Risk Factors for Falls in Community-Dwelling Patients with Alzheimer's Disease and Dementia with Lewy Bodies: Walking with Visuocognitive Impairment May Cause a Fall

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Key Words

Fall • Alzheimer's disease • Dementia with Lewy bodies • Parkinsonism • Hypnotics • Anxiolytics • Visuoception

Abstract

Background/Aims: To identify risk factors for falls in community-dwelling patients with Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). **Patients:** 78 consecutive patients (51 AD, 27 DLB) were recruited from the Niigata Rehabilitation Hospital memory clinic. **Methods:** We assessed the number of falls each patient had had in the previous 4 months. The data for DLB patients without motor parkinsonism were analyzed both as part of the whole DLB group and separately to determine the effect of parkinsonism alone on falls. **Results:** Of 78 patients, 17 (21.8%) reported at least 1 fall during the period. A diagnosis of DLB, visual hallucinations, parkinsonism and cognitive fluctuation were significant predictors, but none of them was significant in the stepwise multivariate analysis. After excluding patients with parkinsonism, the use of hypnotics-anxiolytics and a worse score on the constructional task were significant and independent predictors of falling. **Conclusion:** Parkinsonism was a major risk factor for falls. When AD or DLB patients walk with incongruent visual information, they may increase their postural

sway or instability, because of their executive dysfunction. If elementary and/or higher-order visuocognitive impairment in AD or DLB patients alters visual information sufficiently, they may fall when walking.

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Introduction

A fall can cause a significant decline in the activities of daily living in older people. Not only can it result in serious injury or fracture, a fall may restrict an older person's activity and confine him/her to home for fear of falling (postfall syndrome) [1–3]. The risk factors for falling in older people include: aging, motor disability, visual disturbance, cognitive dysfunction, a history of falls and environmental hazards such as obstacles or uneven surfaces [3–6].

Dementia is one of the most widely accepted risk factors for falls, but the mechanism of falling in demented patients remains controversial [7–15]. Another problem is that most studies of falling and dementia do not take the etiology of the dementia into account. However, recent evidence suggests that patients with dementia with Lewy bodies (DLB), the second most common cause of

neurodegenerative dementia after Alzheimer's disease (AD), are at higher risk of falling than are patients with AD [16, 17]. The clinical diagnostic criteria of DLB include repeated falls as a supportive feature [18].

We examined community-dwelling patients with a clinical diagnosis of AD or DLB based on formal diagnostic criteria and neuropsychological assessments to better understand the cause of falling in patients with dementia. Our aim was to identify cognitive and noncognitive factors associated with falling in AD and DLB patients and to evaluate the risk of falls in patients without parkinsonism.

Patients and Methods

Patients

We recruited 78 consecutive, community-dwelling patients who attended the Niigata Rehabilitation Hospital memory clinic (Niigata City, Japan). The eligibility criteria for the study were: (1) a diagnosis of probable AD based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association [19] or a diagnosis of possible or probable DLB based on the clinical criteria of the Consortium on DLB International Workshop [18]; (2) a score of 10 or more on the Mini Mental State Examination (MMSE) [20, 21]; (3) the ability to walk without a cane or walker; (4) the absence of profound deterioration of visual or hearing acuity; (5) living in community with one or more caregivers as a reliable informant for the activities of daily living of the patient. In the initial assessment, each patient underwent a neurological examination, a neuropsychological assessment, a brain MRI or CT scan, an electroencephalogram, and a blood analysis including vitamin B₁, B₁₂ and thyroid function. Formal clinical criteria were used to exclude patients with vascular dementia, Parkinson's disease with dementia, and other dementias.

Fall Assessment

During the 4-month study period, we assessed the incidence of falls in each patient using a structured interview in which the fall was defined as 'an event reported either by the faller or a witness, resulting in a person inadvertently coming to rest on the ground or another lower level, within or without loss of consciousness or injury' [5]. We showed and read aloud the written definition to a reliable informant for each patient and then asked if the patient had fallen in the previous 4 months. If the informant answered yes, the patient was classified as a faller. We also asked and recorded information about fall-related injuries, multiple falls during the study period and possible factors for falling in the activities of their daily living.

Clinical Assessments

We used the Unified Parkinson's Disease Rating Scale [22] to rate resting tremor, cogwheel or lead-pipe rigidity, bradykinesia and postural instability. Motor parkinsonism was defined as the presence of 1 or more of the 4 symptoms rated as 2, or 2 or more of the symptoms rated as 1. The cognitive function of each patient

was assessed using digit span, the MMSE and the Alzheimer's Disease Assessment Scale (ADAS) [23, 24]. The ADAS includes the constructions subtest which consisted of copy tasks of 4 line-drawing geometric figures (a circle, a rhombus, two crossed rectangles and a transparent cube). Visual hallucinations were assessed using the Neuropsychiatric Inventory [25, 26], which was a structured interview to each patient's informant. Information on medications (hypnotics-anxiolytics, antidepressants, neuroleptics, donepezil and antiparkinsonian drugs) was obtained from the informant. The referring behavioral neurologist determined the presence or absence of cognitive fluctuation based on the information provided by the informant and the descriptive definition in the Consortium on DLB International Workshop criteria [18].

The Consortium on DLB International Workshop criteria [18] include 3 core features: visual hallucinations, cognitive fluctuation and motor parkinsonism. One of these is necessary for a diagnosis of possible DLB, and any 2 constitute a diagnosis of probable DLB. In this study, we defined DLB patients as those with a diagnosis of possible or probable DLB.

The study protocol was approved by the ethics committee of Niigata University of Health and Welfare.

Data Analysis

Between-group comparisons were made of the demographic and clinical characteristics of the AD and DLB groups, both including and excluding patients with parkinsonism, using Mann-Whitney U and Fisher's exact probability tests. The relative risk of each factor associated with falling was determined by a repeated measures analysis using a univariate logistic regression model in which the factors (diagnosis, gender, age at onset, age at examination, disease duration and the results of the clinical assessments) were the independent variables and the classification of faller/nonfaller was the dependent variable. This statistical model allowed us to express the relative risk of fall as an odds ratio. The relationship between two or more significant factors was examined using a stepwise multivariate logistic regression model. Parkinsonism is reported to be a risk factor for falls in older people in general [3] as well as in those with dementia [11]. Dementia is also reported to be a predictor of falls in patients with parkinsonism [27]. According to the diagnostic criteria for this study, all patients with parkinsonism were classified as DLB cases; therefore, statistical analyses that included and excluded patients with parkinsonism were performed to determine the effect of parkinsonism alone on falls.

Statistical analyses were conducted using Statistica software (Statsoft Japan, Tokyo), and significance was defined as $p < 0.05$. We did not correct the significance level for multiple comparisons because of the exploratory nature of this study.

Results

We examined a total of 51 AD and 27 DLB patients (5 possible and 22 probable). Table 1 shows the demographic characteristics and the results of the clinical assessments in the 3 patient groups (AD, total DLB and DLB without parkinsonism). The mean age of the total DLB

Table 1. Demographic and clinical characteristics of AD and DLB groups

	AD (n = 51)	Total DLB (n = 27)	DLB without parkinsonism (n = 12)
Male/female	17/34	10/17	5/7
Age at onset, years	74.1 ± 6.4 (63–89)	78.9 ± 7.5 (65–94)**	79.6 ± 7.1 (69–89)*
Age at examination, years	78.2 ± 6.4 (66–93)	83.2 ± 6.6 (73–96)**	83.0 ± 7.2 (73–93)*
Disease duration, years	4.1 ± 2.4 (0–12)	4.3 ± 2.5 (1–10)	3.4 ± 1.5 (1–6)
Visual hallucination absent/present	51/0	10/17**	2/10**
Parkinsonism absent/present	51/0	12/15**	12/0
Cognitive fluctuation absent/present	51/0	4/23**	1/11**
Drugs absent/present			
Hypnotics-anxiolytics	43/8	22/5	9/3
Antidepressants	42/9	22/5	9/3
Neuroleptics	48/3	26/1	12/0
Donepezil	23/28	11/16	7/5
Antiparkinsonian agents	51/0	23/4	12/0
Digit span forward	4.9 ± 1.1 (3–8)	4.6 ± 0.8 (3–7)	4.6 ± 0.7 (3–5)
MMSE (max. 30)	19.2 ± 4.2 (10–28)	16.9 ± 3.7 (12–27)*	16.9 ± 3.8 (12–24)
ADAS			
Total (0–70)	18.4 ± 9.0 (5–42)	22.6 ± 11.4 (3–47)*	22.8 ± 12.5 (3–37)
Word recall (0–10)	6.5 ± 1.6 (3.3–10)	6.6 ± 1.8 (3.3–10)	6.3 ± 2.2 (2.7–10)
Following commands (0–5)	1.0 ± 1.0 (0–3)	1.5 ± 1.2 (0–4)*	1.5 ± 1.4 (0–4)
Naming (0–5)	0.1 ± 0.4 (0–2)	0.2 ± 0.6 (0–3)	0.3 ± 0.9 (0–3)
Constructions (0–5)	0.8 ± 0.8 (0–4)	1.6 ± 1.1 (0–5)**	1.6 ± 1.5 (0–5)*
Ideational praxis (0–5)	1.4 ± 1.7 (0–5)	3.0 ± 2.0 (0–5)**	2.8 ± 2.2 (0–5)*
Orientation (0–8)	3.9 ± 2.0 (0–8)	5.0 ± 2.2 (0–8)*	4.9 ± 2.4 (0–8)

Data are shown as means ± SD, with ranges in parentheses. ADAS: higher score means worse degree of dysfunction.

* $p < 0.05$, ** $p < 0.01$: statistically significantly different from AD group.

and the DLB without parkinsonism groups was significantly higher than that of the AD group. In addition, the DLB groups scored worse on constructions and ideational praxis subtests in the ADAS. Overall cognitive severity assessed by the mean MMSE and total ADAS scores was worse in the total DLB group than in the AD group. The number of patients using neuroleptics or antiparkinsonian drugs was so small (4 patients each) that they were not included in further analysis.

During the 4-month study, 17 of 78 patients (21.8%) reported falls. Five were AD patients (9.8% of AD) and 12 were in the DLB group (44.4% of total DLB). Eight DLB patients had multiple falls and 2 of them fell 6 or more times. A fall-sustained fracture was reported in 1 AD and 1 DLB patient, and other fall-related injuries were reported in 2 AD and 3 DLB patients. The caregivers of 7 DLB fallers with parkinsonism reported possible environmental factors for the fall, such as obstacles and uneven surfaces. Table 2 shows the results of the univariate logistic regression analysis in all patients. A diagnosis of DLB,

visual hallucinations, parkinsonism and cognitive fluctuation were significantly associated with falling. Among the univariate models including each of the 4 factors as the independent variable, the model with parkinsonism showed best log likelihood. Thus, as the stepwise analysis, we examined the multivariate models which include parkinsonism and each of the remaining 3 factors as the independent variables. None of the multivariate models showed a significantly better log likelihood than did the univariate model, and none of the factors was a significant predictor in the multivariate models.

After excluding the 15 patients with parkinsonism, 9 of the remaining 63 patients (14.3%) were classified as fallers, including 4 of the remaining 12 DLB patients (33.3%). The univariate logistic regression analysis revealed that visual hallucinations and cognitive fluctuation did not present a significant relative risk for falling, and a diagnosis of DLB was just below the significance level ($p < 0.06$; table 3). However, the use of hypnotics-anxiolytics and a worse score in the constructions subtest

Table 2. Possible factors associated with falling in the total patients

	Fallers (n = 17)	Nonfallers (n = 61)	Relative risk of fall		
			OR	95% CI	p value
Diagnosis AD/DLB	5/12	46/15	7.36	2.18–24.78	<0.01
Male/female	3/14	24/37	3.02	0.77–11.91	0.11
Age at onset, years	77.0 ± 7.6 (65–94)	75.4 ± 7.0 (63–89)	1.03	0.96–1.11	0.41
Age at examination, years	81.8 ± 6.5 (73–96)	79.4 ± 6.9 (66–93)	1.05	0.98–1.14	0.20
Disease duration, years	4.8 ± 2.8 (1.5–10)	4.0 ± 2.3 (0–12)	1.13	0.92–1.41	0.23
Visual hallucination absent/present	10/7	51/10	3.57	1.07–11.84	<0.05
Parkinsonism absent/present	9/8	54/7	6.85	1.95–24.07	<0.01
Cognitive fluctuation absent/present	6/11	49/12	5.83	1.80–18.84	<0.01
Drugs absent/present					
Hypnotics-anxiolytics	12/5	53/8	2.76	0.76–10.14	0.12
Antidepressants	12/5	52/9	2.40	0.67–8.66	0.18
Donepezil	7/10	27/34	1.13	0.38–3.43	0.82
Digit span forward	4.7 ± 0.7 (4–6)	4.9 ± 1.1 (3–8)	0.84	0.48–1.49	0.56
MMSE (max. 30)	17.3 ± 3.4 (12–27)	18.7 ± 4.3 (10–28)	0.92	0.80–1.05	0.22
ADAS					
Total (0–70)	22.3 ± 8.7 (8–37)	20.0 ± 10.1 (3–47)	1.03	0.99–1.08	0.17
Word recall (0–10)	6.5 ± 1.2 (4.3–9)	6.5 ± 1.8 (3.3–10)	0.98	0.71–1.35	0.88
Following commands (0–5)	1.1 ± 1.1 (0–3)	1.0 ± 0.9 (0–4)	0.87	0.52–1.46	0.59
Naming (0–5)	0.2 ± 0.4 (0–1)	0.1 ± 0.5 (0–3)	1.28	0.45–3.69	0.63
Constructions (0–5)	1.4 ± 1.2 (0–5)	1.0 ± 0.9 (0–4)	1.50	0.91–2.51	0.11
Ideational praxis (0–5)	2.3 ± 2.0 (0–5)	1.9 ± 2.0 (0–5)	1.15	0.84–1.45	0.47
Orientation (0–8)	4.6 ± 1.9 (0–7)	4.2 ± 2.2 (0–8)	1.11	0.86–1.46	0.41

Data are shown as means ± SD, with ranges in parentheses. OR = Odds ratio; CI = confidence interval. ADAS: higher score means worse degree of dysfunction.

of the ADAS were significant predictors for falling. The univariate model with the constructions subtest showed a better log likelihood than did the model with the use of hypnotics-anxiolytics. As the stepwise analysis, we examined the multivariate model including the 2 factors as the independent variables. This model showed a significantly better log likelihood than did the univariate model ($p < 0.05$), and the 2 factors remained significant predictors in the multivariate analysis. The adjusted odds ratio (and 95% confidence interval, CI) was 6.37 (95% CI 1.12–25.74, $p < 0.05$) for hypnotics-anxiolytics and 1.95 (95% CI 1.04–3.66, $p < 0.05$) for the constructions subtest score.

DLB patients are reported to have disproportionately severe visuocognitive impairment compared to AD patients [28–30]. The DLB patients had worse scores in the constructions subtest of the ADAS (table 1). We performed two-way analysis of variance (ANOVA) to examine the relationship among falling, diagnosis and visuocognitive impairment. Diagnosis (AD or DLB with-out parkinsonism) and fall classification (faller/nonfaller)

were the independent variables, and the constructions subtest score was the dependent variable. There was a significant effect of diagnosis ($F = 9.4$, $p < 0.01$) and fall ($F = 6.3$, $p < 0.05$) and an interaction ($F = 5.7$, $p < 0.05$). A post-hoc comparison indicated that the DLB patients who had fallen had a significantly worse score than did the patients in the other 3 groups ($p < 0.05$; fig. 1).

Discussion

In this consecutive, clinic-based study, 21.8% of 78 community-dwelling Japanese patients with AD or DLB had at least 1 fall during the 4-month study period. The incidence of falling is 2–3 times higher in people with dementia than in the general population of elderly people in Japan [31, 32]. Our findings are consistent with the previous estimates that the annual incidence of falling (70–85%) is approximately twice as high for patients with cognitive impairment and dementia as it is for people with no cognitive impairment [3, 6]. The incidence of falls re-

Table 3. Possible factors associated with falling in the patients without parkinsonism

	Fallers (n = 9)	Nonfallers (n = 54)	Relative risk of fall		
			OR	95% CI	p value
Diagnosis AD/DLB	5/4	46/8	4.60	0.99–21.55	0.05
Male/female	1/8	21/33	5.09	0.57–45.63	0.14
Age at onset, years	78.1 ± 5.4 (69– 86)	74.6 ± 6.9 (63– 89)	1.07	0.97–1.20	0.17
Age at examination, years	81.8 ± 6.0 (73– 92)	78.6 ± 6.8 (66–93)	1.07	0.97–1.19	0.21
Disease duration, years	3.7 ± 1.7 (2–6)	4.0 ± 2.4 (0–12)	0.94	0.67–1.30	0.68
Visual hallucination absent/present	6/3	47/7	3.35	0.66–17.12	0.14
Cognitive fluctuation absent/present	6/3	47/7	3.34	0.66–17.12	0.14
Drugs absent/present					
Hypnotics-anxiolytics	5/4	47/7	6.37	1.12–25.74	<0.05
Antidepressants	6/3	45/9	2.50	0.51–12.27	0.25
Donepezil	4/5	26/28	1.16	0.28–4.93	0.84
Digit span forward	4.8 ± 0.7 (4– 6)	4.9 ± 1.1 (3–8)	0.90	0.44–1.84	0.76
MMSE (max. 30)	17.6 ± 2.7 (12– 21)	19.0 ± 4.4 (10–28)	0.92	0.78–1.09	0.34
ADAS					
Total (0–70)	21.2 ± 7.8 (14–37)	19.1 ± 10.1 (3–47)	1.02	0.96–1.09	0.54
Word recall (0–10)	6.1 ± 1.0 (4.3–8)	6.5 ± 1.8 (2.7–9.7)	0.88	0.58–1.34	0.55
Following commands (0–5)	1.0 ± 1.1 (0–3)	1.1 ± 1.1 (0–4)	0.91	0.45–1.81	0.77
Naming (0–5)	0.2 ± 0.4 (0–1)	0.1 ± 0.5 (0–3)	1.35	0.14–4.47	0.62
Constructions (0–5)	1.7 ± 1.6 (0–5)	0.8 ± 0.9 (0–4)	1.95	1.04–3.66	<0.05
Ideational praxis (0–5)	2.0 ± 1.9 (0–5)	1.6 ± 1.9 (0–5)	1.10	0.77–1.61	0.58
Orientation (0–8)	4.4 ± 1.3 (2–6)	4.1 ± 2.2 (0–8)	1.10	0.77–1.58	0.60

Data are shown as means ± SD, with ranges in parentheses. OR = Odds ratio; CI = confidence interval. ADAS: higher score means worse degree of dysfunction.

Fig. 1. Mean (± SD) score of the ADAS construction task in each group of patients without parkinsonism. Higher score means worse degree of constructional disturbances. The DLB patients with falls showed a significantly higher score than the other 3 groups ($p < 0.05$; two-way ANOVA and post-hoc comparison).

ported in this and other Japanese studies is somewhat lower than that reported in the other countries.

The univariate analysis of all of the patients confirmed previous findings that DLB and comorbid parkinsonism

are risk factors for falling in patients with dementia [11, 16, 17]. Visual hallucinations and cognitive fluctuation were also predictors for falling. The model with parkinsonism showed the best log likelihood among the uni-

variate models of the 4 factors. However, in the stepwise analysis, none of the multivariate models showed a significantly better log likelihood, and none of the factors remained a significant predictor in the multivariate models. This may be explained by the fact that all of the patients with parkinsonism, visual hallucinations or cognitive fluctuation were classified as DLB cases. These findings suggest that parkinsonism is one of the major risk factors for falling in patients with dementia; thus, the effect of parkinsonism should be ruled out when investigating other factors that contribute to falling. Our results also recommend that parkinsonism and a diagnosis of DLB should be taken into consideration in studies to assess fall or fall-related events in patients with cognitive impairment and dementia.

Community-dwelling patients with AD or DLB without parkinsonism who used hypnotics-anxiolytics and who had worse scores on the visuoconstructional subtest in the ADAS were at an increased risk of falling. A meta-analysis [33] found that hypnotics and anxiolytics increased the risk of falling in elderly people with no cognitive impairment, as well as in patients with dementia.

Among the cognitive factors, visuoconstructional impairment was a significant predictor of falling, but two-way ANOVA with a post-hoc comparison indicated that a worse score on the visuoconstructional task predicted falling only in DLB patients (fig. 1). The distinctive nature of visuocognitive impairment in DLB may account for this finding. Patients with DLB have a deficiency in elementary visual perception, such as visual form discrimination, as well as in higher-order visuocognitive function [29, 30]. Such a type of visuocognitive impairment may increase the risk of a fall in patients with DLB. Two recent studies reported that patients in dementia wards who had worse scores on the Clock Drawing Test or failed to copy a figure in the MMSE were more likely to fall [13, 15]. These findings may apply to DLB patients with visuocognitive impairment, because there was no differential diagnosis in these studies and they may have included a number of DLB patients. In contrast, we assessed visuocognitive function using the constructions subtest of the ADAS and did not directly assess elementary visual perception. The relationship between falling and the various types of visuocognitive impairment remains to be elucidated.

The characteristics of our patient population may have influenced the study's outcome. The AD patients lived in the community and had a mean score of 19.2 on the MMSE (table 1), indicating that overall cognitive impairment was mild compared to the DLB patients in this

study and the patients in the previous studies [13, 15]. Visuocognitive impairment may predict falls in AD patients with comparable cognitive impairment to DLB patients. The AD patients in our study showed a mean age at onset of 74.1 years. Fujimori et al. [34] reported that AD patients with younger age at onset scored worse on visuoconstructional tasks. In patients with early-onset AD, visuocognitive impairment may be a significant risk for falling.

Patients with profound visual problems in their activities of daily living were excluded from our study. Thus, patients with visuocognitive impairment did not fall because they were unable to 'see' environmental hazards. The link between visuocognitive impairment and falling in AD and DLB patients needs to be clarified.

Recently, several studies have investigated postural sway or instability in walking with a concurrent and unrelated cognitive activity in people with no cognitive impairment [35–38]: postural sway or instability was more prevalent in older than younger subjects. The results of these studies indicate that the attentional resources of older subjects are so finite that performing two tasks simultaneously (dual task) results in a competition for limited resources, with a subsequent reduction in performance [3]. The concept of limited attentional resources is classified as an executive dysfunction in clinical neuropsychology [39]. On the other hand, patients with cognitive impairment and dementia have significantly more balance and limb coordination problems than do elderly people with no cognitive impairment [40]. Chong et al. [41] compared AD, Parkinson's disease and normal control patients using Sensory Organization Tests [42]. This protocol examines a subject's ability to maintain balance in place. They reported that the sway increased when both visual and somatosensory inputs were incongruent in AD patients [41]. The authors concluded that AD patients have a decreased ability to suppress incongruent visual stimuli when trying to maintain balance. Though these reports do not distinguish DLB from AD, the results can be explained by further restriction of executive function in the patients when compared with normal older subjects [39, 43].

Walking, as opposed to just standing in place, requires executive function [39]. To walk, a person must process inputs from sensory and cognitive systems such as somatosensory information from the physical interaction between foot and floor, visual information to avoid obstacles and cognitive information to complete a purposive behavior. We consider that when patients with AD or DLB walk, they are susceptible and vulnerable to altered

and incongruent visual information and increase their postural sway or instability, because of their impaired executive function [39, 43]. Therefore, if elementary and/or higher-order visuo-cognitive impairment in patients with AD or DLB alters visual information sufficiently to become incongruent as sensory information, they may fall when walking. Thus, walking with visuo-cognitive impairment can cause falls in patients with AD or DLB. We think that this hypothesis is worth further examination.

An important limitation of our study should be mentioned: the number of the subjects was so small that we could not examine the factors for falls in AD and DLB patients separately. As our results suggested, the risk fac-

tors and the mechanisms for falls should be delineated in each disorder having different features. In further studies, the relationship and interaction among fall, visuo-cognitive impairment and executive dysfunction should be addressed in a larger population of patients with AD, DLB and other dementias.

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