

Fig. 3. Mean changes in NPI scores. * $p < 0.05$ vs. baseline (paired t test). Vertical bars indicate standard deviations. **a** Overall mean change during the treatment period ($n = 104$). **b** Mean change in the placebo group in the preceding RCT ($n = 28$). **c** Mean cumulative changes by treatment group in the preceding RCT throughout both the preceding RCT and this extension study (no statistical test was performed).

Changes in NPI scores during the treatment period are shown in figure 3a. The mean (SD) changes at 52 weeks and at the final evaluation (LOCF) from baseline were -1.9 ± 9.8 and -0.7 ± 11.1 , respectively. A significant improvement in the scores compared to baseline was observed at 8–40 weeks, and the largest change was observed at 16 weeks (-3.6 ± 9.9). In the PLA-DON group, significant improvement was demonstrated at 8, 16, and 40 weeks, and at the final evaluation point (LOCF; fig. 3b). The mean changes at 52 weeks and at the final evaluation point (LOCF) were -4.1 ± 10.1 and -4.3 ± 9.7 , respectively. During the entire treatment period, combining both the preceding study and this extension study, improvement was maintained in all the DON-DON groups, even though there was up to an 8-week washout period (fig. 3c).

The changes in CFI scores during the treatment period are shown in figure 4a. Significant improvement compared to baseline was observed at 24 and 32 weeks, and this improvement was maintained throughout the treatment period. In the PLA-DON group, significant improvement was demonstrated at 8 and 16 weeks (fig. 4b). The mean (SD) changes at 52 weeks and at the final evaluation point (LOCF) were -1.0 ± 2.7 and -1.0 ± 2.6 , respectively, and the largest change was observed at 8 weeks (-1.4 ± 1.8). If the results are analyzed by defining week 0 of the preceding RCT as baseline, CFI scores in all the DON-DON

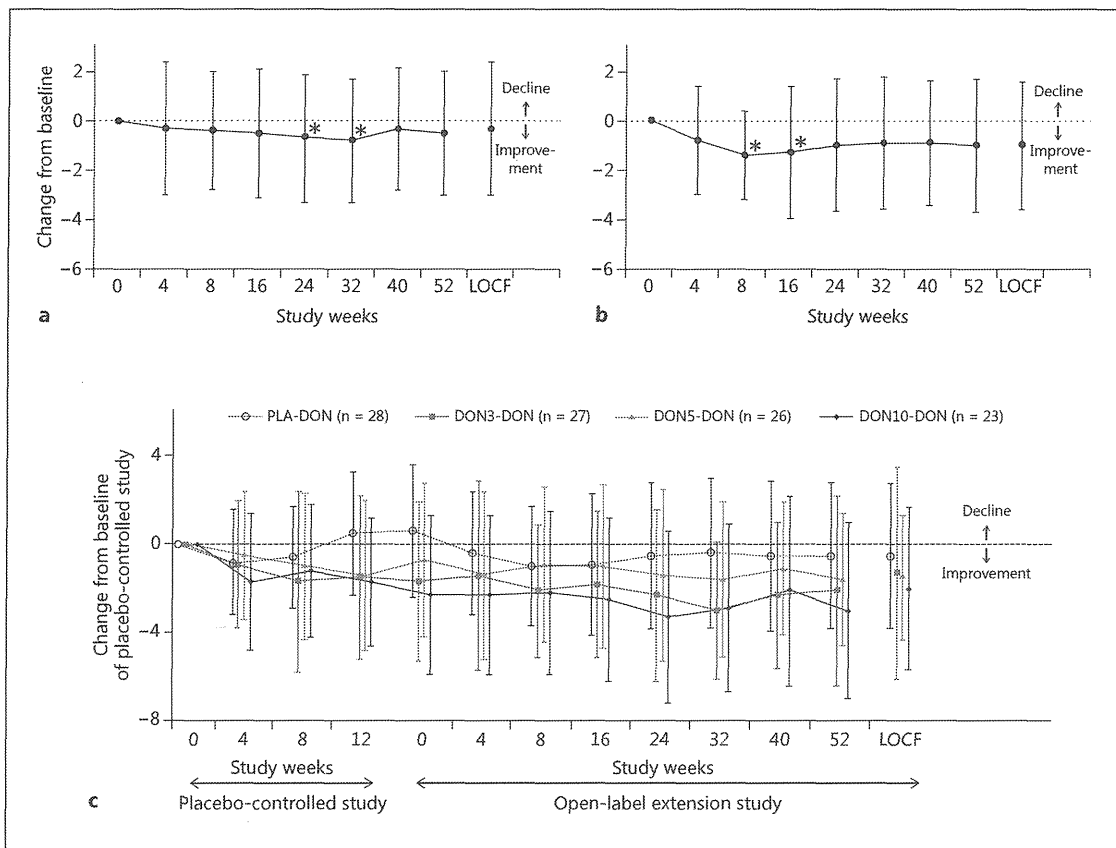


Fig. 4. Mean changes in CFI scores. * $p < 0.05$ vs. baseline (paired t test). Vertical bars indicate standard deviations. **a** Overall mean change during the treatment period ($n = 104$). **b** Mean change in the placebo group in the preceding RCT ($n = 28$). **c** Mean cumulative changes by treatment group in the preceding RCT throughout both the preceding RCT and this extension study (no statistical test was performed).

groups improved throughout the RCT and the subsequent 52-week extension study (fig. 4c).

With regard to caregiver burden, a significant deterioration was demonstrated at 52 weeks and at the final evaluation point (LOCF) compared to baseline (fig. 5a). In the PLA-DON group, however, improvements in scores were observed during the treatment period, although they were not statistically significant (fig. 5b). In the DON-DON groups, ZBI scores were likely to be improved during the preceding RCT; however, this degree of improvement disappeared during the extension period (fig. 5c).

Safety

The incidence of AEs in the safety analysis set was 94.4% (102/108). Incidence rates of AEs did not differ among the four groups stratified according to the preceding RCT (89.7% in PLA-DON, 96.4% in DON3-DON, 92.6% in DON5-DON, and 100.0% in DON10-DON). Twenty-seven serious AEs were reported in 25 patients. Serious AEs observed in more than 1 patient included compression fractures ($n = 3$), pneumonia ($n = 3$), and dehydration ($n = 2$). Four events (myocardial infarction, subarachnoid hemorrhage, asphyxia, and acute pancreatitis) resulted in the deaths of 3 patients. Myocardial infarction and acute pancreatitis were deter-

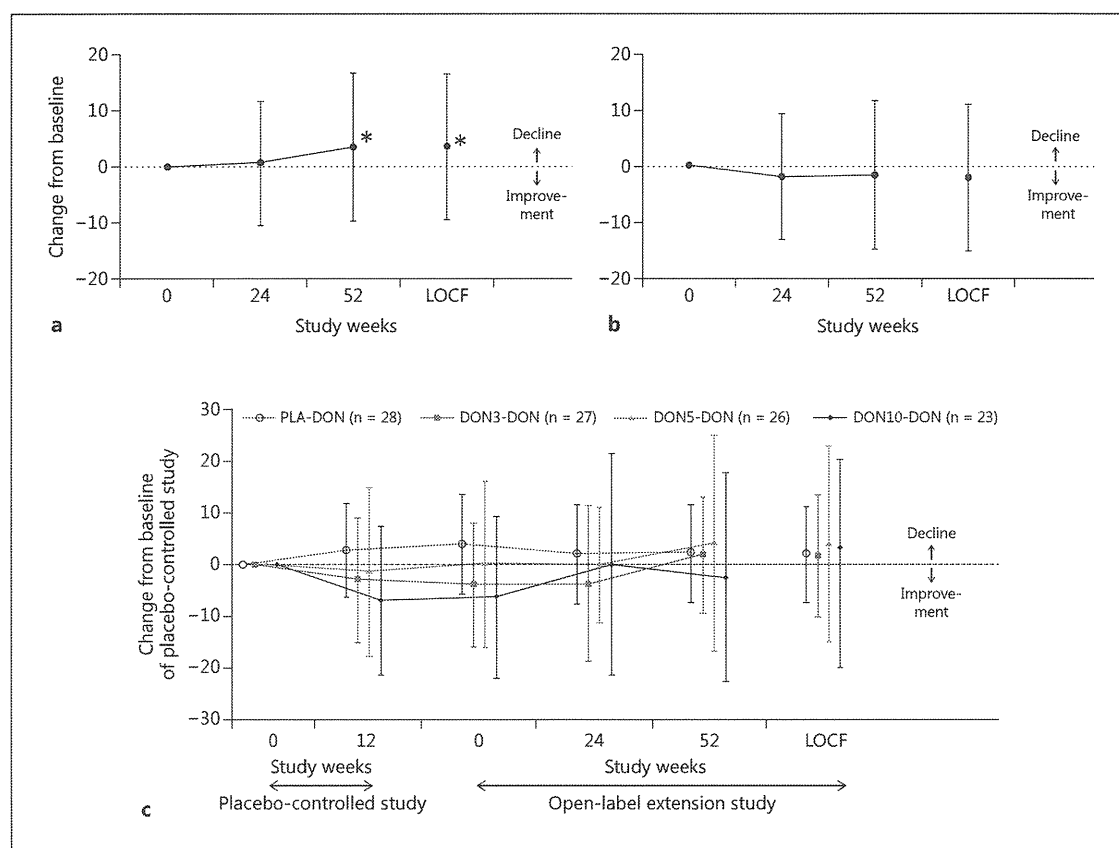


Fig. 5. Mean changes in ZBI scores. * $p < 0.05$ vs. baseline (paired t test). Vertical bars indicate standard deviations. **a** Overall mean change during the treatment period ($n = 103$). **b** Mean change in the placebo group in the preceding RCT ($n = 28$). **c** Mean cumulative changes by treatment group in the preceding RCT throughout both the preceding RCT and this extension study (no statistical test was performed).

mined to be the results of adverse drug reactions. Major frequently observed AEs are shown in table 3. They included increased blood creatine phosphokinase and contusion (12 patients each, 11.1%), followed by nasopharyngitis, blood pressure increase, fall (11 patients each, 10.2%), and diarrhea (10 patients, 9.3%).

AEs associated with parkinsonism were reported in 12.0% ($n = 13$) of the patients throughout the study period. Most of them (12/13) were mild to moderate in severity. No notable increase in these AEs was observed according to the treatment period. A modest and insignificant rise in the mean UPDRS score (range: 0.5–1.1) was noted at 24 and 52 weeks, and at the final evaluation point (LOCF).

The incidence of abnormal changes in pulse rate and abnormal electrocardiograms was 1.9 (2 patients) and 7.5% (8 patients), respectively. The mean pulse rate decreased modestly at every evaluation point compared to baseline (range: -0.3 to -1.8). AEs related to them included prolonged QT (2 patients), supraventricular extrasystoles (2 patients), first-degree atrioventricular block (1 patient), bradycardia (1 patient), sinus bradycardia (1 patient), and ventricular extrasystoles (1 patient) on electrocardiogram. None of these events was serious or clinically significant (e.g., leading to discontinuation or dose reduction).

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.

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Prevalence of delirium among outpatients with dementia

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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

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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

DIAGNOSIS	PATIENTS (n = 206)		PATIENTS WITH DELIRIUM (n = 40)		DELIRIUM IN EACH DEMENTIA TYPE
	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; FTLT: 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 FTLT 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 FTLT 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 FTL. 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 \times 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**	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; **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 lability, 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 (MacLulich *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.

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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

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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年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

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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 Pick¹ 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, Warrington² 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 al³ 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 al⁶ 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

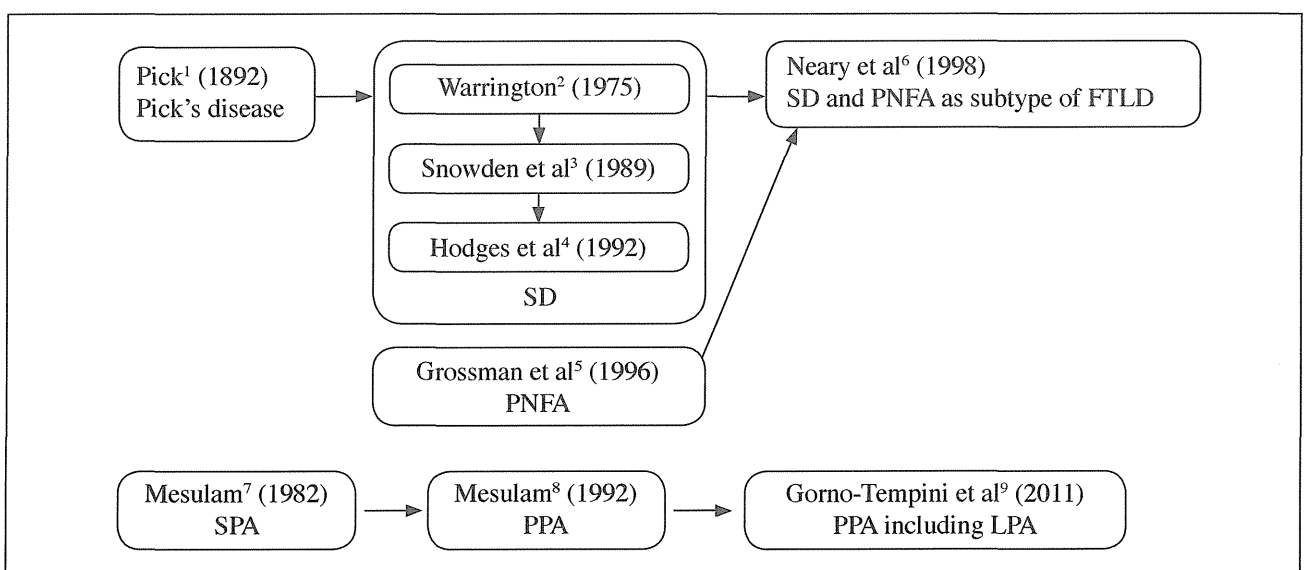


Figure 1. The concepts of classification of progressive aphasia.

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 FTLTLD.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 criteria⁹: 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

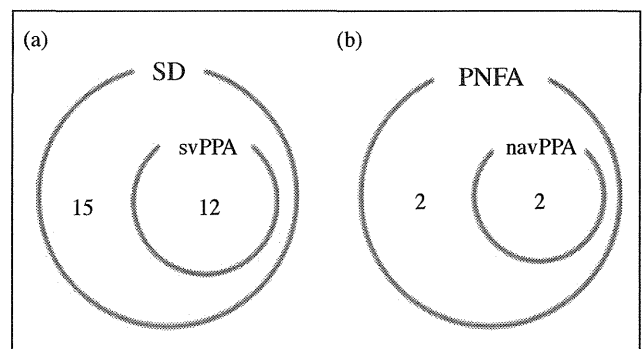


Figure 2. The conceptual diagrams of neurodegenerative dementia showing association between: (a) semantic dementia (SD) and semantic variant primary progressive aphasia (svPPA) groups; and (b) progressive non-fluent aphasia (PNFA) and non-fluent / agrammatic variant PPA (navPPA) groups.

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 parkinsonism⁹ 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.

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