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Ⅲ. 研究成果の刊行物・別刷

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The usefulness of monitoring sleep talking for the diagnosis of dementia with Lewy bodies

Kazuki Honda,[1] Mamoru Hashimoto,[2] Yusuke Yatabe,[2] Keiichiro Kaneda,[2] Seiji Yuki,[2] Yusuke Ogawa,[2,3] Shiho Matsuzaki,[1] Atsuko Tsuyuguchi,[1] Hibiki Tanaka,[1] Hiroko Kashiwagi,[1] Noriko Hasegawa,[1,4] Tomohisa Ishikawa[2] and Manabu Ikeda[2]

[1] *Department of Neuropsychiatry, Graduate School of Medical Science, Kumamoto University, Kumamoto, Japan*
[2] *Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan*
[3] *Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine, Kyoto, Japan*
[4] *Department of Psychiatry, Kobe University Graduate School of Medicine, Hyogo, Japan*

ABSTRACT

Background: Dementia with Lewy bodies (DLB) is the second most common type of neurodegenerative dementia. It is frequently difficult to differentiate DLB from Alzheimer's disease (AD) and other types of dementia. This study examined the usefulness of monitoring sleep talking for the diagnosis of DLB.

Methods: A total of 317 patients with dementia were selected from a consecutive series at the Dementia Clinic of Kumamoto University Hospital. Diagnostic categories consisted of probable DLB (n = 55), probable AD (n = 191), frontotemporal lobar degeneration (FTLD) (n = 16), vascular dementia (VaD) (n = 18), and other/unspecified dementia (n = 37). We evaluated sleep talking in all dementia patients and normal elderly subjects (n = 32) using an originally designed sleep talking questionnaire.

Results: Sleep talking occurred most frequently in the DLB group (61.8%), followed by the VaD group (33.3%), other/unspecified dementia group (27.0%), AD group (18.8%), FTLD group (12.5%), and normal elderly subjects group (6.3%). The prevalence of sleep talking in the DLB group was significantly higher than in other groups, except in the VaD group. The sleep talking yielded high specificity (81.2%) and some sensitivity (61.8%) for the differential diagnosis of DLB from AD. Furthermore, loud sleep talking may improve the specificity (96.9%). For the differentiation of DLB from all other dementia types, the specificity of sleep talking and loud sleep talking was also high (79.4% and 95.8% respectively).

Conclusions: Assessing sleep talking, especially the volume of sleep talking, may be useful in the clinical discrimination of DLB from not only AD but also from all other types of dementia.

Key words: dementia with Lewy bodies, Alzheimer's disease, differential diagnosis, sleep talking

Introduction

Dementia with Lewy bodies (DLB) is the second most common type of neurodegenerative dementia in late life after Alzheimer's disease (AD) and accounts for 10.9%–22.0% of all causes of dementia (Stevens *et al.*, 2002; Rahkonen *et al.*, 2003). DLB has a more malignant course in terms of the rate of cognitive decline (Williams *et al.*, 2006), mortality (Williams *et al.*, 2006), quality of life (Boström *et al.*, 2007a), and resource utilization compared to AD (Boström *et al.*, 2007b). The accurate antemortem diagnosis of DLB is particularly important because of the development of interventions and specific pharmacologic treatments and outcome evaluations.

The clinical diagnostic criteria for DLB were first published in 1996 (McKeith *et al.*, 1996), and were modified in 2005 (McKeith *et al.*, 2005). The central or core symptoms in DLB are progressive cognitive decline, marked fluctuations in cognition, recurrent visual hallucinations, and spontaneous features of Parkinsonism (McKeith *et al.*, 1996). However, a recent study exploring the early symptoms of DLB reported that memory impairment was the most common presenting symptom (57%) in DLB, followed by visual hallucinations (44%) (Auning *et al.*,

Correspondence should be addressed to: Dr Manabu Ikeda, MD, Department of Neuropsychiatry, Kumamoto University Graduate School of Medical Science, 1-1-1 Honjo, Kumamoto-City, Kumamoto, 860-8556, Japan. Phone: +81-96-373-5184; Fax: +81-96-373-5186. Email: mikeda@kumamoto-u.ac.jp.
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2011). Therefore, when the initial presentation of DLB is impaired cognition, it is difficult to differentiate DLB from AD during the early course of the illness. Although Single Photon Emission Computed Tomography (SPECT) and Iodine-123 Metaiodobenzylguanidine (123I-MIBG) myocardial scintigraphy are useful in the differential diagnosis of DLB (Lobotesis *et al.*, 2001; Yoshita *et al.*, 2001), these examinations are too expensive to be utilized generally.

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by a loss of normal skeletal muscle atonia during REM sleep with prominent motor activity accompanying dreaming (American Academy of Sleep Medicine, 2005). This condition is considered to be frequently associated with an underlying synucleiopathy such as DLB, Parkinson's disease, or multiple system atrophy and only rarely with other neurodegenerative disorders (Boeve *et al.*, 2003a). Revised criteria for the clinical diagnosis of DLB have included RBD in suggestive features (McKeith *et al.*, 2005). Furthermore, Ferman *et al.* (2011) reported that the inclusion of RBD as a core feature improved the diagnostic accuracy of autopsy-confirmed DLB. Polysomnography (PSG) is necessary to confirm the diagnosis of RBD. However, it is impractical to perform PSG routinely on patients suspected of having DLB.

Sleep talking is a major symptom of RBD. A questionnaire concerning sleep talking could easily be asked from all caregivers of patients with dementia in daily medical practice. However, there have been few studies of sleep talking in patients with DLB and other types of dementia. We hypothesized that patients with DLB would exhibit a higher frequency of sleep talking compared with other demented patients, including AD, and examined the usefulness of the questionnaire for the differential diagnosis of DLB.

Methods

Subjects

The whole procedure followed the 2010 Clinical Study Guidelines of the Ethics Committee of Kumamoto University Hospital and was approved by the Internal Review Board. After a complete description of all procedures of the present study, written informed consent was obtained from the patients or their caregivers.

This study was a prospective dementia referral center-based cohort study. A total of 317 patients with dementia were selected from a consecutive series of 573 patients who underwent a medical examination at the Dementia Clinic of the Department of Neuropsychiatry, Kumamoto University Hospital between January 2010 and December 2011. All patients were examined comprehensively by senior neuropsychiatrists with sufficient experience in examining patients with dementia, and all patients underwent routine laboratory tests, standard neuropsychological examinations, including the Mini-Mental State Examination (MMSE). Brain magnetic resonance imaging (MRI) or computed tomography (CT) and SPECT were also performed. The following patients were excluded from the current study: (1) those with developmental abnormalities, serious psychiatric diseases, such as schizophrenia or major depression, or substance abuse before the onset of dementia; (2) those living alone or in a nursing home; (3) those whose caregivers had hearing loss; and (4) those without a reliable informant.

Dementia was diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition-revised (DSM-III-R). Probable DLB was diagnosed on the basis of the international working group criteria (McKeith *et al.*, 1996). To avoid circularity, we did not use the revised criteria in 2005 (McKeith *et al.*, 2005), in which RBD was included as a suggestive feature. Brain SPECT was also used to support the clinical diagnosis of DLB. In this study, patients whose dementia developed 12 months or later after the onset of Parkinson's disease (Parkinson's disease with dementia) were classified into the DLB group because they usually have underlying Lewy body pathology and their number was too small to analyze separately (n = 3). Patients were diagnosed as having AD if they met the criteria of the National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) guidelines (McKhann *et al.*, 1984). Patients who fulfilled both probable AD and possible DLB were classified into the AD group (n = 6). Diagnoses of frontotemporal lobar degeneration (FTLD) were based on the consensus clinical diagnostic criteria in an international workshop on FTLD (Neary *et al.*, 1998) and brain SPECT was used to support the clinical diagnosis of FTLD as described earlier (Pickut *et al.*, 1997). Probable vascular dementia (VaD) was diagnosed on the basis of the Criteria for the Diagnosis of Ischemic Vascular Dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) (Chui *et al.*, 1992). Patients who fulfilled the criteria of probable AD and, in addition, displayed cerebrovascular disease (CVD) on brain MRI or CT that did not meet the criteria of VaD were classified in the AD group. Diagnostic categories consisted of probable DLB (n = 55), probable AD (n = 191), FTLD (n = 16), VaD

Table 1. Sleep talking questionnaire

Screening question
Q. Does the patient talk in his/her sleep?
Sleep talking is defined as present if the patient talks in his/her sleep for over 10 seconds, and once a month or more.
Sub-questions
Q1. Does the patient talk in his/her sleep in a loud voice?
Loud sleep talking is defined as present if sleep talking is loud enough to hear even in the next room.
Q2. Does the patient talk in his/her sleep frequently?
Frequent sleep talking is defined as present if the patient talks in his/her sleep once a week or more.
Q3. Has the patient's sleep talking occurred for more than 10 years?

(n = 18), and other/unspecified dementias (O/U dementias) (n = 37). The O/U dementia group consisted of patients with probable progressive supranuclear palsy (PSP) (n = 5; Litvan *et al.*, 1996), probable corticobasal degeneration (CBD) (n = 2; Boeve *et al.*, 2003b), and unspecified etiology (n = 30).

Normal elderly subjects

Thirty-two normal elderly subjects (NE subjects) were recruited from the community (14 males and 18 females). They showed normal cognitive functions (25 or above on the MMSE), normal findings in the physical and neurologic examinations, no history of psychiatric disorders, and no risk factors for CVD (hypertension, heart disease, and diabetes mellitus). All NE subjects had their family members in the same household.

Evaluation of sleep talking

We evaluated sleep talking in dementia patients and NE subjects by using a questionnaire that had originally been designed to assess sleep talking easily (Table 1). The questionnaire asks a screening question to confirm whether the subject has any sleep talking or not. If the screening question is answered in affirmative, three sub-questions about the feature of sleep talking (volume, frequency, and duration of sleep talking) are asked. The questionnaire is based on the *International Classification of Sleep Disorders*, diagnostic criteria for RBD (American Academy of Sleep Medicine, 2005), and some questionnaires that adequately screen for RBD (Boeve *et al.*, 2002; Li *et al.*, 2010). Sleep talking was assessed by a single psychiatrist (Kazuki Honda) who was blinded to all clinical information, including the dementia diagnosis.

Evaluation of sleep disturbances

In dementia patients, sleep and nighttime behavior disorder (SNBD) were assessed by using the Japanese version of the 12-item Neuropsychiatric Inventory (NPI) (Cummings, 1997). We focused on the sleep and nighttime behavior item of the NPI. This item asks the following: (1) "Does the patient have difficulty sleeping (do not count as present if the patient simply gets up once or twice per night only to go to the bathroom and falls back asleep immediately)?"; (2) "Is he/she up at night?"; and (3) 'Does he/she wander at night, get dressed, or disturb your sleep?"; these questions could be answered with "yes" or "no," and SNBD was categorized as present or absent.

Statistical analysis

Differences in patient characteristics between the six groups (DLB, AD, FTLD, VaD, O/U dementia, and NE subjects groups) were analyzed by one-way analysis of variance (ANOVA) or compared by Fisher's exact probability test. Difference in the usage of psychotropic drugs was analyzed by Fisher's exact probability test in five dementia groups.

To examine the prevalence of sleep talking, loud sleep talking, frequent sleep talking, long-term sleep talking, and SNBD, we used Fisher's exact probability test and Bonferroni Z-test for each comparison when an overall group difference was significant. A multiple logistic regression analysis was applied to identify significant independent predictors for sleep talking. Valuables entered were diagnosis (DLB or not), age, sex, duration of illness, MMSE score, the use of cholinesterase inhibitors, benzodiazepine anxiolytics, antipsychotics and antidepressant, and bedroom sharing. In addition, we calculated the sensitivity and specificity of sleep talking, three features of sleep talking, and SNBD for the differential diagnosis of DLB from AD and that of DLB from all other dementias. A significance level of 0.05 was set for all analyses. All analyses were carried out using SPSS for Windows, version 17.0.

Table 2. Demographic and clinical valuables in five dementia groups and the NE subjects group

	DLB (n = 55)	AD (n = 191)	FTLD (n = 16)	VAD (n = 18)	O/U DEMENTIA (n = 37)	NE SUBJECTS (n = 32)	P-VALUE
Age (in yrs.)	79.4 ± 5.4	75.4 ± 8.6	64.6 ± 9.6	77.7 ± 7.6	78.0 ± 7.9	74.7 ± 7.5	<0.001[a]
Male	32 (58.1%)	82 (41.9%)	10 (62.5%)	12 (66.7%)	15 (40.5%)	14 (43.8%)	0.107[b]
Duration (in yrs.)	3.6 ± 2.3	3.3 ± 2.1	4.1 ± 3.0	4.4 ± 4.6	3.5 ± 2.4	n.a.	0.287[a]
MMSE score	17.6 ± 6.3	18.3 ± 5.7	18.9 ± 6.3	18.6 ± 4.5	18.4 ± 6.2	27.9 ± 1.8	<0.001[a]
Medication							
Cholinesterase inhibitors	19 (34.5%)	50 (26.2%)	8 (50.0%)	3 (16.7%)	4 (10.8%)	n.a.	0.017[b]
Benzodiazepine anxiolytics	16 (29.1%)	28 (14.7%)	3 (18.8%)	3 (16.7%)	6 (16.2%)	n.a.	0.195[b]
Antipsychotics	6 (10.9%)	5 (2.6%)	2 (12.5%)	1 (5.6%)	6 (16.2%)	n.a.	0.004[b]
Antidepressants	7 (12.7%)	19 (9.9%)	2 (12.5%)	1 (5.5%)	2 (5.4%)	n.a.	0.798[b]
Bedroom sharing with patients	29 (52.7%)	110 (57.6%)	12 (75.0%)	4 (22.2%)	16 (43.2%)	n.a.	0.011[b]

Notes: Values are n (%), or mean ± SD.
DLB: dementia with Lewy bodies; AD: Alzheimer's disease; FTLD: frontotemporal lobar degeneration; VaD: vascular dementia; O/U dementia: other/unspecified dementia; NE subjects: normal elderly subjects; MMSE: Mini-Mental State Examination; n.a.: not applicable.
Analysis by [a]one-way ANOVA or [b]Fisher's exact probability test.

Table 3. Frequency of sleep talking, loud sleep talking, frequent sleep talking, long-term sleep talking, and SNBD in five dementia groups and the NE subjects group

SLEEP FEATURES	DLB (n = 55)	AD (n = 191)	FTLD (n = 16)	VAD (n = 18)	O/U DEMENTIA (n = 37)	NE SUBJECTS (n = 32)	p-VALUE
Sleep talking	34 (61.8%)	36 (18.8%)	2 (12.5%)	6 (33.3%)	10 (27.0%)	2 (6.3%)	<0.001*
Loud sleep talking	22 (40.0%)	6 (3.1%)	0 (0%)	1 (5.6%)	4 (10.8%)	1 (3.1%)	<0.001†
Frequent sleep talking	20 (36.4%)	16 (8.4%)	1 (6.3%)	3 (16.7%)	6 (16.2%)	2 (6.3%)	<0.001‡
Long-term sleep talking	14 (25.5%)	13 (6.8%)	1 (6.3%)	4 (22.2%)	4 (10.8%)	1 (3.1%)	0.002§
SNBD	27 (49.1%)	35 (18.3%)	5 (31.3%)	8 (44.4%)	12 (32.4%)	n.a.	<0.001§

Notes: Values are n (%).
DLB: dementia with Lewy bodies; AD: Alzheimer's disease; FTLD: frontotemporal lobar degeneration; VaD: vascular dementia; O/U dementia: other/unspecified dementia; NE subjects: normal elderly subjects; SNBD: sleep and night-time behavior disorder; n.a.: not applicable.
Analysis by Fisher's exact probability test and Bonferroni Z-test.
*DLB significantly higher than AD, FTLD, O/U dementia, and NE subjects.
†DLB significantly higher than AD, O/U dementia, and NE subjects (FTLD was not compared with other groups).
‡DLB significantly higher than AD and NE subjects.
§DLB significantly higher than AD.

Results

Table 2 presents the demographic and clinical indices of the subjects. Five dementia and NE subject groups were involved in the present study. There were significant differences in age, MMSE, and the ratio of bedroom sharing in six groups. As for medication, there was a significant difference in the frequency of cholinesterase inhibitors and antipsychotics prescription, but no significant differences were observed in the frequency of other drug usage in five dementia groups. Memantine or melatonin was not prescribed to any patient in this study.

Table 3 shows the prevalence of sleep talking, three features of sleep talking, and SNBD in all the

Table 4. Results of multiple logistic regression analysis associated with sleep talking

FACTORS	WALD	EXP (B)	95% CONFIDENCE INTERVAL	P-VALUE
Diagnosis (DLB or not)	32.323	6.967	3.568–13.603	<0.001
Age	0.359	1.011	0.976–1.046	0.549
Duration	0.004	0.996	0.889–1.116	0.947
MMSE score	0.017	0.997	0.950–1.046	0.897
Bedroom sharing	0.576	0.784	0.419–1.469	0.448
Cholinesterase inhibitors	0.767	0.758	0.407–1.410	0.381
Benzodiazepine	0.276	1.212	0.591–2.485	0.599
Antipsychotic	0.165	0.795	0.262–2.413	0.685
Antidepressant	0.130	0.840	0.327–2.160	0.718

Note: DLB: dementia with Lewy bodies; MMSE: Mini-Mental State Examination.

Table 5. Sensitivity and specificity of sleep talking, three features of sleep talking, and SNBD for the differentiation of DLB from AD or all other dementias

	DIFFERENTIATION OF DLB FROM AD		DIFFERENTIATION OF DLB FROM ALL OTHER DEMENTIAS	
	SENSITIVITY (%)	SPECIFICITY (%)	SENSITIVITY (%)	SPECIFICITY (%)
Sleep talking	61.8	81.2	61.8	79.4
Loud sleep talking	40.0	96.9	40.0	95.8
Frequent sleep talking	36.4	91.6	36.4	90.1
Long-term sleep talking	25.5	93.2	25.5	91.6
SNBD	49.1	81.7	49.1	77.1

Note: DLB: dementia with Lewy bodies; AD: Alzheimer's disease; SNBD: sleep and nighttime behavior disorder.

six groups. Sleep talking occurred most frequently in the DLB group, followed by the VaD group. It is noteworthy that only 6.3% of the NE subjects presented with sleep talking. There was a significant difference in the prevalence of sleep talking in these six groups. The prevalence of sleep talking in the DLB group was significantly higher than in other groups, except for the VaD group. Of the 34 DLB patients who had sleep talking, 22 patients (64.7%) showed loud sleep talking and the prevalence of loud sleep talking in the DLB group was significantly higher than that in the AD, O/U dementia, and NE subject groups. SNDB occurred most frequently in the DLB group and the prevalence of SNDB was significantly higher in the DLB group than in the AD group.

Multiple logistic regression analysis showed that a diagnosis of DLB was significantly associated with the presence of sleep talking (Table 4). There was no association between age, sex, duration of disease, MMSE score, bedroom sharing, or psychotropic drug usage and the presence of sleep talking.

Table 5 shows the sensitivity and specificity of sleep talking, three features of sleep talking, and SNBD for the differential diagnosis of DLB from AD and that of DLB from all other types of dementia. The sleep talking yielded high specificity (81.2%) and some sensitivity (61.8%) for the differential diagnosis of DLB from AD. The loud sleep talking could improve the specificity (96.9%), but the sensitivity would decrease (40.0%). Even with the differentiation of DLB from all other dementias, the specificity of sleep talking and loud sleep talking did not change (79.4% and 95.8% respectively).

Discussion

Sleep talking is not necessarily a pathological symptom, and it often occurs in normal healthy people. Bjorvatn *et al.* (2010) reported that sleep talking occurs at least once a week in 6.3% of adults in the general population. In the present study, 6.3% of NE subjects showed sleep talking, which is very similar to Bjorvatn *et al.*'s data. These findings indicate that the high prevalence of sleep talking in patients with dementia may be associated with some underlying pathological changes.

In this study, the prevalence of sleep talking differed according to the diagnostic group. In

the DLB group, more than 60% of patients exhibited sleep talking, and the prevalence was significantly higher than in any other dementia types. Although the pathophysiology of sleep talking is not well understood, sleep talking is reported to be seen with high frequency in patients with RBD (Li *et al.*, 2010). Boeve (2010) summarized demographics and clinical phenomenology of RBD, and demonstrated that abnormal vocalization is considered to characterize RBD, which is considered to be frequently associated with an underlying synucleinopathy, such as DLB (Boeve *et al.*, 2003a), and rarely with other neurodegenerative disorders. Ferman *et al.* (2011) reported that a history of RBD was present in 76% of autopsy-confirmed DLB patients. Therefore, RBD may be responsible for sleep talking in people with DLB.

We observed a high specificity of sleep talking (81.2%) for the differentiation of DLB from AD. In particular, the presence of loud sleep talking showed extremely high specificity (96.9%). Even in the differentiation of DLB from all other dementias, the specificity of loud sleep talking was kept high (95.8%). These findings suggest the usefulness of sleep talking to discriminate patients with DLB from those with other types of dementia. Although the utilization of SPECT and 123I-MIBG myocardial scintigraphy are limited to well-equipped hospitals, screening questions concerning sleep talking are easy to ask in clinical practice. Thus, patients suspected of having DLB should be questioned about the presence of sleep talking, in particular, the volume of sleep talking.

There was no significant difference between the DLB and VaD groups in the prevalence of sleep talking. This result may reflect low statistical power due to small sample size in the VaD group. However, the prevalence of sleep talking in the VaD group (33.3%) was higher than in NE subjects (6.3%), which did not reach statistical significance. To our knowledge, there have been no reports that investigated the prevalence of RBD in patients with VaD. Although RBD is frequently seen in patients with neurodegenerative diseases, RBD in patients with a pure pontine infarction has also been reported (Xi and Luning, 2009). Some vascular damage around the pons may cause RBD in patients with VaD, and this might explain a certain prevalence of sleep talking in the VaD group.

Sleep disturbance occurs in many forms of dementia. Guarnieri *et al.* (2012) reported that over 60% of persons with cognitive decline had one or more sleep disturbances. In this study, we also investigated the prevalence of sleep and nighttime behavior disorder. In the VaD and FTLD groups, the prevalence of SNBD was higher than that of sleep talking. On the other hand, in the DLB group, the prevalence of SNBD was lower than that of sleep talking. Severe daytime sleepiness predicts VaD (Guarnieri *et al.*, 2012), and sleep-disordered breathing was frequent in VaD patients (Elwood *et al.*, 2011). Anderson *et al.* (2009) have demonstrated sleep–wake disturbance in patients with FTD, who showed increased nocturnal activity and decreased morning activity. These findings suggest that each form of dementia may have a disease-specific sleep disturbance. Ferman and Boeve (2007) reported that sleep disturbance is helpful in differentiating DLB from AD early in the disease course. However, it may be more efficient to focus on sleep talking than to assess overall sleep disturbances for the differentiation of DLB from other dementias.

A recent review of RBD has described that the commonly used medications may induce or unmask latent RBD, and antidepressants are most commonly implicated in altering muscle control during REM and causing RBD (Trotti, 2010). On the other hand, based on a large case series and clinical experience, benzodiazepine clonazepam is considered the first-line treatment for RBD (Chenck and Mahowald, 1990). In the present study, no significant differences were observed in the frequency of benzodiazepine anxiolytics and antidepressant usage between the dementia groups. However, there were significant differences in the frequency of cholinesterase inhibitors and antipsychotic prescriptions. To our knowledge, there are no reports that indicate an association between antipsychotics and RBD. As for cholinesterase inhibitors, Boeve *et al.* (2003c) reported that among 50 patients with DLB and RBD who were treated with donepezil, none experienced significant benefit. Furthermore, multiple logistic regression analysis did not reveal any significant association between the use of these psychotropic drugs and the presence of sleep talking. Therefore, the difference in the frequency of sleep talking between different dementia types cannot be attributed to the effect of psychotropic drugs.

Several methodological issues limit the interpretation of results of this study. First, the diagnosis relied solely on clinical basis without histopathologic confirmation, with inevitably some uncertainty about the rate of misclassification. Although clinical studies are in fact influenced by the quality of clinical diagnosis, clinical studies with prospective clinical data collection can assess patients' sleep disturbances more accurately than can autopsy studies with retrospective data review. Moreover, we supplemented clinical diagnosis with neuroimaging studies. Second, we obtained

information about sleep talking from patients' caregivers. However, nearly half of the caregivers did not share their bedroom with the patients. This condition may make it more difficult for the caregivers to note patients' sleep talking and would increase the false-negative rate of sleep talking. In our study, approximately 60% of the patients with DLB had sleep talking, but this rate might be lower than the true rate. Third, although we considered that RBD was primarily responsible for sleep talking in the dementia patients, no patient with sleep talking was confirmed by PSG whether they had RBD or not. Therefore, the relationship between sleep talking and RBD can only be hypothesized. However, our main aim was to find an alternative to PSG, which can discriminate DLB from AD or all other dementias easily. In the future study, sleep talking in people with dementia need to be evaluated by PSG.

Despite these limitations, we believe that our findings are quite reliable because they are based on a prospective study design and on a consecutive patient series whose diagnosis was carefully made using widely accepted clinical criteria.

Conclusion

The questionnaire about sleep talking, especially the volume of sleep talking, may be useful in the clinical discrimination of DLB from not only AD but also from all other types of dementia.

Conflict of interest

None.

Description of authors' role

Kazuki Honda designed this study, worked on data analysis, and wrote the paper. Yusuke Yatabe, Keiichiro Kaneda, Seiji Yuki, Yusuke Ogawa, Shiho Matuzaki, Atsuko Tsuyuguchi, Hibiki Tanaka, Hiroko Kashiwagi, Noriko Hasegawa, and Tomohisa Ishikawa helped in collecting the data. Mamoru Hashimoto supervised this study. Manabu Ikeda was responsible for the statistical design of the study.

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RESEARCH ARTICLE

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Association of cerebral small vessel disease with delusions in patients with Alzheimer's disease

Yusuke Ogawa[1], Mamoru Hashimoto[2], Yusuke Yatabe[2], Keiichiro Kaneda[2], Kazuki Honda[1], Seiji Yuuki[1], Toshinori Hirai[3] and Manabu Ikeda[2]

[1]Department of Psychiatry and Neuropathobiology, Graduate School of Medical Science, Kumamoto University, Kumamoto, Japan
[2]Department of Psychiatry and Neuropathobiology, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan
[3]Department of Diagnostic Radiology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan
Correspondence to: Manabu Ikeda, E-mail: mikeda@kumamoto-u.ac.jp

Background: Cerebral small vessel disease (SVD) is frequently observed in patients with Alzheimer's disease (AD). However, the association between SVD and clinical symptoms exhibited by patients with AD remains unclear. This study examined the association of SVD as observed on magnetic resonance imaging (MRI) with behavioural and psychological symptoms of dementia and cognitive function of patients with probable AD.

Methods: A total of 163 consecutive patients (55 men, 108 women) with probable AD were included in this cross-sectional study of a prospective cohort. Patients were divided into two groups based on the presence or absence of cerebral SVD [white matter hyperintensities (WMH) grade 0/1 (Fazekas scale) and no lacunes: SVD absent, WMH grade 2/3 (Fazekas scale) or the number of lacunes ≥1: SVD present]. Cognitive functions were assessed using the Mini mental state examination, word recall and recognition subtests in the Alzheimer's Disease Assessment Scale—Cognitive Subscale, as well as the letter fluency task and the category fluency task. Psychiatric symptoms were rated according to Neuropsychiatric Inventory.

Results: Patients with probable AD with cerebral SVD had significantly more delusions and depression than those without SVD. No significant differences were observed in other neuropsychiatric symptoms, MMSE or word recall and recognition tests between both groups.

Conclusions: Our results suggest that cerebral SVD observed on MRI of patients with AD is associated with delusions and depression.

Key words: Alzheimer's disease; small vessel disease; delusion; depression
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Introduction

Cerebral small vessel disease (SVD), including subcortical lacunar infarcts (lacunes) and white matter hyperintensities (WMH), is commonly observed on brain magnetic resonance imaging (MRI) of older people with and without dementia. Numerous post-mortem studies have shown that WMH correspond to several heterogeneous pathological substrates with a varying extent of demyelination, arteriolosclerosis and gliosis representing not only incomplete infarctions but also tissue degeneration (Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study, 2001; Fernando and Ince, 2004). Lacunes are small cavities located in the white matter or subcoritical gray matter. They have been considered small ischemic infarcts; however, several pathogenetic mechanisms have been proposed (Wardlaw *et al.*, 2003). Incidence of SVD increases with age and vascular risk factors (Pantoni and Garcia, 1995).

In older people, Alzheimer's disease (AD) is considered the most common cause of dementia, characterised by gradual progressive cognitive impairment (McKhann *et al.*, 1984). In addition to cognitive

impairment, behavioural and psychological symptoms of dementia (BPSD) are important manifestations of AD. These symptoms have been shown to be associated with a reduced quality of life (Shin *et al.*, 2005), a higher cost of care (Beeri *et al.*, 2002), institutionalisation (Steele *et al.*, 1990) and increased caregiver burden (Robert *et al.*, 2005). Vascular risk factors including hypertension (Skoog *et al.*, 1996; Kivipelto *et al.*, 2001), diabetes (Luchsinger *et al.*, 2001), hypercholesterolemia (Kivipelto *et al.*, 2001) and tobacco smoking (Ott *et al.*, 1998) are also associated with increased AD risk and their treatment reduces AD risk (Li *et al.*, 2011). Furthermore, examination of several patients with AD at autopsy has shown a high prevalence of undiagnosed vascular lesions (Lim *et al.*, 1999; Fernando and Ince, 2004).

MRI has revealed that SVD is more prevalent in patients with AD than in older people without dementia (Scheltens *et al.*, 1992; Jellinger and Mitter-Ferstl, 2003). SVD may play a role, at least to some extent, in the clinical symptoms of AD. WMH are known to affect frontal lobe function, resulting in executive dysfunction in patients with AD (Pantel *et al.*, 2004; Tullberg *et al.*, 2004). However, it is still unclear whether SVD is associated with other symptoms such as BPSD in AD. Reports about the roles of SVD and BPSD in AD have been conflicting. Associations among the following conditions have been reported: WMH and depression (O'Brien *et al.*, 2000); apathy (Scheltens *et al.*, 1992); suicidal ideation (Lopez *et al.*, 1997); delusional misidentification (Lee *et al.*, 2006); aberrant motor behaviour (Hirono *et al.*, 2000); and anxiety, aberrant motor behaviour and night-time disturbance (Berlow *et al.*, 2010). However, these studies had relatively small sample sizes, and only few of them could confirm the results of previous studies. Moreover, some studies failed to find any association between WMH and BPSD (Harrell *et al.*, 1991; Lopez *et al.*, 1992; Staekenborg *et al.*, 2008).

In this study, we assessed the relationship of SVD observed on MRI with BPSD and cognitive functions in a relatively large sample of patients with AD attending a memory clinic.

Methods

Subjects

All procedures followed the Clinical Study Guidelines of the Ethics Committee of Kumamoto University Hospital and were approved by the internal review board. A complete description of all procedures was provided to the patients, and written informed consent was obtained from them or their caregivers.

In this cross-sectional study of a prospective cohort, a total of 163 patients with probable AD were selected from a consecutive series of 1253 patients who underwent a medical examination at the Dementia Clinic of the Department of Neuropsychiatry, Kumamoto University Hospital, from April 2007 to May 2011. All patients were examined comprehensively by two senior neuropsychiatrists (M. I. and M. H.), having sufficient experience in examining patients with dementia. Routine laboratory and standardised neuropsychological tests, such as the Mini mental state examination (MMSE) (Folstein *et al.*, 1975) and Alzheimer's Disease Assessment Scale—Cognitive Subscale Japanese version (ADAS-J cog; Honma *et al.*, 1992) were also conducted. Brain MRI, brain MR angiography and single photon emission computed tomography for cerebral perfusion were also performed. Information on patient demographics including prescribed medications collected from caregivers and investigative data were entered prospectively into the Kumamoto University Dementia Follow-up Registry in a standardised manner. Patients had to meet the criteria of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (McKhann *et al.*, 1984) for probable AD to be included in this study. Patients under 60 years of age; those who had any evidence suggestive of vascular dementia (VaD), such as focal neurological signs, abrupt deterioration or stepwise progression of cognitive deficits; those with focal vascular lesions except SVD, such as hematomas; significant neurologic antecedents, such as brain trauma, brain tumour, epilepsy or inflammatory disease; those with serious psychiatric diseases, substance abuse or developmental abnormalities; those who had severe behavioural or communication problems that would make clinical or MRI examination difficult or those without a reliable informant were excluded from the study.

The subjects consisted of 108 women and 55 men with a mean age of 76.3 ± 7.2 years and a mean educational attainment of 10.5 ± 2.7 years. The mean duration of symptoms determined through interviews with caregivers was 2.5 ± 1.8 years. Forty-one patients (25.2%) were prescribed cholinesterase inhibitors at examination. The Clinical Dementia Rating scale (CDR; Hughes *et al.*, 1982) revealed a functional severity of very mild in 75 patients, mild in 71, moderate in 16 and severe in 1.

Subjects were divided into two groups based on the presence or absence of SVD, and cognitive functions and BPSD were compared between the two groups.

Assessment of cognitive functions

All patients underwent neuropsychological tests to assess their general cognitive functioning as well as memory and executive functions. General cognitive functioning was assessed using MMSE. Memory function was assessed using ADAS-J cog word recall and recognition subtests. ADAS-J cog word recall subtest is equivalent to a verbal learning test in which the retention of a list of 10 written words was measured using free immediate recall after each of the three learning trials. The score is the mean number of correct responses in three repeated trials. In the ADAS word recognition subtest, the subject was asked to read aloud 12 written high-imagery words and then to select the target words among 24 words randomly mixed with 12 irrelevant words. The score is the mean number of correct responses in three repeated trials. Executive function was assessed using the letter fluency task and the category fluency task. In the letter fluency task, subjects were instructed to say as many words as possible that begin with the letter 'Ka' for 1 min. The score was the number of different words listed. In the category fluency task, the subjects were asked to list as many animals as possible within 1 min. The score was the number of different animals listed.

Assessment of behavioural and psychological symptoms of dementia

We evaluated the comprehensive BPSD semiquantitatively through interviews with their caregivers using the Japanese version of the Neuropsychiatric Inventory (NPI) (Cummings *et al.*, 1994; Hirono *et al.*, 1997). In NPI, the following 10 BPSD were rated on the basis of the patients' condition in the month before interviews: delusions, hallucinations, agitation, depression (dysphoria), anxiety, euphoria, apathy, disinhibition, irritability and lability and aberrant motor behaviour. According to the criteria-based rating scheme, severity of each manifestation was classified into four grades (from 1 to 3; 0 if absent), whereas frequency was classified into five (from 1 to 4; 0 if absent). The NPI score (severity × frequency) was calculated for each manifestation (range of possible scores, 0–12). Thus, the maximum total score for the 10 manifestations is 120.

Assessment of small vessel disease

Scans were made on a 3.0-T MR scanner. Fluid-attenuated inversion recovery (FLAIR), T2-weighted, diffusion-weighted, magnetization-prepared rapid acquisition of gradient echo imaging and susceptibility-weighted imaging were performed. The presence of lacunes and the extent of WMH were determined by a neuroradiologist who was blinded to the clinical data, including cognitive test results and NPI scores. The extent of WMH severity was rated visually on axial FLAIR images using the Fazekas scale as grade 1 (punctate), grade 2 (early confluent) or grade 3 (confluent) (Fazekas *et al.*, 1987). In this study, WMH were considered present if the Fazekas grade was 2 or 3 (Pompili *et al.*, 2008; Staekenborg *et al.*, 2008). Changes in the basal ganglia were rated in the same way and considered as white matter lesions even if they were located in the gray matter nuclei. Lacunes were defined as lesions with diameters of more than 2 mm with hyperintensity on T2-weighted images with central hypointensity on FLAIR images. Seventy-nine patients (48.0%) showed WMH, whereas 54 patients (33.1%) showed with lacunes. Both WMH and lacunes were observed in 40 patients (24.5%). Patients were divided into two groups based on the presence or absence of SVD (WMH grade 0/1 and no lacunes: SVD absent, WMH grade 2/3 or the number of lacunes ≥ 1: SVD present).

Statistical analysis

Group differences were analysed using two-tailed Student t test, two-tailed Mann–Whitney U test or χ^2 test. $p < 0.05$ was considered to be statistically significant. No correction for multiple comparisons was performed because of the exploratory nature of the study. In the present study, patients with SVD were significantly older than those without SVD. Therefore, we also analysed group differences in the neuropsychological tests and NPI scores using analysis of covariance (ANCOVA) with age as the covariate. Furthermore, we performed ANCOVA, with age, sex, years of education, disease duration, cholinesterase inhibitor usage and CDR as covariates, as these variables might affect cognition and BPSD. Statistical analysis was performed with SPSS for Windows, version 17.0 (IBM Corporation, Armonk, NY, USA).

Results

Demographic variables of the two groups (patients with SVD and patients without SVD) are shown in Table 1. Patients with SVD were significantly older than those without SVD ($p = 0.005$); however, no significant differences were observed for the male to female ratio, mean level of education, duration of

Table 1 Patient demographics

	Total ($n = 163$)	SVD present ($n = 93$)	SVD absent ($n = 70$)	p
Age (years)	76.3 ± 7.2	77.8 ± 6.1	74.4 ± 8.1	0.005[a,**]
Sex (male/female)	55/108	33/60	22/48	0.588[b]
Education (years)	10.5 ± 2.7	10.3 ± 2.8	10.8 ± 2.5	0.208[a]
Duration of history (years)	2.5 ± 1.8	2.4 ± 1.9	2.6 ± 1.7	0.596[a]
Cholinesterase inhibitor use	41 (25.2)	20 (21.5)	21 (30)	0.216[b]
CDR	0.88 ± 0.47	0.94 ± 0.53	0.80 ± 0.38	0.116[c]
WMH present (Fazekas score ≥2)	79 (48.5)	79	0	
Lacunes present	55 (33.7)	55	0	

Values are presented as mean ± SD, n (%) or n.
SVD, small vessel disease; CDR, Clinical Dementia Rating; WMH, White Matter Hyperintensities
[a]t test; [b]χ^2 test; [c]Mann–Whitney U test; **$p < 0.01$.

symptoms and percentage of patients who were prescribed cholinesterase inhibitors between both groups.

Results of neuropsychological tests are shown in Table 2. No significant differences were observed for MMSE and ADAS-J cog word recall and recognition subtests between both groups. In contrast, patients with SVD were significantly more impaired than those without SVD on the letter fluency task ($p = 0.013$). This difference remained significant after adjustment for age ($p = 0.021$, ANCOVA), but the significance disappeared after adjustment for age, sex, years of education, disease duration, cholinesterase inhibitor usage and CDR ($p = 0.065$, ANCOVA).

Results of NPI are given in Table 3. In the total cohort of 163 patients, prevalence of any BPSD was 90.8%, with a median NPI score of 7 (range, 0–63). Furthermore, apathy was found to be the most common symptom, whereas euphoria was the rarest (affecting 67% and 1% of the patients, respectively). Delusions were present in 39 patients (23.9%). The total NPI score was significantly higher in patients with SVD than in those without SVD after adjustment for age, sex, years of education, disease duration, cholinesterase inhibitor usage and CDR ($p = 0.042$, ANCOVA). Patients with SVD had significantly higher scores than those without SVD in the delusion domain ($p = 0.013$), and the difference remained significant even after adjustment for age ($p = 0.036$, ANCOVA), and age, sex, years of education, disease duration, cholinesterase inhibitor usage and CDR ($p = 0.049$, ANCOVA). In addition, patients with SVD had significantly higher scores than those without SVD in the depression domain after adjustment for age, sex, years of education, disease duration, cholinesterase inhibitor usage and CDR ($p = 0.044$, ANCOVA).

Discussion

The most remarkable finding of this study was that patients with AD and SVD had significantly more delusions than those without SVD. In the present

Table 2 Neuropsychological performances of subjects

	SVD present ($n = 93$)	SVD absent ($n = 70$)	p	Adjusted $p1$	Adjusted $p2$
MMSE scores	19.7 ± 4.5	20.2 ± 4.1	0.425[a]	0.232	0.633
ADAS-J cog					
Word recall (correct response)	4.1 ± 1.6	3.9 ± 1.4	0.415[a]	0.456	0.166
Word recognition (correct response)	7.7 ± 3.0	8.2 ± 2.8	0.285[a]	0.522	0.888
LFT scores ('Ka')	5.3 ± 3.0	6.5 ± 3.1	0.013[a,*]	0.021*	0.065†
CFT scores (animals)	9.0 ± 4.0	9.8 ± 3.3	0.210[a]	0.317	0.571

Values are presented as mean ± SD.
SVD, small vessel disease; MMSE, Mini mental state examination; ADAS-J cog, Alzheimer's Disease Assessment Scale—Cognitive subscale (Japanese version); LFT, letter fluency task; CFT, category fluency task.
[a]t test; age adjustment was performed using analysis of covariance and is represented as adjusted $p1$. Adjustment of age, sex, years of education, disease duration, cholinesterase inhibitor usage and Clinical Dementia Rating scale using analysis of covariance is represented as adjusted $p2$.
*$p < 0.05$; †$p < 0.10$.

Table 3 Prevalence of behavioural and psychological symptoms of dementia and mean composite scores (frequency × severity) of individual Neuropsychiatric Inventory symptoms in patients

	SVD present ($n = 93$)	SVD absent ($n = 70$)	p	Adjusted $p1$	Adjusted $p2$
NPI total scores ≥1	84 (90.3)	64 (91.4)	0.809[b]		
NPI scores					
Total score	11.7 ± 11.4	8.3 ± 9.2	0.036[a*]	0.053[†]	0.042*
Delusion	1.5 ± 3.0	0.5 ± 1.6	0.013[a*]	0.036*	0.049*
Hallucination	0.3 ± 1.0	0.1 ± 0.6	0.288[a]	0.421	0.839
Agitation/aggression	0.9 ± 1.9	0.9 ± 2.1	0.912[a]	0.938	0.860
Depression/dysphoria	1.5 ± 2.8	0.9 ± 1.6	0.075[a†]	0.062[†]	0.044*
Anxiety/indifference	0.9 ± 2.6	0.8 ± 2.0	0.726[a]	0.749	0.828
Euphoria	0.0 ± 0.0	0.1 ± 0.5	0.321[a]	0.471	0.358
Apathy	3.9 ± 4.0	3.2 ± 3.2	0.202[a]	0.248	0.332
Disinhibition	0.6 ± 2.0	0.3 ± 1.6	0.373[a]	0.528	0.354
Irritability/lability	1.0 ± 1.8	0.8 ± 1.9	0.521[a]	0.536	0.304
Aberrant motor behaviour	1.2 ± 2.8	0.7 ± 1.9	0.222[a]	0.210	0.478

Values are presented as mean ± SD or n (%).
SVD, small vessel disease; NPI, Neuropsychiatric Inventory.
[a]t test; [b]χ^2 test; age adjustment was performed using analysis of covariance and is represented as adjusted $p1$. Adjustment of age, sex, years of education, disease duration, cholinesterase inhibitor usage and Clinical Dementia Rating scale using analysis of covariance is represented as adjusted $p2$.
*$p < 0.05$; [†]$p < 0.10$.

study, patients with SVD were significantly older than those without SVD. Both WMH and lacunes have been shown to be associated with aging (Fazekas *et al.*, 1988; Longstreth *et al.*, 1998). Some studies have found a significant association between psychosis in AD and age (Levy *et al.*, 1996; Bassiony *et al.*, 2000) and age at onset of AD (Hwang *et al.*, 1996; Gormley and Rizwan, 1998). However, delusions in patients with AD and SVD were significantly more severe than in those without SVD after adjustment for age in this study. Therefore, the present results cannot be explained by the differences of age between the two groups.

Previous studies have reported relationships between delusions and severity of white matter changes observed on MRI (Lee *et al.*, 2006) and between delusions and lacunar infarcts of white matter observed on computed tomography (Binetti *et al.*, 1995) in patients with AD. Furthermore, one study reported that a history of hypertension increased the risk of delusions in patients with AD (Treiber *et al.*, 2008), and another showed an association between delusions and the use of antihypertensives in patients with AD (Bassiony *et al.*, 2000). Thus, it can be suggested that SVD is a risk factor of delusions in patients with AD.

Mechanisms underlying delusions in patients with AD remain unclear. However, some neuroimaging studies have suggested an association between psychotic symptoms in AD and frontal lobe dysfunction (Sultzer *et al.*, 1995; Mega *et al.*, 2000; Sultzer *et al.*, 2003). Mentis *et al.* (1995) suggested that delusional misidentification in patients with AD are caused because of the abnormal integration of perceptual information from multimodal association cortices with affective information from paralimbic–limbic structures. White matter changes may result in a disruption of the functional connections between the frontal cortex and other related cortices or paralimbic–limbic structures, thus resulting in delusions. Furthermore, white matter changes in basal ganglia may alter connections between the frontal cortex and subcortical regions, resulting in development of delusions (Mentis *et al.*, 1995; McMurtray *et al.*, 2008). Further studies are needed to localise areas on MRI and single-photon emission computed tomography and support this hypothesis.

In this study, there was a trend for patients with SVD to be more impaired on the letter fluency task (for evaluating executive dysfunction) compared with those without SVD. No significant differences were observed in MMSE (for evaluating general cognitive functioning) and ADAS-J cog word recall and recognition subtests (for evaluating memory function) between both groups. In older people, appearance of SVD and incident lacunes on MRI have been reported to be associated with decreases in executive function and processing speed but not in memory or global cognition (Prins *et al.*, 2005; Jokinen *et al.*, 2011). In patients with AD, white matter lesions observed on MRI have been reported to be associated with impaired frontal lobe function, regardless of their

location (Tullberg *et al.*, 2004). These findings were consistent with our results, which suggest that SVD was associated with the impairment of executive function but not to impairments of global cognitive and memory functions. In a study examining the association between cognitive function and BPSD assessed by NPI, the letter fluency task and the category fluency task scores were significantly associated with changes in the psychosis subdomain but not in other subdomains (Tsai *et al.*, 2010). In addition, Swanberg *et al.* (2004) reported that symptoms of psychosis were more frequent in patients with AD with executive dysfunction than in those without. The lesions of the dorsolateral prefrontal circuit mainly involved in executive function are associated with performances of verbal fluency (Duffy and Campbell, 1994; Tekin and Cummings, 2002). In addition, lesions in the dorsolateral prefrontal circuit are associated with psychosis in patients with AD (Sultzer *et al.*, 1995). These previous neuroimaging and cognitive findings and the present result suggest that executive dysfunction due to SVD may be associated with delusions in patients with AD.

In the present study, patients with AD with SVD had significantly more depression than those without SVD after adjustment estimated covariates. Previous study suggests that white matter lesions confer an increased risk for depression in AD (O'Brien *et al.*, 2000). In this study, we did not find evidence to support the previously reported association of WMH with apathy (Scheltens *et al.*, 1992), aberrant motor behaviour (Hirono *et al.*, 2000) as well as anxiety and aberrant motor behaviour (Berlow *et al.*, 2010) in patients with AD. Unlike our study, previous studies failed to find any association between WMH and BPSD (Harrell *et al.*, 1991; Lopez *et al.*, 1992; Staekenborg *et al.*, 2008). Results obtained in our and previous studies may have differed because of the small sample sizes of the previous studies. An advantage of our study is the relatively large study cohort.

This study had some limitations. First, despite the exclusion of patients with any evidence suggestive of VaD, probably a few patients with VaD was included. However, patients with AD have been reported to have more delusions than patients with VaD (Lyketsos *et al.*, 2000; Ikeda *et al.*, 2004), suggesting that a combination of AD pathology and SVD may contribute to delusions. Second, WMH and lacunes are collectively treated as SVD. In this study, 40 patients (43.0% of patients with SVD) had both WMH and lacunes. Because our main aim was to investigate the effect of SVD on clinical symptoms in patients with AD, we analysed the two major representations of SVD together. In the future, WMH and lacunes need to be evaluated separately in order to investigate their independent effect on BPSD of patients with AD in a larger population. Third, in order to measure the extent of WMH, we used a visual rating scale, which may not be as accurate as the MRI volumetric method. However, the Fazekas rating scale, which was used in the present study, is widely accepted and has been shown to provide good global assessments of WMH. In an overview of 26 rating scales used to evaluate WMH on MRI, it was suggested that the simplicity of the Fazekas scale might make it robust, even for images of poorer quality (Scheltens *et al.*, 1998). In addition, simple rating scales, such as the Fazekas scale, have been shown to be comparable with complex measures of WMH in terms of associations with clinical outcome measures (Gouw *et al.*, 2006). Importantly, histopathological analyses have been used to validate this rating scale (Fazekas *et al.*, 1991; Fazekas *et al.*, 1993). Fourth, the study results might be able to be biased because all patients were recruited in only one dementia clinic.

Conclusion

Our results suggest that cerebral SVD observed on MRI is associated with symptoms of delusions and depression in patients with AD.

Key points

- Cerebral SVD in patients with AD is associated with symptoms of delusions and depression.
- No significant differences were observed in other neuropsychiatric symptoms, memory or global cognition between patients with AD with SVD and those without SVD.

Conflict of interest

None declared.

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