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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

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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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ORIGINAL ARTICLE

Efficacy of increasing donepezil in mild to moderate Alzheimer's disease patients who show a diminished response to 5 mg donepezil: a preliminary study

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Abstract

Background: With the recent approval of several new drugs, pharmacological management of Alzheimer's disease has become more complicated in Japan. The efficacy and safety of increasing the dose of donepezil to 10 mg daily were assessed in an open-label study of patients with mild to moderate Alzheimer's disease who were showing a diminished response to 5 mg daily.

Methods: The subjects included 27 patients with mild to moderate probable Alzheimer's disease whose primary caregivers had confirmed progression of symptoms during treatment with donepezil 5 mg daily. The dose of donepezil was increased to 10 mg daily, and the Alzheimer's disease assessment scale-cognitive subscale (Japanese version), Neuropsychiatric Inventory, and Zarit caregiver burden interview scores were compared before and after dose escalation. Adverse events were also investigated.

Results: Efficacy was evaluated in 24 patients; three dropped out because of adverse reactions. The Alzheimer's disease assessment scale score showed significant improvement after dose escalation of donepezil (P = 0.006). The total score of the Neuropsychiatric Inventory and the Zarit score showed no significant changes. However, the anxiety score of the Neuropsychiatric Inventory showed a significant increase (P = 0.028). Safety assessment revealed that the dropout rate was 11.1% and adverse reactions occurred in 40.7%. Nausea (29.6%) and loss of appetite (22.2%) were common adverse reactions.

Conclusions: Because cognitive function showed improvement after increasing the dose of donepezil, the dosage of this drug should probably be adjusted based on the overall severity of Alzheimer's disease as well as the progression of cognitive dysfunction.

Key words: *Alzheimer's disease, behavioural and psychological symptoms of dementia, cognitive function, donepezil, dose escalation.*

INTRODUCTION

Donepezil is used to delay the progression of cognitive dysfunction in Alzheimer's disease (AD). In Japan, this drug was first marketed in 1999 with the indication of 'mild to moderate' AD, because the number of acetylcholinergic cells was thought to be decreased in severe AD, which results in a weaker response to donepezil. Subsequently, a clinical study of donepezil was performed in patients with severe AD using higher doses, and satisfactory results were obtained with regard to both cognitive function and general symptoms.[1] As a result, treatment with donepezil 10 mg daily was approved for severe AD in August 2007. In 2011, three new anti-dementia drugs (galantamine, rivastigmine and memantine) became available in Japan. This increased range of choices for anti-dementia therapy has enabled clinicians to treat patients who could not tolerate donepezil because of

adverse reactions. However, it has also made the treatment of AD more complicated, and clinicians are now required to select the most appropriate drug for each patient. When a treatment for AD is selected, it is not only important to choose an appropriate drug type for each patient and disease stage, but also to adjust the dosage based on the progression of symptoms.

It has often been found that symptoms can be controlled for some time by donepezil 5 mg daily in patients with mild to moderate AD, but symptoms eventually begin to progress again. In such clinical situations, co-administration of memantine may be one choice for patients with moderate AD. However, because symptom progression was initially inhibited by donepezil, it could be that the dose may be too low and should be increased to 10 mg daily. In the present study, the daily dose of donepezil was increased from 5 mg to 10 mg, and its efficacy and safety were evaluated in patients with mild to moderate AD who had shown a decreased response to donepezil at 5 mg.

METHODS

Subjects

All procedures of this study strictly followed the Clinical Study Guidelines of the Ethics Committee of Kumamoto University Hospital (Kumamoto, Japan) and were approved by the committee. After patients or their caregivers were provided with a complete description of all procedures of this study, including the fact that administration of donepezil 10 mg daily for mild to moderate AD involved off-label use of the drug, written informed consent was obtained.

The subjects were selected from patients who presented to the dementia outpatient clinics of the Department of Neuropsychiatry at Kumamoto University Hospital and two outpatient clinics of the Kumamoto Prefectural Dementia-Related Disease Medical Center between April 2008 and March 2011. Patients were required to meet all of the following inclusion criteria:

- patients who met the diagnostic criteria of the National Institute of Neurological and Communicative Disease and Stroke and Alzheimer's Disease and Related Disorders Association for probable AD[2]
- patients with mild to moderate AD, which was defined by a Mini-Mental State Examination score ≥10 and a Clinical Dementia Rating ≤2[3,4]
- patients who had been taking donepezil 5 mg daily for at least 3 months
- patients who had had symptom progression confirmed by family members (caregivers) living with them
- patients whose primary caregiver lived with them and could bring them to hospital throughout the study period.

Because the study involved off-label use of donepezil, patients were excluded if the attending physician considered them unsuitable for treatment with a large dose of the drug. This meant excluding patients over 80 years old, patients with serious complications (bradycardia, asthma, gastric ulcer and hepatic dysfunction), and patients whose mental symptoms were expected to worsen after dose escalation.

A total of 27 patients (6 men, 21 women) who met the above inclusion criteria were enrolled in this study. Their mean age was 66.6 ± 7.6 years, mean duration of education was 10.8 ± 2.4 years, and mean duration of AD was 3.0 ± 1.1 years. The mean Mini-Mental State Examination score was 18.6 ± 3.3 points. The Clinical Dementia Rating was 0.5, 1 and 2 in 7 patients, 19 patients, and 1 patient, respectively. The mean treatment period with donepezil 5 mg daily was 13.9 ± 8.3 months. The mean age of their caregivers was 63.1 ± 11.7 years. Most caregivers were spouses (n = 21), followed by children (n = 3), daughters-in-law (n = 2) and parents (n = 1).

Dose escalation protocol

In this open-label study, the dose of donepezil was increased from 5 mg to 10 mg daily after consent was obtained. Donepezil was administered orally once daily after breakfast under the supervision of the patient's caregiver. Information about compliance was obtained from the caregiver by interview. If patients discontinued treatment for at least 1 week for any reason, they were classified as dropouts and excluded from the efficacy evaluation.

Evaluation of efficacy

For evaluation of efficacy, cognitive function was assessed by the Alzheimer's Disease Assessment Scale-cognitive subscale (Japanese version) (ADAS-J cog),[5,6] behavioural and psychological symptoms of dementia (BPSD) were investigated by the Neuropsychiatric Inventory (Japanese version) (NPI),[7,8] and the burden on the caregivers was determined by the

Zarit Caregiver Burden Interview (Japanese version) (ZBI).[9,10] These assessments were performed within 4 weeks before the dose of donepezil was increased and 8 weeks after dose escalation, and the results were compared. In addition, impressions about the patients after dose escalation were obtained from the caregivers by interview.

Evaluation of safety

Information about adverse events that occurred during the study period was obtained by interviewing patients and their primary caregivers at 8 weeks after dose escalation or at the time of dropout from the study. In addition, a 12-lead electrocardiogram was recorded within 4 weeks before and at 8 weeks after dose escalation.

Statistical analysis

The paired *t*-test was used to compare the ADAS-J cog score, NPI total score and ZBI score before and after increasing the dose of donepezil. Wilcoxon signed rank test was used to compare the scores for NPI subscales. The number of patients with each adverse event (including electrocardiogram findings) was determined, and percentages were also calculated. A significance level of 0.05 (two-tailed) was set for all analyses, which were carried out using SPSS for Windows, version 17.0 (SPSS, Chicago, IL, USA).

RESULTS

Evaluation of efficacy

Efficacy was evaluated in 24 patients (6 men, 18 women; mean age: 64.9 years; mean Mini-Mental State Examination score: 17.8), after excluding the three who dropouts as a result of adverse events. The mean ADAS-J cog total score was 17.1 ± 7.5 before dose escalation of donepezil. It improved to 15.3 ± 6.9 after dose escalation, a significant difference (P = 0.006) (Table 1). The NPI total score showed no significant change after dose escalation, but the score for anxiety became significantly worse among the NPI subscales (P = 0.028). However, scores for other NPI subscales showed no significant change after dose escalation (Table 2). The mean ZBI score was 16.1 ± 11.6 before dose escalation and 17.6 ± 13.3 points after escalation, showing no significant difference (P = 0.224). Caregivers evaluated the response to the increased dose of donepezil in a positive manner, as follows: 'the patient has become slightly more cheerful', 'the patient has become more positive', 'the patient wants to increase the frequency of day service' and 'the patient feels that progression of symptoms has stopped'.

Table 1 ADAS-J cog scores before and after dose escalation of donepezil

	Before	After	*P*-value
Word recall	6.4 ± 1.4	6.0 ± 1.7	0.177
Word recognition	3.4 ± 2.6	2.9 ± 2.3	0.352
Orientation	3.4 ± 2.0	3.0 ± 1.9	0.233
Recall of test instructions	0.4 ± 1.1	0.3 ± 0.8	0.083
Following commands	0.9 ± 0.9	0.7 ± 0.7	0.203
Naming objects/fingers	0.2 ± 0.5	0.2 ± 0.6	0.328
Word finding difficulty	0.2 ± 0.4	0.2 ± 0.5	1.000
Spoken language ability	0.0 ± 0.2	0.0 ± 0.0	0.328
Comprehension	0.1 ± 0.4	0.1 ± 0.6	0.328
Construction	0.9 ± 0.8	0.7 ± 0.6	0.213
Praxis	1.3 ± 1.6	1.2 ± 1.5	0.610
Total ADAS-J cog	17.1 ± 7.5	15.3 ± 6.9	0.006

Data are shown as the mean ± SD. ADAS-J cog, Alzheimer's Disease Assessment Scale-cognitive subscale (Japanese version).

Table 2 NPI scores before and after dose escalation of donepezil

	Before	After	*P*-value
Delusions	0.5 ± 1.2	0.1 ± 0.3	0.102
Hallucinations	0.0 ± 0.0	0.0 ± 0.0	1.000
Agitation	1.0 ± 1.6	1.0 ± 2.1	0.823
Depression	0.8 ± 1.3	1.3 ± 2.3	0.301
Anxiety	0.4 ± 1.1	1.4 ± 2.6	0.028
Euphoria	0.0 ± 0.0	0.0 ± 0.0	1.000
Apathy	3.2 ± 3.9	3.0 ± 3.5	0.943
Disinhibition	0.0 ± 0.2	0.2 ± 0.8	0.414
Irritability	0.4 ± 0.8	0.9 ± 2.3	0.676
Aberrant motor behaviour	0.9 ± 2.3	0.6 ± 1.6	0.500
Total NPI score	7.1 ± 7.1	8.3 ± 9.5	0.483

Data are shown as the mean ± SD. NPI, Neuropsychiatric Inventory.

Evaluation of safety

Of the 27 patients, three were classified as dropouts and the discontinuation rate was 11.1%. In two dropouts (women aged 57 and 79 years), the dose of donepezil was reduced to 5 mg daily because of the onset of nausea and loss of appetite within 1 week after dose escalation. In the other patient (a woman aged 76 years), loss of appetite occurred after dose escalation. Subsequently, she suffered a compression fracture of the lumbar spine and developed depression. At the request of her family, the dose of donepezil was reduced to 5 mg daily after 5 weeks of

treatment at 10 mg. In all three dropouts, gastrointestinal symptoms resolved rapidly after dose reduction.

The following adverse events were noted in 11 (40.7%) of the 27 patients (including the dropouts): nausea occurred in eight patients (29.6%), loss of appetite in six patients (22.2%), pollakiuria in three patients (11.1%), excitement in two patients (7.4%), and diarrhoea in one patient (3.7%). In one patient (3.7%), the electrocardiogram revealed supraventricular extrasystoles after dose escalation.

DISCUSSION

In this study, the ADAS-J cog score showed significant improvement after the daily dose of donepezil was increased from 5 mg to 10 mg. It has already been confirmed that the efficacy of this drug is dose-dependent. In earlier studies of the correlation between the dose and efficacy of donepezil, the ADAS score showed significant improvement in the 10 mg group compared with the 5 mg group.[11–13] Unlike these studies, the dose-response effect of donepezil in the present study was investigated in a group of patients who had shown progression of symptoms. Their symptoms had been stable for some time on donepezil 5 mg daily, but began to worsen again over time. Therefore, this study was focused on countermeasures for a common problem in clinical practice. Our results suggest that increasing the dose of donepezil to 10 mg daily is reasonable in patients with mild to moderate disease who have become less responsive to the drug at 5 mg daily.

Although cognitive function improved after dose escalation, the NPI total score showed no improvement and the anxiety score became worse. There have been some reports about the efficacy of donepezil for BPSD in patients with mild to moderate AD.[14,15] For example, in an earlier study, improvement of BPSD (including anxiety) was noted.[14] Also, Hori *et al.* reported that administration of donepezil to AD patients could improve cognitive function and lead to a better understanding of their problems, but this resulted in an increase in anxiety, a phenomenon known as 'awakening'.[16] The aggravation of anxiety observed in the present study might have been ascribable to this phenomenon. Attention is often focused on apathy when evaluating the efficacy of donepezil for BPSD. Apathy is considered to be related to a decrease of acetylcholine.[17] It has been reported that cholinesterase inhibitors are effective for apathy and that donepezil 10 mg daily was effective for apathy in AD patients.[18–21] In the present study, improvement of apathy was not seen among the NPI subscales. However, some caregivers noted improvement in apathy in their patients. For example, they stated that the 'patient became more cheerful', 'the patient became more positive' or 'the patient wanted to increase the frequency of day service'. Accordingly, further studies are needed concerning the influence of a higher dose of donepezil on apathy. In this study, the NPI data suggested that increasing the dose of donepezil to 10 mg should not be performed with the expectation of improving BPSD in patients with mild to moderate AD and that attention should be paid to the risk of aggravation of anxiety.

After the dose of donepezil was increased in this study, cognitive function improved, but the ZBI score did not. Germain *et al.* investigated the burden on the caregivers of 1091 patients with mild to moderate AD using the ZBI. They reported that the relative influence on the burden placed on the caregivers was in the following order: BPSD, difficulty in performing activities of daily living, caring time, caregiver characteristics (such as age and sex) and cognitive dysfunction.[22] This suggests that it is probably difficult to reduce the caregiver burden by improving cognitive function in AD patients. If the results of the present study are taken into consideration as well, the effect of high-dose donepezil on cognitive dysfunction is probably not strong enough to materially reduce the caregiver burden. This may be a general limitation of current anti-dementia drugs.

Evaluation of safety showed that the incidence of adverse events was 40.7% after dose escalation of donepezil, which was lower than the incidence of 47% reported in Japanese patients with severe AD receiving donepezil 10 mg daily.[1] This difference in incidence of adverse events was presumably related to the difference in the severity of AD and also to the lower mean age of the patients in our study (67 years vs 75 years). In the present study, the discontinuation rate as a result of adverse events was 11.1%, which was similar to the rate for the donepezil 10 mg group in the above-mentioned study (14%).[1] Furthermore, an earlier Japanese study of donepezil 10 mg daily for mild to severe AD showed that the incidence of adverse events requiring discontinuation was 12%.[23] These results suggest that the percentage of patients who cannot tolerate donepezil at 10 mg daily is

around 10% irrespective of age and the severity of AD.

It should be noted that this study had some limitations. First, it was an open-label uncontrolled study, so the reliability of our results is lower than if we had done a placebo-controlled double-blind study. Second, progression of symptoms was assessed by the subjective evaluation of caregivers (not combined objective evaluation such as neuropsychological examinations of patients). The caregivers lived with the patients and could directly observe any changes at close range, so their impressions were likely to be suitable for determining efficacy of donepezil dose escalation. Future studies will need to use neuropsychological assessments in addition to the caregivers' impressions. Similarly, quantitative assessments such as the caregiver-rated Clinical Global Impression of Change might be necessary in the objective evaluation of caregivers' impression. Third, the ADAS-cog data needs to be assessed in the context of a practice effect influence from repeated neuropsychological testing. However, a practice effect on the ADAS has not been noted in AD patients with memory impairment, but it has been reported healthy volunteers.[24] Fourth, because administration of donepezil 10 mg for mild to moderate AD involves off-label use, we excluded patients with a higher risk of aggravation of BPSD (such as those with delusions, agitation and irritability) and patients aged over 80 years. Accordingly, our results cannot be applied to the overall population with mild to moderate AD.

Despite these limitations, the finding that ADAS-J cog showed significant improvement after dose escalation of donepezil suggests a useful approach to the treatment of cognitive dysfunction in AD patients. Therefore, we propose that the dose of donepezil should not only be adjusted on the basis of the severity of AD but also by taking into account the progression of cognitive dysfunction. In contrast, we found no improvement of BPSD when the dose of donepezil was increased to 10 mg in our patients with mild to moderate AD. Thus, if progression of BPSD occurs during treatment with donepezil 5 mg, a beneficial effect cannot be expected by increasing the dose. In conclusion, treatment of AD has become more complicated since the release of several anti-dementia drugs, so it is necessary to conduct further studies to establish the optimum regimens for using the new drugs.

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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

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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

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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 $\leqq$ 40); (ii) preservation of overall cognitive functions at near normal levels when tested by MMSE ($\geqq$24); (iii) a total CDR score of 0.5; and (iv) intact functioning in ADL measured by the IADL (male: $\geqq$4, female: $\geqq$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.

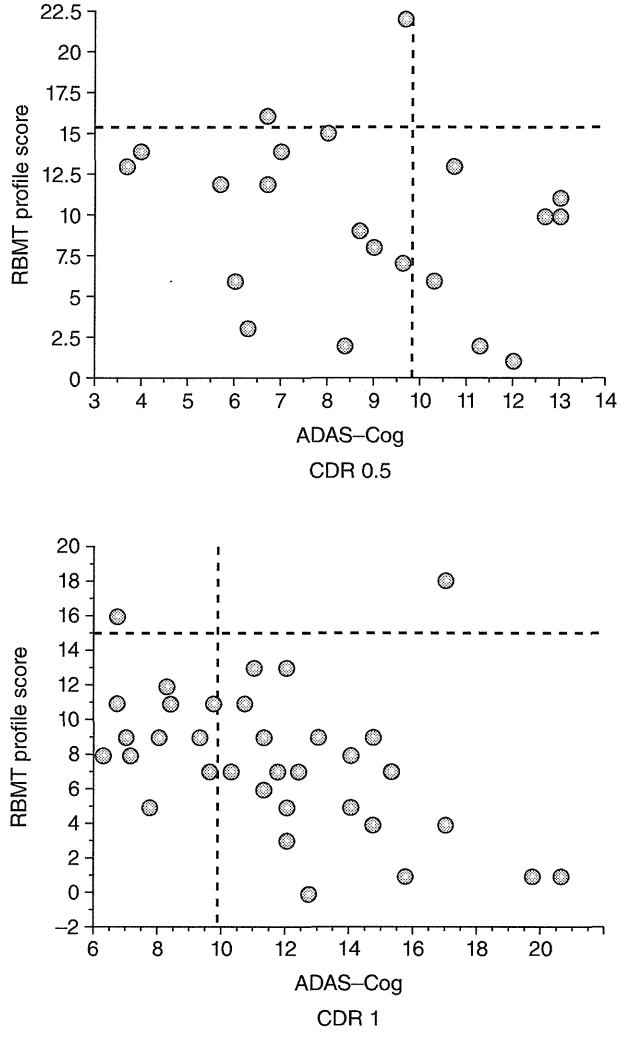

Figure 1. Comparison of the Rivermead Behavioural Memory Test (RBMT) profile score vs the Alzheimer's Disease Assessment Scale-Cognitive part (ADAS-Cog) score. In cases with Clinical Dementia Rating (CDR) 0.5, each score of the profile score of RBMT, the screening score of RBMT, and the ADAS-Cog correctly classified 90.9%, 81.8%, and 31.8% of subjects, respectively. Meanwhile, in cases with CDR 1, each score of the profile score of RBMT, the screening score of RBMT, and the ADAS-Cog correctly classified 94.1%, 91.2%, and 64.7% of subjects, respectively.

profile score of RBMT correctly classified 94.1% of subjects and the screening score of RBMT correctly classified 91.2%. In comparison, only 64.7% of the subjects were correctly classified by ADAS-Cog. The false negative rate was improved in all scores, especially in ADAS-Cog (35.3%).

DISCUSSION

In this study, we evaluated the screening ability of RBMT and ADAS-Cog in MCI or very mild AD, and in more severe cases of AD. There was evident superiority of the RBMT, especially in cases of MCI or very mild AD. The RBMT profile score overlooked only two cases (9.1%), compared to 15 cases (68.2%) overlooked by the ADAS-Cog. ADAS-Cog remains very appropriate for evaluation in typical AD cases, as reported previously,[11] and might be suitable for following the disease progression.

Detecting AD in the very early stages is becoming more important, since there are indications that postponement between MCI and manifest dementia could result in short-term economic costs of $5300 per patient per year.[21] Moreover, a recent report demonstrated that anti-amyloid therapies will be ineffectual in AD and it may be time to change treatment models from curative to prevention at least from the MCI stage.[22]

Our results indicate that everyday memory tests, such as RBMT, may be more appropriate for the evaluation of very mild AD or MCI because the performance on such tasks will be more vulnerable than that on retrospective memory or other cognitive function tests in the early stages of AD or MCI. Salloway *et al.* reported that the modified ADAS-Cog total score was sufficiently sensitive to be useful in studies of MCI patients.[23] They also described a number of reports[1,2,24] showing that, relative to normal elderly, patients with MCI had measurable cognitive deficits that extended beyond the memory domain. However, in our cases, which were considered as showing milder disturbance only in memory domain, there were different results related to the ability of ADAS-Cog. Although not examined this time, RBMT may be more reliable for pharmacometrics than ADAS-Cog. These points should be examined in future studies.

In the present study, a weak point of RBMT was also revealed. Our results showed no significant difference between CDR 0.5 and CDR 1 cases in RBMT scores. This is because an RBMT score falls in the very early stage and the range of RBMT score is rather narrow. As a result, evaluating status and following the progression in more severe cases is difficult. In contrast to RBMT, the ADAS-Cog score has a wide range and can evaluate and follow the severity in more severe cases. Actually, in our results, there is significant difference in ADAS-Cog scores between

CDR 0.5 and CDR 1 cases. A recent report[25] indicated that ADAS-Cog could follow exactly the change of treatment as the primary outcome. However, the RBMT story recall subtest was not able to show evident change. Naturally, as this was the only subtest of RBMT used in the study, this result cannot be treated generally. However, one of the inclusion criteria of the study population was between 18 and 24 in the MMSE score, similar to the range of our CDR 1 group. As for severity, RBMT is not able to follow the change properly because it only evaluates the memory domain. Thus, attention to the advantages and faults of these tests is important in their usage.

Although our results are encouraging, there are some methodological issues. First, the sample size was small because the exclusion criteria was extremely restricted in order to focus this study on MCI or very mild AD. Subjects who showed other symptoms, such as parkinsonism, visual hallucination, abnormal eating behaviors, disinhibition, or a history of stroke, which indicated the possibility of other types of dementia, were excluded from this study. Second, in this kind of study, controls would help interpret the results. However, no normal controls were incorporated in this study. For these reasons, we could not state the sensitivity and specificity in both the RBMT and ADAS-Cog. Third, the constitutive factors included in RBMT, such as the prospective memory, might be useful and easy for screening scale. In a future study with larger samples, the evaluation of the screening ability in these factors is desirable. Fourth, there is the possibility that the result might vary if the subjects are restricted to actual converters from MCI to dementia in larger samples.

Although the diagnostic criteria of MCI are controversial, the criteria that we used in this study are composed of a combination of multiple modalities, such as clinical features, neuropsychological testing, and neuroimaging. We believe our results came from the best possible evaluation and indicated that RBMT is particularly more sensitive to detect or evaluate patients with MCI or very mild AD.

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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

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*

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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 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

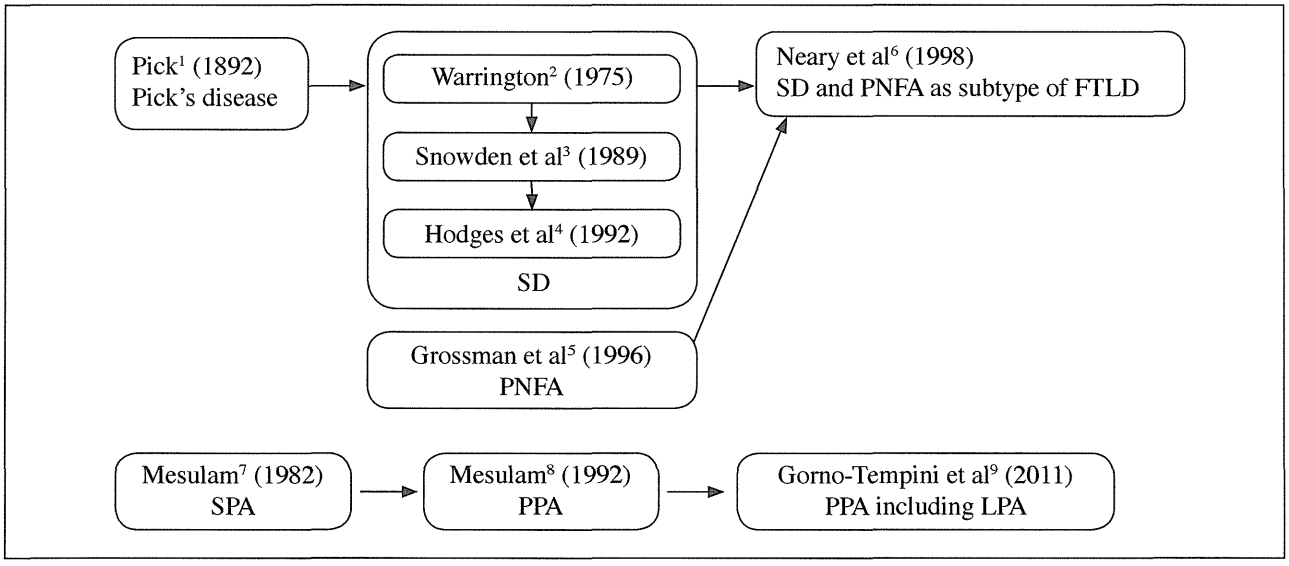

Figure 1. The concepts of classification of progressive aphasia.

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.

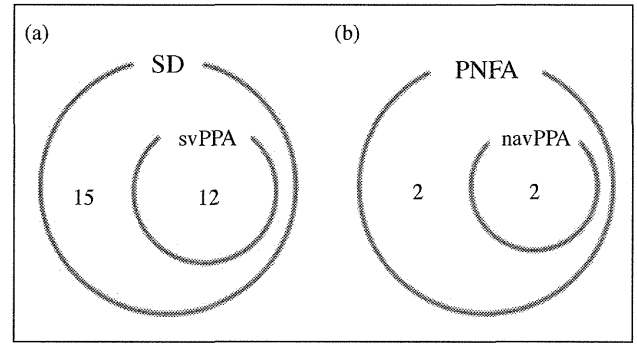

Figure 2. The conceptual diagrams of neurodegenerative dementia showing association between: (a) semantic dementia (SD) and semantic variant primary progressive aphasia (svPPA) groups; and (b) progressive non-fluent aphasia (PNFA) and non-fluent / agrammatic variant PPA (navPPA) groups.

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 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