

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

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

<sup>1</sup>Department of Neuropsychiatry, Graduate School of Medical Science, Kumamoto University, Kumamoto, Japan

<sup>2</sup>Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

<sup>3</sup>Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine, Kyoto, Japan

<sup>4</sup>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. Received 15 Nov 2012; revision requested 8 Jan 2013; revised version received 14 Jan 2013; accepted 24 Jan 2013.

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 synucleinopathy 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, FTL, 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. Variables 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 <sup>a</sup>
Male	32 (58.1%)	82 (41.9%)	10 (62.5%)	12 (66.7%)	15 (40.5%)	14 (43.8%)	0.107 <sup>b</sup>
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 <sup>a</sup>
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 <sup>a</sup>
Medication							
Cholinesterase inhibitors	19 (34.5%)	50 (26.2%)	8 (50.0%)	3 (16.7%)	4 (10.8%)	n.a.	0.017 <sup>b</sup>
Benzodiazepine anxiolytics	16 (29.1%)	28 (14.7%)	3 (18.8%)	3 (16.7%)	6 (16.2%)	n.a.	0.195 <sup>b</sup>
Antipsychotics	6 (10.9%)	5 (2.6%)	2 (12.5%)	1 (5.6%)	6 (16.2%)	n.a.	0.004 <sup>b</sup>
Antidepressants	7 (12.7%)	19 (9.9%)	2 (12.5%)	1 (5.5%)	2 (5.4%)	n.a.	0.798 <sup>b</sup>
Bedroom sharing with patients	29 (52.7%)	110 (57.6%)	12 (75.0%)	4 (22.2%)	16 (43.2%)	n.a.	0.011 <sup>b</sup>

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 <sup>a</sup>one-way ANOVA or <sup>b</sup>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 <sup>†</sup>
Frequent sleep talking	20 (36.4%)	16 (8.4%)	1 (6.3%)	3 (16.7%)	6 (16.2%)	2 (6.3%)	<0.001 <sup>‡</sup>
Long-term sleep talking	14 (25.5%)	13 (6.8%)	1 (6.3%)	4 (22.2%)	4 (10.8%)	1 (3.1%)	0.002 <sup>§</sup>
SNBD	27 (49.1%)	35 (18.3%)	5 (31.3%)	8 (44.4%)	12 (32.4%)	n.a.	<0.001 <sup>§</sup>

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.

<sup>†</sup>DLB significantly higher than AD, O/U dementia, and NE subjects (FTLD was not compared with other groups).

<sup>‡</sup>DLB significantly higher than AD and NE subjects.

<sup>§</sup>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. SNBD occurred most frequently in the DLB group and the prevalence of SNBD 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 <sup>123</sup>I-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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CASE REPORT

**Mirtazapine improves visual hallucinations in Parkinson's disease: a case report**

**Kenji TAGAI, Tomoyuki NAGATA, Shunichiro SHINAGAWA, Norifumi TSUNO, Motohiro OZONE and Kazuhiko NAKAYAMA**

Department of Psychiatry, Jikei University School of Medicine, Tokyo, Japan

Correspondence: Dr Kenji Tagai MD, Department of Psychiatry, Jikei University School of Medicine, 3-25-8 Nishi-Shimbashi, Minato-ku, Tokyo 105-8461, Japan. Email: k-tagai@jikei.ac.jp

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**Key words:** *Lewy bodies, mirtazapine, Parkinson's disease, psychosis, visual hallucinations.*

**Abstract**

Psychotic symptoms often occur as a complication in Parkinson's disease patients, and a set of criteria for Parkinson's disease with psychosis (PDPsy) has been established. Among these criteria, hallucinations are one of the specific symptoms, with visual hallucinations being the most common. While atypical antipsychotic agents are often used for the treatment of PDPsy, adverse effects, including extrapyramidal symptoms, often hinder its continuation or tolerance. There have been some reports and reviews indicating that antidepressants may be effective for PDPsy and other forms of dementia with psychosis. In this report, we present a patient with PDPsy who was treated with one of the new-generation antidepressants, mirtazapine. Mirtazapine improved the patient's refractory psychotic symptoms, especially her visual hallucinations, without worsening her motor symptoms.

**INTRODUCTION**

Psychotic symptoms often occur as a complication in Parkinson's disease (PD) patients, and a set of criteria for PD with psychosis (PDPsy) has been established.<sup>1</sup> Among these criteria, hallucinations are one of the specific symptoms, with visual hallucinations (VH) being the most common.<sup>2-5</sup> While atypical antipsychotic agents are often used for the treatment of PDPsy, adverse effects, including extrapyramidal symptoms (EPS), often hinder its continuation or tolerance.<sup>6</sup> There have been some reports and reviews indicating that antidepressants may be effective for PDPsy and other forms of dementia with psychosis.<sup>7-9</sup> In this report, we present a patient with PDPsy who was treated with one of the new-generation antidepressants, mirtazapine. Mirtazapine improved the patient's refractory psychotic symptoms, especially her VH, without worsening her motor symptoms.

**CASE REPORT**

Herein, we report the case of an 83-year-old woman whose illness started when she was 72 years old. The initial symptom was an upper limb resting tremor, with the subsequent development of rigidity and bradyki-

nesia. Her illness was diagnosed as PD, and antiparkinsonian agents were prescribed, although the details of her prescription are unknown.

When she was 82 years old, her husband died, and she became depressed and began to talk about water being the colour of blood. Five months later, she entered a nursing home and began to experience VH. Her VH sometimes varied, and included that a child was peering at her over a door and a man coming for an interview. The person in her VH was always the same person, and the hallucinations were accompanied by feelings of being monitored. Although a previous doctor had prescribed antipsychotic agents including aripiprazole and risperidone, the patient had also developed delusions of persecution by the time she visited our hospital.

When she visited our outpatient clinic, she was recognized as having mild parkinsonism (Yahr II; Unified Parkinson's Disease Rating Scale:<sup>10</sup> total score 68), psychosis with VH, and depression. In particular, she was very agitated. Her prescription at that time was for trihexyphenidyl 6 mg/day. Unfortunately, we do not have details regarding her former prescriptions. She was not being treated with levodopa at

the time of her entrance to the nursing home. A Mini-Mental State Examination and a Frontal Assessment Battery were performed; her scores were 21 points and 8 points, respectively.<sup>11,12</sup> She could not complete the clock-drawing test. Cranial magnetic resonance imaging, an electroencephalogram and routine serum laboratory tests were normal for her age. We decreased the dosage of trihexyphenidyl to 3 mg/day and prescribed quetiapine 50 mg/day. However, the patient began to insist that she had committed a serious crime, and she did not eat very much at meal-times. Furthermore, the staff of the nursing home reported that her EPS had worsened. After two months, she attempted suicide; she was subsequently admitted to the psychiatric department of our hospital.

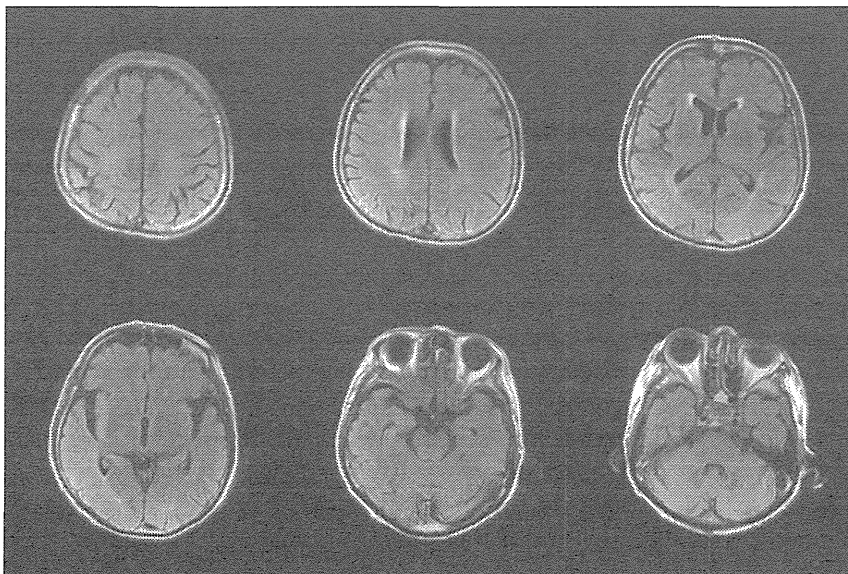
After admittance, a second cranial magnetic resonance imaging (Fig. 1), electroencephalogram and routine serum laboratory tests were performed, but no changes were noted. As a further examination, single-photon emission computed tomography imaging with technetium-99m-ethyl cysteinate dimer was performed. The results of the single-photon emission computed tomography were analyzed with the easy Z-score imaging system (Fig. 2), and a decrease in the regional cerebral blood flow was seen in bilateral prefrontal cortices.

We prescribed risperidone 2 mg/day and trazodone 50 mg/day. On day 9, EPS appeared, and the patient's depression and agitation worsened. We con-

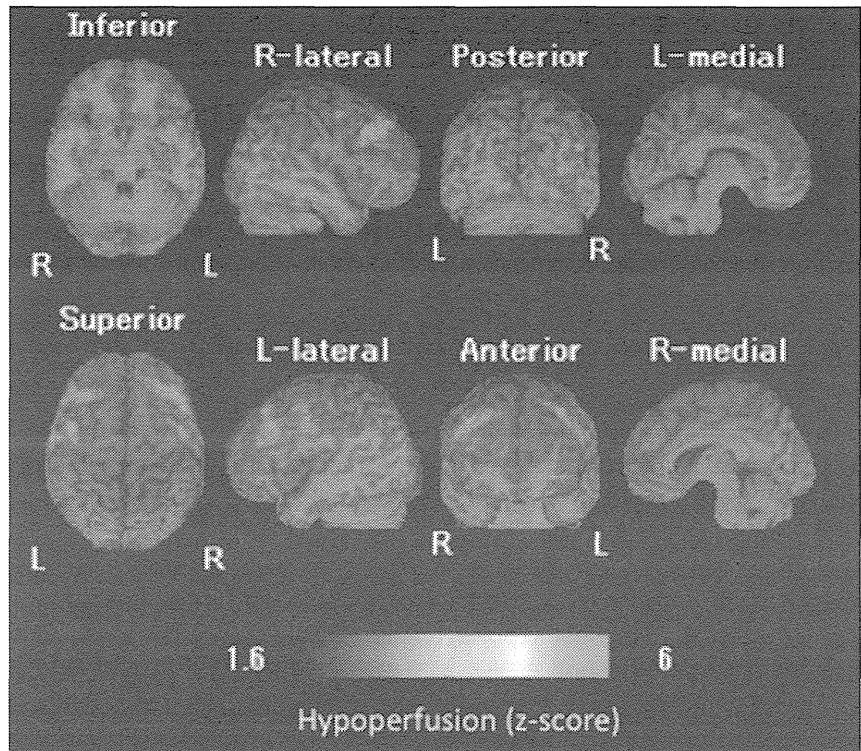
sequently started treatment with mirtazapine 15 mg/day for both symptoms and increased the dosage to 30 mg/day over 7 days. In addition, we tapered the risperidone dosage over 15 days. On day 29, the patient showed a decrease in her psychotic symptoms, which consisted mainly of VH (Behavioural Pathology in Alzheimer's Disease total scores: from 21 to 10 points; delusion scores: from 3 to 2 points, hallucination scores: from 3 to 0 points).<sup>13</sup> There was no increased aggravation of her EPS. The patient's depression also improved slightly (21-item Hamilton Rating Scale for Depression : from 38 to 29 points).<sup>14</sup> She continued taking mirtazapine for 70 days, but her depression did not improve any further. However, she did not experience further VH, and her scores improved on the Mini-Mental State Examination (from 21 to 28 points) and Frontal Assessment Battery (from 8 to 14 points). These results suggested that her cognitive impairment might have arisen from her psychiatric symptoms (Fig. 3).

## DISCUSSION

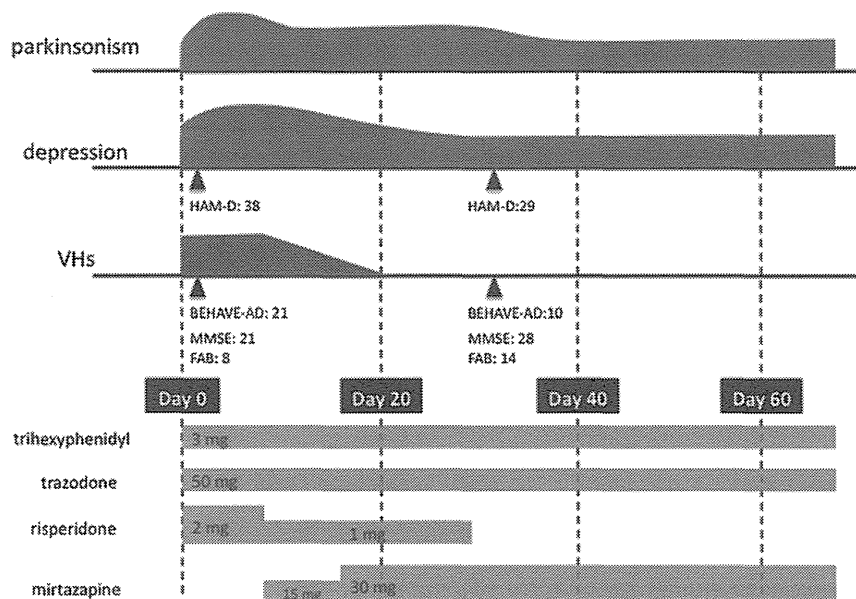
In this case, treatment with mirtazapine improved VH rather than depression in a patient with PD with chronic episodes for more than 10 years. PDPsy typically occurs in advanced PD patients 10 or more years after the initial PD diagnosis.<sup>15</sup> Some triggers or risk factors are known. Among pharmacological factors, the introduction or dose increment of antiparkinsonian agents often triggers PDPsy.<sup>15,16</sup> Among disease-



**Figure 1** Fluid-attenuated inversion recovery view obtained during magnetic resonance imaging of a series of horizontal sections showing mild cortical atrophy.



**Figure 2** Single-photon emission computed tomography analysis with the easy Z-score imaging system shows marked hypoperfusion in bilateral prefrontal cortices. L, left; R, right.



**Figure 3** Timeline of administered tests (including scores) and pharmacological treatments. BEHAVE-AD, Behavioural Pathology in Alzheimer’s Disease; FAB, Frontal Assessment Battery; HAM-D, Hamilton Rating Scale for Depression; MMSE, Mini-Mental State Examination; VH, visual hallucinations.

related factors, cognitive impairment is strongly associated with PDPsy. In particular, an association has been found among visuoperceptual, executive, reality monitoring, and memory tasks.<sup>16</sup> Psychiatric disorders, especially depressive disorders, are also

strongly associated with PDPsy.<sup>17</sup> In our case, the VH may have been induced by the trihexyphenidyl. However, the VH did not improve by when the dosage of trihexyphenidyl was reduced, and instead, her psychotic symptoms worsened somewhat.

PDPsy increases the caregiver's burden and the patient's risk of mortality.<sup>18,19</sup> Therefore, this symptom must be managed. Several approaches to treatment exist. First, stopping or reducing the antiparkinsonian agents can be effective, though motor function may worsen.<sup>6,16</sup> Second, atypical antipsychotic agents can be effective.<sup>6,15,20,21</sup> Several double-blind placebo-controlled trials have been performed, and some reviews report that clozapine can be effective and does not appear to worsen EPS. Quetiapine appears to be less effective than clozapine but may not worsen EPS, but other agents such as risperidone, olanzapine or aripiprazole may worsen such signs.<sup>6,15,20,21</sup> Third, some studies have reported that cholinesterase inhibitors also can be mildly effective for the treatment of Parkinson's disease with dementia or dementia with Lewy bodies with hallucinations.<sup>22-24</sup> A few reports have also indicated that antidepressants may be effective.<sup>7,8</sup> In these reports, antidepressants, such as clomipramine and citalopram, may actually improve psychotic symptoms, especially in patients with concurrent depression. In contrast, some previous studies have shown that antidepressants, including mirtazapine, caused or exacerbated psychotic symptoms.<sup>25,26</sup> In these studies, the patients received dopamine-replacement therapy. In the absence of dopamine-replacement therapy in our case, mirtazapine might have improved the patient's VH, rather than her depression.

The neural mechanisms underlying psychotic symptoms remain unclear. Of the brain's neurotransmitters, not only dopamine but also serotonin and acetylcholine may also play a role in the emergence of psychotic symptoms. In particular, serotonin's contribution to PDPsy has been suggested by some treatment experiences.<sup>15,16</sup> Atypical antipsychotic agents are dopamine receptor antagonists as well as serotonin 2A and 2C receptor antagonists. Also, ondansetron, a serotonin 3 receptor antagonist, has been found to be successful in improving PDPsy,<sup>27,28</sup> and a positron emission tomography study found increased serotonin 2A receptor binding in the ventral visual pathway of PD patients with VH.<sup>29</sup> Mirtazapine acts by antagonizing alpha2-adrenoreceptors as well as serotonin type 2 and type 3 receptors.<sup>30</sup> In our case, this action of antagonizing serotonin type 2 and type 3 receptors may have helped to decrease her psychotic symptoms, especially her VH. However, her depression did not improve significantly. As far as we

know, there have been no published papers indicating that mirtazapine improves depression in PD. In addition, the chronically cyclic deficiency of dopamine in PD may influence fluctuations in motor activity linked to psychogenic symptoms (e.g. depressive mood) or cognitive function.<sup>31</sup> Therefore, dopaminergic agonists, such as pramipexole and pergolide, also improve depression in PD.<sup>32</sup> In our case, the dosage of antiparkinsonian agents had been reduced to mitigate the distress of the VH, and the treatment of the patient's motor symptoms may have been insufficient. Such deficiencies of dopamine might have caused the insufficient efficacy for depression and prevented the exacerbation of the VH.

Our report has some limitations. We could not perform <sup>123</sup>I-metaiodobenzylguanidine cardiac scintigraphy or single-photon emission computed tomography imaging with technetium-99 m-ethyl cysteinate dimer after treatment. Furthermore, no details were available regarding the patient's clinical course prior to her visit to our outpatient clinic. Thus, other parkinsonian syndromes cannot be ruled out.

Regardless of these limitations as a treatment for psychosis in PD patients with VH and depression in PD, we were able to alleviate her distress and prevent its recurrence without any remarkable adverse effects. In conclusion, our case report highlights the effectiveness of mirtazapine and indicates that mirtazapine may be useful for clinicians treating patients with PD with refractory VH.

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✧ ORIGINAL ARTICLE ✧

# *Degree of ambulation and factors associated with the median distance moved per day in Alzheimer's disease patients*

**Shiori Nishikata BSN MS**

*Staff Nurse, Department of Clinical Nursing, Division of Health Sciences, Graduate School of Medicine, Osaka University, Osaka, Japan*

**Miyae Yamakawa RN PhD**

*Associate Professor, Department of Clinical Nursing, Division of Health Sciences, Graduate School of Medicine, Osaka University, Osaka, Japan*

**Kazue Shigenobu MD PhD**

*Psychiatrist, Department of Psychiatry, Asakayama General Hospital, Osaka, Japan*

**Shunji Suto PhD**

*Lecturer, Department of Community Medicine, Nara Medical University, Nara, Japan*

**Kiyoko Makimoto RN PhD**

*Professor, Department of Clinical Nursing, Division of Health Sciences, Graduate School of Medicine, Osaka University, Osaka, Japan*

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**Degree of ambulation and factors associated with the median distance moved per day in Alzheimer's disease patients**

The Integrated Circuit tag monitoring system became available to measure wandering in terms of the distance moved by dementia patients. The purposes of the study were to describe degree of ambulation in patients with Alzheimer's disease (AD) and to examine factors associated with the distance moved. AD patients were recruited at a dementia care unit in Asakayama Hospital, Osaka, Japan. The monitoring system generated the distance moved per day. Demographic and clinical data were abstracted from medical records. Mini-Mental State Examination was used to measure cognitive function. A multiple linear regression was used to predict the distance moved per day. The research was approved by the ethics committee of the university and the hospital, and written informed consent was obtained from the patients' proxies. Majority of the AD subjects monitored had moderate to advance stage of dementia. Patients' age and cognitive function were predictors of the median distance moved/day, and these two variables explained almost half of the variance. Older age and lower cognitive function were associated with reduced median distance moved per day in AD patients.

**Key words:** Alzheimer's disease, monitoring, objective measurement, risk factors, wandering.

*Correspondence:* Kiyoko Makimoto, Department of Clinical Nursing, Graduate School of Medicine, Osaka University, 1-7 Yamadaoka, Suita, Osaka, 565-0871 Japan. Email: kmakimot@sahs.med.osaka-u.ac.jp

## INTRODUCTION

Wandering is one of well-known behavioural and psychological symptoms of dementia (BPSD) and is a risk factor of falls and injuries.<sup>1</sup> Because of safety concerns, wandering in people with dementia (PWD) requires close-attention by the caregivers, leading to severe care burden.<sup>2-4</sup> However, interventions to reduce wandering have not offered enough evidence.<sup>5</sup> Some of the major barriers in evaluating the effectiveness of interventions are a lack of universally acceptable definition of wandering and inadequacy of tools to objectively measure wandering.<sup>6</sup>

Wandering has been described in four major constructs, namely: purpose of ambulation, care burden, quantitative aspects of ambulation and spatial movements.<sup>6</sup> 'Aimless' or 'purposeless' was mainly used to characterize wandering in PWD in the perspective of observers. Wandering behaviours associated with care burden include 'exit seeking', 'eloping' and 'boundary transgression'.<sup>6</sup> These are safety concerns as well.

In terms of quantitative aspects of wandering, the term 'frequent', 'constant' or 'excessive' has been used to describe wandering, although the quantitative measurement using monitoring devices or systems was rarely attempted mainly due to difficulty in getting cooperation from PWD.<sup>6</sup> By videotaping ambulation of institutionalized PWDs, Martino-Saltzman and associates identified a travel pattern.<sup>7</sup> These are direct, random, pacing and lapping. Except for 'direct', all are considered as 'inefficient travel' which was significantly related to cognitive status. Pacing and lapping refer to certain types of repetitive spatial movements,<sup>6</sup> and pacing is regarded as a sign of agitation.<sup>8</sup>

Algase and associates developed Algase Wandering Scale (AWS) to measure an array of wandering behaviours including these spatial movements.<sup>9</sup> However, this scale has not been well used to evaluate interventions to reduce wandering, and scales developed to measure a set of BPSDs have been used for intervention studies. Some of the widely used scales are Cohen-Mansfield Agitation Inventory,<sup>7</sup> Neuropsychiatric Inventory (NPI),<sup>10</sup> and The Behavioural pathology in Alzheimer's Disease Scale (BEHAVE-AD).<sup>11</sup> These scales contain only one item for wandering asking the frequency of pacing or wandering without giving detail definition of wandering. Regardless of the scales used, the following factors were reported to be associated with wandering: age, gender, cognitive function, depression, hallucination, agitation and sleep disturbances.<sup>12-15</sup>

Quantification of wandering is important to examine factors associated with wandering and to evaluate interventions to reduce wandering. There is a quantitative aspect of wandering expressed in subjective terms such as excess or frequent<sup>6</sup> which can be measured by objective methods. We have conducted a series of monitoring studies of dementia patients using the Integrated Circuit (IC) tag monitoring system (Matrix Co, Osaka, Japan), and revealed a wide variation in the degree of wandering and day-to-day fluctuations of the distance moved.<sup>16-18</sup>

A study in Japan showed that assessment of wandering by the staff using the Algase Wandering Scale Japanese version (AWS-J) was not accurate when compared with the IC tag monitoring data. Primary nurses rated the frequency of wandering using the AWS-J in institutionalized PWDs and compared it with the IC tag data; there were good concordance between the AWS-J scale scores and the mean distance moved per time period during day-shift hours, but not hours during evening shift and early morning hours.<sup>19</sup> Agreement between the AWS-J scale scores and the IC tag monitoring data was very poor for spatial movement items, such as pacing, lapping and 'goes to the same location over and over'.<sup>19</sup>

Accurate assessment of the distance moved per day or a pattern of spatial movements in PWDs might not be necessary. However, the degree of ambulation could have impact on body weight of PWDs. The other IC tag monitoring study reported that the median distance moved per day measured the IC tag monitoring system was inversely correlated with the weight change per month ( $r = -0.52$ ;  $P < 0.05$ ), and the mean food intake per day was 97.2%.<sup>20</sup> This study suggests that the degree of ambulation has a potential impact on physical conditions, and it is worthwhile to investigate the distance moved per day for extended period.

The purposes of this study were (i) to describe the degree of ambulation in terms of the median distance moved per day and (ii) to examine the factors associated with the median distance moved per day as an indicator of wandering in institutionalized patients with Alzheimer's-type dementia.

## METHODS

This study was conducted at a dementia special care unit at Asakayama General Hospital in Osaka, Japan. The unit had 60 beds and patients were hospitalized with BPSD unmanageable at home. Once patients were stabilized, they were discharged home or to long-term care facilities.

Monitoring was conducted in two time periods due to the availability of funding: (i) November 2006 to March 2007 and (ii) September 2008 to August 2009.

Eligibility criteria were: (i) those who could ambulate by oneself and (ii) those who were diagnosed as AD by using McKhann *et al.*'s criteria.<sup>21</sup> Exclusion criteria were: (i) those whose median distance moved per day < 200 m and (ii) those who were monitored < 20 days. Those who moved < 200 m per day indicated little autonomous ambulation, and only moved when they were prompted by the staff to the dining room. The distance < 200 m meant round trips to the dining room five times a day (three meals and two snacks) and participating in one activity session a day. Those whose monitoring period was < 20 days might not be sufficient to determine usual pattern of the median distance moved per day because the previous IC tag monitoring studies showed fluctuations in the distance moved per day.<sup>16–18</sup>

### IC tag monitoring system

The IC tag monitoring system was used to describe wandering behaviour in terms of the distance moved consecutively around the clock in AD patients during the two study periods. Thirty-six antennas were set up on the ceiling of the unit to capture the movement of the patient throughout the unit. The antenna received the signal from the IC tag when the patient passed under the antenna and the signal was sent to the computer placed in the nursing station. When the patient moved out of the room, he/she was detected by the antenna by the door. If the patient did not reach the antenna which was closest to the patient's room, and returned to his/her own room, no distance was calculated. The software generated the distance moved per day by summing the distance between the two antennas. Adhesive tape was used to attach the IC tag to the patient's clothes so that the tag could be reattached easily after changing clothes. Reliability and validity of the system were published previously.<sup>16–18</sup> Attachment of the IC tag was checked three times daily. The tag was reattached to the patient's cloth during the bathing or following incontinence episode by the research assistant or unit staff.

### Data collection

Demographic characteristics were abstracted from the medical records. Duration of AD was calculated by subtracting the date of admission from the date when dementia-related symptom manifested. At admission as a

part of a routine clinical data collection, Mini-Mental State Examination (MMSE)<sup>22</sup> was administered by the experienced clinical psychologist, and Clinical Dementia Rating (CDR) was evaluated by a primary physician.<sup>23</sup> CDR assessed the following six domains of functions: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. CDR was developed to stage the severity of AD, and the score ranged from 0 (none) to 3 (severe). Memory is designated as the primary category, with the other five categories secondary categories in the scoring algorithm.

BPSD measured by the Neuropsychiatric Inventory Nursing Home Japanese version (NPI-NH)<sup>24</sup> was evaluated every month as a part of routine evaluation of the patient by the unit staff in a team conference. NPI-NH consists of the following 12 BPSDs: hallucinations, delusions, agitation/aggression, dysphoria/depression, anxiety, irritability, disinhibition, euphoria, apathy, aberrant motor behaviour, sleep and night-time behaviour change, and appetite and eating change. Each BPSD has a screening question for each BPSD, and if 'yes' is checked, then frequency and severity of the behaviour is asked for subsets of questions. For example, 'agitation/aggression' has three screening questions such as 'Does XX have periods when s/he refuses to let people help him/her?' The responses were as follows: 1 NO (go to next page), 2 DON'T KNOW, 3 YES (proceed with subquestions). In this study, if 'yes' was checked for a screening question in 12 subscales, it was considered 'positive' for that BPSD.

### Data analyses

Wilcoxon rank sum test was used to test the differences in the median distance moved per day between two groups, and Kruskal–Wallis test was used to test the differences among three groups or more. Spearman correlation coefficients were obtained to examine the association between the median distance moved per day and the other variables.

Multiple linear regression was used to predict the median distance moved per day using the variables which were significant at univariate analysis.

In order to examine the association between BPSD and the median distance moved per day, the median distance moved per day in the 7 days prior to NPI-NH evaluation was tabulated. For each 12 NPI-NH subscale, median distance moved per day for those rated positive was compared with that for those rated negative.



**Table 1** Demographic characteristics of the study subjects ( $N = 40$ )

Variables		November 2006–March 2007 ( $n = 19$ )	September 2008–August 2009 ( $n = 21$ )
Gender	Male	9	14
	Female	10	7
Age (years) <sup>†</sup>		68.3 ± 10.1	73.8 ± 9.3
Median distance moved/day	Mean ± SD (m)	3160 ± 3728	1621 ± 1655
	Min (m)	997	377
	Median (m)	1737	922
	Max (m)	12 336	5168
Duration of dementia (years) <sup>†</sup>		3.7 ± 7.5	3.9 ± 2.1
Mini-Mental State Examination <sup>†</sup>		10.5 ± 8.2	8.9 ± 6.8
Clinical Dementia Rating	1 (Mild)	6	2
	2 (Moderate)	7	12
	3 (Severe)	6	7

Note: <sup>†</sup> Mean ± SD.

$P$  value < 0.05 was used to determine the statistical significance. Excel 2007 (Microsoft Corporation, Redmond, WA, USA) and JMP Ver. 8.0 (SAS Institute, Cary, NC, USA) for Windows were used for statistical analysis.

### Ethical considerations

The study was approved by the human subject committee of the Osaka University, School of Allied Health Sciences and Asakayama General Hospital. On the date of admission, the research assistant explained to patients' primary caregivers in the family the purpose of the study, study protocol, data handling and ethical consideration. In addition, refusal to participate would not affect treatment and right to withdraw at any time were explained. Written informed consent was obtained from the family member. If the patient did not have a family, a legal guardian was contacted to obtain informed consent. Patients were explained about study in plain language before attaching the IC tag. If the patient appeared to try to remove the tag, it was considered refusal and was dropped from the study.

### RESULTS

There were 45 patients who met inclusion criteria. However, five were excluded because the median distance moved per day was < 200 m ( $n = 4$ ) and the duration of monitoring was < 20 day ( $n = 1$ ). The remaining 40 patients were analyzed. The mean duration of monitoring was  $76.1 \pm 41.5$  days, ranging from 21 to 191 days.

Demographic characteristics of the patients by study period are displayed in Table 1. The distribution of patients' age, gender, median distance moved per day, MMSE and CDR did not differ significantly between two time periods, although a proportion of men in the 2nd period was higher than that in the 1st period and distribution of the median distance moved per day in the 1st period was longer than that in the 2nd period (Table 1). The distribution of the median distance moved per day was skewed for some patients, and median distance moved per day was used for all the analysis related to the median distance moved per day.

Figure 1 displays a box plot of the median distance moved per day in 40 subjects. Median distance moved per day ranged from a low of 278 m to a high of 12 336 m with a wide variability in interquartile.

### Association between the median distance moved per day and demographic/clinical characteristics

The median distance moved per day was moderately correlated with patients' age ( $r = -0.461$ ,  $P < 0.01$ ) and inversely correlated with MMSE ( $r = -0.379$ ,  $P < 0.05$ ), whereas it was not correlated with the duration of dementia. The duration of dementia was weakly and negatively associated with MMSE score ( $r = -0.370$ ,  $P < 0.05$ ).

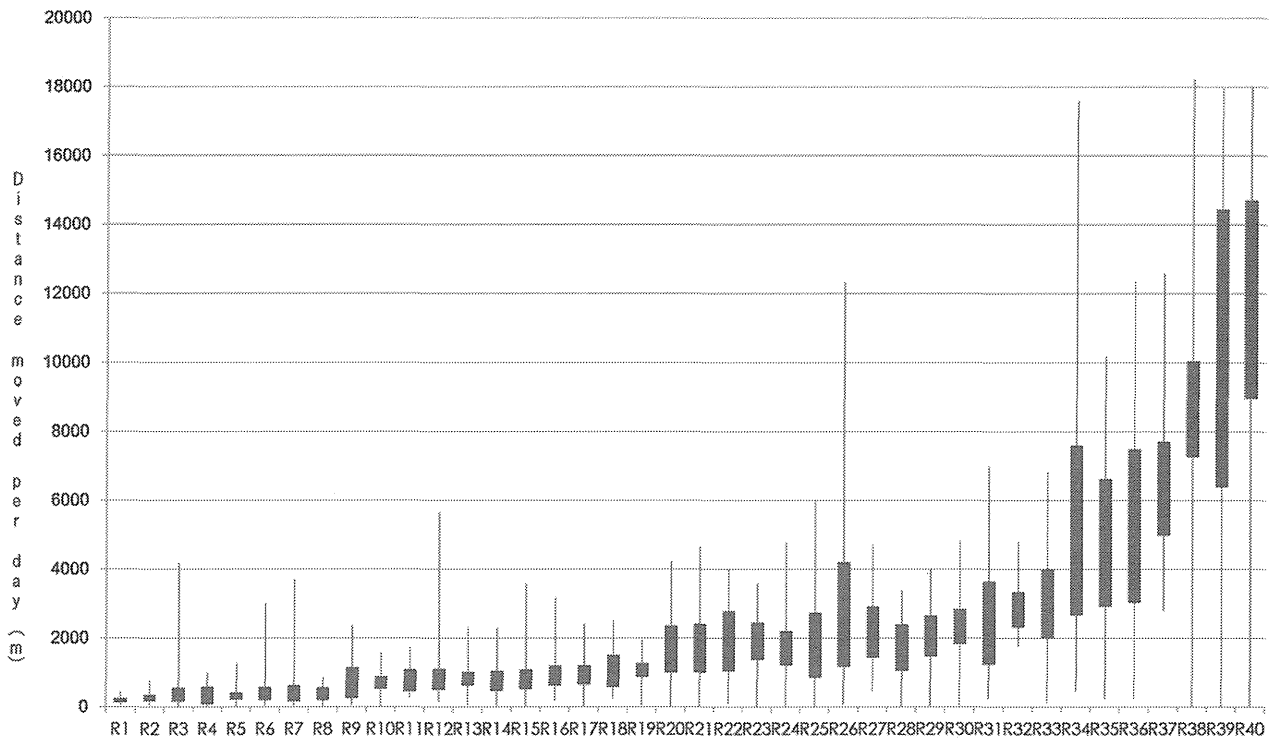


Figure 1. Box plot of the median distance moved per day in 40 subjects with AD.

Table 2 Wilcoxon rank sum test for Clinical Dementia Rating (N = 40)

	Clinical Dementia Rating			P-value
	1 (Mild) (n = 9)	2 (Moderate) (n = 19)	3 (Severe) (n = 12)	
Median of the median distance moved per day	1479 ± 1518	2009 ± 2648	3670 ± 3716	0.23
Age	69 ± 10.1	75.1 ± 9.2	67.2 ± 9.9	0.09
Mini-Mental State Examination	20.7 ± 4.1	9.9 ± 4.3	3.6 ± 4.8	0.0002*
Duration of dementia	2.3 ± 4.0	4.0 ± 2.2	4.5 ± 2.3	0.06

\* P < 0.001.

Then, the differences in the distribution of these variables among three levels of CDR were examined, and only MMSE reached the statistical significance. There were tendency that patients with mild dementia had shorter duration of dementia than those with moderate to severe dementia (P = 0.06) (Table 2).

Multiple linear regressions were used to predict the median distance moved per day using the variable significantly associated with the median distance moved per day. Patients' age and MMSE score were retained in the final model, which explained 47% of the variance (Table 3).

Table 3 Standard regression coefficient of multiple regression analysis for the prediction of the median distance moved per day (N = 40)

Predictors	β	Standard error	P
Age (years)	-0.589	43.2	0.002*
Mini-Mental State Examination	-0.360	59.9	0.0139**
R <sup>2</sup>	0.471		

\* P < 0.001; \*\* P < 0.05.

**Table 4** Prevalence of BPSD and median of the median distance moved per day according to the presence or absence of BPSD in descending order of prevalence ( $n = 28$ )

NPI-NH subscales	Prevalence of BPSD (%)	Median of the median distance moved per day (m)		
		BPSD (+)	BPSD (-)	<i>P</i> -value <sup>†</sup>
Agitation	50	3667	2695	0.71
Apathy	39	2317	3190	0.94
Irritability	36	4628	1858	0.70
Aberrant motor behaviour	32	4572	2030	0.77
Night-time behaviours	32	4649	1994	0.08
Appetite changes	32	3495	2706	0.63
Disinhibition	21	4991	2262	0.042 <sup>†</sup>
Delusions	18	1527	3134	0.17
Hallucinations	18	2868	2843	0.12
Depression	11	4714	3189	0.20
Anxiety	7	2091	2905	0.67
Euphoria	7	6570	2547	0.17

<sup>†</sup> Wilcoxon rank sum test. BPSD, behavioural and psychological symptoms of dementia; NPI-NH, Neuropsychiatric Inventory Nursing Home Japanese version.

### Association between the median distance moved per day and BPSD

Of 40 patients, 12 patients were excluded from this analysis because consecutive 7-day monitoring data could not be obtained due to (i) leaving hospital for the weekend or (ii) being isolated in the private room during NPI-NH evaluation period. Of the remaining 28 patients, the median of the median distance moved per day was 2936 m.

The prevalence of BPSD varied greatly (Table 4). Agitation was the most common BPSD, followed by apathy and irritability. Conversely, euphoria and anxiety were the least common BPSD. When the median distance moved per day for those with each positive BPSD was compared with those with negative BPSD, only disinhibition reached statistical significance (Table 4).

### DISCUSSION

The current study found a wide variation in the median distance moved per day in 40 AD patients measured by the IC tag monitoring system, and age and cognitive function explained 47% of the variance. Severity and duration of dementia, and of the 12 symptoms measured by NPI-NH, only disinhibition was significantly associated with the median distance moved per day.

A major strength of our study was a quantification of wandering in terms of the median distance moved per day in AD patients around the clock for over 2 month period. There are studies which direct observation of dementia patients was used. However, observation per session was short in duration and total duration of observation was mostly few days.<sup>6</sup> Further, scales used to measure wandering were administered by caregivers with various definition of wandering.<sup>12-14</sup> This makes it difficult to compare among studies.

Physical stamina to walk will decrease with advancing age, and our finding is in accordance with this hypothesis. However, previous studies reported contradictory findings. There was an inverse association between age and wandering in a US study,<sup>14</sup> whereas the other multicenter US study reported positive association.<sup>25</sup> In a Taiwanese study no association was found.<sup>10</sup>

These inconsistencies might reflect the differences in the definition and measurement of wandering. All aforementioned studies used different scales to measure BPSDs. In one US study by Colombo *et al.*,<sup>14</sup> aberrant motor behaviour, one of the 12 NPI-NH subscales, was used to measure wandering in institutionalized PWD. Aberrant motor behaviour has seven items which primarily evaluates repetitive activities, and pacing (back

and forth movements) is one of them. In the other US study by Cooper *et al.*, the definition of wandering was not described in the paper whereas reporting patient's age was a positive predictor of wandering ( $P < 0.041$ ) with adjustment for an MMSE ( $P < 0.001$ ) in a logistic model.<sup>25</sup> In the Taiwanese study,<sup>12</sup> BEHAVE-AD was used to measure wandering, in which wandering was defined as 'wandering around the ward or wandering from home or caregiver'.

Cognitive declines are also a predictor of the median distance moved per day in our study, and it is in concordance with all the previous studies.<sup>12–15</sup> Although measurement of wandering differed among studies, these scales measure BPSDs which manifest as the cognitive function decline.

Duration of dementia was expected to be associated with the median distance moved per day; however, this hypothesis was rejected in our study. Progression of AD might differ between those with young onset and those with late onset. Our sample size was too small to control for age at onset of AD. The US study by Cooper *et al.* also found a lack of association between the duration of dementia and wandering.<sup>25</sup> A few factors might explain a lack of association. Firstly, at institutional settings, patients with dementia are admitted for a variety of reasons, which could not be related to the duration of dementia. Secondly, onset of dementia symptoms might not be accurately reported if the patient had not had household members.

Severity of dementia measured by CDR was not associated with the median distance moved per day mainly due to the variability within the group. Further, CDR is a qualitative evaluation of mental function as well as usual activities such as social function and self-care.<sup>23</sup> These activities did not directly relate to the median distance moved per day.

With the exception of disinhibition, the median distance moved per day did not differ significantly between those with and without BPSDs measured by NPI-NH. Some of the subscales related to agitation, such as nighttime behaviour, might have been type 2 error due to the low prevalence.

Our study was limited to the measurement of the median distance moved per day, and other dimensions of wandering were not measured. In the future study, wandering related to care burden needs to be quantified with objective measurement in order to evaluate interventions. There are patients with excessive ambulation, and this group of patients needs to be examined further for

appropriateness of the activity levels. These excessive wandering could be related to the region of the brain affected which could be identified with advancing technology. The other limitation is that the patient's movement within their room was not monitored, and our study might have underestimated the ambulation in some patients who tended to move around in their room.

In summary, the IC tag monitoring system was used to describe the degree of ambulation in terms of the median distance moved per day in institutionalized AD patients over a 2 month period, and factors associated with the median distance moved per day were explored. In total, 40 patients were monitored. The median distance moved per day varied from 276 m to 12 336 m, with a median of 1610 m. In a multiple linear regression, patients' age and cognitive function explained 47% of the variance in the median distance moved per day. In terms of BPSD, only disinhibition reached the statistical significance.

## CONFLICT OF INTEREST

None.

## DESCRIPTION OF AUTHORS' ROLES

The first author analyzed and drafted the paper. The second and third authors implemented the research. The fourth author assisted the logistics and data analysis. The last author supervised the whole project and edited the paper.

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