivers and a major reason for hospitalization.^{3,4} Additionally, disuse syndrome is triggered by psychological factors associated with dementia, such as a depressive and apathetic mood.⁵⁻⁹ Disuse syndrome can lead to deterioration of cognitive and physical function, which can result in repeated hospitalization.

To break the vicious cycle of repeated hospitalization, effective rehabilitation just after discharge from hospital is required, and Roken was singled out as the appropriate facility for the rehabilitation. Thus, in 2006, the Japanese Long-term Care Insurance system introduced intensive rehabilitation for individuals with dementia who were newly admitted to Roken, consisting of personal rehabilitation three times a week for 3 months. This rehabilitation has become widely practiced since its introduction. However, the efficacy has not been examined, although the rehabilitation is payable under long-term insurance. Thus, a model project was organized to examine the efficacy of the rehabilitation for dementia in Roken throughout Japan.

Methods

Study members

Study committee members were researchers excluding stakeholders of any Roken, and committee observers were staff of the Health and Welfare Bureau for the

Elderly, Ministry of Health, Labour and Welfare. The committee designed the research, selected 36 Rokens, and interpreted the data. Data were collected by rehabilitation staff in the 36 Rokens.

Participants

The study was carried out between July 2007 and February 2008. The flow of participants is shown in Figure 1. Survey slips were sent to the facilities in July 2007. The facilities were required to send them back after the pre-intervention and post-intervention assessment, respectively. Inclusion criteria of the intervention group were: (i) newly admitted patients with dementia diagnosed by *The Diagnostic and Statistical Manual of Mental Disorders IV*; (ii) with Mini-Mental State Examination (MMSE) or Hasegawa Dementia Scale revised (HDS-R) score between 5 and 25 at pre-intervention assessment; and (iii) who claimed Long-Term Care Insurance for three consecutive months. Inclusion criteria of the control group were: (i) and (ii), and (iii) who did not receive interventions. The participants were not randomized. We received 271 responses, and among them, 212 individuals met the inclusion criteria (158 in intervention group and 54 in control group; Table 1). Informed consent was given from all participants or their responsible care giver. The research plan was approved by the Ethics Board of the Japan Association of Geriatric Health Services Facilities.

Assessment

The assessment was minimized to reduce the burden of facilities staff. As the interventions were carried out by therapists during working time, it would have been

Table 1 Demographic data

		Intervention	Control	
<i>n</i>		158	54	
Male/female (%)		30.2/69.8	39.6/60.4	NS
Age		84.1 ± 7.1	87.3 ± 7.1	P = 0.005 [†]
Dementia	AD	22	7	NS
	VD	52	15	NS
	DLB	3	0	NS
	FTD	2	0	NS
	Others/unknown	79	32	NS

[†]Significant difference by two-sample *t*-test. AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FTD, front-temporal dementia; M/F, male/female; NS, no significant difference by χ^2 -test; VD, vascular dementia.

difficult to collect many data if the assessment were complicated. The assessment scales were chosen based on preliminary studies, which were carried out in the last 2 years.

Cognitive tests

The MMSE and HDS-R were carried out. HDS-R is similar to MMSE, but lays more weight on memory than does MMSE.

Questionnaires

For the assessment of subjective mood, the participants were required to answer the interview of a short version of the Geriatric Depression Scale (GDS;¹⁰ scores are between 0–5, high scores indicate more depressive mood). Facility care staff assessed activities of daily living (ADL), BPSD, N-Memory Scale (NM),¹¹ vitality index¹² and the Social Activity Scale. ADL was assessed using the Barthel Index (scoring was changed: total assistance of 0 to independence of 3 for each item, and full score of 15).¹³ In addition to ADL, the capacity for social interaction was measured using the Social Activity Scale, whose sub-items were conversation with facility staff members, conversation with other residents, organizing own belongings, participation in recreational activities, and outings (total assistance of 0 to independence of 3 for each item, and full score of 15). BPSD was evaluated using a short version of the Dementia Behavior Disturbance Scale (DBD;¹³ “never” of 0 to “usually” of 3 for each item and full score of 48).¹⁴ The NM Scale is an observational scale, which evaluates the stages of dementia in five domains: housework, social interaction and interest, communication, memory, and orientation (“impossible” of 0 to “normal” of 10 and full score of 50). The Vitality Index evaluates motivation in daily living, with sub-items of waking up, greetings, having meals, elimination, and participation in rehabilitation and/or recreation (“indifferent” of 0 to “voluntarily” of 2 and full score of 10).

Intervention

Before commencement of the study, a training workshop was held to introduce the intervention methods, whose efficacy was suggested by previous studies: such as reminiscence, reality orientation, memory rehabilitation, music therapy, physical exercise, occupational therapy, speech communication therapy and learning sessions.

The intervention was carried out in an individualized tailor-made manner.¹⁵ First, the individual functional profiles were assessed with regard to both abilities and disabilities to evaluate how to enhance the abilities and compensate for disabilities. Second, training activities were selected; the decision was shared between therapists and participants. Each personal session was took place three times a week for 3 months after admission by physical, occupational or speech therapists. Individuals in the control group took usual group therapies including exercise, singing songs and games.

Analysis of data

The data were analyzed using the Japanese version of SPSS for Windows version 19.0 (IBM Corporation, Armonk, NY, USA). For an initial baseline comparison between the intervention and control groups, two-sample *t*-tests were carried out; there was no significant difference between the two groups for any outcome measure. Participants who underwent the initial baseline and post-intervention assessments were included in the final analysis; dropout participants were excluded from the analysis. Repeated measures analysis of covariance (ANCOVA) with the covariate of age was used to analyze the completed cases. Age was used as a covariate, because the ages were significantly different between the two groups (Table 1). The interaction was examined to assess the differential effect between the intervention and control groups, and post-hoc “within subjects” analysis was carried out with Bonferroni correction. Regarding the measures where significant

interaction was shown, intention-to-treat analysis was also carried out; the participants who received the intervention but did not claim Long-Term Care Insurance for three consecutive months were included in the intention-to-treat analysis. A significant difference was set as $P < 0.05$.

Results

Demographic data of the participants are shown in Table 1. Analysis of 158 participants in the intervention group and 54 in the control group was carried out (Fig. 1). The number of participants who took donepezil during the intervention/observation period was two in both groups ($P = 0.269$, χ^2 -test).

Cognitive tests

Participants in the intervention group showed significant improvement in HDS-R score compared with those in the control group (interaction $F[1, 196] = 5.190$, $P = 0.024$; post-hoc intra-subject analysis: intervention group, $P = 0.001$, control group $P = 0.480$). There were no significant differences observed in MMSE (Table 2).

Questionnaire

The intervention group showed significant improvement compared with the control group in DBD¹³ ($F[1,197] = 4.506$, $P = 0.035$; post-hoc intra-subject analysis: intervention group, $P = 0.004$, control group $P = 0.413$) and NM Scale ($F[1,198] = 9.550$, $P = 0.002$; post-hoc intra-subject analysis: intervention group, $P < 0.001$, control group $P = 0.380$). Regarding the sub-items of the NM Scale, significant differences in interaction were observed for social interaction ($F[1,198] = 15.736$, $P < 0.001$), memory ($F[1,198] = 7.635$, $P = 0.006$) and orientation ($F[1,198] = 4.220$, $P = 0.041$).

Although the interaction was not significant, comparison between pre- and post-intervention showed significant improvement in ADL (Barthel Index), Social Activity Scale, motivation (Vitality Index) and mood (GDS) only in the intervention group after multiple correction (Table 2).

Intention-to-treat analysis

Significant differences remained in the intention-to-treat analysis in the HDS-R and NM Scale; HDS-R, interaction ($F[1, 230] = 4.466$, $P = 0.036$), post-hoc analysis within subjects: intervention group $P < 0.001$, control group $P = 0.585$; NM Scale, interaction ($F[1, 236] = 8.113$, $P = 0.005$), post-hoc analysis: intervention

Table 2 Outcome of intensive cognitive rehabilitation

	Intervention group		Control group		Interaction F (DF)	P	Intra-subject [†]	
	Pre mean ± SD	Post mean ± SD	Pre mean ± SD	Post mean ± SD			Intervention	Control
Cognitive test								
MMSE	19.1 ± 4.5	19.4 ± 5.5	19.5 ± 4.9	18.2 ± 7.4	1.780 (1,110)	0.185	0.542	0.234
HDS-R	16.9 ± 5.7	17.9 ± 6.5	17.0 ± 5.9	16.7 ± 6.3	5.190 (1,196)	0.024*	0.001**	0.480
Questionnaire								
NM	30.4 ± 9.1	32.1 ± 9.5	31.4 ± 9.8	30.7 ± 10.9	9.550 (1,198)	0.002**	$P < 0.001$ ***	0.380
ADL	16.4 ± 7.1	17.3 ± 7.1	15.7 ± 7.0	15.9 ± 6.9	1.448 (1,202)	0.230	0.001**	0.621
Activity	8.6 ± 3.3	8.8 ± 3.4	8.5 ± 3.1	8.6 ± 3.2	1.169 (1,200)	0.281	0.038*	0.972
Vitality	8.0 ± 1.7	8.2 ± 1.6	8.1 ± 1.8	8.2 ± 1.8	1.792 (1,199)	0.182	0.004**	0.864
DBD	4.5 ± 5.1	4.0 ± 4.1	4.5 ± 4.2	4.8 ± 4.7	4.506 (1,197)	0.035*	0.004**	0.413
GDS	2.5 ± 1.8	2.4 ± 1.9	2.3 ± 1.5	2.4 ± 1.5	2.048 (1,196)	0.154	0.042*	0.634

[†]Intra-subject; post-hoc analysis of intra-subject (comparison between pre- and post-intervention analysis) * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. Activity, Original Activity Scale; ADL, Activities of daily living; DBD, Dementia Behavior Disturbance Scale; DF, degree of freedom; GDS, Geriatric Depression Scale; HDS-R, Hasegawa Dementia Scale revised; MMSE, Mini-Mental State Examination; NM, N-Memory Scale; Post, post-intervention assessment; Pre, pre-intervention assessment; Vitality, Vitality Index.

group $P < 0.001$, control group $P = 0.410$. The interaction of DBD was marginal; interaction ($F[1, 232] = 3.717, P = 0.055$), post-hoc analysis: intervention group $P = 0.007$, control group $P = 0.439$.

Discussion

Significant improvement by the intervention was shown in multiple domains; therefore, the intensive rehabilitation for dementia was beneficial for the individuals with dementia and also their caregivers. Pharmacological effects were thought to be negligible, as just two participants in both groups took donepezil during the intervention/observation period.

Regarding cognitive function, the effects of intensive rehabilitation for dementia were shown in both a cognitive test and observational evaluation of memory and orientation measured by NM Scale. In the symptomatic treatment of dementia, amelioration in daily living rather than in neuropsychological factors should be the therapeutic objectives, and thus the emphasis would be laid on improving performance in everyday life rather than on scores of cognitive tests.¹⁶ Besides, it is often pointed out that scores of cognitive tests cannot always be generalized to daily living, although cognitive tests are moderately predictive of functional status in everyday life.¹⁷ Therefore, mere enhancement of cognitive test scores is not sufficient, and beneficial changes in daily living are required. In the present study, cognitive improvement was shown in observational evaluation, in addition to a cognitive test. Cognitive enhancement is also beneficial for caregivers, because the severity of cognitive impairment could be a predictor of burden, in addition to BPSD.^{18,19} The effects of non-pharmacological approaches on cognitive function have not yet been established,^{16,19} and the present study could provide additional evidence for their benefit.

Amelioration of BPSD was also attained in the present study. Care for demented individuals requires allocation of longer times than for care of the elderly suffering from physical diseases. In particular, the presence of BPSD might induce more stress than do medical problems,^{4,20-23} and could result in depression or strain in caregivers.²⁴ Consequently, caregivers' burden is associated with an increased risk of institutionalization.²⁵ However, institutionalization could not solve caregivers' distress; a year after institutionalization, distress still persisted in caregivers.²⁶ In contrast, treatment of BPSD could help diminish caregiver burden.²⁷ Thus, it is beneficial both for individuals with dementia and their caregivers to reduce BPSD by rehabilitation in intermediate facilities between hospital and home.

In addition to enhancement of cognitive function and reduction of BPSD, improvement of social functioning and quality of life (QOL) should be the main outcomes of rehabilitation for dementia.¹⁶

Social isolation is associated with increased risk of mental decline,²⁸ whereas a rich social network and interaction might protect against mental decline.^{29,30} In demented individuals, symptoms of depression were a consistent predictor of QOL.³¹ In the present study, the intervention group showed improvement of social functioning measured by the Social Activity Scale, and amelioration of depressive mood measured by GDS.

Regarding the intervention, individualized tailor-made therapies were carried out, because the aim of the present study was to enhance each participant's ability to meet their individual needs, and not to show the efficacy of any specific method. Personally-relevant goals were identified, and the therapist worked with the individuals with dementia to devise strategies to cope with difficulties in their everyday lives by building on the person's strengths and developing ways of compensating for impairment.¹⁵ Personal selection was considered an essential therapeutic element to enhance the motivation and optimize the emotional impact of the training. Changing and combining methods were allowed during the intervention period.

The present study showed that intensive rehabilitation should be beneficial for both individuals with dementia and caregivers. To promote community-based care and dehospitalization, continuity of rehabilitation is desirable to maintain function after returning home; another mission of Roken is to offer community-based rehabilitation and various care services to support home-based care.

As a limitation, the participants were not randomized. By data cleaning, data including missing values were excluded so that the numbers of valid data were different among assessments. Finally, for evaluation of the effects on dehospitalization, a longitudinal follow-up study is required.

Acknowledgment

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Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Cerebrospinal fluid levels of phosphorylated tau and A β 1-38/A β 1-40/A β 1-42 in Alzheimer's disease with PS1 mutations

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Abstract

We studied seven cases of Alzheimer's disease (AD). Six of the patients had presenilin 1 (PS1) mutations (PS1AD). Three novel PS1 mutations (T99A, H131R and L219R) and three other missense mutations (M233L, H163R and V272A) were found in the PS1AD group. We measured the levels of phosphorylated tau (ptau-181, ptau-199) and A β (A β 1-42, A β 1-40 and A β 1-38) in the cerebrospinal fluid (CSF) of PS1AD patients, early-onset sporadic AD (EOSAD), late-onset sporadic AD (LOSAD) and non-demented subjects (ND). The CSF levels of A β 1-42 in the three AD groups were significantly lower than those of the ND group ($p < 0.0001$). CSF levels of A β 1-42 in the PS1AD group were significantly lower than those in the two sporadic AD groups. The A β 1-40 and A β 1-38 levels in the CSF of the PS1AD group were significantly lower than those of the three other groups ($p < 0.0001$, respectively). The levels of A β 1-40, A β 1-38 and A β 1-42 in the CSF of the PS1AD group remained lower than those of the ND group for 4 years. Not only CSF A β 1-42, but also A β 1-40 and A β 1-38 decreased in the advanced stages of PS1AD.

Abbreviations: A β , amyloid β protein; AD, Alzheimer's disease; ADL, activities of daily living; ApoE, apolipoprotein E; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; EOSAD, early-onset sporadic AD; LOSAD, late-onset sporadic AD; MCI, mild cognitive impairment; ND, non-demented subject; PIB-PET, Pittsburgh compound B-positron emission tomography; PS1, presenilin 1; ptau, phosphorylated tau; PS1AD, Alzheimer's disease patient with presenilin 1 mutation; S.D., standard deviation; ^{99m}Tc-ECD SPECT, ^{99m}Tc-ethyl cysteinate dimer single photon emission computerized tomography

Introduction

The extracellular deposition of amyloid- β (A β) peptides (preferentially A β 42) into neuritic plaques and the formation of neurofibrillary tangles consisting of phosphorylated tau (ptau) are hallmarks of Alzheimer's disease (AD) [1,2]. In cases of AD with autosomal dominant inheritance, presenilin 1 (PS1) is the most prevalent causative gene for early-onset familial AD [3–6]. The major component of neurofibrillary tangles is tau, a microtubule-associated protein that undergoes

excessive phosphorylation at multiple sites (e.g. ptau-199, ptau-181 and ptau-231) and aggregates into paired helical filaments in the brains of AD patients [7,8]. In the cerebrospinal fluid (CSF) of AD patients, the levels of A β 1-42 are selectively reduced [9,10] and the CSF levels of total-tau and ptau were reported to be elevated [11–13]. Carboxy-terminal truncated A β peptides other than A β 1-40/42, A β 1-37/38/39 have been identified physiologically in CSF [14]. A β 1-42, A β 1-40 and A β 1-38 have been reported in the CSF in AD, dementia with Lewy bodies (DLB) and progressive aphasia (PA) [15–17]. In the present study, we found that the CSF levels of A β 1-40 and A β 1-38 in AD patients with PS1 mutations were significantly decreased compared to those of early- or late-onset sporadic AD patients and subjects without

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Keywords

Alzheimer's disease, amyloid β protein, cerebrospinal fluid, phosphorylated tau, presenilin 1

History

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AD. We also obtained longitudinal data showing the low levels of A β 1-40 and A β 1-38 in the CSF of the four PS1AD patients with a long-term duration of illness.

Materials and methods

Subjects

This study complied with the Declaration of Helsinki and was approved by the Institutional Review Boards (IRB) of Gunma University Graduate School of Medicine, Geriatrics Research Institute and Hospital, and Maebashi Red Cross Hospital. The spouse or family members of each AD patient provided written informed consent for the patient to participate in the study. One hundred and twenty-seven subjects (40 early-onset sporadic AD (EOSAD) patients, 40 late-onset sporadic AD (LOSAD) patients, 40 subjects without dementia and seven PS1AD patients), who underwent lumbar punctures, were recruited at Gunma University Graduate School of Medicine, Geriatrics Research Institute and Hospital (Maebashi, Gunma, Japan), and Maebashi Red Cross Hospital (Maebashi, Gunma, Japan). Upon entering the study, subjects underwent a standardized clinical assessment, including medical history, physical and neurological examinations, Mini-Mental State Examination (MMSE) [18], brain MRI and/or CT scan. AD was diagnosed for patients scoring 23 points or less on the MMSE [19], combined with caregivers' information of patients' daily activities. Diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) were used for AD [20]. Subjects were classified as non-demented (ND) if they scored more than 24 points on MMSE, and if, based upon information on activities of daily living (ADL) provided by the family, they were considered to have a normal daily life not requiring any intellectual assistance. The ND group comprised patients suffering from tension headache (14 cases), polyneuropathy (eight cases), epilepsy (seven cases), spinal canal stenosis (five cases), myasthenia gravis (three cases) and migraine (three cases). Lumbar puncture and follow-up assessments were performed once a year for 4 years after obtaining informed consent annually.

The AD patient group comprised patients with PS1AD (seven AD patients in six AD families, referred to as GFAD1-6), EOSAD (younger than 64 years at onset) and LOSAD (65-years-old and older at onset). Genetic analyses revealed the following PS1 mutations in the seven patients with familial AD (Table 1): GFAD1-1 (M233L), GFAD1-2 (M233L), GFAD2 (H163R), GFAD3 (L219R), GFAD4 (H131R), GFAD5 (V272A) and GFAD6 (T99A). L219R,

H131R and T99A in the PS1 gene are novel mutations, and the clinical information for these three AD patients is described in the supplementary data. Mutations of M233L, H163R and V272A in the PS1 gene were already reported elsewhere [6]. In the seven cases of PS1AD, the mean age of onset was 44.43 ± 5.74 years; the mean age of first CSF examination of PS1AD was 51.43 ± 4.35 years; the mean MMSE score at first CSF examination of PS1AD was 6.86 ± 4.34 ; and the mean duration between onset and the first CSF examination was 7.43 ± 2.44 years. In the 40 cases of EOSAD, the mean age of onset was 57.4 ± 5.13 years; the mean age of CSF examination was 62.73 ± 5.54 years; the mean MMSE score at the CSF examination was 16.67 ± 2.35 ; and the mean duration between onset and CSF examination was 5.33 ± 2.35 years. In the 40 cases of LOSAD, the mean age of onset was 72.07 ± 3.94 years; the mean age of CSF examination was 75.9 ± 4.01 years; the mean MMSE score at the CSF examination was 16.27 ± 2.55 ; and the mean duration between onset and CSF examination was 3.80 ± 1.81 years. In the ND group, the 40 subjects had a mean age of onset as 65.77 ± 9.02 years; MMSE score at the CSF examination was 29.90 ± 0.38 .

Genetic analysis of PS1 and apolipoprotein E

After obtaining informed consent for genetic testing, we purified genomic DNA from lymphocytes in the peripheral blood of affected subjects. For the analysis of apolipoprotein E, purified genomic DNA was examined as previously described [21]. DNA fragments containing Exon 3-13 of PS1 were amplified by PCR using primers [3–5].

Measurement of CSF A β 1-42, A β 1-40 and A β 1-38

CSF was obtained by a lumbar puncture in the L3/L4 or L4/L5 intervertebral space. CSF samples were centrifuged for 10 min at 1800g at 4 °C within 3 h of collection. Samples were divided into aliquots of 0.5 mL in polypropylene tubes and stored at -80°C until analysis with an ELISA kit for human CSF A β 1-40 (Wako Pure Chemical Industries, Tokyo, Japan), human CSF A β 1-42 (Wako Pure Chemical Industries) and human CSF A β 1-38 (IBL, Gunma, Japan) [22–24].

Measurement of CSF phosphorylated tau 199 and 181

Quantitative measurement of CSF levels of tau protein phosphorylated at serine 199 (CSF ptau-199) by a sandwich ELISA is an excellent biomarker for distinguishing AD patients from non-AD patients [11]. Measurement of ptau-181 in CSF was also performed by the sandwich ELISA (Innogenetics, Ghent, Belgium) as described elsewhere [25].

Table 1. Clinical features of seven PS1AD cases.

Patient	#1	#2	#3	#4	#5	#6	#7	
PS1 mutation	M233L	M233L	H163R	L219R	H131R	V272A	T99A	
Gender	Female	Female	Male	Female	Female	Female	Male	Mean \pm S.D.
Age of Onset	41	37	41	51	45	53	43	44.43 ± 5.74
MMSE*	8	3	6	16	5	4	6	6.86 ± 4.34
Age*	48	47	49	57	55	56	48	51.43 ± 4.35
Duration (years)	7	10	8	6	10	3	8	7.43 ± 2.44

This table shows PS1 mutations, gender, age of onset, MMSE, age at CSF first lumbar puncture (*) and duration (years) in seven PS1AD cases.

Statistical analysis

Differences between AD groups (PS1AD, EOSAD, LOSAD) and subjects without dementia (ND group) were compared using a two-way ANOVA with the Bonferroni correction for multiple comparisons. The level of significance was set at $p < 0.05$. All analyses were performed with the GraphPad Prism Software (GraphPad Prism Version 5.0, GraphPad software, San Diego, CA).

Results

Apolipoprotein E genotypes

The apolipoprotein E genotypes of PS1AD patients were M233L-1 ($\epsilon 3/\epsilon 4$), M233L-2 ($\epsilon 3/\epsilon 4$), H163R ($\epsilon 3/\epsilon 4$), L219R ($\epsilon 3/\epsilon 4$), H131R ($\epsilon 3/\epsilon 3$), V272A ($\epsilon 3/\epsilon 4$) and T99A ($\epsilon 3/\epsilon 4$).

Comparative analysis of CSF data from ND, PS1AD, EOSAD and LOSAD groups

The CSF levels of ptau-199 were significantly higher in the AD groups (PS1AD (M233L-1, M233L-2, H163R, L219R), 6.66 ± 3.12 pg/ml; EOSAD, 9.89 ± 4.69 pg/ml; LOSAD, 9.39 ± 4.15 pg/ml) than in the ND group (2.64 ± 0.44 pg/ml) (Figure 1(A), $p < 0.01$, $p < 0.0001$, $p < 0.0001$, respectively). The CSF levels of ptau-181 in the AD groups (PS1AD, 50.31 ± 19.03 pg/ml; EOSAD, 72.01 ± 36.30 pg/ml; LOSAD, 67.19 ± 33.93 pg/ml) were significantly higher than in the ND group (32.27 ± 12.56 pg/ml) (Figure 1(B), $p < 0.01$, $p < 0.0001$, $p < 0.0001$).

The CSF levels of A β 1-42 in the AD groups (PS1AD, 68.10 ± 22.59 pg/ml; EOSAD, 117.52 ± 64.32 pg/ml; LOSAD, 144.57 ± 70.03 pg/ml) were significantly lower than in the ND group (309.05 ± 105.02 pg/ml) (Figure 1(C), $p < 0.0001$, respectively). The CSF level of A β 1-42 in the PS1AD group was significantly lower than the levels in the EOSAD and LOSAD groups ($p < 0.01$, $p < 0.01$, respectively).

In terms of the CSF levels of A β 1-40, there were no significant differences amongst the EOSAD groups (3163.27 ± 1442.55 pg/ml), the LOSAD group (3072.37 ± 1674.86 pg/ml) and the ND group (2995.52 ± 1227.93 pg/ml) (Figure 1(D)). The CSF level of A β 1-40 in the PS1AD group (1011.06 ± 392.61 pg/ml) was significantly lower than that in the ND group ($p < 0.0001$), the EOSAD group ($p < 0.0001$) and the LOSAD group ($p < 0.0001$) (Figure 1(D)). The CSF level of A β 1-38 in the PS1AD group (655.17 ± 253.62 pg/ml) was significantly lower than the levels in the EOSAD group (2337.27 ± 1048.33 pg/ml), the LOSAD group (2511.47 ± 1221.74 pg/ml) and the ND group (2113.35 ± 1028.57 pg/ml) (Figure 1(E), $p < 0.0001$, $p < 0.0001$, $p < 0.0001$, respectively).

Combined ratios of A β molecules and ptau-181

The ratios of CSF A β 1-42/A β 1-40 in the CSF of the EOSAD, LOSAD and PS1AD were significantly lower than that of the ND group (Figure 2(A), $p < 0.0001$, $p < 0.0001$, $p < 0.001$, respectively). The ratios of A β 1-42/A β 1-38 in the CSF of the EOSAD and LOSAD groups were significantly lower than that of the ND group (Figure 2(B), $p < 0.0001$, $p < 0.0001$). There was no significant difference in the A β 1-38/A β 1-40

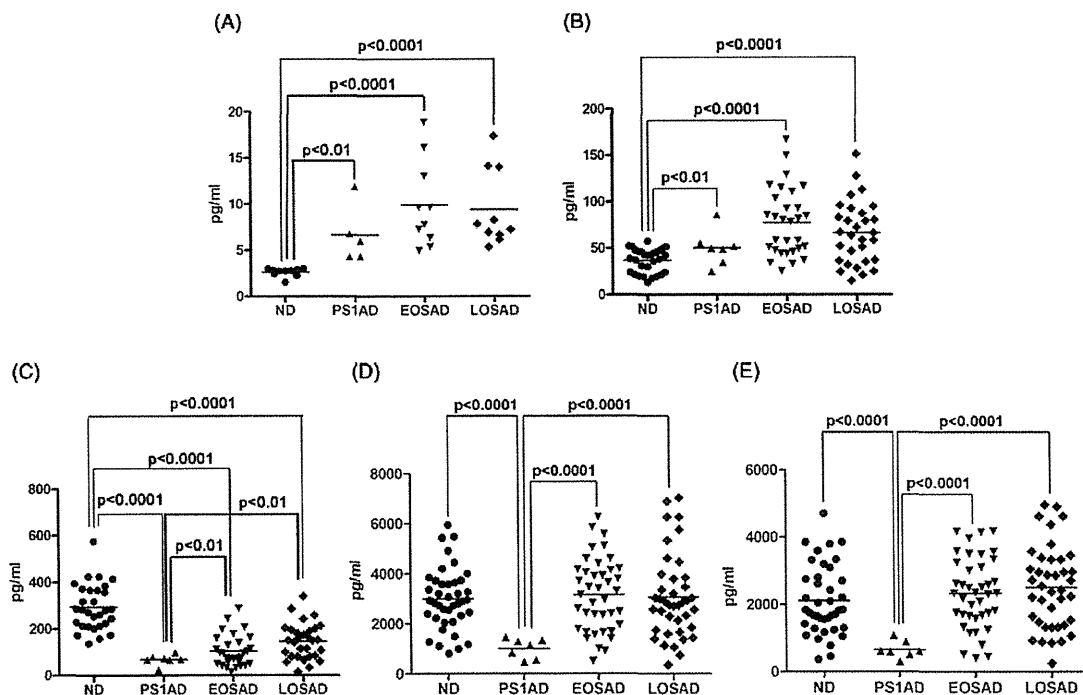


Figure 1. Measurement of CSF A β molecules and phosphorylated tau (PS1AD, EOSAD, LOSAD and ND). (A) CSF levels of ptau-199 and (B) ptau-181 showed significant increases in the AD groups (PS1AD, EOSAD, LOSAD) compared to the ND group ($p < 0.01$, $p < 0.0001$, $p < 0.0001$). (C) CSF level of A β 1-42 in the AD groups (PS1AD, EOSAD, LOSAD) showed a significant decrease compared to the ND group ($p < 0.0001$, $p < 0.0001$, $p < 0.0001$). The CSF level of A β 1-42 in the PS1AD group was significantly decreased as compared to the EOSAD, LOSAD groups (shown in bold lines, $p < 0.01$, $p < 0.01$, respectively). (D) The CSF level of A β 1-40 in the PS1AD group was significantly decreased as compared to the sporadic AD groups (EOSAD, LOSAD) ($p < 0.0001$, $p < 0.0001$) and the ND group ($p < 0.0001$). (E) The CSF level of A β 1-38 in the PS1AD group was significantly decreased compared to the sporadic AD groups (EOSAD, LOSAD) ($p < 0.001$, $p < 0.0001$) and the ND group ($p < 0.0001$).

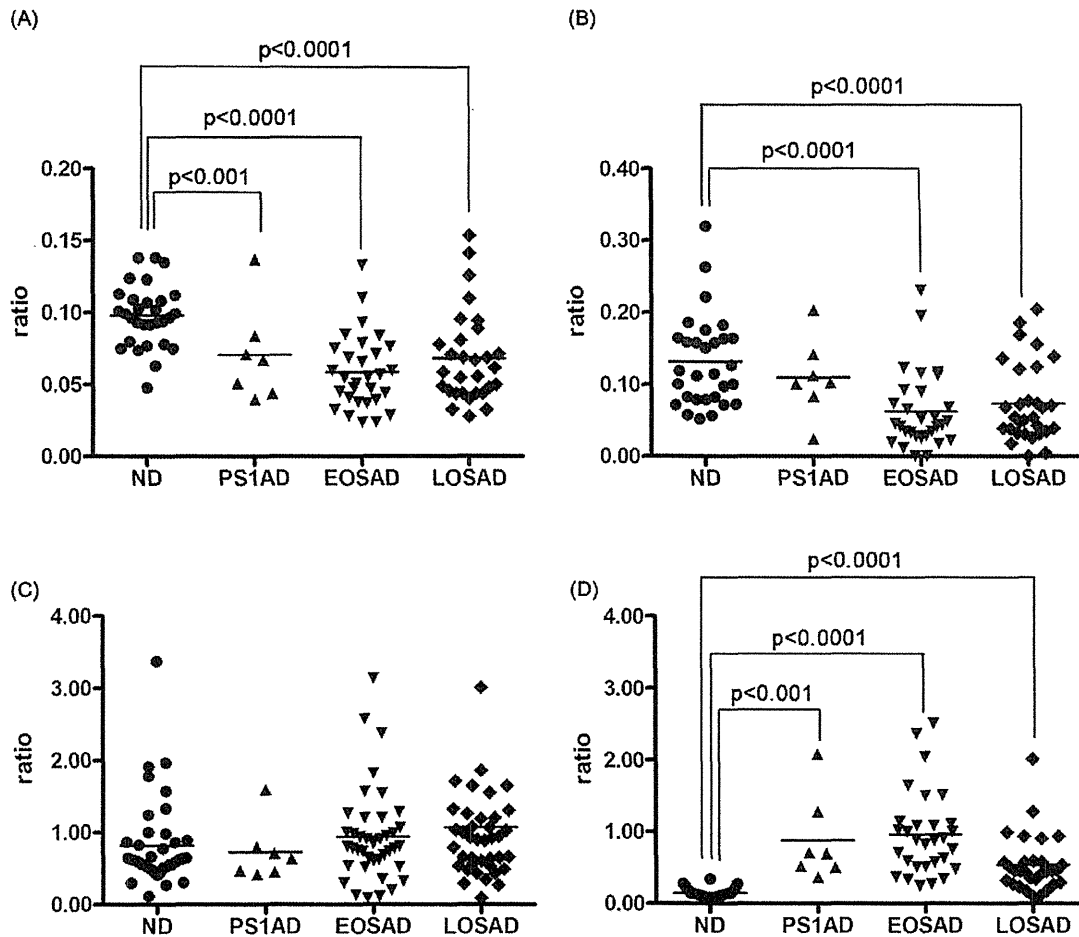


Figure 2. Ratios of CSF A β molecules and phosphorylated tau (ptau-181). (A) The ratio of A β 1-42/A β 1-40 significantly decreased between the PS1AD and the ND ($p < 0.001$) groups and between the sporadic AD (EOSAD and LOSAD) and the ND group ($p < 0.0001$, $p < 0.0001$, respectively). (B) The ratio of A β 1-42/A β 1-38 of the sporadic AD groups (EOSAD and LOSAD) significantly decreased compared to those of the ND group ($p < 0.0001$, $p < 0.0001$, respectively). (C) No significant difference in the ratio of A β 1-38/A β 1-40 in CSF was observed amongst EOSAD, LOSAD and PS1AD. (D) The ratio of ptau-181/A β 1-38 significantly increased between the three AD groups (PS1AD, EOSAD, LOSAD) compared to the ND group ($p < 0.001$, $p < 0.0001$, $p < 0.0001$).

ratios in the CSF of the four groups (Figure 2C). The ptau-181/A β 1-42 ratios in CSF of the EOSAD, LOSAD and PS1AD were significantly higher than that of the ND group (Figure 2(D), $p < 0.001$, $p < 0.0001$, $p < 0.0001$, respectively).

Temporal profiles of MMSE scores and CSF levels of A β molecules and ptau-181 in the PS1AD group

MMSE scores of four PS1AD patients (M233L-1, M233L-2, H163R, L219R) who underwent CSF analysis every year, decreased over the 4-year study period (Figure 3A). The CSF levels of ptau-181 in four PS1AD patients were significantly higher than those of ND subjects (Figure 3(B), $p < 0.01$), while the CSF levels of A β 1-42, A β 1-40 and A β 1-38 of four PS1AD patients were lower than those of ND subjects (Figure 3(C), (D), (E), $p < 0.0001$, respectively).

Discussion

The most reliable AD biomarkers are CSF A β 1-42 and PIB-PET of imaging studies, followed by CSF ptau-181 and the total tau included in the new AD criteria [26,27]. In our study,

the CSF level A β 1-42 in the three AD groups was significantly lower than that of the ND group, with the PS1AD group having a lower level than the two sporadic AD groups. The CSF levels of A β 1-42, A β 1-40 and A β 1-38 in the PS1AD group were significantly lower than those of the other three groups (ND, EOSAD and LOSAD). The ratios of A β 1-42/A β 1-40 in the three AD groups were lower than that in the ND group. The ratios of CSF A β 1-42/A β 1-38 in the CSF of the EOSAD and LOSAD groups were significantly lower than that of the ND group. This suggests that the CSF level of A β 1-38 increased in the sporadic AD groups as compared to the ND group, although the increase was not statistically significant. In contrast to these results, the CSF ratio of A β 1-38/A β 1-40 did not show a significant difference amongst the four groups (ND, PS1AD, EOSAD and LOSAD). In the PS1AD patients, the level of A β 1-38 was lower than that in other sporadic AD groups; therefore, the ratio of A β 1-42/A β 1-38 in PS1AD did not differ from ND, while it did differ between ND and the other AD groups.

We analyzed the temporal profiles of CSF (ptau-181, A β 1-42, A β 1-40, A β 1-38) in four PS1AD patients for 4 years. The CSF levels of A β 1-42, A β 1-40 and A β 1-38 were lower in

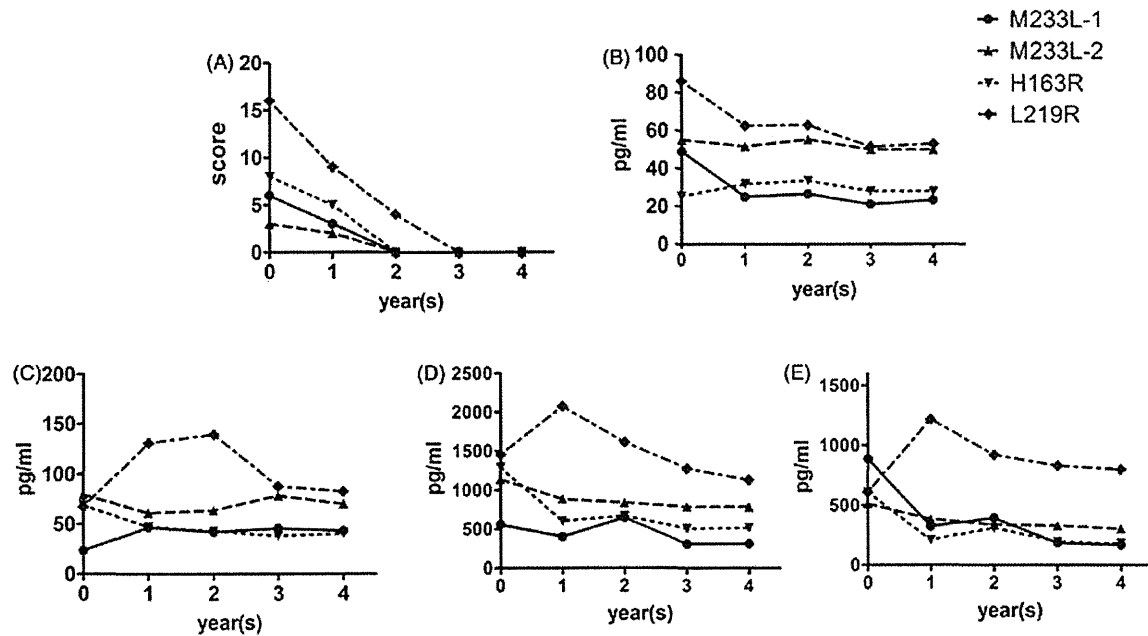


Figure 3. Temporal change of MMSE scores and CSF levels (ptau-181, A β 1-38, A β 1-40, A β 1-42) in PS1AD. (A) Four PS1AD patients (M233L-1, M233L-2, H163R, L219R) who underwent CSF analysis, have shown a decrease in MMSE scores over the 4-year period. (B) First CSF levels of ptau-181 of these four PS1AD patients were significantly higher than those of ND subjects as shown in Figure 1(B) ($p < 0.01$). (C) The CSF level of A β 1-42 was stable in M233L-1, M233L-2 and H163R, while in L219R, it increased and then decreased to levels lower than those in ND subjects. First CSF levels of A β 1-42 of these four PS1AD patients were significantly lower than those of ND groups as shown in Figure 1(C) ($p < 0.0001$). (D) The CSF level of A β 1-40 of PS1AD patients was less than 2500 pg/ml, which was lower than that in the ND group. First CSF levels of A β 1-40 of these four PS1AD patients were significantly lower than those of ND groups as shown in Figure 1(D) ($p < 0.0001$). (E) The CSF levels of A β 1-38 of PS1AD patients were less than 1500 pg/ml, which was lower than those of the ND group. First CSF levels of A β 1-38 of these four PS1AD patients were significantly lower than those of ND groups as shown in Figure 1(E) ($p < 0.0001$).

these patients as compared to the ND group during the 4-year period (Figure 3C, D, E). Unlike our results, it was reported that CSF A β 1-42 in patients with AD, mild cognitive impairment (MCI) and subjective complaints (SC) increased during 1–3.5 years [28]. The reasons for the differences from our results of PS1AD might be associated with the long duration of the illness and severe aggregative AD biochemical change, likely due to PS1 mutations. Age differences amongst the three AD groups (EOSAD, LOSAD and PS1AD), age of onset and duration of the illness might contribute to differences in the levels of CSF markers, with or without genetic background (PS1 mutation in this study).

In a recent article, the ratio of A β 1-42/A β 1-38 was largely proportional to that of A β 1-40/A β 1-43, and the two cleavage processes are tightly coupled. Therefore, both the CSF A β 1-40 and A β 1-38 were generally higher in MCI/AD patients compared with control subjects, the CSF A β 1-43 and A β 1-42 decreased in MCI/AD patients [24].

In our study, PS1AD patients with long-term severe dementia presented and remained characterized by lower CSF A β 1-42, A β 1-40 and A β 1-38 in the examined period, as compared to sporadic AD and subjects without dementia. Unlike Kakuda's article [24], our results of PS1AD presumably reflect more severe pathological processes during the long-term duration of the illness.

To date, only A431E mutation of PS1AD showed a decrease of CSF A β 1-38 and A β 1-42 [29]. Pathologically, PS1AD brains frequently showed aggravating Lewy bodies [30,31]. Some relationship between α -synuclein and A β 1-38

might be of pathological relevance for A β aggregation [32]. They may generate a nucleation center for subsequent A β amyloidogenesis and the formation of Lewy bodies. In long-term PS1AD, various molecular relationships amongst A β 1-38/40/42 molecules with aberrant accumulation of α -synuclein and tau still require further elucidation.

Conclusion

In PS1AD patients with severe dementia and advanced stage disease, CSF levels of A β 1-42, A β 1-40 and A β 1-38 were significantly lower than those of ND subjects, in which CSF levels of A β 1-40 and A β 1-38 were significantly lower than sporadic AD (EOSAD and LOSAD). We showed that CSF levels of ptau-181 in PS1AD patients were significantly higher than the ND subjects, but were not as high as in patients with sporadic AD (EOSAD and LOSAD). These findings were observed in known mutations (M233L, H163R and V272A) as well as novel mutations (T99A, H131R and L219R).

Declaration of interest

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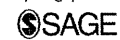
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Communicative Competence in Alzheimer's Disease: Metaphor and Sarcasm Comprehension

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Abstract

The purpose of this study was to evaluate the deficits of metaphor and sarcasm comprehension in Alzheimer's disease (AD), as pragmatic interpretation such as metaphor and sarcasm comprehension is required in social communication. A total of 31 young normal controls, 104 aged normal controls (ANC), 42 patients with amnesic mild cognitive impairment (aMCI), and 30 patients with mild AD were evaluated by Metaphoric and Sarcastic Scenario Test, which consists of 5 metaphoric and 5 sarcastic questions with 5 answer choices. Scores were analyzed using the repeated measures analysis of variance (metaphor/sarcasm vs 4 participant groups). Sarcasm comprehension, which requires second-order Theory of Mind (ToM), started to deteriorate in ANC, and metaphor comprehension, which requires first-order ToM, started to deteriorate in aMCI, and both deteriorated as disease progressed. Literal interpretation of pragmatic language is characteristic in patients with mild AD. Such misinterpretation would result in social miscommunication, even if they still retained semantic-lexical competence.

Keywords

Alzheimer's disease, theory of mind, empathy, communication difficulties, pragmatic competence

Introduction

Communicative competence occupies a central place in participation in social activities and it can be impaired in patients with Alzheimer's disease (AD). In AD, lexical-semantic competence is deteriorated as a result of cognitive decline.¹ However, patients could also have communicative difficulties even from the stage where lexical-semantic competence is still preserved. In social communication, literal lexical-semantic comprehension is not sufficient.² Comprehension of nonliteral implication is often required to infer a speaker's intended meaning (Theory of Mind [ToM]),³ which is not always expressed explicitly.

Theory of Mind is considered to consist of 2 stages, first-order ToM is the ability to grasp the intentions of the speaker and second-order ToM is the ability to infer the speakers' evaluation for an attributed thought.⁴⁻⁷ Metaphor and sarcasm comprehension are considered to be appropriate materials of ToM.⁸ First-order ToM is sufficient for metaphor comprehension.⁹ Metaphor suggests meanings through mental linkage and comparison of similarities between different expressions normally not related to each other.^{10,11} Second-order ToM is required for sarcasm comprehension.⁵ Sarcasm expresses something other than explicitly stated and especially the opposite of the literal meaning of the utterance.¹² Thus comprehension of sarcasm requires the ability to reflect on the speakers' evaluation about the attributed thought, adding to utterance intention.⁴

Metaphoric and sarcastic competence has been mainly studied to evaluate the social communicative competence in the phases of development and its disorders,¹³ as interaction with other people is critical for normal neurocognitive development.¹⁴ In the phase of aging and degeneration, it is also meaningful to evaluate the decline of social communicative competence. However, a recent review on nonliteral language in AD noted a severe lack of evidence.¹⁵ Furthermore, previous reports on metaphor and sarcasm comprehension are inconsistent; for example, deficits in metaphor comprehension were reported from early stages of AD,¹⁶⁻¹⁸ whereas concerning irony and sarcasm, previous studies did not find a significant impairment relative to an aged control group,^{19,20} which is surprising because irony involves more cognitive processes than metaphor.²¹

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The controversy could be partly due to the material in the test; it is a prerequisite that difficulty level of lexical-semantic aspects is even among sentences used in the tests. Thus, we conducted the present study to evaluate the deficits of metaphor and sarcasm in AD using a questionnaire that consists of the same type of sentences with similar difficulty levels and whose efficacy was validated for differential diagnosis of developmental disorders in children.²² For a better understanding of characteristics of AD, error patterns were analyzed. We hypothesized that comprehension might be deteriorated at the early stages of disease and sarcasm comprehension might be deteriorated earlier than metaphor comprehension.

Methods

Participant

The participants were 31 young normal controls (YNC), 104 aged normal controls (ANC), 42 patients with amnesic mild cognitive impairment (aMCI), and 30 patients with mild AD in Clinical Dementia Rating scale (CDR) 1. The YNC were university students and ANC were recruited from community dwellers, who underwent clinical interviews by a clinician who specialized in evaluation of dementia. Patients were recruited from the outpatient clinics. The exclusion criteria were psychiatric diseases and delirium. Verbal incomprehension was also an exclusion criterion. The participants were required to read out the questions and those who lacked fluency were excluded. Concerning language ability, the participants received the Mini-Mental State Examination (MMSE) and were confirmed to have the capacity to name simple objects, repeat phrases, follow written commands, and write a sentence with a noun and a verb. The participants were diagnosed based on the criteria for AD by National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association²³ and on the criteria for aMCI by the report of the International Working Group on Mild Cognitive Impairment.²⁴ Patients with aMCI were limited to those free from objective symptoms of other types of dementia such as dementia with Lewy bodies or frontotemporal dementia. The Ethics Board of the Gunma University School of Health Sciences approved all procedures (No. 21-26), and written informed consent was obtained from all the participants.

Task

Metaphor and sarcasm comprehension was evaluated by the Metaphoric and Sarcastic Scenario Test (MSST), which was developed for discrimination of high functioning pervasive developmental disorders from attention deficit/hyperactivity disorders in young children.²² This test consists of 5 metaphoric and 5 sarcastic sentences; metaphoric sentences are odd numbered and sarcastic sentences even. The words and sentences in MSST were selected from standard textbooks of Japanese language (Mitsumura Press) for 1st, 2nd, and 3rd grades in elementary school. Therefore, the lexical-semantic components were not above the levels for those who completed

6 years of elementary school education. The test employed a multiple-choice style, that is, 1 choice was correct and 4 were incorrect. The wrong choices included a literal interpretation, an answer associated with part of the sentence, misunderstanding of the sentence, and not knowing. The number of correct answers represented the metaphor score and sarcasm score, respectively. Each pattern of incorrect answers was totaled. Cognitive performance was assessed using MMSE.

Analysis

Group comparison of scores and the 4 error scores were conducted using the repeated measures analysis of variance (metaphor/sarcasm vs 4 participant groups).

Among aged groups, we conducted the repeated measures analysis of covariance (metaphor/sarcasm vs 3 participant groups) with covariates of age, sex, education, and MMSE scores. A post hoc test was conducted with multiple comparisons with Bonferroni correction. All analyses were conducted using the Japanese version of SPSS for Windows version 19.0 (IBM Corporation, New York). Significance was set as $P < .05$.

Results

Demographic scores are shown in Table 1. The results of the MSST are shown in Table 2 and Figure 1. The main effect indicated that sarcasm was more difficult to comprehend than metaphor ($F_{1,203} = 54.634, P < .001$), and interaction with participant groups was also significant ($F_{3,203} = 3.354, P = .020$). According to within-subject post hoc analysis, no significant difference was observed between metaphor and sarcasm scores in YNC ($P = .442$), whereas in ANC, aMCI, and mild AD, scores of sarcasm was significantly lower than that of metaphor ($P < .001$ in all the groups). According to between-subject post hoc analysis, metaphor scores were not different between YNC and ANC, whereas metaphor scores were significantly better in ANC than in aMCI ($P = .011$) and in aMCI than mild AD ($P < .001$). Sarcasm scores were significantly better in YNC than in ANC ($P = .040$), in ANC than in aMCI ($P = .005$), and in aMCI than in mild AD ($P = .002$).

Concerning the error patterns, group differences were observed only in literal interpretation and there were no group differences in the other 3 error patterns (an answer associated with a part of the sentence, misunderstanding of the sentence, and not knowing; Table 3, Figure 2). The main effect was significant ($F_{1,203} = 34.283, P < .001$) and interaction was also significant ($F_{3,203} = 6.887, P < .001$). According to the between-subject post hoc analysis, frequency of the errors of literal interpretation of metaphor and sarcasm comprehension were not different between YNC and ANC ($P = 1.000$ in both), and ANC and aMCI ($P = .115, P = .349$, respectively), whereas a significant difference was observed between aMCI and mild AD ($P < .001$ in both). According to within-subject post hoc analysis, the errors of literal interpretation were more in sarcasm than in metaphor in aMCI ($P = .038$) and in mild AD ($P < .001$), whereas there was no significant difference in YNC ($P = .187$) and in ANC ($P = .072$).

Table 1. Demographic Data.^a

	n	Age	Gender	Education	MMSE
		Mean ± SD	Male, Female	Mean ± SD	Mean ± SD
YNC	31	19.3 ± 1.4	M10, F21	13.3 ± 0.6	
ANC	104	72.1 ± 4.2	M25, F79	12.0 ± 2.3	28.4 ± 1.4
aMCI	42	74.0 ± 5.4	M18, F24	11.1 ± 3.0	25.8 ± 1.7
AD	30	78.0 ± 7.2	M6, F24	9.3 ± 2.3	21.4 ± 4.0

Abbreviations: YNC, young normal controls; ANC, aged normal controls; aMCI, amnesic mild cognitive impairment; AD, patients with mild Alzheimer's disease in clinical dementia rating I; MMSE, Mini-Mental State Examination; SD, standard deviation.

^a The rate of gender difference was not different among the groups ($P = .088$, chi-squared statistic). Concerning age, there was no difference between ANC and aMCI, but patients with mild AD were significantly older than ANC and aMCI ($P < .001$, $P = .004$, respectively). Concerning years of education, there was no difference between ANC and aMCI, but patients with mild AD received significantly shorter education than the patients with ANC and aMCI did ($P < .001$, $P = .006$, respectively). Scores of MMSE was significantly different among groups ($P < .001$, among all the groups).

Table 2. Correct Answers.

	Metaphor		Sarcasm		P Value ^b
	Mean ± SD	P Value ^a	Mean ± SD	P Value ^a	
YNC	5.0 ± 0.2		4.8 ± 0.4		.442
YNC vs ANC		1.000		.040*	
ANC	4.8 ± 0.7		4.1 ± 1.2		<.001**
ANC vs aMCI		.011*		.005*	
aMCI	4.3 ± 1.2		3.4 ± 1.3		<.001**
aMCI vs AD		<.001**		.002*	
AD	3.3 ± 1.2		2.3 ± 1.6		<.001**

Abbreviations: YNC, young normal controls; ANC, aged normal controls; aMCI, amnesic mild cognitive impairment; AD, patients with mild Alzheimer's disease in clinical dementia rating I; SD, standard deviation.

^a The difference among groups analyzed by between-subject post hoc analysis of 2 × 4 analysis of variance (metaphor and sarcasm; 4 groups).

^b The difference between metaphor and sarcasm analyzed by within-subject post hoc analysis of 2 × 4 analysis of variance (metaphor and sarcasm; 4 groups).

* $P < .05$.

** $P < .001$.

There was weak correlation between MMSE scores and metaphor ($r = .362$, $P < .001$) and sarcasm scores ($r = .337$, $P < .001$).

The difference among the aged groups of ANC, aMCI, and mild AD remained by the repeated measures analysis of covariance with covariates of age, sex, education, and MMSE scores. According to within-subject post hoc analysis, in ANC, aMCI, and mild AD, scores of sarcasm was significantly lower than that of metaphor ($P < .001$, $P < .001$, $P = .004$, respectively). According to between-subject post hoc analysis, metaphor scores were significantly better in ANC than in aMCI ($P = .040$) and in aMCI than mild AD ($P = .002$). Sarcasm comprehension was significantly better in ANC than in aMCI ($P = .021$) and in aMCI than in mild AD ($P = .023$).

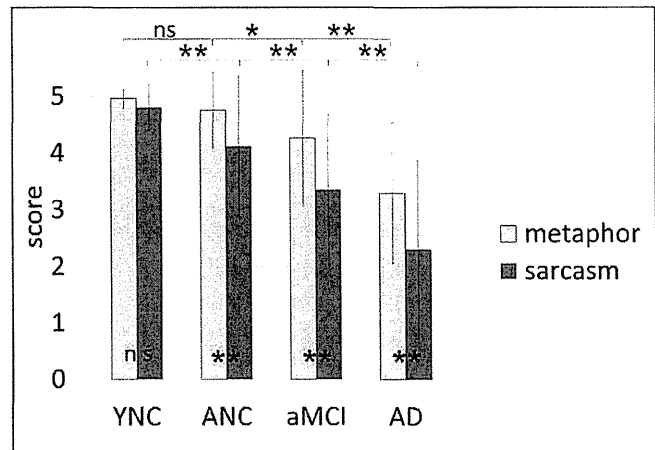


Figure 1. Scores of correct answers. Sarcasm scores were significantly lower in ANC than YNC, whereas metaphor scores were not different between the 2 groups. Metaphor scores were deteriorated from MCI. Post hoc analysis of 2 × 4 analysis of variance (metaphor and sarcasm; 4 groups) was conducted; * in upper row indicates statistical significance of between subject analysis of metaphor, * in middle row indicates that of sarcasm, and * in the bottom row indicates statistical significance calculated by intrasubject analysis. * $P < .05$, $P < .001$. YNC indicates young normal controls; ANC, aged normal controls; aMCI, amnesic mild cognitive impairment; AD, patients with mild Alzheimer's disease in clinical dementia rating I.

Table 3. Errors of Literal Answers.

	Metaphor		Sarcasm		
	Mean ± SD	P Value ^a	Mean ± SD	P Value ^a	P Value ^b
YNC	0.00 ± 0.00		0.19 ± 0.40		.187
YNC vs ANC		1.000		1.000	
ANC	0.05 ± 0.21		0.19 ± 0.44		.072
ANC vs aMCI		.115		.349	
aMCI	0.21 ± 0.47		0.48 ± 0.77		.038*
aMCI vs AD		<.001**		<.001**	
AD	0.87 ± 0.82		1.77 ± 1.72		<.001**

Abbreviations: YNC, young normal controls; ANC, aged normal controls; aMCI, amnesic mild cognitive impairment; AD, patients with mild Alzheimer's disease in clinical dementia rating I; SD, standard deviation.

^a The difference among groups analyzed by between-subject post hoc analysis of 2 × 4 analysis of variance (metaphor and sarcasm; 4 groups).

^b The difference between metaphor and sarcasm analyzed by within-subject post hoc analysis of 2 × 4 analysis of variance (metaphor and sarcasm; 4 groups).

* $P < .05$.

** $P < .001$.

Discussion

Scores for both metaphor and sarcasm were not significantly different from each other in YNC, which confirmed that the difficulty level of metaphor and sarcasm comprehension tested by MSST was not different, at least among young participants.

The result suggested that deterioration of sarcasm comprehension was an age-related change. Sarcasm scores were

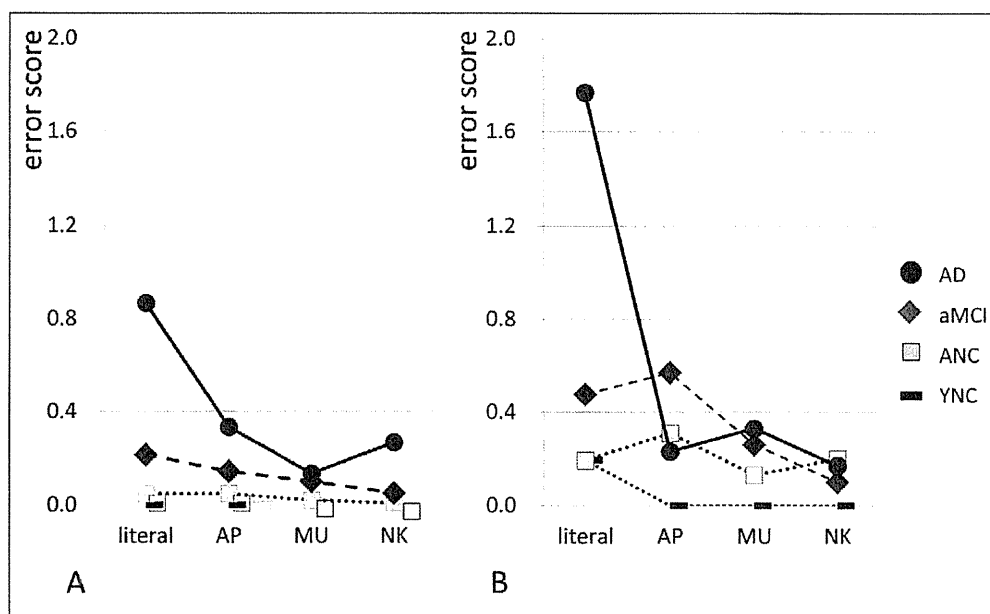


Figure 2. Error patterns. Error patterns of metaphor (A) and sarcasm (B). Significant differences among groups were observed in literal errors in both metaphor and sarcasm and the other 4 patterns of error were not significantly different among groups. AD indicates patients with mild Alzheimer's disease in clinical dementia rating 1; aMCI, amnesic mild cognitive impairment; ANC, aged normal controls; YNC, young normal controls; literal, literal interpretation; AP, answers associated with part of the sentence; MU, misunderstanding of the sentence; NK, not knowing.

significantly lower in ANC than in YNC, whereas no difference was observed in metaphor comprehension. Empirical developmental studies of normal children have found that metaphors are comprehended at an earlier age than ironies.⁴ One factor critical for understanding verbal irony (sarcasm) is an individual's ability to attribute appropriate second-order ToM.⁴ The success of the second-order ToM task emerges at around age 5 or 6²⁵ and it has been revealed that age-related decline occurred directly in the second-order ToM and indirectly in the first-order ToM.²⁶ The influence of difference in difficulty level could not be ruled out. Colston and Gibbs have shown that it takes healthy adults longer to read ironic than metaphoric statements, which suggests that irony (sarcasm) processing requires more cognitive load than metaphor processing.⁵

Age-related decline in metaphor comprehension was not shown in the present study. The deterioration was reported in the early stage of AD by a study that did not include the participants with MCI,¹⁶⁻¹⁸ and the present study showed that comprehension begins to decline even during aMCI, the prodromal stage of AD.

Another issue was with the comprehension of conventional metaphor. In the present study, conventional metaphor comprehension was deteriorated as well as nonconventional novel expressions, as shown in previous studies.^{16,17} However, Amanzio et al reported the deficits in nonconventional novel metaphors, while no impairment was observed in conventional metaphors.¹⁸ The study assumed that conventional metaphors might be interpreted automatically through frequent usage, whereas novel metaphors recruited ToM

processes. However, the patients might tend to avoid complicated pragmatic wording and without usage in everyday speech, conventional metaphors could recruit ToM processes as novel metaphors.

Deficits of AD were characterized by literal interpretation; concerning error patterns, group differences were observed only in the pattern of literal interpretation. Decline of inhibition could be related to choosing literal interpretation. Metaphor and sarcasm comprehension requires contextual coherence judgment, as literal interpretation can be taken out of context. It has been proposed that both the literal and the nonliteral meaning are activated concurrently and the inappropriate meaning is inhibited by the context.²⁷⁻³¹ However, patients with AD had difficulty suppressing inappropriate literal interpretation, which is concurrently activated.^{32,33} Literal interpretation of metaphor causes misunderstanding and that of sarcasm could be more problematic. In sarcastic expression, the speakers say the opposite of what they mean¹⁵ and thus the patients with AD may interpret the utterance as admiration, which would be opposite to the speakers' intention. Such misinterpretation would result in social miscommunication.

Miscommunication between patients and caregivers could lead to behavioral and psychological symptoms of dementia (BPSD) in patients and distress in caregivers.³⁴⁻³⁷ Therefore, caregivers' understanding of decreased communication abilities in patients may reduce BPSD and caregiver distress.^{38,39}

As a limitation, the groups of the present study were not matched for age and education. Based on the results of the present study, further study is required with a larger group of participants for consideration of clinical relevance.