Table 3. AEs [n (%)] reported by ≥5% of patients during the entire period (all causality)

	Overall (n = 108)	Time of onset		
		0–12 weeks (n = 108)	12–24 weeks (n = 98)	24–52 weeks (n = 90)
Blood CPK increase	12 (11.1)	8 (7.4)	3 (3.1)	3 (3.3)
Contusion	12 (11.1)	4 (3.7)	5 (5.1)	4 (4.4)
Nasopharyngitis	11 (10.2)	4 (3.7)	4 (4.1)	3 (3.3)
Blood pressure increase	11 (10.2)	8 (7.4)	3 (3.1)	1 (1.1)
Fall	11 (10.2)	5 (4.6)	1 (1.0)	7 (7.8)
Diarrhea	10 (9.3)	3 (2.8)	5 (5.1)	3 (3.3)
Constipation	8 (7.4)	2 (1.9)	4 (4.1)	2 (2.2)
Parkinsonism	8 (7.4)	1 (0.9)	2 (2.0)	6 (6.7)
Blood urine present	7 (6.5)	2 (1.9)	3 (3.1)	3 (3.3)
Protein urine present	7 (6.5)	2 (1.9)	2 (2.0)	4 (4.4)
Decreased appetite	6 (5.6)	1 (0.9)	1 (1.0)	4 (4.4)
Insomnia	6 (5.6)	2 (1.9)	1 (1.0)	3 (3.3)
Compression fracture	6 (5.6)	2 (1.9)	0	4 (4.4)

CPK = Creatine phosphokinase.

AEs associated with gastrointestinal symptoms were reported in 34 patients (31.5%). Diarrhea (10 patients, 9.3%), constipation (8 patients, 7.4%), and decreased appetite (6 patients, 5.6%) were observed relatively frequently.

AEs associated with psychiatric symptoms were noted in 25 patients (23.1%). Six patients (5.6%) experienced insomnia. Visual hallucinations and psychiatric symptoms were recorded as AEs in 5 patients (4.6%), respectively. Incidence rates by onset time did not reveal any notable imbalance.

Discussion

This is the first study to examine long-term safety and efficacy of donepezil in patients with DLB. Overall, 108 patients with DLB who had completed the 12-week, double-blind, comparative RCT subsequently participated in this extension study. The results presented here demonstrate that cognitive function and dementia-related behavioral symptoms, including cognitive fluctuations, were improved after the start of donepezil treatment, and maintained for 52 weeks, or up to 64 weeks if the preceding treatment period is included. Our findings suggest that treatment efficacy of donepezil for these symptoms may be maintained even after the treatment in patients who were followed in this extension study, since no linear decrease in evaluation scores was observed. In accordance with our results, the study of long-term use of rivastigmine in DLB patients revealed that the reduction in MMSE scores was gradual and without statistical significance compared to baseline for 96 weeks [8]. Additionally, no significant worsening of NPI scores was demonstrated, although the decline in the scores seemed sharper after 72 weeks [8]. In contrast, when donepezil was administered to patients with AD for 52 weeks, it was reported that cognitive function, as assessed by the MMSE or Severe Impairment Battery [19], started to decline after 24 weeks [20, 21]. Progression of cognitive impairment in DLB and AD patients has been compared in several studies, but results differ from study to study. Olichney et al. [22] reported that there was a significant difference between DLB and AD groups in mean MMSE decline per year (–5.8 ± 4.5

for the DLB group and −4.1 ± 3.0 for the AD group). Ballard et al. [23] reported that more deterioration in the mean MMSE score per year was observed in an AD group (−4.9 ± 3.6) than a DLB group (−4.3 ± 4.2), although no statistical difference was shown. Furthermore, a similar cognitive decline between a DLB and an AD group was reported by Walker et al. [24]. The mean decline in the MMSE score per year was −3.1 ± 4.3 for the DLB group and −2.6 ± 4.0 for the AD group, with no statistically significant difference. These results indicate that cognitive decline in DLB may be faster than or at least similar to that in AD patients, and, in this respect, patients with DLB might be more likely to benefit from donepezil treatment compared to AD patients. With regard to burden on caregivers, no obvious improvement was shown in ZBI scores, while the treatment effect on cognitive functions, as well as neuropsychiatric symptoms, were improved or at least maintained. Accumulation of caregiving burden over time may prevent caregivers from realizing that a decrease in burden has occurred. However, it is noteworthy that burden on caregivers did not increase throughout the cumulative observational period in our two studies.

Unsurprisingly, a relationship between the washout period and attenuation in the treatment effect was suggested. Among patients who were assigned to the donepezil treatment groups in the preceding RCT, cognitive function and behavioral/psychiatric symptoms deteriorated more in patients with a longer washout period. This could indicate that the treatment effect might eventually diminish if donepezil administration was stopped for a long period of time.

Since there was no significant imbalance in the AE incidence analyzed by onset time, it is therefore suggested that delayed onset of AE induced by long-term donepezil administration is unlikely to appear in these patients. Patients with DLB may be at increased risk of bradyarrhythmia resulting from treatment with ChEIs though [14]. In this long-term study, however, only 2 patients experienced abnormal changes in pulse rate (1 bradycardia and 1 sinus bradycardia), and neither of these were serious. Also, long-term administration of donepezil is unlikely to worsen parkinsonian symptoms since UPDRS scores did not worsen over 52 weeks. Furthermore, only 3 patients received dose reductions to 3 mg/day due to AEs. Two of them completed this study with the reduced dose, thereby enabling the patients to continue treatment with donepezil by reducing the dosage to 3 mg/day. In comparison to a study of donepezil in patients with AD, AEs reported in this study were similar to those reported in the study of AD patients, except for parkinsonism [20].

The major limitation of this study is its open-label, single-arm design. Clearly, a blinded, comparative study is necessary to confirm our findings; however, due to the progressive nature of this disease, leading to acceleration of mortality, allocating patients to a placebo is not appropriate for long periods of time. Because improvement in MMSE scores and NPI scores after donepezil administration in the PLA-DON group showed a similar trend with the results presented in the preceding double-blind RCT, despite the open-label design used in this study, we believe that our results reliably indicate the efficacy of donepezil. It should also be noted that this study cannot determine which donepezil dose might contribute to a better outcome on a long-term basis. Since the preceding RCT suggested the benefit of the administration of a 10-mg dose in a particular group of patients, compared to 3 or 5 mg, further research would be helpful to assess the long-term benefits of administration of 10-mg doses.

In conclusion, the long-term administration of donepezil at 5 mg/day was safe in patients with DLB, and is expected to exhibit lasting effects on improving impaired cognitive function and psychiatric symptoms.

Acknowledgments

We are deeply grateful for the participation of the patients and their caregivers. We also thank all investigators and site staff for their contributions, and the Eisai study team (M. Hayashi, T. Kobayashi, S. Taniguchi, and E. Ebisawa) for their assistance. This study was sponsored by Eisai Co., Ltd. (Tokyo, Japan).

Donepezil-DLB Study Investigators

Sadao Katayama (Hiroshima-nishi Medical Center), Yasuto Higashi (Himeji Central Hospital), Tatsuo Yamada (Fukuoka University Hospital), Yuichi Maruki (Saitama Neuropsychiatric Institute), Satoshi Orimo (Kanto Central Hospital), Aoi Yoshiiwa (Oita University Hospital), Haruo Hanyu (Tokyo Medical University Hospital), Masayuki Yokochi (Ebara Hospital), Takemi Kimura (Kikuti National Hospital), Koichi Mizoguchi (Shizuoka Institute of Epilepsy and Neurology), Aki Nakanishi (Osaka City Kosaiin Hospital), Tadashi Tsukamoto (National Center of Neurology and Psychiatry), Norio Taniguchi (Asakayama General Hospital), Koichi Okamoto (Gunma University Hospital), Tatsuru Kitamura (Takamatsu Hospital), Yoko Nakano (Sukoyaka-Silver Hospital), Tomonobu Kato (Osaka Red Cross Hospital), Kenichi Shimada (Hyogo Brain and Heart Center), Masanori Hiji (Vi-hara Hananosato Hospital), Yasumasa Yoshiyama (Chiba-East Hospital), Yuri Kitamura (Nanohana Clinic), Satoshi Takahashi (Iwate Medical University Hospital), Masahiro Akishita (Tokyo University Hospital), Yukihiko Washimi (National Center for Geriatrics and Gerontology), Yasuji Yamamoto (Kobe University Hospital), Miyuki Kobayashi (Komoro Kogen Hospital), Fukashi Udaka (Sumitomo Hospital), Yasushi Osaki (Kochi University Hospital), Hiroaki Hino (Yokohama Hoyu Hospital), Takashi Kanda (Yamaguchi University Hospital), Toshifumi Kishimoto (Nara Medical University Hospital), Hiroaki Oguro (Shimane University Hospital), Toshimasa Matsuoka (Kurume University Hospital), Yasuhiro Tsugu (Toyokawa City Hospital), Naoki Fujii (Omuta Hospital), and Yasuhiro Kawase (Kawase Neurology Clinic).

Disclosure Statements

M.I.: grants/grants pending, Daiichi Sankyo, Eisai, FUJIFILM RI, Janssen, Nihonmediphysics, Novartis, Pfizer, Takeda, Tsumura; speaking fees, Daiichi Sankyo, Eisai, FUJIFILM RI, Janssen, MSD, Nihonmediphysics, Novartis, Ono, Pfizer, Takeda, Tsumura.

E.M.: consultancy, Lundbeck; grants/grants pending, Eisai, FUJIFILM RI, Nihonmediphysics; speaking fees, Eisai, FUJIFILM RI, Janssen, Johnson & Johnson, Lundbeck, Nihonmediphysics, Novartis.

K.K.: board membership, Dainippon Sumitomo, Eisai, Novartis, Tsumura; speaking fees, Daiichi Sankyo, Eisai, FUJIFILM RI, Janssen, Novartis, Nihonmediphysics, Ono, Pfizer, Tsumura; paid manuscript preparation, Tsumura.

E.I.: grants/grants pending, Daiichi Sankyo, Eisai, Nihonmediphysics, Novartis, Ono, Takeda, Tsumura; speaking fees, Daiichi Sankyo, Eisai, Janssen, Nihonmediphysics, Novartis, Ono, Takeda.

M.H.: speaking fees, Daiichi Sankyo, Eisai, FUJIFILM RI, Janssen, Nihonmediphysics, Novartis, Pfizer.

N.M.: grants/grants pending, Daiichi Sankyo.

K.M., M.N.: employees of Eisai.

References

1 McKeith I, Mintzer J, Aarsland D, Burn D, Chiu H, Cohen-Mansfield J, Dickson D, Dubois B, Duda JE, Feldman H, Gauthier S, Halliday G, Lawlor B, Lippa C, Lopez OL, Carlos Machado J, O'Brien J, Playfer J, Reid W: International Psychogeriatric Association Expert Meeting on DLB. Dementia with Lewy bodies. Lancet Neurol 2004;3:19–28.

2 McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen EN, Ballard C, de Vos RA, Wilcock GK, Jellinger KA, Perry RH: Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;47:1113–1124.

3 Perry EK, Haroutunian V, Davis KL, Levy R, Lantos P, Eagger S, Honavar M, Dean A, Griffiths M, McKeith IG, et al: Neocortical cholinergic activities differentiate Lewy body dementia from classical Alzheimer's disease. Neuroreport 1994;5:747–749.

4 Perry EK, Irving D, Kerwin JM, McKeith IG, Thompson P, Collerton D, Fairbairn AF, Ince PG, Morris CM, Cheng AV, et al: Cholinergic transmitter and neurotrophic activities in Lewy body dementia: similarity to Parkinson's and distinction from Alzheimer disease. Alzheimer Dis Assoc Disord 1993;7:69–79.
5 Thomas AJ, Burn DJ, Rowan EN, Littlewood E, Newby J, Cousins D, Pakrasi S, Richardson J, Sanders J, McKeith IG: A comparison of the efficacy of donepezil in Parkinson's disease with dementia and dementia with Lewy bodies. Int J Geriatr Psychiatry 2005;20:938–944.
6 Mori S, Mori E, Iseki E, Kosaka K: Efficacy and safety of donepezil in patients with dementia with Lewy bodies: preliminary findings from an open-label study. Psychiatry Clin Neurosci 2006;60:190–195.
7 Rowan E, McKeith IG, Saxby BK, O'Brien JT, Burn D, Mosimann U, Newby J, Daniel S, Sanders J, Wesnes K: Effects of donepezil on central processing speed and attentional measures in Parkinson's disease with dementia and dementia with Lewy bodies. Dement Geriatr Cogn Disord 2007;23:161–167.
8 Grace J, Daniel S, Stevens T, Shankar KK, Walker Z, Byrne EJ, Butler S, Wilkinson D, Woolford J, Waite J, McKeith IG: Long-term use of rivastigmine in patients with dementia with Lewy bodies: an open-label trial. Int Psychogeriatr 2001;13:199–205.
9 Edwards K, Royall D, Hershey L, Lichter D, Hake A, Farlow M, Pasquier F, Johnson S: Efficacy and safety of galantamine in patients with dementia with Lewy bodies: a 24-week open-label study. Dement Geriatr Cogn Disord 2007;23:401–405.
10 McKeith I, Del Ser T, Spano P, Emre M, Wesnes K, Anand R, Cicin-Sain A, Ferrara R, Spiegel R: Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. Lancet 2000;356:2031–2036.
11 Mori E, Ikeda M, Kosaka K: Donepezil-DLB Study Investigators. Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial. Ann Neurol 2012;72:41–52.
12 Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, De Deyn PP, Durif F, Kulisevsky J, van Laar T, Lees A, Poewe W, Robillard A, Rosa MM, Wolters E, Quarg P, Tekin S, Lane R: Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med 2004;351:2509–2518.
13 Dubois B, Tolosa E, Katzenschlager R, Emre M, Lees AJ, Schumann G, et al: Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study. Mov Disord 2012;27:1230–1238.
14 Rosenbloom MH, Finley R, Scheinman MM, Feldman MD, Miller BL, Rabinovici GD: Donepezil-associated bradyarrhythmia in a patient with dementia with Lewy bodies (DLB). Alzheimer Dis Assoc Disord 2010;24:209–211.
15 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.
16 Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J: The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–2314.
17 Zarit SH, Reever KE, Bach-Peterson J: Relatives of the impaired elderly: correlates of feelings of burden. Gerontologist 1980;20:649–655.
18 Fahn S, Elton RL; UPDRS Development Committee: Unified Parkinson's Disease Rating Scale; in Fahn S, Marsden CD, Calne D, Goldstein M (eds): Recent Developments in Parkinson's Disease. Florham Park, Macmillan Healthcare Information, 1987, vol 2, pp 153–163, 293–304.
19 Panisset M, Roudier M, Saxton J, Boller F: Severe impairment battery. A neuropsychological test for severely demented patients. Arch Neurol 1994;51:41–45.
20 Tohgi H, Homma A, Imai Y, Udaka F, Takeda M, Nishimura T, Kameyama M, Hasegawa K: Long-term safety and efficacy of acetylcholinesterase inhibitor E2020 in patients with Alzheimer-type dementia. 52-week open label study. Clin Eval 2000;28:97–126.
21 Homma A, Imai Y, Tago H, Asada T, Shigeta M, Iwamoto T, Takita M, Arimoto I, Koma H, Takase T, Ohbayashi T: Long-term safety and efficacy of donepezil in patients with severe Alzheimer's disease: results from a 52-week, open-label, multicenter, extension study in Japan. Dement Geriatr Cogn Disord 2009;27:232–239.
22 Olichney JM, Galasko D, Salmon DP, Hofstetter CR, Hansen LA, Katzman R, Thal LJ: Cognitive decline is faster in Lewy body variant than in Alzheimer's disease. Neurology 1998;51:351–357.
23 Ballard C, O'Brien J, Morris CM, Barber R, Swann A, Neill D, McKeith I: The progression of cognitive impairment in dementia with Lewy bodies, vascular dementia and Alzheimer's disease. Int J Geriatr Psychiatry 2001;16:499–503.
24 Walker Z, McKeith I, Rodda J, Qassem T, Tatsch K, Booij J, Darcourt J, O'Brien J: Comparison of cognitive decline between dementia with Lewy bodies and Alzheimer's disease: a cohort study. BMJ Open 2012;2:e000380.

International Psychogeriatrics (2013), 25:11, 1877–1883 © International Psychogeriatric Association 2013
doi:10.1017/S1041610213001191

Prevalence of delirium among outpatients with dementia

N. Hasegawa,[1,2,3] M. Hashimoto,[2] S. Yuuki,[2,3] K. Honda,[2] Y. Yatabe,[2] K. Araki[3] and M. Ikeda[2,3]

[1] *Department of Psychiatry, Kobe University Graduate School of Medicine, Hyogo, Japan*
[2] *Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan*
[3] *Kumamoto Mental Health Hospital, Kumamoto, Japan*

ABSTRACT

Background: Delirium and dementia are highly interrelated. However, few comprehensive epidemiological studies have examined this altered state of consciousness superimposed on dementia. We investigated the frequency of delirium in patients with dementia, its prevalence in patients with each dementia type, and its association with cerebrovascular disease (CVD) in patients with neurodegenerative dementias.

Methods: We studied 261 consecutive outpatients in the memory clinic of a psychiatric hospital between April 2010 and September 2011. All patients underwent routine laboratory tests and computed tomography (CT), and their Mini-Mental State Examination, Neuropsychiatric Inventory (NPI), Physical Self-Maintenance Scale (PSMS), and Delirium Rating Scale – Revised 98 scores were recorded. The diagnosis of delirium was based on the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision. CVD was detected by CT.

Results: Among the 206 patients with dementia, delirium was present in 40 (19.4%). The proportion of patients who experienced episodes of delirium was 14.7% in the Alzheimer's disease, 34.4% in the vascular dementia, 31.8% in the dementia with Lewy bodies, and none in frontotemporal lobar degeneration. Delirium was frequently observed in patients with dementia and CVD. The NPI total and agitation subscale scores were significantly higher in dementia patients with delirium than in those without delirium. PSMS scores were significantly lower for patients with delirium than for patients without delirium.

Conclusions: The frequency of delirium varies with each dementia type. In addition, delirium decreases activities of daily living, exaggerates behavioral and psychological symptoms dementia, and is associated with CVD in patients with neurodegenerative dementias.

Key words: delirium, dementia, cerebrovascular disease, behavioral and psychological symptoms of dementia, neuropsychiatric inventory

Introduction

There is a strong interrelationship between delirium and dementia, both pathophysiologically and clinically (Young and Inouye, 2007). Delirium superimposed on dementia is common but frequently unrecognized, and these patients reportedly exhibit an accelerated decline in cognitive and functional abilities, a greater need for institutionalization, a greater re-hospitalization risk, and increased mortality (Fick *et al.*, 2002).

According to a recent review article, the prevalence of delirium in elderly individuals aged ≥65 years is 1–2%, and it increases up to 22% in elderly individuals with dementia (de Lange *et al.*, 2012). The prevalence of delirium superimposed on dementia ranges from 22 to 89% in community and hospital populations (Fick *et al.*, 2002).

Although dementia is generally considered a major risk factor for delirium, the relationship between delirium and dementia remains unclear. We hypothesized that the frequency of delirium varies with each dementia type, and is associated with cerebrovascular disease (CVD) with neurodegenerative dementias. This study aimed to investigate the frequency of delirium superimposed on dementia in patients with each dementia type and examines the association between delirium and CVD in patients with neurodegenerative dementias.

Methods

All procedures followed the Clinical Study Guidelines of the Ethics Committee of Kumamoto

Correspondence should be addressed to: Dr. Manabu Ikeda, MD, PhD, Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan. Phone: +81-96-373-5184; Fax: +81-96-373-5186. Email: mikeda@kumamoto-u.ac.jp. Received 1 Jul 2012; revision requested 27 Sep 2012; revised version received 14 Jun 2013; accepted 17 Jun 2013. First published online 22 July 2013.

Mental Health Hospital and were approved by the internal review board. A complete description of all procedures was provided to the patients, and written informed consents were obtained from all patients or their caregivers prior to participation.

This study was a prospective, dementia referral center-based, cohort study. The participants were 206 consecutive patients with dementia. These patients were defined at the time of initial assessment and selected on the basis of inclusion/exclusion criteria from a consecutive series of 261 patients who had undergone medical examination at the memory clinic of Kumamoto Mental Health Hospital from April 2010 to September 2011. All patients were examined by senior neuropsychiatrists (M. Ikeda and Y. Yatabe) using routine laboratory tests, computed tomography, and standard neuropsychological examinations, the results of which included Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975) and Physical Self-Maintenance Scale (PSMS; Lawton and Brody, 1969; Hokoishi *et al.*, 2001) scores. Behavioral and psychological symptoms of dementia (BPSD) were assessed by the Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994; Hirono *et al.*, 1997). In addition, we investigated antipsychotic and benzodiazepine use at the time of initial assessment. We also assessed delirium severity using the Delirium Rating Scale – Revised 98 (DRS-R98; Trzepacz *et al.*, 2001; Kato *et al.*, 2010). The DRS-R98 severity scale score ranges from 0 to 39, with higher scores indicating more severe delirium and a cut-off score of ≥ 15 being consistent with a diagnosis of delirium (Meagher *et al.*, 2010).

The diagnosis of delirium was based on the criteria for delirium outlined in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR; American Psychiatric Association, 2000). All patients with delirium fulfilled the following core criteria: (a) disturbance of consciousness, (b) changes in cognition, (c) development of disturbances over a short period of time, with a fluctuating course during the day, and (d) evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequence of general medical condition or drug effect. The criteria for delirium state that the condition should not be better explained by a pre-existing dementia, whereas the criteria for dementia state that prior delirium should be excluded.

Therefore, dementia was diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, third edition-revised (DSM-III-R; American Psychiatric Association, 1987) after improvement of consciousness by clinical treatments. If dementia existed, each dementia type was diagnosed according to the international consensus criteria. Patients were divided into those with probable Alzheimer's disease (AD), defined according to the National Institute for Neurological and Communicative Disorders and Stroke and Alzheimer's disease and Related Disorders Association (NINCDS–ADRDA; McKhann *et al.*, 1984); probable vascular dementia (VaD), defined according to the NINCDS and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS–AIREN) criteria (Román *et al.*, 1993); probable dementia with Lewy bodies (DLB), defined according to the consensus criteria for the clinical diagnosis of DLB, 2005 (McKeith *et al.*, 2005); frontotemporal lobar degeneration (FTLD), defined according to the international collaborative workshop on FTLD, 1998 (Neary *et al.*, 1998); or other types. In patients where it was difficult to determine whether symptoms were due to delirium or DLB were diagnosed as DLB without delirium. Therefore, the prevalence of delirium in patients with DLB could have been underestimated in this study. The presence of CVD, including multiple lacunar infarcts and leukoencephalopathy, was determined by a senior neuropsychiatrist (M. Hashimoto), who was blinded to the clinical data. As suggested by a number of previous studies (Bennett *et al.*, 1990; Román *et al.*, 1993; Yoshitake *et al.*, 1995; Leys *et al.*, 1999), we used a semi-standardized measure and classified CVD on the basis of computed tomography (CT) findings as follows (Ikeda *et al.*, 2001): multiple lacunar infarcts, leukoencephalopathy with or without lacunar infarcts, multiple infarcts, strategic single infarct, large cortical infarcts, cerebral hemorrhage, and subarachnoid hemorrhage.

Exclusion criteria for this study included the following: (a) absence of dementia according to DSM-III-R, (b) those with developmental abnormalities, serious psychiatric diseases, such as schizophrenia or major depression, or substance abuse before the onset of dementia, (c) absence of reliable informants, and (d) inability to obtain informed consent from patient and caregiver.

Statistical differences in age, education, and MMSE, PSMS, NPI total, and NPI subscale scores between patients with dementia and delirium and those with dementia without delirium were assessed by Student's *t*-tests. The χ^2 for independence test was conducted to compare sex; presence of CVD; use of donepezil, antipsychotics, or benzodiazepines; presence of CVD with neurodegenerative dementias; and the prevalence of delirium in patients with each dementia type. A significance level of 0.05 (two-tailed) was set for all analyses, which were conducted with SPSS for Windows, version 17.0 (IBM Corporation,

Table 1. Prevalence of delirium in patients with each dementia type

	PATIENTS (n = 206)		PATIENTS WITH DELIRIUM (n = 40)		DELIRIUM IN EACH DEMENTIA TYPE
DIAGNOSIS	n	%	n	%	%
AD	129	62.6	19	47.5	14.7
(AD)	(83)	(40.3)	(9)	(22.5)	(10.8)
(AD with CVD)	(46)	(22.3)	(10)	(25.0)	(21.7)
VaD	32	15.5	11	27.5	34.4
DLB	22	10.7	7	17.5	31.8
(DLB)	(12)	(5.8)	(3)	(7.5)	(25.0)
(DLB with CVD)	(10)	(4.9)	(4)	(10.0)	(40.0)
FTLD	5	2.4	0	0	0
(FTLD)	(4)	(1.9)	(0)	(0)	(0)
(FTLD with CVD)	(1)	(0.5)	(0)	(0)	(0)
Others	18	8.7	3	7.5	16.7

Notes: AD: Alzheimer's disease, CVD: cerebrovascular disease, VaD: vascular dementia, DLB: dementia with Lewy bodies; FTLD: frontotemporal lobar degeneration.

Armonk, NY, USA). In addition, two-way analysis of variance (ANOVA) was used to analyze the effects of each diagnosis with or without delirium and their interaction effects on scores for individual items in the NPI. The significance level was set at 0.01 or less. Scheffe's post hoc test was performed to detect any significant differences between diagnoses.

Results

Among the 206 patients, there were 142 women and 64 men with a mean age of 81.4 years (standard deviation (SD), 6.0), a mean educational attainment period of 8.5 years (SD, 2.1), and a mean MMSE score of 15.9 points (SD, 6.0). AD was observed in 62.6% (129/206) patients, VaD in 15.5% (32/206) patients, DLB in 10.7% (22/206) patients, and FTLD in 2.4% (5/206) patients.

Forty patients (19.4%) suffered from delirium. The frequency of delirium varied with dementia type, as shown in Table 1. The proportion of patients who experienced episodes of delirium was 14.7% in the AD group, 34.4% in the VaD group, and 31.8% in the DLB group, whereas no patient with FTLD experienced these episodes, indicating that the prevalence of delirium was significantly diverse for each dementia type ($p = 0.022$). Furthermore, delirium was more frequent in patients with CVD than in those without ($p = 0.006$); 21.7% of AD with CVD and 40.0% of DLB with CVD developed delirium, while 10.8% of AD without CVD and 25.0% of DLB without CVD developed delirium.

Demographic characteristics of the patients with and without delirium are shown in Table 2. There were no significant differences between the two groups with regard to age, sex, education, MMSE score, and use of donepezil, while patients with delirium more frequently used antipsychotics and benzodiazepines compared with those without delirium. PSMS scores were significantly lower for patients with delirium than for those without delirium ($p = 0.013$), while DRS-R98 severity was significantly higher for patients with delirium than for those without delirium ($p < 0.001$). With regard to NPI scores, NPI total scores ($p = 0.019$) and NPI agitation subscale scores ($p = 0.026$) were significantly higher for patients with delirium than for those without delirium.

Table 3 shows scores for individual NPI subscales among patients with each dementia type with or without delirium. Two-way ANOVA revealed statistically significant differences in scores for hallucinations among patients with each dementia type ($p < 0.001$) and in scores for agitation between patients with and without delirium ($p = 0.008$). Scheffe's post hoc comparisons revealed that DLB patients with delirium exhibited significantly higher scores for hallucinations compared with AD or VaD patients with delirium ($p < 0.01$). Overall, no significant differences were observed in individual NPI scores between patients with each dementia type with or without delirium ($p > 0.01$).

Discussion

To the best of our knowledge, this is the first study to investigate the disease-specific frequency of delirium superimposed on dementia on an outpatient basis. Delirium was present in approximately 20% outpatients with dementia,

Table 2. Demographic characteristics of patients with dementia with or without delirium

	PATIENTS (n = 206)	DEMENTIA WITHOUT DELIRIUM (n = 166)	DEMENTIA WITH DELIRIUM (n = 40)	p-VALUE
Age, years (SD)	81.4 (6.0)	81.0 (6.1)	82.8 (5.3)	0.090
Male, sex, n (%)	64 (31.1)	54 (32.5)	10 (25.0)	0.356
Years of education, y (SD)	8.5 (2.1)	8.5 (2.2)	8. 3 (1.8)	0.540
MMSE (SD)	15.9 (6.0)	16.1 (6.0)	14.7 (6.1)	0.162
Treatment with donepezil (%)	40 (19. 4)	32 (19.3)	8 (20.0)	0.917
Treatment with antipsychotic agent (%)	16 (7.8)	8 (4.8)	8 (20.0)	0.001*
Treatment with benzodiazepine (%)	23 (11.2)	8 (4.8)	15 (37.5)	<0.001*
PSMS (SD)	4.0 (1.9)	4.2 (1.9)	3.3 (2.1)	0.013*
CVD, n (%)	94 (45.6)	68 (41.0)	26 (65.0)	0.006*
DRS-R98 severity (SD)	10.8 (5.4)	8.9 (3.4)	18.5 (5.0)	<0.001*
NPI total score (SD)	11.1 (12.4)	9.8 (11.2)	16.2 (15.7)	0.019*
NPI subscale score, frequency × severity (SD)				
Delusions		1.3 (2.5)	1.9 (2.6)	0.161
Hallucinations		0.7 (1.9)	1.2 (2.5)	0.260
Agitation		1.1 (2.3)	2.3 (3.2)	0.026*
Dysphoria		0.8 (1.5)	1.5 (2.7)	0.114
Anxiety		1.0 (1.9)	2.0 (3.0)	0.062
Euphoria		0.1 (0.5)	0.1 (0.6)	0.807
Apathy		2.4 (2.8)	3.5 (3.9)	0.103
Disinhibition		0.4 (1.4)	0.2 (1.0)	0.426
Irritability		1.2 (2.5)	2.1 (3.5)	0.107
Aberrant motor behavior		0.9 (2.4)	1.5 (2.9)	0.265

Notes: *$p < 0.05$.
CVD: cerebrovascular disease, MMSE: Mini-Mental State Examination,
PSMS: Physical Self-Maintenance Scale, DRS-R98: Delirium Rating Scale-Revised 98, NPI: Neuropsychiatric inventory.

although the prevalence of delirium was diverse for each dementia type: 14.7% in patients with AD, 34.4% in patients with VaD, 31.8% in patients with DLB, and 0% in patients with FTLD. The prevalence of delirium among AD and DLB patients with CVD was 1.6 times higher than that in AD and DLB patients without CVD. The findings suggest that delirium decreases activities of daily living (ADL) and exaggerates BPSD in patients with dementia.

In a study that examined patients (n = 175) admitted to a neuropsychiatric unit (Robertsson *et al.*, 1998), the overall prevalence of recurrent delirium was 37%: 57% in patients with late-onset AD, 14% in patients with early-onset AD, 19% in patients with frontotemporal dementia, and 40% in patients with VaD. Among patients with acute medical illness, delirium was observed in 26% patients with primary degenerative dementia and 52% patients with dementia associated with vascular changes, i.e., VaD (Erkinjuntti *et al.*, 1986). However, there have been no studies that have investigated the prevalence of delirium in patients with DLB. Among the patients with neurodegenerative dementias in this study, the prevalence of delirium was highest in the DLB group. It can be particularly difficult to distinguish delirium from DLB because some features such as hallucinations and symptom fluctuation are common to both (Young and Inouye, 2007). In the current study, dementia was diagnosed immediately after it was determined that the symptoms of delirium had subsided. Moreover, DRS-R98 severity scores were significantly higher for DLB patients with delirium (mean, 19.6; SD, 5.2; range, 15–28) than for DLB patients without delirium (mean, 11.7; SD, 2.6; range, 5–14; p = 0.006). No DLB patient with delirium exhibited a score of <15, whereas no DLB patient without delirium exhibited a score of ≥15. DLB patients with delirium exhibited significantly higher scores for the hallucination subscale of the NPI compared with AD and VaD patients with delirium. However, overall differences in individual NPI scores among patients with each dementia type with or without delirium were not significant. Dementia researchers need to assess any delirium component more carefully

Table 3. Mean composite scores (frequency × severity) of individual Neuropsychiatric Inventory (NPI) items among patients with each dementia type with or without delirium

NPI SUBSCALES	DEMENTIA WITHOUT DELIRIUM (n = 166)	DEMENTIA WITH DELIRIUM (n = 40)	p-VALUE	TWO-WAY ANOVA; p-VALUE		
				EACH TYPE	WITH/WITHOUT DELIRIUM	INTERACTION
Delusions						
AD	1.39 (2.63)	1.53 (2.53)	0.835	0.026	0.176	0.646
VaD	0.86 (1.93)	1.91 (2.17)	0.170			
DLB	2.67 (2.85)	3.71 (3.30)	0.453			
Hallucinations						
AD	0.46 (1.67)	0.58 (1.92)	0.786	<0.001*[a]	0.539	0.937
VaD	0.48 (1.21)	0.64 (1.43)	0.741			
DLB	3.53 (2.90)	4.00 (3.87)	0.755			
Agitation						
AD	1.23 (2.46)	2.89 (3.50)	0.059	0.042	0.008*	0.676
VaD	0.33 (0.91)	1.09 (2.59)	0.366			
DLB	1.20 (2.01)	3.00 (3.22)	0.122			
Dysphoria						
AD	0.88 (1.65)	1.58 (3.06)	0.344	0.635	0.117	0.987
VaD	0.62 (1.16)	1.18 (2.44)	0.381			
DLB	1.07 (1.79)	1.71 (2.36)	0.483			
Anxiety						
AD	1.12 (2.19)	1.53 (2.97)	0.479	0.275	0.010	0.355
VaD	0.57 (1.17)	2.09 (2.63)	0.092			
DLB	1.33 (1.50)	3.14 (3.93)	0.278			
Euphoria						
AD	0.12 (0.57)	0.00 (0.00)	0.370	0.453	0.472	0.131
VaD	0.00 (0.00)	0.36 (1.21)	0.341			
DLB	0.00 (0.00)	0.00 (0.00)	-			
Apathy						
AD	2.41 (2.79)	3.47 (4.16)	0.294	0.594	0.228	0.634
VaD	3.00 (3.39)	2.91 (3.73)	0.945			
DLB	1.47 (2.33)	2.86 (2.80)	0.234			
Disinhibition						
AD	0.34 (1.33)	0.42 (1.43)	0.800	0.822	0.351	0.573
VaD	0.48 (1.54)	0.00 (0.00)	0.171			
DLB	0.40 (1.55)	0.00 (0.00)	0.508			
Irritability						
AD	1.24 (2.60)	2.89 (4.19)	0.110	0.333	0.067	0.443
VaD	1.24 (2.19)	1.36 (2.20)	0.879			
DLB	0.60 (1.30)	2.00 (3.46)	0.336			
Aberrant motor behavior						
AD	0.88 (2.41)	1.74 (3.12)	0.268	0.037	0.281	0.586
VaD	0.57 (1.57)	0.36 (0.92)	0.690			
DLB	1.87 (3.87)	3.00 (4.04)	0.535			

Notes: Values are presented as mean (SD).
AD: Alzheimer's disease; AD without delirium (n = 110), AD with delirium (n = 19).
VaD: Vascular dementia; VaD without delirium (n = 21), VaD with delirium (n = 11).
DLB: Dementia with Lewy bodies; DLB without delirium (n = 15), DLB with delirium (n = 7).
*p < 0.01; [a]DLB versus AD or VaD as per Scheffe's post hoc test.

and utilize instruments that capture characteristics that differentiate delirium and dementia disorders (Meagher and Trzepacz, 2007).

In the 263 post-stroke patients of the Helsinki Stroke Aging Memory cohort study, patients with delirium were more likely to have pre-stroke cognitive decline compared with patients without delirium (28.0% vs. 4.2%), and the former group developed post-stroke dementia more frequently than the latter group (50.0% vs. 16.9%; Melkas *et al.*, 2012). In addition, the findings of this study suggest that CVD in patients with neurodegenerative dementias, such as AD and DLB, are at an increased risk of delirium. However,

the association of CVD with neurodegenerative dementia and delirium remains unclear. Delirium may be a disorder of corticostriatal loops, and a central cholinergic deficiency may be a major factor in its development (Robertsson *et al.*, 1998). In patients with CVD accompanied by neurodegenerative dementias, the cortex is probably partly disconnected from deeper structures, and this causes cortical and subcortical dysfunction and a decrease in cholinergic activity. Cerebrovascular disease may be one of the major risk factors causing vulnerability to delirium.

In this study, NPI scores, particularly agitation subscale scores, were higher in patients with delirium than in those without ("pure" dementia). In a previous study, the scores for a wide range of DRS-R98 non-cognitive items, such as sleep–wake cycles, perceptual abnormalities, affective liability, thought process abnormalities, motor agitation, and motor retardation, were more severe in patient groups with dementia and comorbid delirium than in patient groups with "pure" dementia (Meagher *et al.*, 2010). Taking into account these findings, delirium has an additive impact on the phenomenological profile of patients with dementia. Delirium has been shown to accelerate the trajectory of cognitive decline during the follow-up course of memory-clinic patients with AD (Fong *et al.*, 2009). In addition, delirium is highly prevalent among hospitalized patients with AD and is associated with an increased rate of cognitive deterioration in these patients (Weiner, 2012). Moreover, delirium itself is a cause of long-term cognitive impairment. However, the key question of whether delirium is a risk factor for new-onset dementia remains unanswered (MacLullich *et al.*, 2009). In a true population-based study, delirium has been shown to be a strong risk factor for the incidence of dementia and cognitive decline, but the relationship did not appear to be mediated by the classic neuropathologies associated with dementia (Davis *et al.*, 2012). In a longitudinal future study, we should carefully investigate the relationship between delirium and onset of dementia.

A previous study demonstrated an increased risk of admission to long-term care facilities among patients with delirium superimposed on dementia than among patients with "pure" dementia or only delirium (Fick *et al.*, 2002). This study suggests that delirium superimposed on dementia exaggerates BPSD and decreases patients' ADL. Therefore, delirium superimposed on dementia can become a major burden to long-term care services.

This study had some limitations. First, we did not have pathological confirmations of dementia subtype in our patients. Second, the results may have been biased because all patients were recruited from the dementia outpatient clinic of a mental hospital, and the prevalence of delirium varies depending on the care settings. Hospital admission is one of the major risk factors for delirium, and most previous studies have examined hospitalized patients. A well-defined dementia cohort in an outpatient clinic is the strength of our study. However, taking account of the number of people with delirium due to medical problems severe enough to preclude coming to the memory clinic, the prevalence of delirium with dementia in this study may estimate low. Third, in order to identify CVD, we used a visual assessment method using CT, which may not be as accurate as assessments conducted using magnetic resonance imaging (MRI). Fourth, our sample size with regard to patients with each dementia type was relatively small for analysis. We had to exclude FTLD and other types of dementia for statistical analysis. However, an advantage of our study was the relatively large study cohort. A future investigation similar to this one should be conducted with a larger number of patients.

In summary, the findings of this study suggest that the frequency of delirium varies among patients with different types of dementia. In addition, these findings suggest that delirium decreases ADL, exaggerates BPSD, and is associated with CVD in patients with neurodegenerative dementias.

Conflict of interest

None.

Description of authors' roles

N. Hasegawa collected and analyzed the data and prepared the first draft of the paper. S. Yuuki, K. Honda, Y. Yatabe, and K. Araki assisted with the data collection and defining the diagnoses. M. Hashimoto evaluated the signs of CVD on CT scans. M. Ikeda conducted the literature review and assisted with the design of the study, data collection, definition of diagnoses, and writing of the paper.

Acknowledgments

The present study was undertaken with the support of grants that were provided by the Ministry of Health, Labor and Welfare (Research on dementia; H24-Dementia-General-001) to M. Ikeda. The authors gratefully acknowledge the assistance of the staff of Kumamoto Mental Health Hospital.

References

Bennett, D. A., Wilson, R. S., Gilley, D. W. and Fox, J. H. (1990). Clinical diagnosis of Binswanger's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, 53, 961–965.

Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A. and Gornbein, J. (1994). The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*, 44, 2308–2314.

Davis, D. H. *et al.* (2012). Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study. *Brain*, 135, 2809–2816.

de Lange, E., Verhaak, P. F. and van der Meer, K. (2012). Prevalence, presentation and prognosis of delirium in older people in the population, at home and in long-term care: a review. *International Journal of Geriatric Psychiatry*, 28, 127–134.

Erkinjuntti, T., Wikström, J., Palo, J. and Autio, L. (1986). Dementia among medical inpatients. evaluation of 2000 consecutive admissions. *Archives of Internal Medicine*, 146, 1923–1926.

Fick, D. M., Agostini, J. V. and Inouye, S. K. (2002). Delirium superimposed on dementia: a systematic review. *Journal of American Geriatric Society*, 50, 1723–1232.

Folstein, M. F., Folstein, S. E. and McHugh, P. R. (1975). "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12, 189–198.

Fong, T. G. *et al.* (2009). Delirium accelerates cognitive decline in Alzheimer's disease. *Neurology*, 72, 1570–1575.

Hirono, N. *et al.* (1997). Japanese version of the Neuropsychiatric Inventory: a scoring system for neuropsychiatric disturbance in dementia patients. *No To Shinkei*, 49, 266–271.

Hokoishi, K. *et al.* (2001). Inter-rater reliability of the Physical Self-Maintenance scale and the Instrumental Activities of Daily Living scale in a variety of health professional representatives. *Aging & Mental Health*, 5, 38–40.

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

Kato, M., Kishi, Y., Okuyama, T., Trzepacz, P. T. and Hosaka, T. (2010). Japanese version of the Delirium Rating Scale, Revised-98 (DRS-R98-J): reliability and validity. *Psychosomatics*, 51, 425–431.

Lawton, M. P. and Brody, E. M. (1969). Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*, 9, 179–186.

Leys, D. *et al.* (1999). Vascular dementia: the role of cerebral infarcts. *Alzheimer's Disease Associated Disorders*, 13(Suppl 3), S38–S48.

MacLullich, A. M., Beaglehole, A., Hall, R. J. and Meagher, D. J. (2009). Delirium and long-term cognitive impairment. *International Review of Psychiatry*, 21, 30–42.

McKeith, I. G. *et al.* (2005). Diagnosis and management of dementia with Lewy bodies: third report of the DLB consortium. *Neurology*, 65, 1863–1872.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. and Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS–ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer' disease. *Neurology*, 34, 939–944.

Meagher, D. and Trzepacz, P. T. (2007). Phenomenological distinctions needed in DSM- V: delirium, subsyndromal delirium, and dementias. *The Journal of Neuropsychiatry & Clinical Neurosciences*, 19, 468–470.

Meagher, D. J., Leonard, M., Donnelly, S., Conroy, M., Saunders, J. and Trzepacz, P. T. (2010). A comparison of neuropsychiatric and cognitive profiles in delirium, dementia, comorbid delirium-dementia and cognitively intact controls. *Journal of Neurology, Neurosurgery & Psychiatry*, 81, 876–881.

Melkas, S. *et al.* (2012). Post-stroke delirium in relation to dementia and long-term mortality. *International Journal of Geriatric Psychiatry*, 27, 401–408.

Neary, D. *et al.* (1998). Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*, 51, 1546–1554.

Robertsson, B., Blennow, K., Gottfries, C. G. and Wallin, A. (1998). Delirium in dementia. *International Journal of Geriatric Psychiatry*, 13, 49–56.

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

Trzepacz, P. T., Mittal, D., Torres, R., Kanary, K., Norton, J. and Jimerson, N. (2001). Validation of the Delirium Rating Scale – Revised-98: comparison with the delirium rating scale and the cognitive test for delirium. *Journal of Neuropsychiatry & Clinical Neurosciences*, 13, 229–242.

Weiner, M. F. (2012). Impact of delirium on the course of Alzheimer's disease. *Archives of Neurology*, 17, 1–2.

Yoshitake, T. *et al.* (1995). Incidence and risk factors of vascular dementia and Alzheimer's disease in a defied elderly Japanese population: the Hisayama Study. *Neurology*, 45, 1161–1168.

Young, J. and Inouye, S. K. (2007). Delirium in older people. *BMJ*, 334, 842–846.

The Relationship between Primary Progressive Aphasia and Neurodegenerative Dementia

原发性进行性失语症和大脑渐进式脑退化症之间的关系

N Ichimi, M Hashimoto, M Matsushita, H Yano, Y Yatabe, M Ikeda

Abstract

Objective: To examine the relationship between primary progressive aphasia (PPA) and neurodegenerative dementia.
Methods: Subjects were selected from 1723 consecutive patients who had undergone a medical examination at the Kumamoto University Hospital Dementia Clinic, Japan, from April 2007 to October 2012. First, patients with semantic dementia (SD) and patients with progressive non-fluent aphasia were diagnosed by clinical diagnostic criteria for frontotemporal lobar degeneration. Next, in the same cohort, patients with PPA were diagnosed according to the recent international consensus criteria. The relationship and clinical symptoms including language and psychiatric symptoms in each patient group were then compared.
Results: In all, 12 of 27 SD patients fulfilled both SD and semantic variant PPA criteria (SD+PPA+ group), whereas the other 15 who met the SD criteria could not be included in the semantic variant PPA group due to prominent behavioural disturbances (SD+PPA- group). No significant differences in clinical characteristics and language functions were found between these 2 groups. Neuropsychiatric symptoms were more severe in the SD+PPA- group.
Conclusion: The results suggest the possibility that SD and semantic variant PPA may be identical, regardless of different severities of behavioural disturbance. When considering the language disorder of neurodegenerative dementia, it may be more important to diagnose the subtype of language disorder the patient has than to emphasise isolated language deficits.

Key words: *Aphasia, primary progressive; Dementia; Neuropsychological tests*

摘要

目的：检视原发性进行性失语症与大脑渐进式脑退化症之间的关系。
方法：纳入1723例于2007年4月至2012月10月在日本熊本大学医院脑退化症诊所进行体检的患者。首先以额颞叶退化症的临床诊断标准诊断语意型脑退化（SD）和进行性非流利性失语症（PPA）患者，然后根据近期国际共识标准，于同一队列中确诊PPA患者，再比较不同病人组别之间包括语言和精神症状的关系和临床症状。
结果：27名患者中，12名符合SD和语意型PPA诊断标准（SD+PPA+组），其余15名因明显行为障碍不符合语意型PPA诊断标准（SD+PPA-组）。两组间临床特点和语言功能无显著差异，但SD+PPA-组的神经精神症状较为严重。
结论：研究认为，尽管行为障碍的重度有所不同，SD和svPPA可能是等同的病症。当考虑大脑渐进式脑退化症语言障碍的诊断时，对患者进行语言障碍子型的诊断，可能较独立诊断语言障碍更为重要。

关键词：*原发性进行性失语症、脑退化症、神经心理测试*

Ms Naoko Ichimi, MS, Clinical Psychologist, Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, Japan.
Dr Mamoru Hashimoto, MD, PhD, Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, Japan.
Mr Masateru Matsushita, PhD, Clinical Psychologist, Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, Japan.
Mr Hiroyuki Yano, MS, Clinical Psychologist, Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, Japan.
Dr Yusuke Yatabe, MD, PhD, Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, Japan.
Prof. Manabu Ikeda, MD, PhD, Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, Japan.

Address for correspondence: *Prof. Manabu Ikeda, Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan.*
Tel: (81-96) 373 5184; Fax: (81-96) 373 5184;
email: mikeda@kumamoto-u.ac.jp

Submitted: *19 April 2013;* **Accepted:** *10 June 2013*

Introduction

Progressive aphasia, which results from a neurodegenerative disease, is characterised by a progressive loss of specific language functions with relative sparing of other cognitive

domains. The understanding of this syndrome generally depends on either of the following 2 schools of thought (Fig 1).[1-9]

The first school of thought views progressive aphasia as a subtype of neurodegenerative dementia associated with anterior brain atrophy. This archetype was first described by Pick[1] in the 1890s as a progressive disorder of language with atrophy of the frontal and temporal regions of the left hemisphere and became known as Pick's disease. In 1975, Warrington[2] reported 3 cases with associative agnosia and a fluent-type aphasia characterised by anomia and impaired word comprehension attributed to circumscribed asymmetric atrophy in the anterior temporal lobe, which was considered a selective impairment of semantic memory. Later, this condition was also described by Snowden et al[3] as semantic dementia (SD). In the 1990s, a comprehensive characterisation of SD was provided by Hodges et al.[4] Subsequently, Grossman et al[5,10] reported a different form of progressive language disorder, which was marked by dysfluent and effortful speech, hesitations and errors in the production of speech sounds and termed progressive non-fluent aphasia (PNFA). In 1998, Neary et al[6] developed diagnostic criteria for SD and PNFA in relation to frontotemporal lobar degeneration (FTLD). For several years, cases of progressive aphasia were broadly classified into SD or PNFA.

The second school of thought regarding progressive aphasia was described in 1982 by Mesulam,[7] who discussed a series of cases he referred to with "slowly progressive aphasia without generalised dementia". He used the term 'progressive' to differentiate these patients from those with stroke-caused aphasia, and the word 'slowly' to differentiate them from those with a progressive but a relatively faster course (e.g. due to a neoplasm). The term 'without generalised dementia' was used to highlight differences from typical forms of Alzheimer's disease (AD). After some modifications, he proposed the concept of primary progressive aphasia (PPA).[8,11,12] Primary progressive aphasia could be diagnosed in any patient who had a fluent or non-fluent language disorder (aphasia) due to a neurodegenerative (progressive) disease and in whom aphasia was initially the most salient (primary) clinical feature. Mesulam[7,8,11,12] intended PPA to be a symptomatologically distinct clinical entity that selectively involved the language network. However, a number of studies have revealed that PPA is a clinical syndrome with heterogeneous neuropathological causes.[12-14]

Based on these 2 viewpoints, 3 subtypes of PPA are currently recognised: semantic variant PPA (svPPA), non-fluent / agrammatic variant PPA (navPPA), and logopenic variant PPA (lvPPA). The third clinical variant, termed logopenic progressive aphasia (LPA) by Gorno-Tempini et al,[9,13] is characterised by slow spontaneous speech output with frequent word-finding pauses and phonemic paraphasias. Several investigations have demonstrated that lvPPA is associated with atrophy of the posterior perisylvian and inferior parietal regions in the brain and is closely related to AD pathology.[14]

Despite advances in the concept of PPA, it is still unclear whether it is an independent disease entity or an atypical phenotype of neurodegenerative dementia such as FTLD or AD. This controversy could be addressed to a certain degree by examining the relationship between svPPA and SD. Both syndromes have similar language impairments. Nevertheless, a critical difference is the presence of a visual recognition deficit for faces and objects

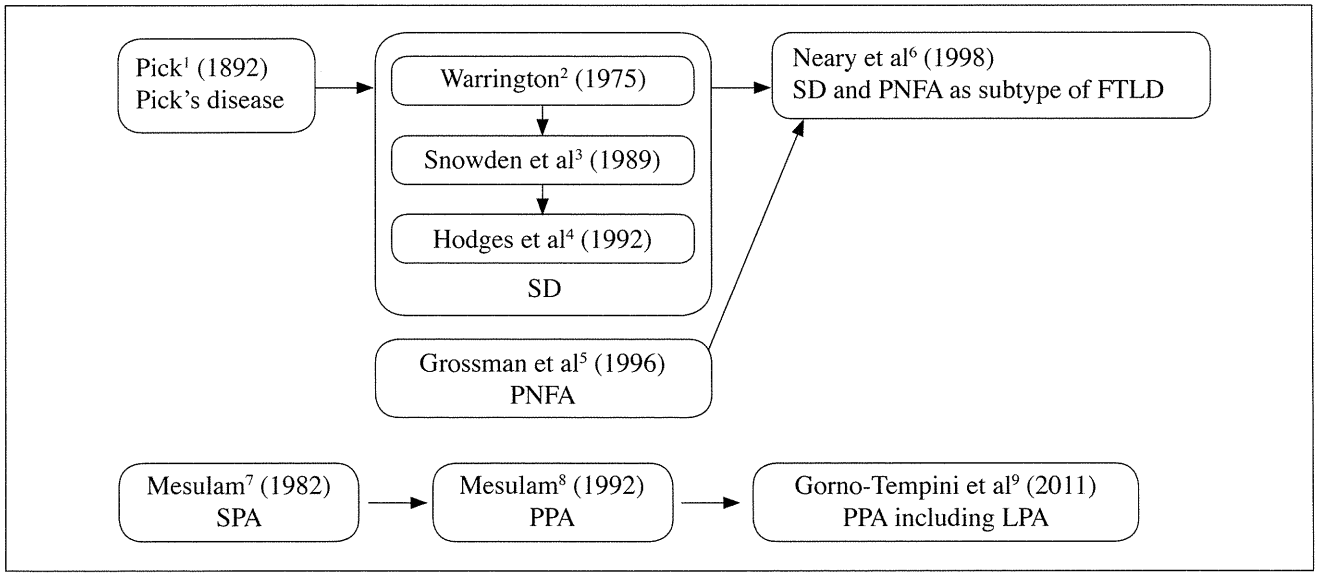

Figure 1. The concepts of classification of progressive aphasia.

Abbreviations: *SD = semantic dementia; PNFA = progressive non-fluent aphasia; FTLD = frontotemporal lobar degeneration; SPA = slowly progressive aphasia; PPA = primary progressive aphasia; and LPA = logopenic progressive aphasia.*

(prosopagnosia and associative agnosia) in SD that is not prominent in svPPA. In addition, some patients with SD, particularly those in whom the right temporal lobe is dominantly involved, exhibit remarkable behavioural changes even in the early stages of the disease. However, it has been pointed out that svPPA patients invariably progress to clear presentations of SD, and both syndromes share a common pathology. These findings suggest that svPPA may be an early phase of SD and it may not be important to differentiate it from SD. A more accurate clinical diagnosis of neurodegenerative dementia based on the background pathology may be required when aetiology-specific treatments become available in the future. In the present study, we reconsidered the relationship between PPA and neurodegenerative dementia by investigating consecutive patients with progressive aphasia in a dementia clinic.

Methods

All procedures in this study strictly followed the Clinical Study Guidelines of the Ethics Committee of Kumamoto University Hospital and were approved by the Internal Review Board. After a complete description of all procedures of the study was provided, written informed consent was obtained from patients or their caregivers.

Subjects were recruited from a consecutive series of 1723 patients who had undergone a medical examination at the Dementia Clinic of the Department of Neuropsychiatry, Kumamoto University Hospital, from April 2007 to October 2012. All patients were examined by senior neuropsychiatrists experienced in assessing dementia and aphasia, and underwent routine laboratory tests and standard neuropsychological examinations, including the Mini-Mental State Examination (MMSE)[15] and Clinical Dementia Rating (CDR) scale.[16] Behavioural and psychiatric symptoms were assessed by structured caregiver interviews using the Neuropsychiatric Inventory (NPI).[17] In addition, stereotypic behaviours were assessed using the Stereotypy Rating Inventory (SRI).[18] Brain magnetic resonance imaging or computed tomographic scans were performed in all patients and single-photon emission computed tomography of the brain was performed in most. The clinical, neuropsychological, and neuroimaging data collected prospectively in a standardised fashion were entered into the Kumamoto University Dementia Follow-up Registry. Selection was then based on inclusion and exclusion criteria as described below.

Clinical Diagnosis of Semantic Dementia and Progressive Non-fluent Aphasia

The diagnoses of SD and PNFA were based on a consensus regarding clinical diagnostic criteria developed by the international workshop on FTLD.[6] The diagnosis of SD required a gradually progressive language disorder characterised by fluent, empty spontaneous speech, loss of word meaning manifested by impaired naming and comprehension, preserved single-word repetition, and preserved ability to read aloud and write down orthographically regular words that were dictated. However, instead of the language disorder, patients with prosopagnosia (impaired recognition of identity of familiar faces) and / or associative agnosia (impaired recognition of object identity) could also be diagnosed as having SD. Other aspects of cognition, including autobiographic memory, could be intact or relatively well preserved. Behavioural and personality changes characterised by loss of sympathy and empathy, narrowed preoccupations, and parsimony were included in the supportive diagnostic features, as these changes were considered characteristic of SD and often associated with high diagnostic specificity. In all, 27 patients met the SD criteria. The clinical characteristics of the SD patients are shown in Table 1. Fifteen patients had left-predominant involvement and 12 had right-predominant involvement.

The diagnosis of PNFA required gradually progressive non-fluent spontaneous speech with at least one of the following symptoms: agrammatism, phonemic paraphasias, or anomia. Other aspects of cognition could be intact or relatively well preserved. Late behavioural changes similar to behavioural variant frontotemporal dementia (bvFTD) were included as supportive diagnostic features. Four patients met the PNFA criteria (Table 1).

Clinical Diagnosis of Primary Progressive Aphasia

The diagnosis and classification of PPA were made with a 2-step process on the basis of the recent international consensus criteria.[9] First, patients were diagnosed with PPA and then divided into clinical variants based on specific speech and language features. A PPA clinical diagnosis required the following 3 conditions: (1) the most prominent clinical feature was difficulty with language; (2) this deficit was the principal cause of impaired daily living activities; and (3) aphasia was the most prominent deficit at symptom onset and during the initial phases of the disease. Based on these criteria, behavioural disturbances could be early features in PPA, but should not be the main complaint or cause of functional impairment. Therefore, we excluded patients who had 3 or more of the following behavioural symptoms: (1) disinhibition, (2) apathy or inertia, (3) loss of sympathy or empathy, (4) perseverative or stereotyped behaviour, and (5) dietary changes at the initial assessment. Three of these 5 behavioural symptoms had to be present to meet the recent international consensus criteria for bvFTD.[19] Similarly, patients with a clear parkinsonian syndrome at the time of diagnosis were excluded from the PPA group. In the present study, 15 patients fulfilled these PPA criteria.

After a PPA diagnosis was established, these 15 subjects were classified into 3 semantic variants according to specific diagnostic criteria[9]: svPPA (n = 12), navPPA (n = 2), and lvPPA (n = 1). The clinical features of each diagnostic category are shown in Table 1.[6,9,13]

Neuropsychological Assessments

Language function of subjects who met the SD, PNFA, or PPA criteria was evaluated using the Japanese Standard

*Table 1. Demographic and clinical profiles of the 5 groups diagnosed based on specific criteria.**

Item	Neary et al's diagnostic criteria[6]		Gorno-Tempini et al's diagnostic criteria[9,13]		
	SD (n = 27)	PNFA (n = 4)	svPPA (n = 12)	navPPA (n = 2)	lvPPA (n = 1)
Age (years)	67.9 ± 7.4	73.8 ± 3.3	66.8 ± 7.0	76.5 ± 0.7	69
Sex					
Male	13	0	6	0	0
Female	14	4	6	2	1
Duration of language disturbance (years)	2.9 ± 3.1	1.8 ± 1.0	2.9 ± 3.2	2.0 ± 1.4	3
Duration of education (years)	11.1 ± 2.5	8.8 ± 0.5	11.2 ± 2.4	8.5 ± 0.7	8
MMSE score	18.2 ± 6.8	14.3 ± 10.7	17.9 ± 8.7	12.5 ± 17.7	10
CDR score					
0.5	16	4	9	2	0
1	11	0	3	0	1
2	0	0	0	0	0
3	0	0	0	0	0
Dominant side of atrophy					
Left	15	4	7	2	1
Right	12	0	5	0	0

* *Data are shown as mean ± standard deviation, unless otherwise specified.*

Abbreviations: *SD = semantic dementia; PNFA = progressive non-fluent aphasia; svPPA = semantic variant primary progressive aphasia; navPPA = non-fluent / agrammatic variant primary progressive aphasia; lvPPA = logopenic variant primary progressive aphasia; MMSE = Mini-Mental State Examination; and CDR = Clinical Dementia Rating scale.*

Language Test of Aphasia consisting of 26 subtests (listening, speaking, reading, writing, and calculating).[20] In addition, the naming and word-comprehension ability of subjects who fulfilled the SD or svPPA criteria were assessed by object naming from 80 line drawings of common everyday objects and 10 colours, as well as word-picture matching with spoken word targets and 10 line drawing choices; the target plus 9 within-category distracters used the same 90 items as in the naming test.[21]

Statistical Analysis

To examine differences between patients with SD and svPPA, we divided the SD patients into 2 groups. One group included patients who met the SD criteria but did not meet the svPPA criteria (SD+PPA-), and the other group met both the SD and svPPA criteria (SD+PPA+). Gender, age, duration of language disturbance, education, MMSE score, CDR score, dominant side of atrophy, and performance on the picture naming and matching tests in the SD patients who did and did not meet the svPPA criteria were compared. Student's t test and the χ^2 test were used as appropriate.

Results

The overlap between the SD and the svPPA groups is shown in Figure 2a. Among the 27 SD patients, 12 fall into the category of SD+PPA+ group, whereas the remaining 15 patients were under SD+PPA- group due to prominent

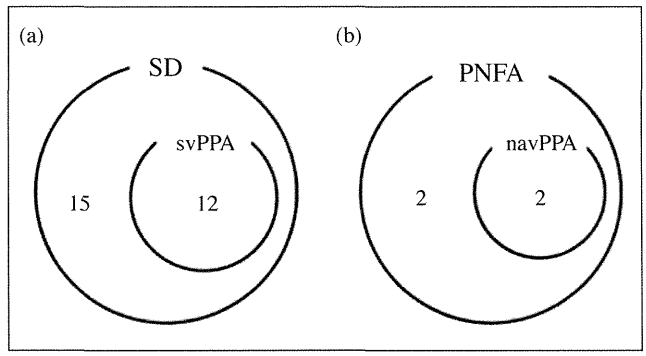

Figure 2. The conceptual diagrams of neurodegenerative dementia showing association between: (a) semantic dementia (SD) and semantic variant primary progressive aphasia (svPPA) groups; and (b) progressive non-fluent aphasia (PNFA) and non-fluent / agrammatic variant PPA (navPPA) groups.

behavioural disturbances. No SD patients had disturbed object identification if they had intact language function. The overlap between the PNFA and navPPA groups is shown in Figure 2b. Among these 4 PNFA patients, 2 met both the PNFA and navPPA criteria whereas the other 2 met only the former criteria due to clear parkinsonian syndrome. The neurological findings in the latter were thought to be

*Table 2. Demographic and clinical profiles of the SD+PPA- and SD+PPA+ groups.**

Item	SD+PPA- (n = 15)	SD+PPA+ (n = 12)	p Value
Age (years)	68.9 ± 7.8	66.8 ± 7.0	0.47
Sex			0.86
Male	7	6	
Female	8	6	
Duration of language disturbance (years)	3.0 ± 3.2	2.9 ± 3.2	0.92
Duration of education (years)	11.1 ± 2.7	11.2 ± 2.4	0.93
MMSE score	18.5 ± 5.2	17.9 ± 8.7	0.84
CDR score			0.15
0.5	7	9	
1	8	3	
2	0	0	
3	0	0	
Dominant side of atrophy			0.79
Left	8	7	
Right	7	5	
Picture naming score	38.4 ± 15.9	40.4 ± 22.9	0.81
Picture matching score	63.6 ± 12.3	67.1 ± 20.2	0.63
NPI score	17.5 ± 15.4	7.8 ± 9.8	0.07
SRI score	8.7 ± 7.5	4.0 ± 8.8	0.18

* *Data are shown as mean ± standard deviation, unless otherwise specified.*

Abbreviations: *SD+PPA- = semantic dementia except for primary progressive aphasia; SD+PPA+ = semantic dementia with primary progressive aphasia; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating scale; NPI = Neuropsychiatric Inventory; and SRI = Stereotypy Rating Inventory.*

better accounted for by corticobasal degeneration (CBD).

The demographic and clinical profiles in the SD+PPA- and the SD+PPA+ groups are shown in Table 2. There were trends for the SD+PPA- group to have higher NPI scores than the SD+PPA+ group (p = 0.07). There were no significant differences with respect to age, gender, duration of language disturbance, MMSE score, CDR score, dominant side of atrophy, performance on the naming and matching tests, and the SRI score between the groups.

Discussion

In this study, patients who presented with severe behavioural disturbances were not labelled as having PPA according to recent diagnostic criteria.[9] However, these criteria do not define the severity and features of the prominent behavioural disturbance. Therefore, we defined behavioural disturbance as prominent when patients had 3 or more of the following behavioural symptoms: (1) disinhibition, (2) apathy or inertia, (3) loss of sympathy or empathy, (4) perseverative or stereotyped behaviour, and (5) dietary changes. According to the recent criteria for bvFTD, we can diagnose patients with this disorder whenever they manifest 3 of the 5 behavioural symptoms.[19] For this reason, the present procedure was considered valid. Results of the present study also show the validity of the PPA criteria that classified those 15 patients into these 3 subgroups: svPPA group, navPPA group, or lvPPA group.

In this study, 15 of 27 patients with SD did not fulfil the svPPA criteria due to prominent behavioural disturbances. It is noteworthy that we found no significant differences in picture naming and matching performances between the SD+PPA- group and SD+PPA+ group. In addition, there were no significant differences between these 2 groups in terms of other clinical characteristics including dominant atrophy side. These results suggest that SD and svPPA may be identical conditions, regardless of their associations with different behavioural disturbance severities.

Two of the 4 PNFA patients fulfilled the navPPA criteria. The other 2 had parkinsonian syndrome and were diagnosed as having CBD. Recently, there have even been reports of non-fluent aphasia due to CBD or progressive supranuclear palsy (PSP).[22] Because it is important to arrive at an early diagnosis and disease-specific care for Parkinson's disease and related disorders such as CBD or PSP, the recent PPA criteria that exclude patients with parkinsonism[9] might well be suitable in clinical practice.

One limitation of this study was that data were based on patients from a dementia clinic, rather than from a

population-based cohort. Thus, it is possible that our results were affected by selection bias. In addition, there were only a small number of patients with PNFA and lvPPA, and behavioural disturbances in these patients were less evident than in patients with SD. However, we believe that the present results provide a good reflection of PPA patients that currently attend dementia clinics.

In this study, more than half of the SD patients were not considered to have PPA, despite presenting with a comparable language disorder. As it is reported that the background pathology of SD and svPPA is common,[9] there is crucial problem in the 2-step diagnostic process for PPA variants when considering disease-modified treatment in any future study. In addition, it is reported that there are many LPA cases with AD pathology. Therefore, it is possible to estimate background pathology by classifying subtypes of language disorder. The results of this study show that it is important to classify which type of language disorder prevails in neurodegenerative dementia, whether or not there is cognitive dysfunction and / or behavioural disorder.

It is impractical to regard PPA as an independent clinical entity because of the symptomathological and neuropathological variations that prevail in patients with this disorder. On the other hand, 3 subtypes of PPA seem to reflect the background pathology at least to some degree. Thus, it is more important to directly identify the subtype of language disorder than to emphasise presentations of isolated language deficits, whenever language disorder of neurodegenerative dementia is being considered.

Acknowledgements

This research was performed as a part of the scientific research conducted by the Ministry of Education, Culture, Sports, Science and Technology of Japan for M.I. (Grant No. 23591718). The authors gratefully acknowledge the assistance of the staff of Department of Neuropsychiatry, Kumamoto University Hospital.

References

1. Pick A. Ueber die Beziehungen der senilen Hirnatrophie zur Aphasie [in German]. Prager Medizinische Wochenschrift 1892;17:165-7.
2. Warrington EK. The selective impairment of semantic memory. Q J Exp Psychol 1975;27:635-57.
3. Snowden JS, Goulding PJ, Neary D. Semantic dementia: a form of circumscribed cerebral atrophy. Behav Neurol 1989;2:167-82.
4. Hodges JR, Patterson K, Oxbury S, Funnell E. Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. Brain 1992;115:1783-806.
5. Grossman M, Mickanin J, Onishi K, Hughes E, D'Esposito M, Ding XS, et al. Progressive nonfluent aphasia: language, cognitive and PET measures contrasted with probable Alzheimer's disease. J Cogn Neurosci 1996;8:135-54.
6. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998;51:1546-54.
7. Mesulam MM. Slowly progressive aphasia without generalized dementia. Ann Neurol 1982;11:592-8.
8. Mesulam MM, Weintraub S. Spectrum of primary progressive aphasia. Baillieres Clin Neurol 1992;1:583-609.
9. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology 2011;76:1006-14.
10. Grossman M, Ash S. Primary progressive aphasia: a review. Neurocase 2004;10:3-18.
11. Mesulam MM. Primary progressive aphasia. Ann Neurol 2001;49:425-32.
12. Mesulam MM. Primary progressive aphasia — a language-based dementia. N Engl J Med 2003;349:1535-42.
13. Gorno-Tempini ML, Dronkers NF, Rankin KP, Ogar JM, Phengrasamy L, Rosen HJ, et al. Cognition and anatomy in three variants of primary progressive aphasia. Ann Neurol 2004;55:335-46.
14. Mesulam M, Wicklund A, Johnson N, Rogalski E, Léger GC, Rademaker A, et al. Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. Ann Neurol 2008;63:709-19.
15. 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.
16. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566-72.
17. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308-14.
18. Shigenobu K, Ikeda M, Fukuhara R, Maki N, Hokoishi K, Nebu A, et al. The Stereotypy Rating Inventory for frontotemporal lobar degeneration. Psychiatry Res 2002;110:175-87.
19. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011;134:2456-77.
20. SLTA Committee. Standard Language Test of Aphasia Manual. Tokyo, Shinkou Igaku Shuppan-sha; 1997.
21. Ito K, Nakagawa Y, Ikeda M, Yamada N, Hashimoto M, Tanabe H. Category-specific word meaning impairment in Gogi aphasics [in Japanese]. Higher Brain Function Res 1994;14:221-9.
22. Deramecourt V, Lebert F, Debachy B, Mackowiak-Cordoliani MA, Bombois S, Kerdraon O, et al. Prediction of pathology in primary progressive language and speech disorders. Neurology 2010;74:42-9.

Psychiatry and Clinical Neurosciences 2013; **67**: 148–153 doi:10.1111/pcn.12034

Regular Article

Comparison of the utility of everyday memory test and the Alzheimer's Disease Assessment Scale-Cognitive part for evaluation of mild cognitive impairment and very mild Alzheimer's disease

Hiroyoshi Adachi, MD, PhD,[1,2] Shunichiro Shinagawa, MD, PhD,[2,3] Kenjiro Komori, MA,[2] Yasutaka Toyota, MD, PhD,[2] Takaaki Mori, MD, PhD,[2] Teruhisa Matsumoto, MD, PhD,[2] Naomi Sonobe, MD, PhD,[2] Tetsuo Kashibayashi, MD, PhD,[2,4] Tomohisa Ishikawa, MD, PhD,[2,5] Ryuji Fukuhara, MD, PhD[2,5] and Manabu Ikeda, MD, PhD[2,5]*

[1]*Department of Psychiatry, Osaka University Health Care Center, Osaka,* [2]*Department of Neuropsychiatry and Neuroscience, Ehime University Graduate School of Medicine, Ehime,* [3]*Department of Psychiatry, Jikei University School of Medicine, Tokyo,* [4]*Department of Rehabilitation, Rehabilitation Nishi-Harima Hospital, Hyogo and* [5]*Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan*

Aim: The purpose of this study was to compare the utility of the Rivermead Behavioural Memory Test (RBMT) and the Alzheimer's Disease Assessment Scale-Cognitive part (ADAS-Cog) for the evaluation of mild cognitive impairment (MCI) or very mild Alzheimer's disease (AD).

Methods: The discriminative abilities of RBMT and ADAS-Cog were compared in the very early stage of AD or MCI patients. Furthermore, we evaluated the difference in both RBMT score and ADAS-Cog score between different severities.

Results: Evident superiority in the false negative rate was observed in RBMT over ADAS-Cog in MCI or very mild AD. In addition, 86.7% of the subjects overlooked by ADAS-Cog were correctly detected by RBMT profile score. However, the RBMT score falls in the very early stages and the range of the RBMT score is rather narrow. As a result, it is difficult to evaluate status and follow the progression in severer cases. In contrast to RBMT, the ADAS-Cog score has a wide range and can evaluate and follow the severity in more severe cases.

Conclusion: RBMT is more useful than ADAS-Cog in evaluating patients with MCI or very mild AD.

Key words: Alzheimer's disease, Alzheimer's Disease Assessment Scale-Cognitive part, everyday memory, mild cognitive impairment, Rivermead Behavioural Memory Test.

MILD COGNITIVE IMPAIRMENT (MCI) is a concept that was introduced by Flicker *et al.*[1] and the Mayo Clinic group[2] to fill the gap between cognitive changes associated with normal aging and those associated with dementia. With increasing attention being paid to MCI, several studies have been conducted in recent years in a variety of research settings. A substantial proportion of patients with MCI develop clinically diagnosable Alzheimer's disease (AD) at a later date.[2] Considering the urgent demands for preventing dementia, detecting MCI in clinical research settings or community-based epidemiological study is very important. There is a need

Correspondence: Manabu Ikeda, MD, PhD, Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan. Email: mikeda@kumamoto-u.ac.jp
Received 13 December 2011; revised 23 April 2012; accepted 28 April 2012.

for sensitive but user-friendly cognitive tests for clinicians.[3]

At present, no consensus exists as to which neuropsychological tests are appropriate for the diagnosis of MCI specifically.[4,5] Everyday memory is a fundamental aspect of cognition that is necessary for people to function effectively in their daily lives. Theoretical accounts of cognitive processes involved in prospective memory, which is included in everyday memory, imply that performance on such tasks is more vulnerable than on retrospective memory tests in the early stage of dementia.[6] Furthermore, Kazui *et al.* reported that everyday memory was impaired in MCI patients.[7] The Rivermead Behavioural Memory Test (RBMT)[8,9] is an instrument for this type of evaluation and was designed to fill the gap between memory impairment observed by the informant and various laboratory assessments of memory. Thus, the implication is that the RBMT assesses specific memory processes tapped by conventional laboratory memory tests. On the other hand, the Alzheimer's Disease Assessment Scale-Cognitive part (ADAS-Cog),[10,11] a well-established evaluating tool, is often employed for assessing the efficacy of drugs in AD treatment. The ADAS-Cog is capable of assessing a wide range of cognitive functions, such as memory, language, ideational praxis, and visuospatial ability. Thus, the ADAS-Cog can evaluate demented patients efficiently. However, in some instances, the appropriate application of ADAS-Cog in evaluating the effect of medication for MCI or very mild AD patients is questionable.

We performed the RBMT and ADAS-Cog on patients with MCI or very mild AD (all cases are Clinical Dementia Rating [CDR] = 0.5) and mild AD patients (all cases are CDR = 1). The purpose of this study was to examine the distribution of the scores from both psychometries in different severities of dementia and to evaluate the screening ability of both tests in MCI or very mild AD. The diagnostic criteria of MCI are controversial, and some reports show that MCI represents early-stage AD.[12] Therefore, in this study, the cases with CDR = 0.5, which was assumed to include both MCI and very mild AD, were selected as the subjects.

METHODS

Subjects

Subjects were consecutive outpatients with a diagnosis of very mild AD or MCI who were referred for evaluation to the Higher Brain Function Clinic for outpatients of the university hospital of Ehime University School of Medicine as a retrospective study. Of 680 demented cases, there were 22 patients with very mild AD or MCI. In addition, 34 AD patients with a severity of CDR 1 were also assessed. From a viewpoint of protecting personal information, we performed the anonymization in an unlinkable fashion. The protocol for this study has been approved by the University of Ehime hospital ethics committee.

General assessment for dementia

Subjects underwent physical and neurological examinations, and a comprehensive neuropsychological test battery. Neuropsychological tests were composed of the Mini-Mental State Examination (MMSE) for evaluation of overall cognitive functions,[13] Short-Memory Questionnaire (SMQ) for objective memory impairment[14] (which was evaluated by caregivers), CDR for dementia severity,[15] RBMT, and ADAS-Cog. In addition, the Instrumental Activities of Daily Living (IADL)[16] scale was administered for evaluation of activities of daily living (ADL). Subjects with significant depression, delusions, or hallucination scores on the Neuropsychiatric Inventory (NPI)[17] were excluded. Cranial magnetic resonance imaging (MRI) was examined for the purpose of exclusion of vascular or other organic lesions. Some of the subjects were examined with a blood test and/or a brain single photon emission computed tomography (SPECT) when necessary.

Definition of MCI or very mild AD

In the present study, a diagnosis of MCI or very mild AD was made according to the following criteria: (i) a memory complaint documented by the patient or collateral source (SMQ ≦ 40); (ii) preservation of overall cognitive functions at near normal levels when tested by MMSE (≧24); (iii) a total CDR score of 0.5; and (iv) intact functioning in ADL measured by the IADL (male: ≧4, female: ≧6), except for items that could be affected by amnesia. Very mild AD was designated to patients who fulfilled the above criteria and satisfied the NINCDS/ADRDA diagnostic criteria[18] for probable AD. A diagnosis of MCI was made when patients fulfilled the above criteria and showed no symptoms of dementia based on a clinical examination and an extensive interview with a knowledgeable informant. In addition, the

criteria of MCI included at least one index of verbal, visual, general memory and delayed recall of the Wechsler Memory Scale-Revised (WMS-R)[19] that was < 77.5, which is 1.5 SD below the age-adjusted normal value according to the manual of the Japanese version of WMS-R.[19,20] Thus, we applied Petersen's criteria for MCI.[2] On the other hand, the mild AD group was defined as patients who satisfied the NINCDS/ADRDA diagnostic criteria for probable AD and CDR 1.

Statistical analysis

The discriminative abilities of RBMT and ADAS-Cog were calculated as the number of disturbed individuals correctly identified by each assessment divided by the number of all subjects. Based on previous studies,[9] impaired functioning was indicated when the profile score of RBMT was ≦15 (age ≧ 60) and ≦16 (age 40–59) or the screening score of RBMT was ≦ 5 (age ≧ 60) and ≦6 (age 40–59). As the false negative rate is a main outcome in the present study, the ADAS-Cog score was considered at an impaired level when it was ≧ 9.8 (which was the score that made the false negative rate minimum). The standardized cut-off score of dementia patients and normal subjects is not set in ADAS-Cog. Homma *et al.* reported that the mean ± SD score of ADAS-Cog in a mild group of dementia patients was 15.5 ± 5.7 in a validation study of a Japanese version of ADAS.[11] Based on this report, the mean − SD (i.e. 15.5–5.7), that is 9.8, was employed as the cut-off score of ADAS-Cog in this study. The demographic and psychometric characteristics were compared between the CDR 0.5 group and the CDR 1 group using the Student's *t*-test. The χ^2-test was used to compare for the categorical variable (sex). Results were considered statistically significant at *P*-values less than 0.05 (two-tailed).

RESULTS

Demographic and psychometric characteristics of the patients are presented in the Table 1. MCI or very mild AD patients included 11 female and 11 male patients (mean age [±SD] 72.9 ± 9.1 years; mean MMSE [±SD] 26.7 ± 1.8). AD patients with severity of CDR 1 included 26 female and eight male patients (mean [±SD] age 74.6 ± 8.5 years; mean [±SD] MMSE 22.8 ± 3.5). There were significant differences between patients with CDR 0.5 and those with CDR 1 in MMSE, SMQ, and ADAS-Cog. However, there was no significant difference between the RBMT profile score and the RBMT screening score. In particular, the average score of the RBMT profile score in patients with CDR 0.5 was prominently below the cut-off point.

With respect to the discrimination in MCI or very mild AD with CDR 0.5, the profile score of RBMT correctly classified 90.9% of subjects, and the screening score of RBMT correctly classified 81.8%. In comparison, only 31.8% of the subjects were correctly classified by ADAS-Cog. In addition, 86.7% of the subjects overlooked by ADAS-Cog were correctly detected by RBMT profile score. On the contrary, none of the subjects that failed to be noticed by either the RBMT profile or screening score was identified by ADAS-Cog (Fig. 1). In the cases with CDR 1, the

Table 1. Demographic and psychometric characteristics of subjects

Characteristic	CDR 0.5 ($n = 22$)	CDR 1 ($n = 34$)	*P*-value
Age, years	72.9 ± 9.1	74.6 ± 8.5	0.47
Education, years	10.6 ± 2.1	10.2 ± 2.2	0.5
Sex, female : male	11:11	26:8	0.04*
MMSE score	26.7 ± 1.8	22.8 ± 3.5	<0.0001*
SMQ score	29.6 ± 8.5	23.5 ± 6.6	0.004*
ADAS-Cog score	8.7 ± 2.8	11.7 ± 3.7	0.002*
RBMT profile score	9.7 ± 5.2	7.8 ± 4.2	0.13
RBMT screening score	3.5 ± 2.5	2.5 ± 2.0	0.08

Values are mean ± SD unless otherwise indicated; *$P < 0.05$.
ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive part; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; RBMT, Rivermead Behavioural Memory Test; SMQ, Short-Memory Questionnaire.