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.

Acknowledgements

The authors thank all the study participants, Dr. Masamitsu Takatama (Geriatrics Research Institute and Hospital, Maebashi), and Rumi Shinohara and Yuko Tsunoda (Gunma University, Maebashi) for their support. Dr. Haruyasu Yamaguchi was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, Culture, and Technology, Japan (23300197 and 22650123) and a Grant-in-Aid for Scientific Research (H22-Ninchisho-Ippan-004) from the Ministry of Health, Labor, and Welfare, Japan.

References

1 Holsinger T, Deveau J, Boustani M, Williams JW Jr: Does this patient have dementia? JAMA 2007;297:2391–2404.
2 Boustani M, Peterson B, Hanson L, Harris R, Lohr KN: Screening for dementia in primary care: a summary of the evidence for the US Preventive Services Task Force. Ann Intern Med 2003;138:927–937.
3 Folstein MF, Folstein SE, McHugh PR: 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
4 Lawrence J, Davidoff D, Katt-Lloyd D, Auerbach M, Hennen J: A pilot program of improved methods for community-based screening for dementia. Am J Geriatr Psychiatry 2001;9:205–211.
5 Espino DV, Lichtenstein MJ, Palmer RF, Hazuda HP: Evaluation of the mini-mental state examination's internal consistency in a community-based sample of Mexican-American and European-American elders: results from the San Antonio Longitudinal Study of Aging. J Am Geriatr Soc 2004;52:822–827.
6 Lorentz WJ, Scanlan JM, Borson S: Brief screening tests for dementia. Can J Psychiatry 2002;47:723–733.
7 Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H: Validation of a short Orientation-Memory-Concentration Test of cognitive impairment. Am J Psychiatry 1983;140:734–739.
8 Kuslansky G, Buschke H, Katz M, Sliwinski M, Lipton RB: Screening for Alzheimer's disease: the memory impairment screen versus the conventional three-word memory test. J Am Geriatr Soc 2002;50:1086–1091.
9 Mograbi DC, Brown RG, Morris RG: Anosognosia in Alzheimer's disease – the petrified self. Conscious Cogn 2009;18:989–1003.
10 Maki Y, Amari M, Yamaguchi T, Nakaaki S, Yamaguchi H: Anosognosia: patients' distress and self-awareness of deficits in Alzheimer's disease. Am J Alzheimers Dis Other Demen 2012;27:339–345.
11 Morris JC: The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–2414.

12 Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P: Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007;6:734–746.
13 McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Londos E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M, Consortium on DLB: Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863–1872.
14 Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF: Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998;51:1546–1554.
15 Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A, et al: Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43:250–260.
16 Reisberg B, Ferris SH, Kluger A, Franssen E, Wegiel J, de Leon MJ: Mild cognitive impairment (MCI): a historical perspective. Int Psychogeriatr 2008;20:18–31.
17 Grundman M, Petersen RC, Ferris SH, Thomas RG, Aisen PS, Bennett DA, Foster NL, Jack CR Jr, Galasko DR, Doody R, Kaye J, Sano M, Mohs R, Gauthier S, Kim HT, Jin S, Schultz AN, Schafer K, Mulnard R, van Dyck CH, Mintzer J, Zamrini EY, Cahn-Weiner D, Thal LJ, Alzheimer's Disease Cooperative Study: Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. Arch Neurol 2004;61:59–66.
18 Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Bäckman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC: Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004;256:240–246.
19 Barberger-Gateau P, Dartigues JF, Letenneur L: Four Instrumental Activities of Daily Living Score as a predictor of one-year incident dementia. Age Ageing 1993;22:457–463.
20 Edelberg HK, Shallenberger E, Wei JY: Medication management capacity in highly functioning community-living older adults: detection of early deficits. J Am Geriatr Soc 1999;47:592–596.
21 Edelberg HK, Shallenberger E, Hausdorff JM, Wei JY: One-year follow-up of medication management capacity in highly functioning older adults: J Gerontol A Biol Sci Med Sci 2000;55:M550–M553.
22 Hutchison LC, Jones SK, West DS, Wei JY: Assessment of medication management by community-living elderly persons with two standardized assessment tools: a cross-sectional study. Am J Geriatr Pharmacother 2006;4:144–153.
23 Lieto JM, Schmidt KS: Reduced ability to self-administer medication is associated with assisted living placement in a continuing care retirement community. J Am Med Dir Assoc 2005;6:246–249.
24 Schmidt KS, Lieto JM: Validity of the Medication Administration Test among older adults with and without dementia. Am J Geriatr Pharmacother 2005;3:255–261.
25 Bassuk SS, Glass TA, Berkman LF: Social disengagement and incident cognitive decline in community-dwelling elderly persons. Ann Intern Med 1999;131:165–173.
26 Wilson RS, Krueger KR, Arnold SE, Schneider JA, Kelly JF, Barnes LL, Tang Y, Bennett DA: Loneliness and risk of Alzheimer disease. Arch Gen Psychiatry 2007;64:234–240.
27 Fratiglioni L, Wang HX, Ericsson K, Maytan M, Winblad B: Influence of social network on occurrence of dementia: a community-based longitudinal study. Lancet 2000;355:1315–1319.
28 Wang HX, Karp A, Winblad B, Fratiglioni L: Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project. Am J Epidemiol 2002;155:1081–1087.
29 Vilalta-Franch J, Calvo-Perxas L, Garre-Olmo J, Turro-Garriga O, Lopez-Pousa S: Apathy syndrome in Alzheimer's disease epidemiology: prevalence, incidence, persistence, and risk and mortality factors. J Alzheimers Dis 2013;33:535–543.
30 D'Onofrio G, Sancarlo D, Panza F, Copetti M, Cascavilla L, Paris F, Seripa D, Matera MG, Solfrizzi V, Pellegrini F, Pilotto A: Neuropsychiatric symptoms and functional status in Alzheimer's disease and vascular dementia patients. Curr Alzheimer Res 2012;9:759–771.
31 Weisman D, McKeith I: Dementia with Lewy bodies. Semin Neurol 2007;27:42–47.
32 Middleton LE, Yaffe K: Promising strategies for the prevention of dementia. Arch Neurol 2009;66:1210–1215.
33 Bassett SS, Folstein MF: Memory complaint, memory performance, and psychiatric diagnosis: a community study. J Geriatr Psychiatry Neurol 1993;6:105–111.
34 Tobiansky R, Blizard R, Livingston G, Mann A: The Gospel Oak Study stage IV: the clinical relevance of subjective memory impairment in older people. Psychol Med 1995;25:779–786.
35 Jonker C, Geerlings MI, Schmand B: Are memory complaints predictive for dementia? A review of clinical and population-based studies. Int J Geriatr Psychiatry 2000;15:983–991.

36 Riedel-Heller SG, Matschinger H, Schork A, Angermeyer MC: Do memory complaints indicate the presence of cognitive impairment? Results of a field study. Eur Arch Psychiatry Clin Neurosci 1999;249:197–204.
37 Geerlings MI, Jonker C, Bouter LM, Ader HJ, Schmand B: Association between memory complaints and incident Alzheimer's disease in elderly people with normal baseline cognition. Am J Psychiatry 1999;156:531–537.
38 St John P, Montgomery P: Is subjective memory loss correlated with MMSE scores or dementia? J Geriatr Psychiatry Neurol 2003;16:80–83.
39 Carr DB, Gray S, Baty J, Morris JC: The value of informant versus individual's complaints of memory impairment in early dementia. Neurology 2000;55:1724–1726.
40 Pearman A, Storandt M: Predictors of subjective memory in older adults. J Gerontol B Psychol Sci Soc Sci 2004; 59:4–6.
41 Jorm AF, Jacomb PA: The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. Psychol Med 1989;19:1015–1022.
42 Hopman-Rock M, Tak EC, Staats PG: Development and validation of the Observation List for early signs of Dementia (OLD). Int J Geriatr Psychiatry 2001;16:406–414.
43 Galvin JE, Roe CM, Powlishta KK, Coats MA, Muich SJ, Grant E, Miller JP, Storandt M, Morris JC: The AD8: a brief informant interview to detect dementia. Neurology 2005;65:559–564.
44 Li M, Ng TP, Kua EH, Ko SM: Brief informant screening test for mild cognitive impairment and early Alzheimer's disease. Dement Geriatr Cogn Disord 2006;21:392–402.
45 Galvin JE, Roe CM, Coats MA, Morris JC: Patient's rating of cognitive ability: using the AD8, a brief informant interview, as a self-rating tool to detect dementia. Arch Neurol 2007;64:725–730.
46 Rapp MA, Dahlman K, Sano M, Grossman HT, Haroutunian V, Gorman JM: Neuropsychological differences between late-onset and recurrent geriatric major depression. Am J Psychiatry 2005;162:691–698.
47 Baune BT, Suslow T, Arolt V, Berger K: The relationship between psychological dimensions of depressive symptoms and cognitive functioning in the elderly – the MEMO-Study. J Psychiatr Res 2007;41:247–254.
48 Porter RJ, Gallagher P, Thompson JM, Young AH: Neurocognitive impairment in drug-free patients with major depressive disorder. Br J Psychiatry 2003;182:214–220.

Geriatrics & Gerontology Medline Indexed

Geriatr Gerontol Int 2013

ORIGINAL ARTICLE

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

Kenji Toba,[1] Yu Nakamura,[2] Hidetoshi Endo,[1] Jiro Okochi,[3] Yukiko Tanaka,[3] Chiyako Inaniwa,[3] Akira Takahashi,[3] Naoko Tsunoda,[3] Kentaro Higashi,[3] Motoharu Hirai,[3] Hiroyuki Hirakawa,[3] Shizuru Yamada,[3] Yohko Maki,[4] Tomoharu Yamaguchi[4] and Haruyasu Yamaguchi[4]

[1]National Center for Geriatrics and Gerontology, Ohbu, [2]Department of Psychiatry, Kagawa University, Takamatsu, [3]Japan Association of Geriatric Health Service Facilities, Tokyo, and [4]Graduate School of Health Sciences, Gunma University, Maebashi, Japan

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

Accepted for publication 20 March 2013.

Correspondence: Dr Kenji Toba MD PhD, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka-cho, Ohbu-city, Aichi Japan 474-8511. Email: toba@ncgg.go.jp

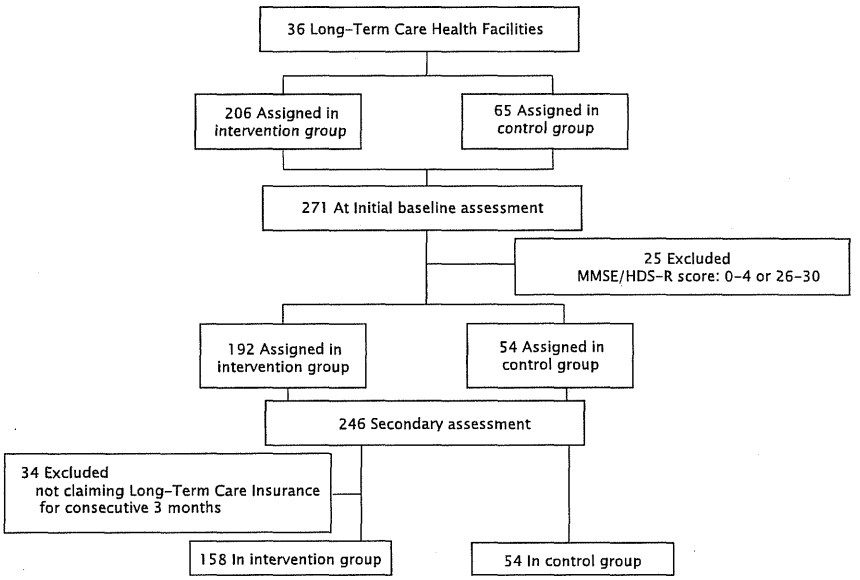

Figure 1 Flow of participants in the intervention and control groups. HDS-R, Hasegawa Dementia Scale revised. MMSE, Mini-Mental State Examination.

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	
n		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 index[12] 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 DBD[13] (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		Intra-subject†	
	Pre	Post	*n*	Pre	Post	*n*	F (DF)	*P*	Intervention	Control
	mean ± SD	mean ± SD		mean ± SD	mean ± SD					
Cognitive test										
MMSE	19.1 ± 4.5	19.4 ± 5.5	100	19.5 ± 4.9	18.2 ± 7.4	13	1.780 (1,110)	0.185	0.542	0.234
HDS-R	16.9 ± 5.7	17.9 ± 6.5	149	17.0 ± 5.9	16.7 ± 6.3	50	5.190 (1,196)	0.024*	0.001**	0.480
Questionnaire										
NM	30.4 ± 9.1	32.1 ± 9.5	149	31.4 ± 9.8	30.7 ± 10.9	52	9.550 (1,198)	0.002**	$P < 0.001$***	0.380
ADL	16.4 ± 7.1	17.3 ± 7.1	152	15.7 ± 7.0	15.9 ± 6.9	53	1.448 (1,202)	0.230	0.001**	0.621
Activity	8.6 ± 3.3	8.8 ± 3.4	150	8.5 ± 3.1	8.6 ± 3.2	53	1.169 (1,200)	0.281	0.038*	0.972
Vitality	8.0 ± 1.7	8.2 ± 1.6	149	8.1 ± 1.8	8.2 ± 1.8	53	1.792 (1,199)	0.182	0.004**	0.864
DBD	4.5 ± 5.1	4.0 ± 4.1	150	4.5 ± 4.2	4.8 ± 4.7	50	4.506 (1,197)	0.035*	0.004**	0.413
GDS	2.5 ± 1.8	2.4 ± 1.9	148	2.3 ± 1.5	2.4 ± 1.5	51	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

This study is partially supported by a Grant-in-Aid from the Ministry of Health Labor and Welfare (#19 Health Promotion Projects for Elderly-169 2-Na).

Disclosure statement

The authors declare no conflict of interest.

References

1 Zekry D, Herrmann FR, Grandjean R *et al.* Does dementia predict adverse hospitalization outcomes? A prospective study in aged inpatients. *Int J Geriatr Psychiatry* 2009; **24**: 283–291.
2 Andrieu S, Reynish E, Nourhashemi F *et al.* Predictive factors of acute hospitalization in 134 patients with Alzheimer's disease: a one year prospective study. *Int J Geriatr Psychiatry* 2002; **17**: 422–426.

3 Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. Behavioral and psychological symptoms of dementia. *Front Neurol* 2012; **3**: 73.
4 Matsumoto N, Ikeda M, Fukuhara R *et al.* Caregiver burden associated with behavioral and psychological symptoms of dementia in elderly people in the local community. *Dement Geriatr Cogn Disord* 2007; **23**: 219–224.
5 Kobayashi T, Kato S. Depression-dementia medius: between depression and the manifestation of dementia symptoms. *Psychogeriatrics* 2011; **11**: 177–182.
6 Vilalta-Franch J, Calvo-Perxas L, Garre-Olmo J, Turro-Garriga O, Lopez-Pousa S. Apathy syndrome in Alzheimer's disease epidemiology: prevalence, incidence, persistence, and risk and mortality factors. *J Alzheimers Dis* 2012; **33** 535–543.
7 Bjoerke-Bertheussen J, Ehrt U, Rongve A, Ballard C, Aarsland D. Neuropsychiatric symptoms in mild dementia with lewy bodies and Alzheimer's disease. *Dement Geriatr Cogn Disord* 2012; **34**: 1–6.
8 Quaranta D, Marra C, Rossi C, Gainotti G, Masullo C. Different apathy profile in behavioral variant of frontotemporal dementia and Alzheimer's disease: a preliminary investigation. *Curr Gerontol Geriatr Res* 2012; **2012**: 719250.
9 Xing Y, Wei C, Chu C *et al.* Stage-specific gender differences in cognitive and neuropsychiatric manifestations of vascular dementia. *Am J Alzheimers Dis Other Demen* 2012; **27**: 433–438.
10 Yesavage JA, Brink TL, Rose TL. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1982; **17**: 37–49.
11 Kobayashi T, Hariguchi S, Nishimura K *et al.* A new clinical scale for rating of mental states and activities of daily living of the elderly (NM scale and N-ADL). *Jpn J Clin Psychiatry* 1988; **17**: 1653–1668. (In Japanese.)
12 Toba K, Nakai R, Akishita M *et al.* Vitality Index as a useful tool to assess elderly with dementia. *Geriatr Gerontol Int* 2002; **2**: 23–29.
13 Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *Md State Med J* 1965; **14**: 61–65.
14 Machida A. Estimation of the reliability and validity of the short form version of the 28-item Dementia Behavior Disturbance scale. *Nippon Ronen Igakkai Zasshi* 2012; **49**: 463–467. (In Japanese, abstract English.)
15 Lam LC, Lui VW, Luk DN *et al.* Effectiveness of an individualized functional training program on affective disturbances and functional skills in mild and moderate dementia–a randomized control trial. *Int J Geriatr Psychiatry* 2010; **25**: 133–141.
16 Woods B, Aguirre E, Spector AE, Orrell M. Cognitive stimulation to improve cognitive functioning in people with dementia. *Cochrane Database Syst Rev* 2012; (2)CD005562.
17 Farias ST, Harrell E, Neumann C, Houtz A. The relationship between neuropsychological performance and daily functioning in individuals with Alzheimer's disease: ecological validity of neuropsychological tests. *Arch Clin Neuropsychol* 2003; **18**: 655–672.
18 Germain S, Adam S, Olivier C *et al.* Does cognitive impairment influence burden in caregivers of patients with Alzheimer's disease? *J Alzheimers Dis* 2009; **17**: 105–114.
19 Aguirre E, Woods RT, Spector A, Orrell M. Cognitive stimulation for dementia: a systematic review of the evidence of effectiveness from randomised controlled trials. *Ageing Res Rev* 2012; **12**: 253–262.
20 Black W, Almeida OP. A systematic review of the association between the Behavioral and Psychological Symptoms of Dementia and burden of care. *Int Psychogeriatr* 2004; **16**: 295–315.
21 Miyamoto Y, Tachimori H, Ito H. Formal caregiver burden in dementia: impact of behavioral and psychological symptoms of dementia and activities of daily living. *Geriatr Nurs* 2010; **31**: 246–253.
22 Marvardi M, Mattioli P, Spazzafumo L *et al.* The Caregiver Burden Inventory in evaluating the burden of caregivers of elderly demented patients: results from a multicenter study. *Aging Clin Exp Res* 2005; **17**: 46–53.
23 Campbell P, Wright J, Oyebode J *et al.* Determinants of burden in those who care for someone with dementia. *Int J Geriatr Psychiatry* 2008; **23**: 1078–1085.
24 Molyneux GJ, McCarthy GM, McEniff S, Cryan M, Conroy RM. Prevalence and predictors of carer burden and depression in carers of patients referred to an old age psychiatric service. *Int Psychogeriatr* 2008; **20**: 1193–1202.
25 Yaffe K, Fox P, Newcomer R *et al.* Patient and caregiver characteristics and nursing home placement in patients with dementia. *JAMA* 2002; **287**: 2090–2097.
26 Elmstahl S, Ingvad B, Annerstedt L. Family caregiving in dementia: prediction of caregiver burden 12 months after relocation to group-living care. *Int Psychogeriatr* 1998; **10**: 127–146.
27 Gitlin LN, Winter L, Dennis MP *et al.* Targeting and managing behavioral symptoms in individuals with dementia: a randomized trial of a nonpharmacological intervention. *J Am Geriatr Soc* 2010; **58**: 1465–1474.
28 Bassuk SS, Glass TA, Berkman LF. Social disengagement and incident cognitive decline in community-dwelling elderly persons. *Ann Intern Med* 1999; **131**: 165–173.
29 Fratiglioni L, Wang HX, Ericsson K, Maytan M, Winblad B. Influence of social network on occurrence of dementia: a community-based longitudinal study. *Lancet* 2000; **355**: 1315–1319.
30 Wang HX, Karp A, Winblad B, Fratiglioni L. Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project. *Am J Epidemiol* 2002; **155**: 1081–1087.
31 Naglie G, Hogan DB, Krahn M *et al.* Predictors of patient self-ratings of quality of life in Alzheimer disease: cross-sectional results from the Canadian Alzheimer's Disease Quality of Life Study. *Am J Geriatr Psychiatry* 2011; **19**: 881–890.

Amyloid
The Journal of Protein Folding Disorders

http://informahealthcare.com/amy
ISSN: 1350-6129 (print), 1744-2818 (electronic)

Amyloid, Early Online: 1–6
 DOI: 10.3109/13506129.2013.790810

informa
healthcare

ORIGINAL ARTICLE

Cerebrospinal fluid levels of phosphorylated tau and Aβ1-38/Aβ1-40/Aβ1-42 in Alzheimer's disease with PS1 mutations

Masaki Ikeda[1], Kimie Yonemura[2,3], Satoko Kakuda[1], Yuichi Tashiro[1], Yukio Fujita[1], Eriko Takai[1], Yukiko Hashimoto[1], Kouki Makioka[1], Natsumi Furuta[1], Koichi Ishiguro[4], Risa Maruki[5], Jun'ichi Yoshida[6], Osamu Miyaguchi[7], Tamao Tsukie[7], Ryouzou Kuwano[7], Tsuneo Yamazaki[8], Haruyasu Yamaguchi[9], Masakuni Amari[10], Masamitsu Takatama[10], Yasuo Harigaya[11], and Koichi Okamoto[1]

[1]Department of Neurology and [2]Department of Psychiatry and Human Behavior, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan, [3]Department of Psychiatry, Yukiguni Yamato Hospital, Minami Uonuma, Niigata, Japan, [4]Department of Neurology, Juntendo University School of Medicine, Bunkyo-ku, Tokyo, Japan, [5]Moroyama Hospital, Moroyama-machi, Saitama, Japan, [6]Sait Pierre Hospital, Takasaki, Gunma, Japan, [7]Genome Science Branch, Centre for Bioresource-Based Researches, Brain Research Institute, Niigata University, Chuo-ku, Niigata, Japan, [8]Department of Occupational Therapy, Gunma University School of Health Sciences, Maebashi, Gunma, Japan, [9]Department of Physical Therapy, Gunma University School of Medicine, Maebashi, Gunma, Japan, [10]Department of Neurology, Geriatrics Research Institute and Hospital, Maebashi, Gunma, Japan, and [11]Department of Neurology, Maebashi Red Cross Hospital, Maebashi, Gunma, Japan

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 Aβ (Aβ1-42, Aβ1-40 and Aβ1-38) 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 Aβ1-42 in the three AD groups were significantly lower than those of the ND group ($p<0.0001$). CSF levels of Aβ1-42 in the PS1AD group were significantly lower than those in the two sporadic AD groups. The Aβ1-40 and Aβ1-38 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 Aβ1-40, Aβ1-38 and Aβ1-42 in the CSF of the PS1AD group remained lower than those of the ND group for 4 years. Not only CSF Aβ1-42, but also Aβ1-40 and Aβ1-38 decreased in the advanced stages of PS1AD.

Abbreviations: Aβ, 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

Keywords

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

History

Received 12 December 2012
Accepted 24 March 2013
Published online 2 May 2013

Introduction

The extracellular deposition of amyloid-β (Aβ) peptides (preferentially Aβ42) 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 Aβ1-42 are selectively reduced [9,10] and the CSF levels of total-tau and ptau were reported to be elevated [11–13]. Carboxy-terminal truncated Aβ peptides other than Aβ1-40/42, Aβ1-37/38/39 have been identified physiologically in CSF [14]. Aβ1-42, Aβ1-40 and Aβ1-38 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 Aβ1-40 and Aβ1-38 in AD patients with PS1 mutations were significantly decreased compared to those of early- or late-onset sporadic AD patients and subjects without

Address for correspondence: Dr Masaki Ikeda, Department of Neurology, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan. Tel: +81-27-220-8068. Fax: +81-27-220-8068. E-mail: mikeda@med.gunma-u.ac.jp

AD. We also obtained longitudinal data showing the low levels of Aβ1-40 and Aβ1-38 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 Diseases 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 Aβ1-42, Aβ1-40 and Aβ1-38

CSF was obtained by a lumbar puncture in the L3/L4 or L4/L5 intervertebral space. CSF samples were centrifuged for 10 min at 1800*g* 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 Aβ1-40 (Wako Pure Chemical Industries, Tokyo, Japan), human CSF Aβ1-42 (Wako Pure Chemical Industries) and human CSF Aβ1-38 (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	L2I9R	H13IR	V272A	T99A	
Gender	Female	Female	Male	Female	Female	Female	Male	Mean ± 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 (ε3/ε4), M233L-2 (ε3/ε4), H163R (ε3/ε4), L219R (ε3/ε4), H131R (ε3/ε3), V272A (ε3/ε4) and T99A (ε3/ε4).

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 Aβ1-42 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 Aβ1-42 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 Aβ1-40, 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 1D). The CSF level of Aβ1-40 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 1D). The CSF level of Aβ1-38 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 Aβ molecules and ptau-181

The ratios of CSF Aβ1-42/Aβ1-40 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 Aβ1-42/Aβ1-38 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 Aβ1-38/Aβ1-40

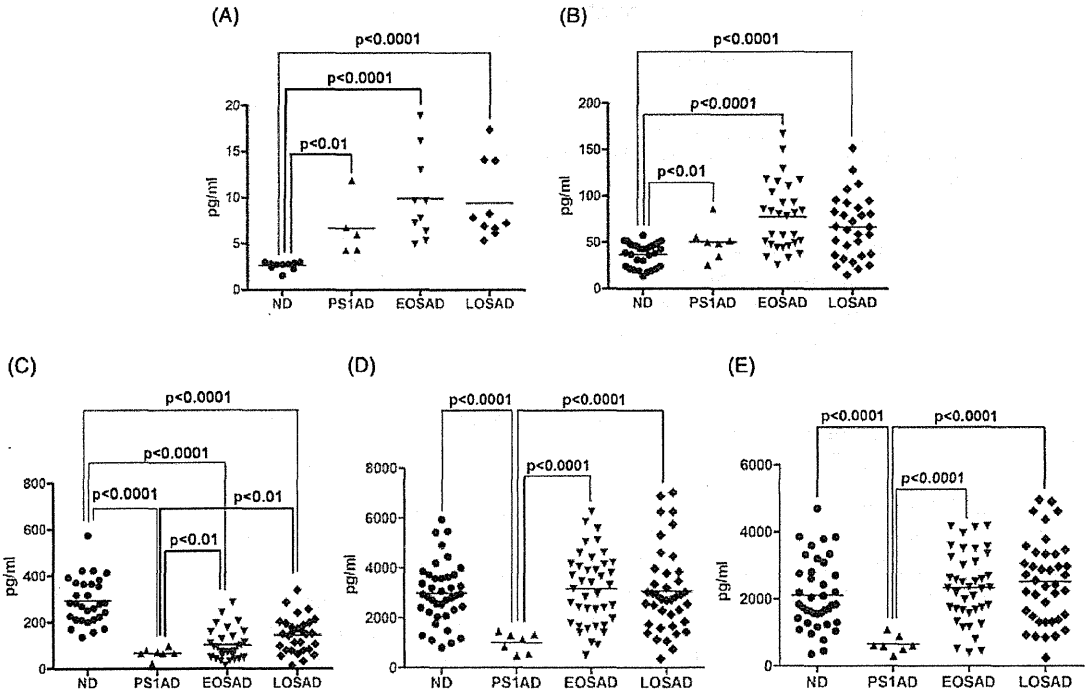

Figure 1. Measurement of CSF Aβ molecules and phosphorylated tau (PS1AD, EOSAD, LOSAD and ND). (A) CSF levels of ptau-199 and (B) ptau-181 showed significant increases in the AD groups (PS1AD, EOSAD, LOSAD) compared to the ND group ($p<0.01$, $p<0.0001$, $p<0.0001$). (C) CSF level of Aβ1-42 in the AD 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 Aβ1-42 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 Aβ1-40 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 Aβ1-38 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 ($p<0.0001$).

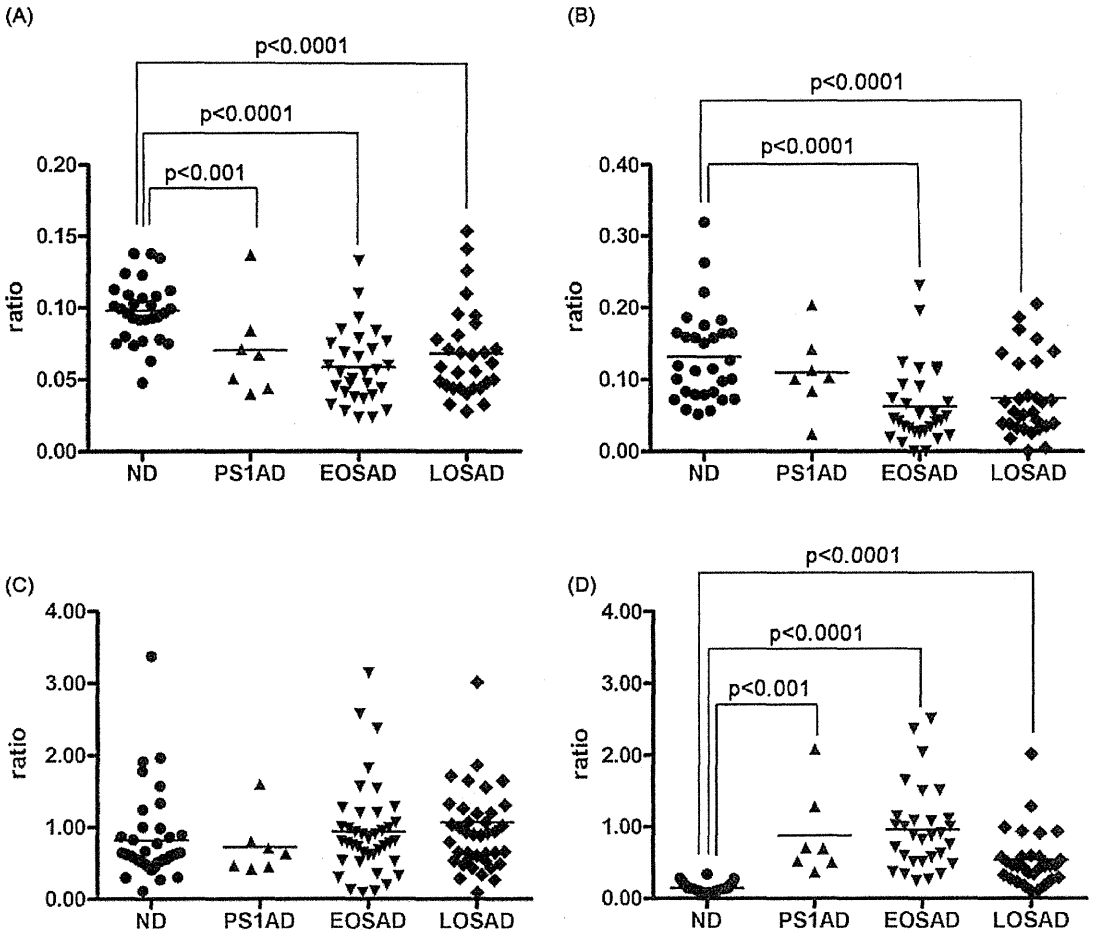

Figure 2. Ratios of CSF Aβ molecules and phosphorylated tau (ptau-181). (A) The ratio of Aβ1-42/Aβ1-40 significantly decreased between the PS1AD and the ND ($p<0.001$) groups and between the sporadic AD (EOSAD and LOSAD) and the ND group ($p<0.0001$, $p<0.0001$, respectively). (B) The ratio of Aβ1-42/Aβ1-38 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 Aβ1-38/Aβ1-40 in CSF was observed amongst EOSAD, LOSAD and PS1AD. (D) The ratio of ptau-181/Aβ1-38 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/Aβ1-42 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 Aβ 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 Aβ1-42, Aβ1-40 and Aβ1-38 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 Aβ1-42 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 Aβ1-42 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 Aβ1-42, Aβ1-40 and Aβ1-38 in the PS1AD group were significantly lower than those of the other three groups (ND, EOSAD and LOSAD). The ratios of Aβ1-42/Aβ1-40 in the three AD groups were lower than that in the ND group. The ratios of CSF Aβ1-42/Aβ1-38 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 Aβ1-38 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 Aβ1-38/Aβ1-40 did not show a significant difference amongst the four groups (ND, PS1AD, EOSAD and LOSAD). In the PS1AD patients, the level of Aβ1-38 was lower than that in other sporadic AD groups; therefore, the ratio of Aβ1-42/Aβ1-38 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, Aβ1-42, Aβ1-40, Aβ1-38) in four PS1AD patients for 4 years. The CSF levels of Aβ1-42, Aβ1-40 and Aβ1-38 were lower in

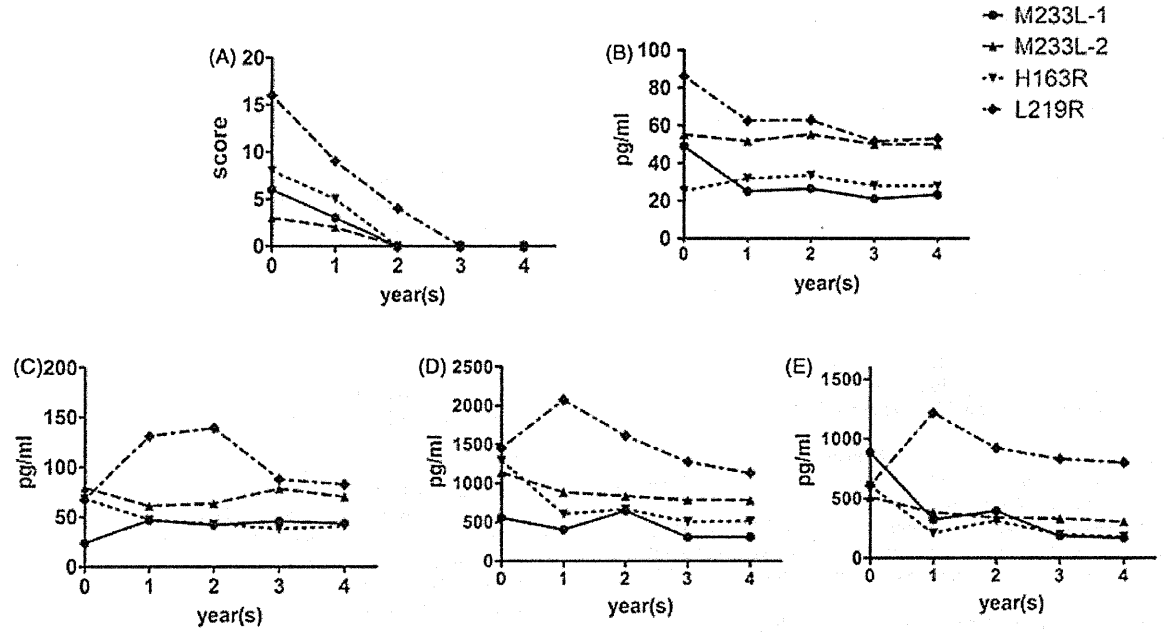

Figure 3. Temporal change of MMSE scores and CSF levels (ptau-181, Aβ1-38, Aβ1-40, Aβ1-42) in PS1AD. (A) Four PS1AD patients (M233L-1, M233L-2, H163R, L219R) who underwent CSF analysis, have shown a decrease in MMSE scores over the 4-year period. (B) First CSF levels of ptau-181 of these four PS1AD patients were significantly higher than those of ND subjects as shown in Figure 1(B) ($p<0.01$). (C) The CSF level of Aβ1-42 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 Aβ1-42 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 Aβ1-40 of PS1AD patients was less than 2500 pg/ml, which was lower than that in the ND group. First CSF levels of Aβ1-40 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 Aβ1-38 of PS1AD patients were less than 1500 pg/ml, which was lower than those of the ND group. First CSF levels of Aβ1-38 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 Aβ1-42 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 Aβ1-42/Aβ1-38 was largely proportional to that of Aβ1-40/Aβ1-43, and the two cleavage processes are tightly coupled. Therefore, both the CSF Aβ1-40 and Aβ1-38 were generally higher in MCI/AD patients compared with control subjects, the CSF Aβ1-43 and Aβ1-42 decreased in MCI/AD patients [24].

In our study, PS1AD patients with long-term severe dementia presented and remained characterized by lower CSF Aβ1-42, Aβ1-40 and Aβ1-38 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 Aβ1-38 and Aβ1-42 [29]. Pathologically, PS1AD brains frequently showed aggravating Lewy bodies [30,31]. Some relationship between α-synuclein and Aβ1-38 might be of pathological relevance for Aβ aggregation [32]. They may generate a nucleation center for subsequent Aβ amyloidogenesis and the formation of Lewy bodies. In long-term PS1AD, various molecular relationships amongst Aβ1-38/40/42 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 Aβ1-42, Aβ1-40 and Aβ1-38 were significantly lower than those of ND subjects, in which CSF levels of Aβ1-40 and Aβ1-38 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

This study received a Grant-in-Aid for Scientific Research (C) (M.I.: 23591231, Y.F.: 21591108, T.Y.: 23500426, H.Y.: 23300197) from the Ministry of Education, Culture, Sports, Science and Technology of Japan and funding from the 'Japanese Alzheimer's Disease Neuroimaging Initiative' of the New Energy and Industrial Technology Development Organization (NEDO) in Japan (R.K.). Dr Okamoto received

research support from the Ministry of Grants-in-Aid from the Research Committee of CNS Degenerative Diseases, the Ministry of Health, Labour and Welfare of Japan. Dr Yonemura, Dr Kakuda, Dr Tashiro, Dr Ishiguro, Dr Hashimoto, Dr Takatama, Dr Amari and Dr Harigaya report no disclosures.

References

1. www.metalife.com/OMIM/104300.
2. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002;297:353–6.
3. Sherrington R, Rogaev EL, Liang Y, Rogaeva EA, Levesque G, Ikeda M, Chi H, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature 1995; 375:754–60.
4. Rogaeva EA, Fafel KC, Song YQ, Medeiros H, Sato C, Liang Y, Chi H, et al. Screening for PSEN1 mutations in a referral-based series of AD cases. Neurology 2001;57:621–5.
5. Ikeda M, Sharma V, Sumi SM, Rogaeva EA, Poorkaj P, Sherrington R, Nee L, et al. The clinical phenotypes of two missense mutations in the presenilin 1 gene in Japanese patients. Ann Neurol 1996;40: 912–17.
6. Alzheimer Reasearch Forum.Available from: http://www.alzforum.org/.
7. Lee VM, Balin BJ, Otvos Jr L, Trojanowski JQ. A68: a major subunit of paired helical filaments and derivatized forms of normal Tau. Science 1991;251:675–8.
8. Ishiguro K, Omori A, Takamatsu M, Sato K, Arioka M, Uchida T, Imahori K. Phosphorylation sites on tau by tau protein kinase I, a bovine derived kinase generating an epitope of paired helical filaments. Neurosci Lett 1992;148:202–6.
9. Kanai M, Matsubara E, Isoe K, Urakami K, Nakashima K, Arai H, Sasaki H, et al. Longitudinal study of cerebrospinal fluid levels of tau, Abeta1-40, and Abeta1-42(43) in Alzheimer's disease: a study in Japan. Ann Neurol 1998;44:17–26.
10. Hulstaert F, Blennow K, Ivanoiu A, Schoonderwaldt HC, Riemenschneider M, De Deyn PP, Bancher C, et al. Improved discrimination of AD patients using β-amyloid(1-42) and tau levels in CSF. Neurology 1999;52:1555–62.
11. Ishiguro K, Ohno H, Arai H, Yamaguchi H, Urakami K, Park JM, Sato K, et al. Phosphorylated tau in human cerebrospinal fluid is a diagnostic marker for Alzheimer's disease. Neurosci Lett 1999;270: 91–4.
12. Itoh N, Arai H, Urakami K, Ishiguro K, Ohno H, Hampel H, Buerger K, et al. Large-scale, multicenter study of cerebrospinal fluid tau protein phosphorylated at serine 199 for the antemortem diagnosis of Alzheimer's disease. Ann Neurol 2001;50:150–6.
13. Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nat Rev Neurol 2010;6:131–44.
14. Wiltfang J, Esselmann H, Bibl M, Smirnov A, Otto M, Paul S, Schmidt B, et al. Highly conserved and disease-specific patterns of carboxyterminally truncated Abeta peptides 1-37/38/39 in addition to 1-40/42 in Alzheimer's disease and in patients with chronic neuroinflammation. J Neurochem 2002;81:481–96.
15. Bibl M, Mollenhauer B, Esselmann H, Lewczuk P, Klafki HW, Sparbier K, Smirnov A, et al. CSF amyloid-beta-peptides in Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia. Brain 2006;129:1177–87.
16. Bibl M, Mollenhauer B, Lewczuk P, Esselmann H, Wolf S, Otto M, Kornhuber J, et al. Cerebrospinal fluid tau, p-tau 181 and amyloid-β38/40/42 in frontotemporal dementias and primary progressive aphasias. Dement Geriatr Cogn Disord 2011;31:37–44.
17. Mulugeta E, Londos E, Ballard C, Alves G, Zetterberg H, Blennow K, Skogseth R, et al. CSF amyloid β38 as a novel diagnostic marker for dementia with Lewy bodies. Neurol Neurosurg Psychiatry 2011; 82:160–4.
18. Folstein MF, Folstein SE, McHugh PR. ''Mini-Mental State''. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
19. Holsinger T, Deveau J, Boustani M, Williams JW. Does this patient have dementia? JAMA 2007;297:2391–404.
20. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–44.
21. Wenham PR, Price WH, Blandell G. Apolipoprotein E genotyping by one-stagePCR. Lancet 1991;337:1158–9.
22. Kasuga K, Tokutake T, Ishikawa A, Uchiyama T, Tokuda T, Onodera O, Nishizawa M, et al. Differential levels of α-synuclein, β-amyloid42 and tau in CSF between patients with dementia with Lewy bodies and Alzheimer's disease. J Neurol Neurosurg Psychiatry 2010;81:608–10.
23. Ikeda M, Hirayanagi K, Arai M, Kakuda S, Makioka K, Furuta N, Takai E, et al. Encephalopathy with amyloid angiopathy and numerous amyloid plaques with low levels of CSF Aβ1-40/Aβ1-42. Amyloid 2012;19:186–90.
24. Kakuda N, Shoji M, Arai H, Furukawa K, Ikeuchi T, Akazawa K, Takami M, et al. Altered γ-secretase activity in mild cognitive impairment and Alzheimer's disease. EMBO Mol Med 2012;4: 344–52.
25. Vanmechelen E, Vanderstichele H, Davidsson P, Van Kerschaver E, Van Der Perre B, Sjögren M, Andreasen N, et al. Quantification of tau phosphorylated at threonine 181 in human cerebrospinal fluid: a sandwich ELISA with α synthetic phosphopeptide for standardization. Neurosci Lett 2000;285:49–52.
26. Jack Jr CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2019;9:119–28.
27. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr CR, Kawas CH, Klunk WE, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7: 263–9.
28. Bouwman FH, van der Flier WM, Schoonenboom NS, van Elk EJ, Kok A, Rijmen F, Blankenstein MA, et al. Longitudinal changes of CSF biomarkers in memory clinic patients. Neurology 2007;69: 1006–11.
29. Portelius E, Andreasson U, Ringman JM, Buerger K, Daborg J, Buchhave P, Hansson O, et al. Distinct cerebrospinal fluid amyloid beta peptide signatures in sporadic and PSEN1 A431E-associated familial Alzheimer's disease. Mol Neurodegener 2010;5:2.
30. Lippa CF, Fujiwara H, Mann DM, Giasson B, Baba M, Schmidt ML, Nee LE, et al. Lewy bodies contain altered alpha-synuclein in brains of many familial Alzheimer's disease patients with mutations in presenilin and amyloid precursor protein genes. Am J Pathol 1998;153:1365–70.
31. Ishikawa A, Piao YS, Miyashita A, Kuwano R, Onodera O, Ohtake H, Suzuki M, et al. A mutant PSEN1 causes dementia with Lewy bodies and variant Alzheimer's disease. Ann Neurol 2005;57: 429–34.
32. Yoshimoto M, Iwai A, Kang D, Otero D, Xia Y, Saitoh T. NACP, the precursor protein of the non-amyloid β/A4 protein (Aβ) component of Alzheimer disease amyloid, binds Aβ and stimulates Aβ aggregation. Proc Natl Acad Sci USA 1995;92:9141–5.

American Journal of Alzheimer's Disease & Other Dementias®
28(1) 69-74

DOI: 10.1177/1533317512467677
aja.sagepub.com
SAGE

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

Yohko Maki, PhD[1,2], Tomoharu Yamaguchi, MA[1,3], Tatsuya Koeda, MD, PhD[4], and Haruyasu Yamaguchi, MD, PhD[1]

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]

[1] Gunma University Graduate School of Health Sciences
[2] Geriatrics Research Institute and Hospital, Gunma, Japan
[3] Department of Rehabilitation, Gunma University of Health and Welfare, Gunma, Japan
[4] Department of Humanity Education, Faculty of Education and Regional Sciences, Tottori University, Tottori, Japan

Corresponding Author:
Haruyasu Yamaguchi, MD, PhD, Gunma University School of Health Sciences, 3-39-15 Showa-machi, Maebashi, 371-8514 Gunma, Japan.
Email: yamaguti@health.gunma-u.ac.jp

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 Association[23] 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 Mean ± SD	Gender Male, Female	Education Mean ± SD	MMSE 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, amnestic mild cognitive impairment; AD, patients with mild Alzheimer's disease in clinical dementia rating 1; 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 not 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 Mean ± SD	Metaphor P Value[a]	Sarcasm Mean ± SD	Sarcasm P Value[a]	P Value[b]
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, amnestic mild cognitive impairment; AD, patients with mild Alzheimer's disease in clinical dementia rating 1; 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 ($P = .023$).

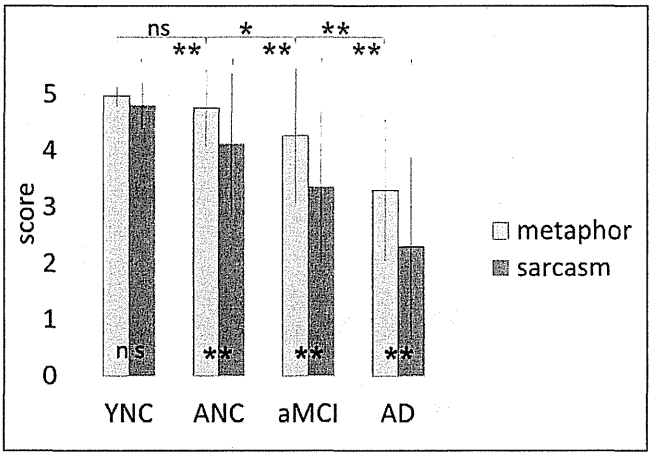

Figure 1. Scores of correct answers. Sarcasm scores were significantly lower in ANC than YNC, whereas metaphor scores were not different between the 2 groups. Metaphor scores were deteriorated from MCI. Post hoc analysis of 2 × 4 analysis of variance (metaphor and sarcasm; 4 groups) was conducted; * 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, amnestic mild cognitive impairment; AD, patients with mild Alzheimer's disease in clinical dementia rating 1.

Table 3. Errors of Literal Answers.

	Metaphor Mean ± SD	Metaphor P Value[a]	Sarcasm Mean ± SD	Sarcasm 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, amnestic mild cognitive impairment; AD, patients with mild Alzheimer's disease in clinical dementia rating 1; 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

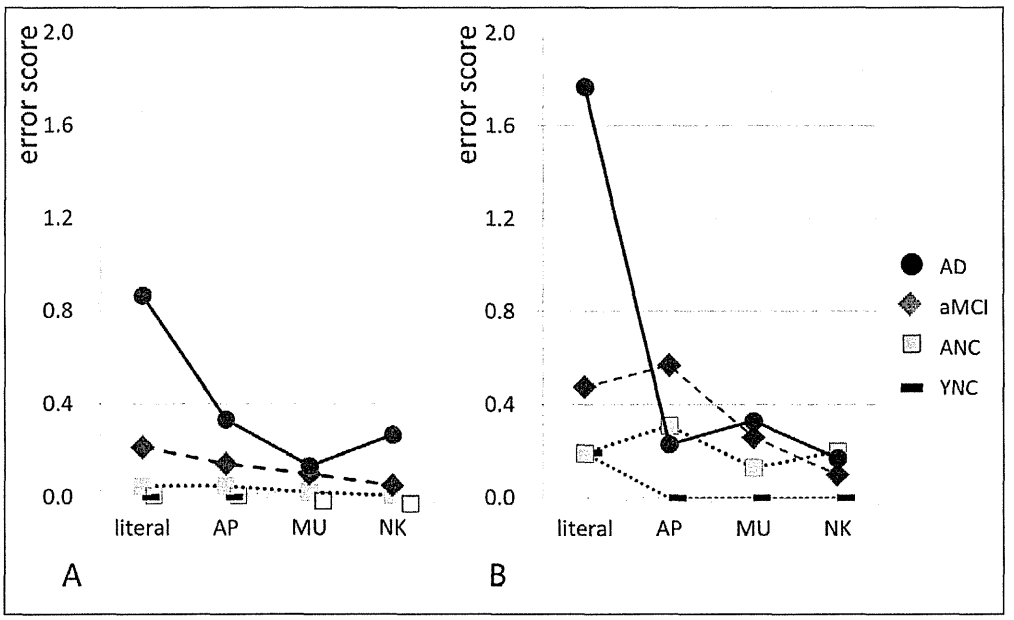

Figure 2. Error patterns. Error patterns of metaphor (A) and sarcasm (B). Significant differences among groups were observed in literal errors in both metaphor and sarcasm and the other 4 patterns of error were not significantly different among groups. AD indicates patients with mild Alzheimer's disease in clinical dementia rating 1; aMCI, amnestic 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 6[25] 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 mean[15] 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.