Table 1. Patient demographics according to studies and specialty centres

	Total (n = 273)	Studies			Specialty centres		
		phase II (n = 135)	phase III (n = 138)	p value[a]	psychiatric (n = 73)	neurological (n = 184)	p value[a]
Sex				0.213			0.006
Male	104 (38.1)	46 (34.1)	58 (42.0)		17 (23.3)	77 (41.8)	
Female	169 (61.9)	89 (65.9)	80 (58.0)		56 (76.7)	107 (58.2)	
Mean age, years	78.3 (5.8)	78.7 (5.6)	77.9 (6.1)	0.259	79.3 (6.0)	78.2 (5.6)	0.164
Mean weight, kg	49.6 (9.9)	48.3 (9.7)	50.9 (9.9)	0.031	48.8 (8.0)	49.6 (10.5)	0.572
Duration since onset of cognitive decline, years							
Mean (SD)	2.3 (2.2)	2.3 (2.4)	2.3 (2.0)	0.851	2.5 (1.7)	2.1 (2.0)	0.176
Range	0.0–20.4	0.1–20.4	0.0–10.8		0.1–7.4	0.0–10.8	
Experience of anti-dementia medication	12 (4.4)	4 (3.0)	8 (5.8)	0.377	5 (6.8)	6 (3.3)	0.302

Figures in parentheses indicate SD or percentage. [a] Fisher's exact or χ^2 test for categorical variables and t test for continuous variables were used.

Results

A total of 273 patients (phase II: 135, phase III: 138) from a total of 89 specialty centres were incorporated for the analysis: 73 patients were enrolled from psychiatric centres, 184 from neurological centres, and 16 from other centres such as gerontological and neurosurgical centres. Demographic characteristics are summarised in table 1.

Diagnostic and Clinical Characteristics Based on the Central and Core Features (Pooled Analysis)

Central Feature

The central feature of DLB is progressive cognitive decline. The CDR of more than half of the patients was 1 (52.4%), followed by 0.5 (27.5%), 2 (19.4%), and 3 (0.7%; table 2). The MMSE score (mean ± SD) was 19.4 ± 4.2 (table 3).

Core Features

The core features of DLB include cognitive fluctuation, visual hallucinations, and parkinsonism. Patients with the respective core features were 94.1% (257/273), 84.6% (231/273), and 86.4% (236/273; table 2). The proportion of patients with all three features was 65.2% (178/273). Of those with two features, the most prevalent was a combination of cognitive fluctuation and parkinsonism (15.4%), followed by cognitive fluctuation and visual hallucinations (13.6%) and visual hallucinations and parkinsonism (5.9%; table 4). In the NPI-plus, cognitive fluctuation showed the highest score (mean ± SD: 3.7 ± 3.0) and the highest proportion of patients with the symptom (score ≥1: 83.9%) among the items (fig. 1). Hallucinations also showed a high mean score of 3.3 ± 3.2, the third highest following cognitive fluctuation and apathy/indifference, and the second highest proportion of patients with the symptom (score ≥1: 75.1%). Regarding parkinsonism, almost half of the patients were at the Hoehn and Yahr stage III (45.3%), followed by stage II (39.4%) and stage I (15.3%; table 2). The UPDRS part III score (mean ± SD) was 19.8 ± 11.4, with the higher subscale scores of akinesia (8.1 ± 4.9) and rigidity (4.2 ± 3.2; table 5). The proportion of patients taking anti-Parkinson drugs was 20.1% (table 6).

Table 2. Clinical characteristics of patients with DLB according to studies and specialty centres

	Total (n = 273)	Studies			Specialty centres		
		phase II (n = 135)	phase III (n = 138)	p value[a]	psychiatric (n = 73)	neurological (n = 184)	p value[a]
Presence of progressive cognitive decline	273 (100.0)	135 (100.0)	138 (100.0)		73 (100.0)	184 (100.0)	
CDR				0.467			0.839
0.5	75 (27.5)	39 (28.9)	36 (26.1)		20 (27.4)	52 (28.3)	
1	143 (52.4)	74 (54.8)	69 (50.0)		38 (52.1)	94 (51.1)	
2	53 (19.4)	21 (15.6)	32 (23.2)		15 (20.5)	36 (19.6)	
3	2 (0.7)	1 (0.7)	1 (0.7)		0	2 (1.1)	
Cognitive fluctuation	257 (94.1)	130 (96.3)	127 (92.0)	0.197	72 (98.6)	170 (92.4)	0.074
Visual hallucinations	231 (84.6)	111 (82.2)	120 (87.0)	0.316	63 (86.3)	155 (84.2)	0.847
Parkinsonism	236 (86.4)	115 (85.2)	121 (87.7)	0.598	52 (71.2)	169 (91.8)	<0.001
Hoehn and Yahr stage				0.587			<0.001
I	36 (15.3)	17 (14.8)	19 (15.7)		13 (25.0)	19 (11.2)	
II	93 (39.4)	42 (36.5)	51 (42.1)		28 (53.8)	57 (33.7)	
III	107 (45.3)	56 (48.7)	51 (42.1)		11 (21.2)	93 (55.0)	
≥IV	0	0	0		0	0	
REM sleep behaviour disorder	107 (39.2)	52 (38.5)	55 (39.9)	0.901	27 (37.0)	70 (38.0)	1.000
Neuroleptic sensitivity	14 (5.1)	7 (5.2)	7 (5.1)	1.000	4 (5.5)	9 (4.9)	1.000
SPECT or PET scan within 3 years prior to consent	142 (52.0)	88 (65.2)	54 (39.1)	<0.001	28 (38.4)	107 (58.2)	0.005
Flow decline in occipital lobe and metabolic decline	118 (83.1)	74 (84.1)	44 (81.5)	0.687	23 (82.1)	88 (82.2)	0.990
Myocardial scintigraphy within 3 years prior to consent	78 (28.6)	37 (27.4)	41 (29.7)	0.690	8 (11.0)	68 (37.0)	<0.001
Decreased myocardial uptake of MIBG	70 (89.7)	31 (83.8)	39 (95.1)	0.141	8 (100.0)	60 (88.2)	0.589
Repeated falls and syncope	56 (20.5)	29 (21.5)	27 (19.6)	0.765	14 (19.2)	41 (22.3)	0.618
Transient loss of consciousness	21 (7.7)	11 (8.1)	10 (7.2)	0.823	3 (4.1)	18 (9.8)	0.205
Severe autonomic dysfunction	61 (22.3)	27 (20.0)	34 (24.6)	0.386	13 (17.8)	43 (23.4)	0.403
Hallucinations in other modalities	103 (37.7)	53 (39.3)	50 (36.2)	0.620	28 (38.4)	71 (38.6)	1.000
Systematised delusion	93 (34.1)	44 (32.6)	49 (35.5)	0.702	21 (28.8)	69 (37.5)	0.196
Depression	103 (37.7)	55 (40.7)	48 (34.8)	0.321	26 (35.6)	71 (38.6)	0.672

Totals may not sum to 100% owing to rounding. Data are presented as n (%). REM = Rapid eye movement. [a] Fisher's exact or χ^2 test for categorical variables and t test for continuous variables were used.

Table 3. Assessment of cognitive, neuropsychiatric, and behavioural function in patients with DLB according to studies and specialty centres

	Total (n = 273)	Studies			Specialty centres		
		phase II (n = 135)	phase III (n = 138)	p value[a]	psychiatric (n = 73)	neurological (n = 184)	p value[a]
MMSE at screening	19.4±4.2	19.4±4.3	19.4±4.1	0.996	19.3±4.4	19.6±4.1	0.606
MMSE				0.855			0.483
≤17	79 (28.9)	39 (28.9)	40 (29.0)		21 (28.8)	54 (29.3)	
≥18, ≤21	99 (36.3)	47 (34.8)	52 (37.7)		30 (41.1)	62 (33.7)	
≥22	95 (34.8)	49 (36.3)	46 (33.3)		22 (30.1)	68 (37.0)	
NPI-2 at baseline	7.0±4.6	6.9±4.6	7.1±4.5	0.833	7.8±4.5	6.8±4.5	0.112
NPI-2				0.784			0.208
≤4	106 (38.8)	52 (38.5)	54 (39.1)		22 (30.1)	76 (41.3)	
≥5, ≤8	82 (30.0)	43 (31.9)	39 (28.3)		23 (31.5)	54 (29.3)	
≥9	85 (31.1)	40 (29.6)	45 (32.6)		28 (38.4)	54 (29.3)	
NPI-10	18.4±12.7	18.2±11.2	18.6±14.0	0.809	19.8±12.4	17.6±12.3	0.188

Totals may not sum to 100% owing to rounding. Data are presented as mean ± SD or n (%). [a] Fisher's exact test for categorical variables and t test for continuous variables were used.

Table 4. Core features of symptoms in patients with DLB at baseline according to studies and specialty centres

	Total (n = 273)	Studies		Specialty centres		
		phase II (n = 135)	phase III (n = 138)	psychiatric (n = 73)	neurological (n = 184)	others (n = 16)
Three symptoms: cognitive fluctuation, visual hallucinations, parkinsonism	178 (65.2)	86 (63.7)	92 (66.7)	41 (56.2)	126 (68.5)	11 (68.8)
Two symptoms: cognitive fluctuation, visual hallucinations	37 (13.6)	20 (14.8)	17 (12.3)	21 (28.8)	15 (8.2)	1 (6.3)
Two symptoms: cognitive fluctuation, parkinsonism	42 (15.4)	24 (17.8)	18 (13.0)	10 (13.7)	29 (15.8)	3 (18.8)
Two symptoms: visual hallucinations, parkinsonism	16 (5.9)	5 (3.7)	11 (8.0)	1 (1.4)	14 (7.6)	1 (6.3)

Totals may not sum to 100% owing to rounding. Data indicate frequency (%).

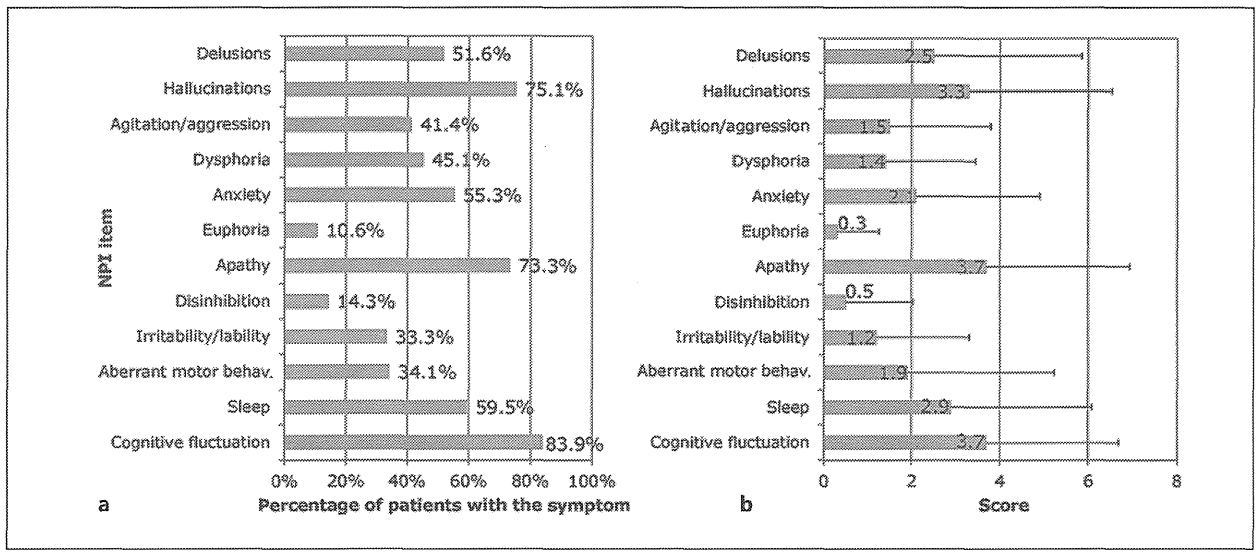

Fig. 1. a Proportions of patients with the presence of NPI symptoms. **b** Mean NPI scores of individual items. T bars indicate standard deviation.

Prevalence of Suggestive and Supportive Features (Pooled Analysis)

Suggestive Features

Patients commonly experienced the rapid eye movement sleep behaviour disorder (RBD; 39.2%) while rarely experiencing neuroleptic sensitivity (5.1%; table 2). Dopamine transporter uptake was not assessed as DaTscan was not approved at the time of study implementation in Japan.

Supportive Features

Patients commonly experienced the following three symptoms: hallucinations in other modalities (37.7%), depression (37.7%), and systematised delusion (34.1%; table 2). Compared with these psychiatric symptoms, prevalence of repeated falls and syncope (20.5%), transient loss of consciousness (7.7%), and severe autonomic dysfunction (22.3%) were relatively low. Single-photon emission computed tomography (SPECT) or positron emission tomography (PET) scan was performed in 52.0% (table 2). Of these, decreased cerebral blood flow or metabolism in the occipital lobes was observed in 83.1%. Similarly, myocardial scin-

Table 5. Assessment of UPDRS part III in DLB patients according to studies and specialty centres

	Total (n = 273)	Studies			Specialty centres		
		phase II (n = 135)	phase III (n = 138)	p value[a]	psychiatric (n = 73)	neurological (n = 184)	p value[a]
Total score	19.8 (11.4)	19.3 (10.5)	20.4 (12.2)	0.425	18.8 (12.5)	20.5 (10.9)	0.296
Tremor[b]	2.1 (3.1)	2.1 (3.1)	2.1 (3.1)	0.943	3.3 (3.9)	1.6 (2.5)	<0.001
Akinesia[c]	8.1 (4.9)	7.8 (4.6)	8.4 (5.2)	0.322	7.7 (5.2)	8.4 (4.9)	0.345
Rigidity[d]	4.2 (3.2)	3.9 (2.9)	4.4 (3.5)	0.194	3.1 (3.1)	4.6 (3.3)	0.001
Postural instability and gait difficulty[e]	3.5 (2.6)	3.4 (2.5)	3.5 (2.7)	0.941	2.9 (2.7)	3.7 (2.6)	0.017

Data indicate mean (SD). [a] T test was used for statistical significance. [b] Tremor includes tremor at rest (face, both sides of hands and feet) and action or postural tremor of hands (right and left), ranging from 0 to 28. [c] Akinesia includes finger taps (left), finger taps (right), hand movement (left), hand movement (right), rapid altering movements of hands (left), rapid altering movements of hands (right), leg agility (left), leg agility (right), and body bradykinesia and hypokinesia, ranging from 0 to 36. [d] Rigidity includes rigidity (neck, lower and upper extremities), ranging from 0 to 20. [e] Postural instability and gait difficulty includes rising from chair, posture erect, gait, and postural stability, ranging from 0 to 16.

Table 6. Concomitant drug at baseline in DLB patients according to studies and specialty centres

	Total (n = 273)	Studies			Specialty centres		
		phase II (n = 135)	phase III (n = 138)	p value[a]	psychiatric (n = 73)	neurological (n = 184)	p value[a]
Anti-Parkinson drugs[b]	55 (20.1)	24 (17.8)	31 (22.5)	0.367	8 (11.0)	45 (24.5)	0.017
Anti-depressants	19 (7.0)	9 (6.7)	10 (7.2)	1.000	4 (5.5)	14 (7.6)	0.787
Anxiolytics	43 (15.8)	19 (14.1)	24 (17.4)	0.508	16 (21.9)	26 (14.1)	0.137
Hypnotics	48 (17.6)	21 (15.6)	27 (19.6)	0.428	14 (19.2)	32 (17.4)	0.722
Cerebral metabolism enhancer	20 (7.3)	8 (5.9)	12 (8.7)	0.487	2 (2.7)	17 (9.2)	0.110

Data indicate n (%). [a] Fisher's exact test was used for statistical significance. [b] Levodopa or dopamine agonists.

tigraphy was performed in 28.6%. Of these, decreased myocardial uptake of ^{123}I-metaiodobenzylguanidine (MIBG) was observed in 89.7%. On magnetic resonance imaging or computed tomography scan, 12.8% showed no atrophy of the cerebral cortex including medial temporal lobe, and 64.8% showed mild atrophy. Data on electroencephalography were not required.

Other Clinical Features

The NPI-10 score (mean ± SD) was 18.4 ± 12.7 (table 3). Among the NPI-plus items, the mean score was highest in cognitive fluctuation (3.7 ± 3.0) and apathy/indifference (3.7 ± 3.2), followed by hallucinations (3.3 ± 3.2), sleep (2.9 ± 3.2), delusions (2.5 ± 3.4) and anxiety (2.1 ± 2.8; fig. 1). The proportion of patients with the symptom (score ≥1) was highest in cognitive fluctuation (83.9%), followed by hallucinations (75.1%), apathy/indifference (73.3%), sleep (59.5%), and anxiety (55.3%).

Comparison of Patient Characteristics between the Phase II and III Studies

Central Feature

The proportions of the CDR 1 were 54.8 and 50.0% in phases II and III, respectively (table 2). The MMSE scores (mean ± SD) were 19.4 ± 4.3 and 19.4 ± 4.1, respectively (table 3).

There was no difference in the distribution of the CDR and MMSE score between the two studies (p = 0.467 and 0.996).

Core Features

Patients with cognitive fluctuation, visual hallucinations, and parkinsonism were 96.3, 82.2, and 85.2% in phase II, and 92.0, 87.0, and 87.7% in phase III, respectively, with no significant differences between the studies (table 2). Patients with all core features were 63.7 and 66.7%, respectively (table 4). In the NPI-plus, the scores (mean ± SD) of cognitive fluctuation were 3.4 ± 3.0 and 3.9 ± 3.0, respectively, and those of hallucinations were 3.5 ± 3.4 and 3.1 ± 3.0, respectively, with no significant differences between the studies (p = 0.151, 0.304). Regarding parkinsonism, patients at the Hoehn and Yahr stage III were 48.7 and 42.1% in phases II and III, respectively (table 2). The UPDRS part III scores (mean ± SD) were 19.3 ± 10.5 and 20.4 ± 12.2, respectively (table 5). There was no difference in the distribution of the Hoehn and Yahr stage and UPDRS part III score between the two studies (p = 0.587, 0.425). The use of anti-Parkinson drugs was also similar: 17.8 and 22.5%, respectively (p = 0.367; table 6).

Other Clinical Features

Regarding suggestive or supportive features, no significant differences were found (table 2). A SPECT or PET scan was performed in more patients in phase II (65.2 vs. 39.1%, p < 0.001), but decreased cerebral blood flow and metabolism in the occipital lobes were observed in similar proportions. Mean NPI-10 scores were 18.2 ± 11.2 and 18.6 ± 14.0 in phases II and III, respectively (table 3). The proportions of patients taking concomitant medications (anti-depressants, anxiolytics, hypnotics, and cerebral metabolism enhancers) were also similar between the studies (table 6).

Comparisons of Patient Characteristics between Psychiatric and Neurological Specialty Centres

Central Feature

The proportions of the CDR 1 were 52.1 and 51.1% in the psychiatric and neurological centres, respectively (table 2). The MMSE scores (mean ± SD) were 19.3 ± 4.4 and 19.6 ± 4.1, respectively (table 3). There was no difference in the distribution of the CDR and MMSE score between types of centres (p = 0.839, 0.606).

Core Features

Patients with cognitive fluctuation, visual hallucinations, and parkinsonism were 98.6, 86.3, and 71.2% in the psychiatric centres, and 92.4, 84.2, and 91.8% in the neurological centres, respectively. The proportion of patients with parkinsonism was significantly higher in the neurological centres (p < 0.001; table 2). More patients with all core features tended to be enrolled from the neurological centres (68.5%) than psychiatric centres (56.2%, p = 0.081; table 4). Conversely, those with a combination of cognitive fluctuation and visual hallucinations were enrolled more in psychiatric centres (28.8 and 8.2%, p < 0.001). In the NPI-plus, the scores (mean ± SD) of cognitive fluctuation were 3.8 ± 3.1 and 3.6 ± 2.9, respectively, and those of hallucinations were 3.9 ± 3.6 and 3.1 ± 3.1, respectively, with no significant differences between types of centres (p = 0.649, 0.073). Regarding parkinsonism, patients at Hoehn and Yahr stage III were 21.2 and 55.0% in the psychiatric and neurological centres, with a significant difference in the distribution of the stage between them (p < 0.001; table 2). The UPDRS part III score (mean ± SD) was not different between types of centres (18.8 ± 12.5 and 20.5 ± 10.9, respectively, p = 0.296); the subscores of rigidity and postural instability and gait difficulty were higher in neurological centres, and that of tremor was higher in psychiatric centres (table 5). Interaction was found in rigidity (neurological: phase II < III, psychiatric:

phase II > III, p = 0.039), with a significant difference between centres only in phase III. The proportion of patients taking anti-Parkinson medications was also significantly higher in the neurological centres (24.5 and 11.0%, p = 0.017; table 6).

Other Clinical Features

Regarding suggestive and supportive features, no significant differences were observed between types of centres (table 2). Myocardial scintigraphy was performed in more patients in the neurological (37.0%) than psychiatric centres (11.0%; p < 0.001), but decreased myocardial uptake of MIBG was observed in similar proportion. The NPI-10 scores (mean ± SD) were 19.8 ± 12.4 and 17.6 ± 12.3 in the psychiatric and neurological centres, respectively (table 3). The proportions of patients taking concomitant medications were also similar between types of centres, although the proportion of patients with concomitant anti-anxiety drugs was slightly higher in the psychiatric centres, but this was not significant (21.9 vs. 14.1%, respectively; table 6).

Discussion

We explored clinical characteristics of patients with DLB using data from the previous phase II and III studies of donepezil for DLB. The results provided detailed descriptions of clinical characteristics of patients with probable DLB based on the original consensus diagnostic criteria [2] and showed a high prevalence of the suggestive and supportive items of the revised criteria [3] in those patients. Furthermore, overall, similar patient characteristics were found between types of specialty centres as well as varying times of study implementation.

Only a few large-scale clinical trials for DLB have been conducted. Compared with AD, it is difficult to enrol a large number of patients into clinical trials, especially RCTs, for DLB owing to its faster progression, wide variety of symptoms including severe BPSD, greater caregiver burden, and easily induced severe adverse events [11, 29–32]. In the previous two RCTs of donepezil, the number of patients enrolled by each centre was generally small (none by 5 and only 1 patient by 14 out of 48 centres in phase II, and none by 14 and only 1 patient by 15 out of 72 centres in phase III). Similar recruitment difficulties impeded an RCT of rivastigmine for DLB [33]. It might be inevitable that patients are recruited from various specialty departments, such as neurology, psychiatry, geriatrics, and so on, of multinational centres for future RCTs in DLB and that enrolment in those studies takes a long time. Therefore, it is very important to confirm the adequacy of using the consensus criteria in those studies by comparing patient characteristics among trials conducted at different times and subjects enrolled from different types of specialty centres.

The phase III study of donepezil was initiated about 3 years after initiating phase II. Nevertheless, patient characteristics of these trials were almost the same except for the proportion of patients in whom a SPECT or PET scan was performed. This difference may be due to the high proportion of patients from clinics and the low proportion from hospitals in phase III.

Clinical characteristics were also similar between psychiatric and neurological centres. The only exception was parkinsonism, specifically the proportions of patients with parkinsonism and in concomitant use of anti-Parkinson medication, and the severity assessed with the Hoehn and Yahr stage, which were significantly higher in neurological centres, as expected. In psychiatric centres, a larger proportion of patients were diagnosed as probable DLB with two core features: cognitive fluctuation and visual hallucinations. The NPI-10 score and the proportion of patients with concomitant administration of anti-anxiety drugs were relatively higher in psychiatric than neurological centres, but the differences were not significant and no difference in any subscale of NPI was also found between them. This may suggest that

patients from psychiatric centres developed anxiety more frequently than those from neurology centres before the entry into the studies.

Core features observed in these studies were also not greatly different from those in the RCTs of rivastigmine conducted in 2000 or earlier in Spain, the UK, and Italy: cognitive fluctuation, 90%; visual hallucinations, 78%; parkinsonism, 90%, and mean MMSE score, approximately 18 [33].

These findings suggest that the consensus diagnostic criteria are reliable and can be used to enrol patients with homogeneous characteristics in clinical trials, which various specialty departments of a large number of multinational centres join with a long enrolment period. They also imply that similar proportions of neurological and psychiatric centres should be included because the presence/absence and severity of parkinsonism may vary depending upon specialty centres.

More than a decade has passed since the consensus diagnostic criteria and their revised version were published [2, 3]. During those years, clinical, neuroimaging, and molecular biological techniques have progressed, leading to major updates in diagnostic criteria for other degenerative dementias, such as AD and behavioural variant frontotemporal dementia. Likewise, updates in the criteria for DLB can be expected. Exploring the prevalence of suggestive as well as supportive features of the current revised criteria for DLB in subjects selected in a strictly controlled environment may be beneficial.

Among the suggestive features, RBD developed in 39.2% of patients. RBD preceded the diagnosis of DLB in almost all cases in which RBD was noted [34], and it was reported that inclusion of RBD as a core clinical feature improved the diagnostic accuracy of autopsy-confirmed DLB [8]. Furthermore, a screening questionnaire for RBD in patients with dementia was recently developed [35]. It seems appropriate that RBD was upgraded to a suggestive feature in the revised criteria [3]. On the other hand, neuroleptic sensitivity was observed in only 5.1%. This might be due to prohibition of antipsychotics during the studies. However, administration of antipsychotics has not been encouraging in a clinical setting since antipsychotics were reportedly associated with increased mortality in elderly patients with dementia. Furthermore, in DLB, hypersensitivity to them has been widely acknowledged, so that atypical antipsychotics, such as quetiapine, olanzapine, clozapine, aripiprazole, which trigger less extrapyramidal symptoms, are selected for patients with DLB if needed. Neuroleptic sensitivity is clinically important, but further research may be needed to evaluate its importance in the future diagnostic criteria.

Of the supportive features, psychiatric symptoms, such as hallucinations in other modalities, depression, and systematised delusion, were observed in approximately 35% of patients. Results of the NPI indicate that anxiety, which has a lower prevalence in other forms of dementia [36–38], was observed in 55.3%, suggesting that this could be added to the diagnostic criteria. Interestingly, an earlier research found that anxiety was a risk factor for DLB [39]. A relatively high prevalence of both repeated falls and syncope (20.5%) and severe autonomic dysfunction (22.3%) was observed, unlike transient loss of consciousness (7.7%). Although imaging tests were not conducted in all patients, decreased cerebral blood flow and metabolism in the occipital lobes and decreased myocardial uptake were found positive in 83.1 and 89.7%, respectively, implying the importance of these items in the criteria.

The present analysis has some limitations. The data were originally collected under a clinical trial setting where strict criteria were employed. In particular, to examine the effect of donepezil on BPSD, the inclusion criteria in 2 studies required at least some degree of BPSD. Furthermore, due to concerns about safety, patients with severe parkinsonism (Hoehn and Yahr stage ≥IV) were excluded. As a result, patients in these studies may be more homogeneous than those in a real-life setting. Future research is needed for further application of the consensus criteria in a real-life setting. Second, among centres which participated in phase II,

31 centres again joined in phase III (total 72 centres) and enrolled 73 out of a total of 138 patients. This may add the possibility that patients with similar clinical profiles tended to be enrolled. Future research without duplicated centres in enrolment may strengthen the present findings. Third, we cannot discuss the adequacy and prevalence of the central and core features because these symptoms are part of the diagnosis process. The prevalence of low dopamine transporter uptake in basal ganglia, one of the suggestive features, was not assessed as DaTscan was not approved at the time of study implementation in Japan. Lastly, regardless of relatively higher values in most parkinsonism-related indices in neurological centres, the UPRDS part III subscore of tremor was solely higher in psychiatric centres. Therefore, there might be a difference in the types of parkinsonian symptoms at the time of patients' centre visit between types of centres. Given that tremor is relatively easy to detect, however, we also cannot deny the possibility that this could be attributed to the difference in training background and hence the sensitivity of the investigators to parkinsonian symptoms, although a rater training for psychiatrists who were less experienced in scoring the UPDRS part III was provided prior to each trial to reduce such variability.

In conclusion, patient characteristics were similar between the phase II and III studies conducted 3 years apart. They were also similar between psychiatric and neurological specialty centres, with the exception of parkinsonism, which was more distinctively observed in neurological centres, reflecting specific characteristics of the specialty centres. The results of the present analysis suggest that it is adequate to employ the consensus criteria in order to enrol homogeneous DLB patients into future clinical trials regardless of the specialty of centres. A few points such as including anxiety for future revision of the consensus criteria may be open to further discussion.

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Disclosure Statement

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Diagnostic Significance of Cortical Superficial Siderosis for Alzheimer Disease in Patients with Cognitive Impairment

Y. Inoue, M. Nakajima, H. Uetani, T. Hirai, M. Ueda, M. Kitajima, D. Utsunomiya, M. Watanabe, M. Hashimoto, M. Ikeda, Y. Yamashita, and Y. Ando

ABSTRACT

BACKGROUND AND PURPOSE: Because the diagnostic significance of cortical superficial siderosis for Alzheimer disease and the association between cortical superficial siderosis and the topographic distribution of cerebral microbleeds have been unclear, we investigated the association between cortical superficial siderosis and clinicoradiologic characteristics of patients with cognitive impairment.

MATERIALS AND METHODS: We studied 347 patients (217 women, 130 men; mean age, 74 ± 9 years) who visited our memory clinic and underwent MR imaging (3T SWI). We analyzed the association between cortical superficial siderosis and the topographic distribution of cerebral microbleeds plus clinical characteristics including types of dementia. We used multivariate logistic regression analysis to determine the diagnostic significance of cortical superficial siderosis for Alzheimer disease.

RESULTS: Twelve patients (3.5%) manifested cortical superficial siderosis. They were older ($P = .026$) and had strictly lobar cerebral microbleeds significantly more often than did patients without cortical superficial siderosis (50.0% versus 19.4%, $P = .02$); the occurrence of strictly deep and mixed cerebral microbleeds, however, did not differ in the 2 groups. Alzheimer disease was diagnosed in 162 (46.7%) patients. Of these, 8 patients (4.9%) had cortical superficial siderosis. In the multivariate logistic regression analysis for the diagnosis of Alzheimer disease, lacunar infarcts were negatively and independently associated with Alzheimer disease ($P = .007$).

CONCLUSIONS: Although cortical superficial siderosis was associated with a strictly lobar cerebral microbleed location, it was not independently associated with Alzheimer disease in a memory clinic setting. Additional studies are required to investigate the temporal changes of these cerebral amyloid angiopathy–related MR imaging findings.

ABBREVIATIONS: AD = Alzheimer disease; CAA = cerebral amyloid angiopathy; cSS = cortical superficial siderosis; DLB = dementia with Lewy bodies; MBs = cerebral microbleeds; MCI = mild cognitive impairment

Cortical superficial siderosis (cSS) is characterized by linear hypointensities on the surface of cerebral cortex gyri on T2*-weighted gradient-echo MR imaging or SWI.[1,2] cSS reflects subtle hemorrhages from amyloid-affected fragile cortical or leptomeningeal vessels and occurs often in patients with cerebral amyloid angiopathy (CAA); associations of cSS with repeat lobar hemorrhages have been reported.[3-5] Several studies showed that patients with cognitive impairment manifested a higher prevalence of cSS compared with the general population.[6,7] cSS, along with lobar cerebral microbleeds (MBs), was described as a characteristic neuroimaging marker of CAA.[8,9]

Alzheimer disease (AD) is the most common cause of dementia in the elderly, and CAA is assumed to have a pivotal function in the underlying pathogenesis of AD.[10] In the aforementioned studies, cSS was associated with the presence of MBs, and the authors speculated that a relatively high prevalence of cSS in patients with AD indicates this pathogenesis.[6,7] We therefore hypothesized that cSS itself may be a significant diagnostic marker of AD and that lobar MBs would be observed more frequently in patients with cSS than in patients without cSS.

The primary aim of the present study was thus to clarify the diagnostic significance of cSS for AD, with the secondary aim being to explore the radiologic markers of small-vessel disease in relation to cSS in patients with cognitive impairment.

MATERIALS AND METHODS

Study Population

This study consisted of a subanalysis of a prospective clinicoradiologic study described previously.[11] Consecutive patients who

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From the Departments of Neurology (Y.I., M.N., M.U., M.W., Y.A.), Diagnostic Radiology (H.U., T.H., M.K., D.U., Y.Y.), and Psychiatry and Neuropathobiology (M.H., M.I.), Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan.

Please address correspondence to Yasuteru Inoue, MD, Department of Neurology, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan; e-mail: yinoue@fc.kuh.kumamoto-u.ac.jp

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attended the Dementia Clinic of the Department of Neuropsychiatry, Kumamoto University Hospital, were recruited prospectively from January 2008 to February 2010. The Ethics Committee of Kumamoto University Hospital approved this study. The patients received information about the purpose and method of the study, and written informed consent for participation in the study was obtained from them or their caregivers.

Patients with cognitive impairment associated with posttraumatic brain injury, brain tumor, idiopathic normal pressure hydrocephalus, history of psychiatric diseases or substance abuse, and neurodegenerative diseases, including Pick disease, corticobasal degeneration, and spinocerebellar degeneration, were excluded from this study. Patients whose MR images had severe motion artifacts and patients who did not provide informed consent were also excluded.

All patients received independent neuropsychological evaluations conducted by 2 neuropsychiatrists (M.I., M.H.). Neuropsychological tests including the Mini-Mental State Examination, brain MR imaging, and SPECT were used for diagnosing dementia. Diagnostic criteria included the following: for AD, criteria from the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association[12]; for vascular dementia, criteria from the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences[13]; for mild cognitive impairment (MCI), general criteria from the International Working Group on Mild Cognitive Impairment[14]; for dementia with Lewy bodies (DLB), clinical criteria from the Consortium on Dementia with Lewy Bodies[15]; and for frontotemporal lobar dementia, the Lund-Manchester criteria for behavioral variant frontotemporal lobar dementia, semantic dementia, or progressive nonfluent aphasia.[16] If results of all clinical investigations were normal, patients were classified in a subgroup labeled "subjective memory symptoms."

MR Imaging Protocol

MR imaging was performed with a 3T whole-body system (Magnetom Trio; Siemens, Erlangen, Germany). Axial SWI, axial FLAIR, axial T2-weighted turbo spin-echo sequences, 3D T1-weighted magnetization-prepared rapid acquisition of gradient echo sequences, diffusion-weighted imaging, MR spectroscopy, and MRA were performed by using the same section thickness, matrix, and parameters as described previously.[11]

Evaluation of cSS and Other Radiologic Data

We defined cSS as linear hypointensities on the surface of cerebral cortex gyri on SWI; cSS related to previous symptomatic subarachnoid hemorrhage, traumatic subdural hematoma, or intracranial surgery was not included. cSS was classified as focal (restricted to 3 sulci) or disseminated (≥4 sulci).

We defined MBs as small (<10 mm in diameter), homogeneous, round foci of low signal intensity. We excluded symmetric hypointensities in the globi pallidi and dentate nuclei, which we identified as physiologic calcifications or iron deposits; we also excluded hypointense signals inside a lesion that were consistent with infarcts. Lacunar infarcts and white matter hyperintensities were defined according to criteria reported previously.[11,17,18] The distribution of MBs was categorized as lobar (frontal, temporal, parietal, and occipital) or deep (thalamoganglionic, brain stem, and cerebellum).

Patients with MBs were divided into 3 groups according to the microbleed distribution. The strictly lobar group had MBs localized exclusively in the lobar region. The strictly deep group had MBs located only in the thalamoganglionic and infratentorial regions. The mixed group had MBs throughout both lobar and deep regions. All radiologic findings were assessed by 2 experienced neuroradiologists (H.U., T.H.) who were blinded to the clinical information.

Clinical Data Collection

Baseline clinical information, including age, sex, history of hypertension, length of education, and Mini-Mental State Examination results, was recorded at registration. Hypertension was defined as a history of hypertension or prescription of antihypertensive medications.

Statistical Analyses

We compared baseline demographics and clinical characteristics for patients with any cSS and patients with no cSS. Categoric data were evaluated by using the χ^2 test and the Fisher 2-tailed exact test. Continuous variables were compared by using the Mann-Whitney U test. We next conducted multivariate logistic regression analysis to investigate the predictors for diagnosing AD. The independent variables included age, sex, hypertension, length of education, distribution of MBs (strictly lobar, strictly deep, or mixed), lacunar infarcts, white matter hyperintensities, and cSS. Backward stepwise logistic regression analysis was performed by adjusting for age,[19-21] sex,[22] length of education,[23] and variables that were automatically selected in a backward stepwise selection method. We performed a backward selection procedure for each outcome by using $P > .10$ of the likelihood ratio test for exclusion of variables. The OR and 95% CI were obtained. The statistical significance level was set at $P < .05$. In addition, we calculated the sensitivity, specificity, positive predictive value, and negative predictive value of cSS for the clinical diagnosis of AD. Statistical analyses were performed by using JMP 9.0 statistical software (SAS Institute, Cary, North Carolina).

RESULTS

Prevalence of cSS

A total of 347 patients (217 women, 130 men; mean age, 74 ± 9 years) with cognitive impairment visited our hospital from January 2008 to February 2010. Of these patients, 12 (3.5%) had cSS.

Clinical Characteristics Related to cSS

Table 1 provides demographic and clinical characteristics of the patients. Patients with cSS were older ($P = .026$) compared with patients without cSS. No significant differences were observed in the occurrence of cSS across different types of dementia ($P = .337$), and a bivariate analysis also demonstrated no differences between patients with and without AD ($P = .239$). Sensitivity, specificity, positive predictive value, and negative predictive value of cSS for the clinical diagnosis of AD were 4.9%, 97.8%, 66.7%, and 54.0%, respectively (4 patients had cSS but no AD, 8 patients had both cSS and AD, 181 patients had no cSS or AD, and 154 patients had AD but no cSS).

Table 1: Demographic and clinical characteristics of patients with or without cSS

Parameter	No. of Patients (%)			P Value
	Total	Any cSS	No cSS	
No. of patients	347	12	335	
Age (yr) (mean)	74 ± 9	79 ± 5	74 ± 9	.026
No. of women	217 (62.5%)	6 (50.0%)	211 (63.0%)	.361
No. of patients with hypertension	160 (46.1%)	9 (75.0%)	151 (45.1%)	.073
Length of education (yr) (mean) (range)	11 (9–12)	11 (9–13)	11 (9–12)	.506
MMSE (mean)	21 ± 5	19 ± 7	21 ± 5	.457
Types of dementia				.337
AD	162 (46.7%)	8 (66.7%)	154 (46.0%)	
DLB	41 (11.8%)	1 (8.3%)	40 (11.9%)	
FTLD	33 (9.5%)	0 (0%)	33 (9.9%)	
VaD	28 (8.1%)	1 (8.3%)	27 (8.1%)	
MCI	51 (14.7%)	2 (16.7%)	49 (14.6%)	
SC	32 (9.2%)	0 (0%)	32 (9.6%)	

Note:—MMSE indicates Mini-Mental State Examination; FTLD, frontotemporal lobar dementia; VaD, vascular dementia; SC, subjective symptoms.

Table 2: Radiologic characteristics of patients with or without cSS

Type of MBs	No. of Patients (%)			P Value
	Total	Any cSS	No cSS	
No. of patients	347	12	335	
Lobar MBs				
Frontal	69 (19.9%)	7 (58.3%)	62 (18.5%)	.003
Temporal	65 (18.7%)	8 (66.7%)	57 (17.0%)	<.001
Parietal	78 (22.5%)	7 (58.3%)	71 (21.2%)	.007
Occipital	63 (18.2%)	7 (58.3%)	56 (16.7%)	.002
Deep MBs				
Thalamoganglionic	62 (17.9%)	3 (25.0%)	59 (17.6%)	.456
Brain stem	32 (9.2%)	3 (25.0%)	29 (8.7%)	.088
Cerebellum	48 (13.8%)	3 (25.0%)	45 (13.4%)	.222
Topographic distribution of MBs				
Strictly lobar	71 (20.5%)	6 (50.0%)	65 (19.4%)	.020
Strictly deep	10 (2.9%)	0 (0%)	10 (3.0%)	1.00
Mixed	79 (22.8%)	5 (41.7%)	74 (22.1%)	.154
No MBs	187 (53.9%)	1 (8.3%)	186 (55.5%)	.002
Lacunar infarcts	71 (20.5%)	6 (50.0%)	65 (19.4%)	.020
WMH (mean)[a]	1.5 ± 0.8	1.9 ± 0.8	1.4 ± 0.8	.053
0	32 (9.2%)	0 (0%)	32 (9.6%)	
1	166 (47.8%)	4 (33.3%)	162 (48.4%)	
2	107 (30.8%)	5 (41.7%)	102 (30.4%)	
3	42 (12.1%)	3 (25.0%)	39 (11.6%)	

Note:—WMH indicates white matter hyperintensities.

[a] WMH were graded according to the scale of Fazekas et al[17]: 0, absent; 1, punctate; 2, early confluent; and 3, confluent.

Location and Topographic Distribution of MBs

Strictly lobar MBs were observed more frequently in patients with cSS than in patients without cSS ($P = .020$), whereas the 2 groups did not differ with regard to the occurrence of strictly deep MBs ($P = 1.00$) and mixed MBs ($P = .154$). MBs in each cerebral lobe (frontal [$P = .003$], temporal [$P < .001$], parietal [$P = .007$], and occipital [$P = .002$]) had a significant association with the presence of cSS. However, patients with cSS and those without cSS showed no significant differences in the presence of thalamoganglionic MBs ($P = .456$), brain stem MBs ($P = .088$), and cerebellar MBs ($P = .222$) (Table 2). We also performed a separate analysis of demographic and clinicoradiologic characteristics in patients with AD and found similar tendencies in location and topographic distribution of MBs for that whole population (On-line Table). Among patients with AD, strictly lobar MBs were observed more frequently in patients with cSS than in patients without cSS ($P = .004$). MBs in each cerebral lobe (frontal [$P = .040$], temporal [$P < .001$], parietal [$P = .040$], and occipital [$P = .006$]) also had a significant association with the presence of cSS.

Clinicoradiologic Characteristics of Patients with cSS

We further investigated the clinicoradiologic characteristics of 12 patients with cSS (6 women, 6 men; mean age, 79 ± 5 years) (Table 3). Of these, AD was diagnosed in 8 patients (66.7%); DLB, in 1 patient (8.3%); vascular dementia, in 1 patient (8.3%); and MCI, in 2 patients (16.7%). cSS was observed in 22 cerebral lobes, and its location corresponded to locations of MBs in 13 lobes (72.2%). We noted a tendency of cSS to occur in temporal and occipital lobes, and the distribution was focal in 7 patients (58.3%) and disseminated in 5 patients (41.7%). Six patients (50%) had strictly lobar MBs, 5 patients (41.7%) had mixed MBs, no patient with cSS had strictly deep MBs, and 1 patient (8.3%) had no MBs (case 2, Table 3). Four patients (33.3%) were classified as having grade 1 white matter hyperintensities; 5 patients (41.7%), grade 2 white matter hyperintensities; and 3 patients (25.0%), grade 3 white matter hyperintensities. No correlations between age-related white matter change rating scores and the location of cSS were found.

Relationship among cSS, MBs, and AD

Table 4 shows the results of multivariate logistic regression analysis for the diagnosis of AD. In the multivariate model, lacunar infarcts (OR, 0.46; 95% CI, 0.25–0.81; $P = .007$) were negatively and independently associated with AD, and the presence of cSS was not associated with AD (OR, 2.99; 95% CI, 0.88–12.0; $P = .08$).

DISCUSSION

This study is the first to investigate the diagnostic significance of cSS for AD and the relationships between cSS and the location of MBs in patients with cognitive impairment. The major new finding was that patients with cSS had strictly lobar MBs significantly more often than patients without cSS.

With respect to spatial distributions of MBs, past histopathologic studies of patients with intracerebral hemorrhage revealed that strictly lobar MBs strongly suggested CAA.[24] The population-based Rotterdam Scan Study showed a tendency for MBs to be located in the lobar region, especially in the temporal lobes.[25] A

Table 3: Clinicoradiologic characteristics of patients with cSS

Subject No.	Type of Dementia	Age (yr)	Sex	Location of cSS	Frontal	Temporal	Parietal	Occipital	Topographic Distribution of MBs	WMH[a]	ARWMC Rating Scale[b] (R/L) Frontal	Temporal	Parieto-Occipital
1	AD	79	M	Right frontal	−	−	+	+	Mixed	1	1/1	1/0	1/1
2	AD	81	F	Left occipital Right occipital	−	−	−	−	No MBs	2	1/0	2/2	2/2
3	AD	84	M	Left temporal	−	+	−	−	Strictly lobar	3	2/2	3/3	2/1
4	AD	83	F	Left temporal	+	+	−	−	Strictly lobar	2	2/2	2/2	2/2
5	AD	78	F	Right temporal	−	+	+	+	Strictly lobar	1	0/0	1/1	0/0
6	AD	80	M	Right frontal Right temporal	+	+	+	+	Strictly lobar	2	2/2	2/2	2/2
7	AD	78	F	Right frontal Right temporal	+	+	+	+	Strictly lobar	1	0/1	1/0	1/1
8	AD	70	F	Right parietal Right occipital	+	+	−	+	Strictly lobar	1	1/1	1/1	1/1
9	DLB	69	F	Right frontal Right temporal	+	−	+	−	Mixed	2	2/2	2/2	2/2
10	VaD	87	M	Right frontal Right temporal Right occipital Left temporal Left occipital	+	+	−	+	Mixed	2	1/1	2/2	2/2
11	MCI	82	M	Right occipital Left occipital	−	−	+	−	Mixed	3	3/3	3/2	3/3
12	MCI	80	M	Left temporal	+	+	+	+	Mixed	3	3/3	3/3	3/3

Note:—ARWMC indicates age-related white matter changes; R/L, right/left; WMH, white matter hyperintensities; VaD, vascular dementia.

[a] WMH were graded according to the scale of Fazekas et al[17]: 0, absent; 1, punctate; 2, early confluent; and 3, confluent.

[b] ARWMC rating scale[18]: 0, no lesions (including symmetric, well-defined caps, or bands); 1, focal lesions; 2, beginning confluence of lesions; 3, diffuse involvement of the entire region, with or without involvement of U fibers.

Table 4: Multivariate logistic regression analysis for AD[a]

Parameter	OR (95% CI)	*P* Value
Age (per 1-yr increase)	0.99 (0.96–1.02)	.400
Female sex	0.88 (0.55–1.41)	.593
Education (per 1-yr increase)	1.72 (0.43–7.02)	.448
Lacunar infarcts	0.46 (0.25–0.81)	.007
cSS	2.99 (0.88–12.0)	.080

[a] The model was adjusted for age, sex, length of education, and variables that showed a relationship to AD in a backward stepwise selection method.

case-control and memory clinic–based cross-sectional study including patients with AD showed that the microbleed topography was significantly predominant in the occipital region.[26] Our study indicated that strictly lobar MBs are closely related to cSS, which was shown to be a marker of CAA. This tendency also persisted among patients with AD with or without cSS, 2 groups who were barely distinguishable from each other except for a higher prevalence of a lobar microbleed location in patients with AD and cSS.

With respect to the diagnostic significance of cSS for AD, though AD was diagnosed in most patients with cSS, multivariate logistic regression analysis showed that neither cSS nor MBs in any location were independent significant predictors for the diagnosis of AD. An explanation of this result is that CAA pathogenesis also occurs in patients with dementias other than AD. Other histopathologic studies reported CAA in patients with DLB and vascular dementia and a low prevalence of CAA in patients with frontotemporal lobar dementia.[27-29] MCI was reportedly a transitional state of AD,[30] so our patients with cognitive impairment may have had CAA pathologic features. Thus, the similar occurrence of cSS and pathologic findings of CAA in patients with cognitive impairment again indicated the same underlying pathophysiologic mechanisms.

As an interesting finding, 1 female patient had AD and cSS without MBs in the present study, whereas all other patients manifested both cSS and MBs. As with convexity subarachnoid hemorrhage, cSS has causes other than CAA: posterior reversible leukoencephalopathy syndrome, reversible cerebral vasoconstriction syndrome, and lupus vasculitis.[31] One study indicated that cSS or convexity subarachnoid hemorrhage does not always reflect CAA pathogenesis.[31] Given the older age and impaired cognition of our patients, however, most cSS in our study presumably resulted from CAA, as in another study that found CAA in >80% of patients with AD.[32] A cross-sectional study including patients with probable or definite CAA, diagnosed on the basis of the Boston criteria,[33] found inverse associations among the severity of cSS, number of MBs, and *apolipoprotein E ε4*.[34] These authors also speculated that cSS may arise from vasculopathic mechanisms different from those associated with CAA-related microbleeds.[34] Because this patient in our study had no history of possible underlying causes of cSS other than CAA, cSS may have manifested as an initial radiologic finding of CAA.

Limitations of the present study included using a relatively small population and a heterogeneous patient population without AD (DLB, frontotemporal lobar dementia, vascular dementia, MCI, and subjective symptoms) as a reference group in the multivariate logistic regression analysis.

Our study results indicated that cSS was associated with a lobar location of MBs and may be an initial radiologic finding of CAA in patients with cognitive impairment. Additional prospective studies to investigate temporal changes of these CAA-related MR imaging findings may help in understanding the mechanisms of cognitive decline.

CONCLUSIONS

The prevalence of cSS was 3.9% in our memory clinic. Most patients with cSS were diagnosed as having AD, and the specificity of cSS for the clinical diagnosis of AD was high. Strictly lobar MBs were observed more frequently in patients with cSS than in patients without cSS.

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Preliminary communication

Suicidal ideation and related factors among dementia patients

Asuka Koyama *, Noboru Fujise, Masateru Matsushita, Tomohisa Ishikawa, Mamoru Hashimoto, Manabu Ikeda

Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

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ABSTRACT

Background: It is generally thought that people with dementia are not able to attempt suicide because of impaired executive function. Little research is available about suicidal ideation among dementia patients. The present study examines 1) the sociodemographic and clinical features of dementia patients with suicidal ideation and 2) the effect of suicidal ideation on caregiver burden.

Methods: A total of 634 dementia outpatients and their family caregivers participated in this study. Comparisons of variables were made among three groups: patients with suicidal ideation, patients with depression without suicidal ideation, and patients with neither suicidal ideation nor depression. Data were collected between April 2007 and July 2013.

Results: Suicidal ideation was seen in 64 patients (10.1%). Patients with suicidal ideation had a significantly higher rate of behavioural and psychological symptoms of dementia (BPSD) ($P<0.001$). Caregivers of patients with suicidal ideation felt a higher caregiver burden, even after adjusting for BPSD score ($P<0.01$).

Limitations: Suicidal ideation was assessed by interview with caregivers, so we may have overlooked people who had suicidal ideation but did not express it to their caregivers.

Conclusions: Suicidal ideation among dementia patients should receive greater attention. Adequate assessment of suicidal ideation and psychological support for both patients with suicidal ideation and their caregivers are needed.

1. Introduction

Dementia is a worldwide problem affecting 44.4 million people. (International Alzheimer's Disease, 2013) Among dementia patients, depression is one of the major neuropsychiatric symptoms.(Pellegrino et al., 2013) Considering that depression sometimes leads to suicidal ideation, it is possible that some dementia patients have suicidal ideation or actually attempt suicide. However, it is generally thought that people with dementia are not able to attempt suicide because of impaired executive function. Haw et al.(Haw et al., 2009) reviewed the relation between dementia and suicidal behaviour and concluded that the relation is unclear. Therefore, suicidality among patients with dementia has received little attention. To date, some researchers have reported a higher rate of suicide among dementia patients, especially for patients with newly diagnosed dementia(Draper et al., 2010; Erlangsen et al., 2008; Lim et al., 2005; Mizukami et al., 2009; Seyfried et al., 2011) or those with specific types of dementia, such as semantic dementia.(Hsiao et al., 2013; Sabodash et al., 2013) Rubio et al. (Rubio et al., 2001)also reported increased Alzheimer pathology in a population of elderly people committing suicide compared with subjects who died of natural causes. Considering that elderly people generally have a higher risk of suicide(Draper, 2014) and that dementia is frequently associated with depression,(Bennett and Thomas, 2014) the issue of suicidality among dementia patients should not be thought of lightly. Most previous studies about suicidality among dementia patients focused on suicidal behaviour, and suicidal ideation was rarely discussed. Having suicidal ideation, which is one of the most important risk factors for suicidal behaviour,(Almeida et al., 2012) would not only decrease patients' quality of life (QOL) but also affect caregivers. Based on the findings that caregivers of dementia patients with depression felt burdened more than those of dementia patients without depression,(Kang et al., 2014; Mohamed et al., 2010) we hypothesised that caring for dementia patients with suicidal ideation would be more stressful for caregivers.

This paper clarifies 1) the sociodemographic and clinical features of dementia patients with suicidal ideation and 2) the effect of suicidal ideation on caregiver burden.

* Correspondence to: Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University 1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan.
E-mail address: asuka@fc.kuh.kumamoto-u.ac.jp (A. Koyama).

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2. Methods

2.1. Participants

This study was approved by the Human Ethics Review Committee of Kumamoto University. After a complete description of all procedures of the study was provided, written informed consent was obtained from patients and their family caregivers.

Participants in this study were outpatients of the Dementia Clinic of the Department of Neuropsychiatry, Kumamoto University Hospital, from April 2007 to July 2013. Inclusion criteria was 1) provision of written informed consent; 2) diagnosed with Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB), or frontotemporal lobar degeneration (FTLD); 3) living at home, that is, not in a nursing home; and 4) both the patient and his/her main caregiver could participate in our survey. Patients who fulfilled the above criteria ($n=634$) were examined by senior neuropsychiatrists with adequate experience with patients with dementia. All patients had undergone routine laboratory tests, neuroimaging studies such as magnetic resonance imaging and single-photon emission computed tomography, and standard neuropsychological examinations. Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition-revised.(APA, 1987) Patients were divided into those with probable AD, defined according to the National Institute for Neurological and Communicative Disorders and Stroke-Alzheimer's disease and Related Disorders Association (McKhann et al., 1984); probable VaD, defined according to the National Institute for Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria(Román et al., 1993); probable DLB, defined according to the Consensus Criteria for the clinical diagnosis of DLB, 2005(McKeith et al., 2005); or probable FTLD, defined according to the Consensus Criteria for the clinical diagnosis of FTLD.(Neary et al., 1998).

2.2. Measures

2.2.1. Suicidal ideation and depression

We used a domain of the Japanese version of the Neuropsychiatric Inventory (NPI) to assess suicidal ideation and objective depression.(Cummings et al., 1994; Hirono et al., 1997) The NPI, which is a semi-structured interview with a caregiver of patients, consists of ten behavioural domains including Depression/Dysphoria. For each domain, several subquestions are explored. For suicidal ideation, we regarded an answer of "yes" to the subquestion of the domain of Depression/Dysphoria, "Does the patient express a wish for death or talk about killing himself/herself ?" as "having suicidal ideation".

2.2.2. Behavioural and Psychological Symptoms of Dementia (BPSD)

NPI was used to assess BPSD (Cummings et al., 1994; Hirono et al., 1997) Besides Depression/Dysphoria above, we evaluated the domains of Hallucinations, Delusions, Agitation/aggression, Anxiety, Euphoria, Apathy, Disinhibition, Irritability/lability, and Aberrant motor behaviour. The score of each domain was calculated by frequency (1=less than once a week, 2=once a week, 3=a few times a week, 4=once a day or more) × severity (1=mild, 2=moderate, 3=severe), and we regarded the sum of all scores of each domain excluding Depression/Dysphoria as the NPI total score (range, 0–108). Higher scores indicate worse conditions.

2.2.3. Caregiver burden

The Japanese version of the Zarit Caregiver Burden Interview (J-ZBI)(Arai et al., 1997), (Zarit et al., 1980) was used. ZBI consists of 22 questions about the impact of the patient's disabilities on the lifestyle of the caregiver. The questions were aimed at eliciting information regarding areas most frequently mentioned by caregivers as problematic, including caregiver health, psychological well-being, finances, social life, and the relationship between the caregiver and recipient of care. For each item, caregivers indicate how often they feel that way (never=0, rarely=1, sometimes=2, quite frequently=3, nearly always=4). The sum of scores ranges from 0 to 88, and higher scores indicate higher burden.

2.2.4. Severity of dementia and cognitive function

The severity of dementia was assessed using the Clinical Dementia Rating (CDR) scale.(Morris, 1993) It is a 5-point scale used to characterise six domains of cognitive and functional performance: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. Based on these domains, an overall CDR score is calculated. The overall CDR assigns cognitive function to five levels: no dementia, CDR 0; questionable dementia, CDR 0.5; mild dementia, CDR 1; moderate dementia, CDR 2; or severe dementia, CDR 3., The Mini-Mental State Examination (MMSE) was used to assess cognitive function.(Folstein et al., 1975) MMSE is one of the most widely used cognitive screening tests that quantitatively assesses the severity of cognitive function. Scores range from 0 to 30, with higher scores indicating better cognitive functioning.

2.2.5. Other variables

Sociodemographic and clinical variables included age, gender, way of living (living alone, living with family), age of dementia onset (younger than 65 years, aged 65 years and older), and duration of illness.

2.3. Statistical analysis

Participants were divided into three groups: the suicidal ideation group (SI+), the no suicidal ideation with depression group (SI-/Dep+), and the neither suicidal ideation nor depression group (SI-/Dep-). Demographic and clinical factors were compared among groups using one-way analysis of variance and Bonferroni's post-hoc test. To compare caregiver burden among the three groups, we conducted one-way analysis of covariance adjusting for NPI total score (except for the Depression/Dysphoria score), which is strongly related to caregiver burden.(Ornstein and Gaugler, 2012) All tests were two-tailed and the significance levels were set at $P<0.05$. All statistical analyses were performed with SPSS 21.0 J for Windows (IBM SPSS Japan, Tokyo, Japan).

3. Results

Of 634 subjects, suicidal ideation was seen in 64 (10.1%). Of 570 subjects who did not have suicidal ideation, 133 (21.0%) had depression (SI-/Dep+ group), and 437 (68.9%) did not (SI-/Dep- group). Table 1 shows demographic and clinical characteristics of groups. The percentage of females was significantly higher in the SI+ and SI-/Dep+ groups than the SI-/Dep- group. Early-onset participants (younger than 65 years) had a significantly higher rate of SI-/Dep+ than late-onset participants and a significantly lower rate of SI-/Dep-. NPI total score except for the Depression/Dysphoria score was significantly lower in the SI-/Dep- group than in the SI+ and SI-/Dep- groups. There were no significant differences among groups in age, duration of illness, diagnoses, severity of dementia, way of living, and cognitive function.

Table 2 shows BPSD symptoms. Symptoms that were significantly more severe in the SI+ group than in the SI-/Dep+ and SI-/Dep- groups were delusions, agitation/aggression, and anxiety. Apathy and irritability/lability were significantly worse in the SI+ group than in the SI-/Dep- group, but were not worse than in the

Table 1
Comparisons of demographic and clinical factors among groups.

	Suicidal ideation (+) n=64	Suicidal ideation (-) n=570		F/χ^2	p
		Depression (+) n=133	Depression (-) n=437		
Age, mean[a]	77.3	74.5	81.5	0.45	0.637
Onset[b]				11.04	0.004
Early (< 65 years), n=95	7.4%] AB	33.7%] B	58.9%] A		
Late (≥65 years), n=539	10.6%] AB	18.7%] B	70.7%] A		
Duration of illness, mean[a]	3.0	2.6	2.6	0.45	0.641
Gender(%)[b]				20.32	<0.001
Male, n=242	5.0%] A	16.1%] A	78.9%] B		
Female, n=392	13.3%] A	24.0%] A	62.8%] B		
Diagnosis (%)[b]				2.59	0.859
AD, n=467	10.3%	21.0%	68.7%		
VaD, n=63	11.1%	19.0%	69.8%		
DLB, n=78	10.3%	19.2%	70.5%		
FTLD, n=26	3.8%	30.8%	65.4%		
Severity (%)[b]				10.00	0.125
Very mild, n=270	7.4%	21.5%	71.1%		
Mild, n=262	11.1%	18.3%	70.6%		
Moderate, n=88	15.9%	27.3%	56.8%		
Severe, n=14	7.1%	21.4%	71.4%		
Way of living (%)[b]				0.66	0.718
Living alone, n=101	7.9%	20.8%	71.3%		
Living with family, n=533	10.5%	21.0%	68.5%		
MMSE score, mean[a]	18.6	19.8	19.8	1.54	0.215
NPI total score (except for Depression/Dysphoria score), mean[a]	16.3[a]	12.5[a]	9.4[b]	14.43	<0.001

Different characters represent significant differences between groups. ($P < 0.05$).
AD: Alzheimer's disease, VaD: vascular dementia, DLB: dementia with Lewy bodies, FTLD: frontotemporal lobar degeneration.
MMSE: Mini-Mental State Examination, NPI: Neuropsychiatric Inventory.
[a]One-way ANOVA and Bonferroni's post-hoc test.
[b]Chi-square and Z test.

Table 2
Comparisons of behavioural and psychological symptoms of dementia between groups.

	Suicidal ideation (+) n=64	Suicidal ideation (-) n=570		F	p
		Depression (+) n=133	Depression (-) n=437		
Delusions	2.1[A]	1.2[B]	1.0[B]	6.3	0.002
Hallucinations	0.8	0.6	0.6	0.3	0.771
Agitation/aggression	1.8[A]	1.0[B]	0.9[B]	5.6	0.004
Anxiety	2.3[A]	1.4[B]	0.8[C]	16.8	<0.001
Euphoria	0.0	0.1	0.1	1.3	0.272
Apathy	4.7[A]	4.1[A]	3.1[B]	7.8	<0.001
Disinhibition	0.5	0.6	0.3	2.2	0.111
Irritability/lability	1.8[A]	1.4[A]	0.8[B]	10.2	<0.001
Aberrant motor behavior	1.1	1.1	1.0	0.1	0.875
Depression/Dysphoria	3.9[A]	3.0[B]	0.0[C]	344.9	<0.001

Different characters represent significant differences between groups. ($P < 0.05$).
One-way ANOVA and Bonferroni's post-hoc test.

Table 3
Comparisons of caregiver burden among groups.

	Suicidal ideation (+) n=64	Suicidal ideation (-) n=570		F	p
		Depression (+) n=133	Depression (-) n=437		
ZBI score, mean[a]	30.9[A]	24.1[B]	20.2[C]	17.2	<0.001
Estimated ZBI score, mean[b]	26.6[A]	22.7	21.2[B]	5.7	0.003

Different characters represent significant differences between groups. ($P < 0.05$).
ZBI: Zarit Caregiver Burden Interview.
[a] ANOVA and Bonferroni's post-hoc test to compare differences among three groups.
[b] ANCOVA adjusting for NPI total score (except for Depression/Dysphoria score), and Bonferroni's post-hoc test to compare differences among three groups.

SI-/Dep+ group. Depression/Dysphoria was significantly worse in the SI+ group than in the SI-/Dep+ group.

In terms of caregiver burden (Table 3), the SI+ group had a significantly higher burden than the SI-/Dep+ and SI-/Dep- groups. After adjusting for NPI total score (except for the Depression/Dysphoria score), the difference was not significant between the SI+ and SI-/Dep+ groups, but the SI+ group had a significantly higher burden than the SI-/Dep- group.

4. Discussion

The present study was the first to show a prevalence of suicidal ideation among dementia patients and the relationship between suicidal ideation and other factors. In our study, a total of 10.1% of dementia patients had suicidal ideation, the number of which is somewhat higher than that of community-dwelling older people. Almeida et al. reported that 4.8% of community-dwelling older people aged 60 years and older acknowledged suicidal ideation. (Almeida et al., 2012) Although the prevalence of suicidal ideation is reported to decrease with advancing age,(Nock et al., 2008) suicidal ideation might not be a rare feeling in the last stage of life. Fässberg et al. reported that 11.8% of elderly people aged 97 years

old without dementia had some levels of suicidal ideation but that most of them did not fulfil the criteria for depression.(Fässberg et al., 2013) Comparisons of the prevalence of suicidal ideation between dementia patients and normal controls are needed in future studies.

Our study revealed that age, gender, and way of living were not related to suicidal ideation. In addition, suicidal ideation was observed regardless of diagnosis, severity, and cognitive function, which is inconsistent with some previous studies that reported a higher risk of suicidal behaviour in early stages of dementia or with a new dementia diagnosis.(Lim et al., 2005; Seyfried et al., 2011) This inconsistency might be explained by the difference between suicidal ideation and suicidal behaviour, although suicidal ideation is one of the most important risk factors of suicidal behaviour.(Almeida et al., 2012) Our results suggest the importance of paying attention to suicidal ideation in every stage and type of dementia.

The dementia patients with suicidal ideation had worse BPSD. In particular, delusion, agitation/aggression, and anxiety were more frequently seen in patients with suicidal ideation than those without suicidal ideation. Although some previous studies examined the effect of BPSD on patients' quality of life, consistent results have not been obtained thus far.(Naglie et al., 2011) However, our results indicate the association between BPSD and suicidal ideation. Some dementia patients with behavioural disturbances might feel uncomfortable about these symptoms, or others may be distressed about the relationship with caregivers over these symptoms.

Patients with suicidal ideation were more depressed than those with depression but accompanying suicidal ideation, which indicates that the severity of depression is associated with suicidal ideation among dementia patients as is the case with the common depression.

Our results showed higher caregiver burden of patients with suicidal ideation. Higher caregiver burden of patients with suicidal ideation was reported in a previous study targeted at bipolar patients.(Chessick et al., 2007) Caring for people who have suicidal ideation might be highly stressful for caregivers regardless of disease. Caregiver burden has been pointed out to be associated with poor outcomes of caregivers such as depression, physical illness, and decreased QOL, along with poor outcomes of dementia patients, such as poor QOL and early nursing home placement.(Etters et al., 2008) A recent study also reported a significant prevalence of suicidal ideation in caregivers of patients with dementia.(O'Dwyer et al., 2013) Psychological support for caregivers of dementia patients with suicidal ideation and care support for patients are needed to alleviate burden.

4.1. Limitations

A major strength of our study is that we clarified the prevalence of and factors related to suicidal ideation among clinical dementia in a large sample. However, some limitations must be considered when interpreting these results. First, we assessed patients' suicidal ideation from the caregivers' interview, so we may have overlooked people who had suicidal ideation but did not express it to their caregivers. Therefore, the prevalence rate of suicidal ideation among our sample of dementia patients might be underestimated. Second, we could not assess the seriousness of suicidal ideation. Third, we dealt with suicidal ideation, not with suicidal attempts. Fourth, we targeted only AD, VaD, DLB, and FTLD and did not examine other minor diseases underlying dementia because the number of each disease was not high enough for statistical analysis.

Although dementia patients are thought to lack insight, it is possible that they are often vaguely aware of their unusual changes after the onset of dementia and lose confidence or feel anxiety. As a result, they might become socially isolated, coupled with apathetic symptoms. Considering that social isolation is reported to be a strong risk factor for suicide in the elderly,(Almeida et al., 2012; Draper, 2014) providing opportunities for going out and communicating with others may be important from the aspect of suicide prevention.

4.2. Conclusions and clinical implications

In conclusion, about 10% of dementia patients had suicidal ideation, regardless of diagnosis, severity, and cognitive function. Caring for dementia patients who have both suicidal ideation and depression was highly burdensome for caregivers. It is important to assess dementia patients' suicidal ideation, expressed or not, adequately and to provide psychological support and as-needed treatment for depression.

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Contributors

AK, MM, and TI collected the data. AK analysed and wrote the paper. NF, MH, and MI provided valuable help on this study. All authors discussed the results and commented on the manuscript.

Declaration of interest

None.

Conflict of interest

None.

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