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Comparison of behavioral and psychological symptoms in early-onset and late-onset Alzheimer's disease

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SUMMARY

Background When comparing with early-onset Alzheimer's disease (EO-AD) and late-onset Alzheimer's disease (LO-AD), some symptomatological differences in clinical features can be seen between them. Rapid progression, more severe language problems or visuospatial dysfunction occur more often in EO-AD patients. However, there have been very few reports about the differences in behavioral and psychological symptoms between these two groups.

Aim The aim of this study was to demonstrate the differences in behavioral symptoms between EO-AD and LO-AD groups.

Method Three hundred and seven consecutive outpatients with AD were put into an EO-AD group (46 patients) or a LO-AD group (261 patients). Comprehensive assessment batteries, including the Neuropsychiatric Inventory (NPI), were administered at the first medical assessment.

Results Significant differences were found between the EO-AD and LO-AD groups in terms of NPI total score (EO-AD: 10.3 ± 10.9, LO-AD: 17.8 ± 17.0, $p = 0.004$) and number of patients who experienced each NPI subscale score (delusion; EO-AD: 13.0%, LO-AD: 50.6%, $p < 0.001$). There were no differences in cognitive functions or dementia severity between two groups.

Conclusion In EO-AD, behavioral and psychological symptoms are relatively fewer than LO-AD at the first medical assessment.

KEY WORDS — early-onset; Alzheimer's disease; Neuropsychiatric Inventry (NPI); behavioral and psychological symptoms of dementia (BPSD); outpatients

INTRODUCTION

In recent years, reports based on large clinicopathologic studies have shown that the pathologies of Alzheimer's presenile dementia and senile dementia of Alzheimer type are not qualitatively different (Newton, 1948; Neumann and Cohn, 1953; Corsellis, 1962). However, when comparing their clinical symptoms in detail, several differences can be found (Chui *et al.*, 1985; Mayeux *et al.*, 1985). Some studies have reported that rapid progression (Jacobs *et al.*, 1994), language problems (Imamura *et al.*, 1998) or visuospatial dysfunction (Fujimori *et al.*, 1998) occur more often in early-onset Alzheimer's disease (EO-AD) patients.

There have been very few reports about the differences of behavioral and psychological symptoms of dementia (BPSD) between EO-AD and late-onset Alzheimer's disease (LO-AD) groups. Ferran *et al.* (1996) reported that in EO-AD patients, delusions,

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hallucinations and disinhibition were under 15%, however, they did not use standardized assessment instruments. Other studies lack standardized instruments for BPSD and operational criteria, too. Therefore, differences of BPSD between EO-AD and LO-AD groups are not clear at the present.

BPSD have been shown to be a major cause of anxiety and concern for caregivers (Deimling and Bass, 1986) and a frequent cause of admission to an institution (Steel *et al.*, 1990; Haupt and Kurz, 1993). Because appropriate management of BPSD may lessen the burden of caregivers (Shigenobu *et al.*, 2002) and may postpone admission to an institution, evaluation and management of BPSD are of considerable importance in practice (Ikeda and Tanabe, 2004). It is also important to assess BPSD of AD patients because of its differential diagnosis from depression, delusional disorders or dementia with Lewy Bodies (DLB) (Mckeith *et al.*, 1996).

In this study we examined a large set of patients with EO-AD and LO-AD to evaluate BPSD using standardized assessment instrument (the Neuropsychiatric Inventory: NPI) (Cummings *et al.*, 1994; Hirono *et al.*, 1997) and attempted to clarify the differences of BPSD between the two groups.

METHOD

Subjects

Study participants were consecutive outpatients with a diagnosis of AD between January 1997 and September 2005. They were referred for evaluation to the Higher Brain Function Clinic, for outpatients of the University Hospital of Ehime University Graduate School of Medicine.

All patients underwent physical and neurological examinations, laboratory blood tests including vitamin B12, folic acid and thyroid function, brain MRI, and HMPAO-SPECT, and were assessed with a comprehensive neuropsychological test battery, including the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975), Alzheimer's Disease Assessment Scale—Cognitive Part (ADAS-cog) (Mohs *et al.*, 1983; Homma *et al.*, 1992) and Raven's Coloured Progressive Matrices (RCPM) (Raven, 1965). Dementia severity was assessed by Clinical Dementia Rating (CDR) (Hughes *et al.*, 1982). BPSD were assessed by the NPI. The age at onset and the duration of the disease were ascertained through an interview with the primary caregiver. Age at onset was defined as the age of the first appearance of symptoms which interfere with social or occupational functioning, and the duration was defined as the amount of time between the onset and the first medical assessment. Patients who satisfied the NINCDS/ADRDA diagnostic criteria for probable AD (Mckhann *et al.*, 1984) were put into the EO-AD group if they were under 65 years old, and into the LO-AD group if they were over 70 years old, at the time of their first assessment. We excluded patients aged between 65 and 70 years at the time of first medical assessment in order to reduce the likelihood of having patients older than 65 years with a disorder that had its onset before that age (Suribhatla *et al.*, 2004), patients without a reliable caregiver, and patients who had a history of mental illness or substance misuse before onset of dementia. This study was conducted after obtaining informed consent from all subjects or their caregivers.

Assessment of BPSD

We assessed the presence of BPSD with a structured caregiver interview using the NPI. The NPI evaluates ten neuropsychiatric disturbances common in dementia: delusion, hallucination, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, and aberrant motor behavior. The severity and frequency of each neuropsychiatric symptom are rated on the basis of scripted questions that the patient's reliable caregiver is asked. A total NPI score is calculated, in addition to the scores for the individual symptom domains. The validity and reliability of the NPI have been proven both in Western countries and Japan (Cummings *et al.*, 1994; Hirono *et al.*, 1997).

Statistical analysis

All statistical analyses were carried out with Stat View, J 5.0.

To compare the differences of EO-AD and LO-AD, we used the Mann–Whitney *U*-tests for CDR, MMSE, ADAS-cog, RCPM, total NPI score and each NPI subscale score. We used the *t*-test for duration of disease and years of education. We used Fisher's exact test for sex and number of patients in each NPI subscale.

A significance level of 0.05 was set for all analyses.

RESULTS

Among the 370 patients who were diagnosed with AD, 27 patients were excluded because information from a reliable caregiver could not be attained. After we

excluded patients 65–70 years old at the time of first medical assessment, 307 patients remained. Of the 307 patients, 46 had EO-AD (24 males and 22 females; the mean age with SD at the time of first medical assessment was 55.3 years, SD 5.2) and 261 had LO-AD (80 males and 181 females, 75.3 years, SD 5.4). Significant differences were found between the EO-AD and LO-AD groups in terms of sex ratio ($p = 0.007$). The background of both groups is presented in Table 1. Significant differences were also found in years of education ($p < 0.001$) between the EO-AD and LO-AD groups. Duration of disease determined by informant-based interviews did not differ significantly ($p = 0.405$).

No significant differences were found between the two groups with CDR ($p = 0.445$), MMSE ($p = 0.231$), ADAS-cog ($p = 0.898$) and RCPM ($p = 0.064$). The mean total NPI score was significantly lower in the EO-AD group ($p = 0.004$). The number of patients who scored each NPI subscale is presented in Table 2. Significant differences were found between EO-AD and LO-AD groups in terms of delusion ($p < 0.001$), hallucination ($p = 0.002$), agitation ($p = 0.037$), disinhibition ($p = 0.039$) and aberrant motor behavior ($p = 0.034$). Each NPI subscale score is shown in Table 3. Significant differences were additionally found in the NPI subscale scores of delusion ($p < 0.001$), hallucination ($p = 0.004$), agitation ($p = 0.009$), disinhibition ($p = 0.037$) and aberrant motor behavior ($p = 0.015$).

Table 1. Comparison of characteristics between EO-AD and LO-AD patients

	EO-AD ($N = 46$)	LO-AD ($N = 261$)	p value
Age at onset (y)	55.3 ± 5.2	75.3 ± 5.4	
Age at examination (y)	58.8 ± 5.0	78.5 ± 5.1	
Duration of illness (y)	3.5 ± 2.0	3.2 ± 2.4	0.405
Sex (M/F)	24/22	80/181	0.007*
Education (y)	11.8 ± 2.7	9.5 ± 2.3	<0.001**
CDR (0.5/1/2/3)	16/15/9/6	66/97/82/16	0.445
MMSE	17.4 ± 7.6	19.0 ± 6.0	0.231
ADAS-cog	18.7 ± 12.1[a]	17.9 ± 10.4[b]	0.898
RCPM	17.9 ± 10.7[c]	21.5 ± 7.6[d]	0.064
total NPI score	10.3 ± 10.9	17.8 ± 17.0	0.004***

mean ± SD or N.
*Significant difference was found by the Fisher exact test ($p < 0.05$);
**Significant difference was found by the t-test ($p < 0.05$);
***Significant difference was found by the Mann–Whitney U-test ($p < 0.05$).
CDR = Clinical Dementia Rating; MMSE = Mini-Mental State Examination; ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive part; RCPM = Raven's Coloured Progressive Matrices; NPI = Neuropsychiatric Inventory.
[a]$N = 39$,
[b]$N = 222$,
[c]$N = 41$,
[d]$N = 204$.

Table 2. Number of patients who scored on each NPI subscale

	EO-AD ($N = 46$)	LO-AD ($N = 261$)	p value
Delusion	13.0% (6)	50.6% (132)	<0.001*
Hallucination	4.3% (2)	22.6% (59)	0.002*
Agitaion	28.3% (13)	44.8% (117)	0.037*
Dysphoria	43.5% (20)	39.1% (102)	0.625
Anxiety	28.3% (13)	38.7% (101)	0.19
Euphoria	8.7% (4)	7.3% (19)	0.761
Apathy	56.5% (26)	64.4% (168)	0.323
Disinhibition	4.3% (2)	16.5% (43)	0.039*
Irritability	19.6% (9)	24.5% (64)	0.574
Aberrant motor behavior	26.1% (12)	43.7% (114)	0.034*

*Significant difference was found by the Fisher exact test ($p < 0.05$).

DISCUSSION

In this study, we examined a large series of patients in EO-AD and LO-AD groups for the evaluation of BPSD and attempted to clarify the differences between these groups. This is the first study which used standardized test batteries to evaluate and compared the BPSD of these two groups as far as we are aware.

Significant differences were found between the EO-AD and LO-AD groups in terms of NPI total score. In the EO-AD group, BPSD were relatively few. Significant differences were also found between the two groups in the NPI subscale scores, such as delusion. Delusions are common BPSD in AD (Wragg

Table 3. Scores of NPI subscale

	EO-AD ($N = 46$)	LO-AD ($N = 261$)	p value
Delusion	0.50 ± 1.59	2.99 ± 3.97	<0.001*
Hallucination	0.15 ± 0.73	1.13 ± 2.72	0.004*
Agitaion	0.57 ± 1.13	1.81 ± 2.88	0.009*
Dysphoria	1.87 ± 2.83	1.30 ± 2.30	0.302
Anxiety	1.20 ± 2.37	1.72 ± 2.80	0.200
Euphoria	0.20 ± 0.75	0.19 ± 0.76	0.755
Apathy	3.17 ± 3.80	3.53 ± 3.62	0.399
Disinhibition	0.33 ± 1.81	0.77 ± 2.22	0.037*
Irritability	0.89 ± 2.06	1.46 ± 3.02	0.369
Aberrant motor behavior	1.41 ± 2.66	2.94 ± 4.09	0.015*

*Significant difference was found by the Mann–Whitney U-test ($p < 0.05$).

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Table 4. Number of patients who experience delusions

	EO-AD patients	LO-AD patients	Total
Male			
With delusion	1	30	31
Without delusion	23	50	73
Total	24	80	104
Female			
With delusion	5	102	107
Without delusion	17	79	96
Total	22	181	203

Significant differences were found between the EO-AD and LO-AD groups, regardless of sex (in male, $p = 0.002$; in female, $p = 0.003$, by the Fisher exact test).

and Jeste, 1989; Migliorelli *et al.*, 1995). However, the mechanism for delusions in AD patients is not well understood. Some studies which did not use an age limit reported that being female is linked to delusions in AD (Hirono *et al.*, 1998; Launer *et al.*, 1999; Ikeda *et al.*, 2003). Therefore, there is a possibility that our results were strongly influenced by sex ratio. We thus sorted females and males and recompared separately (Table 4). Delusions were significantly lower in the EO-AD group, regardless of sex.

Hallucination was significantly lower in EO-AD group. The mechanism of hallucinations in AD patients, like that of delusions, is not well understood. There is a possibility that DLB patients who often hallucinated may have been misdiagnosed with AD, although patients with parkinsonism, fluctuation and deterioration of blood flow in the occipital lobe were excluded as a precaution (Mori *et al.*, 2006). Similar to AD patients, DLB patients show memory disturbance and disorientation, and there are more DLB patients amongst the elderly (Yokota *et al.*, 2005). Therefore, some DLB patients might be diagnosed as LO-AD.

Ropacki and Jeste (2005) reviewed 55 studies published between 1990–2003 that reported that older age was correlated with psychotic symptoms in 12 of 25 studies and was not associated with psychosis in the remaining 13 investigations. Further studies are needed on this issue.

Agitation, disinhibition and aberrant motor behavior were significantly lower in EO-AD group. This may be due to the low frequency of hallucination and delusions (Ballard and Oyebode, 1995).

We could not sufficiently explain the reason why the prevalence of these BPSD in EO-AD is lower than that of LO-AD in this study. A possible explanation for our findings is that age itself, biological, psychosocial or environmental factors may affect BPSD. It is especially important to evaluate BPSD for diagnosis and care in LO-AD patients.

Although BPSD were low in the EO-AD group, dysphoria (43.5%) and apathy (56.5%) occurred with relatively high frequency. Therefore, it is important to introduce a day-care service and plan for keeping daily activities of EO-AD patients similar to LO-AD patients. In examining a young patient with memory disturbance and depression, clinicians should carefully consider the diagnosis of dementing disorders, depression (pseudo-dementia), or complicated versions of both.

No significant differences were found in the duration of disease, CDR, MMSE, ADAS-cog and RCPM. Therefore, levels of cognitive function and severity of dementia were almost the same in the two groups. The education level was significantly higher in EO-AD group. This difference seems to be influenced by the changing of the Japanese education system after World War.

Ropacki and Jeste (2005) reviewed studies that reported the risk factors associated with psychosis of AD and reported that education level showed a weak or inconsistent relationship with psychosis. As Hirono *et al.* (1998) also reported that education level is not related to behavioral and psychological symptoms, this difference of education level might not effect our results.

In general, there are more female AD patients (Launer *et al.*, 1999). In this study as a whole, there was also female predominance. However, looking at the EO-AD group only, no significant difference was found in terms of sex ratio. Some community based surveys about early-onset dementias did not show a difference in sex ratio (Newens *et al.*, 1993), whereas others showed female predominance in EO-AD (Kokmen *et al.*, 1988). Further studies are needed to examine this sex ratio in the future.

Previous PET studies show the differences of regional cerebral glucose metabolism between EO-AD and LO-AD groups. Sakamoto *et al.* (2002) reported that EO-AD group had more severe hypometabolism in the bilateral parietal and posterior cingulated cortices and precuneus region than the LO-AD groups. Yasuno *et al.* (1998) reported that EO-AD patients showed significant hypometabolism in the left dorsal frontal, left lateral temporal, bilateral inferior parietal and left retrosplenial areas compared to the LO-AD patients. There is a possibility that these results are associated with the differences of BPSD between two groups. Further studies with strictly controlled experimental designs are needed to reveal

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the regions responsible for psychotics (Fukuhara *et al.*, 2001).

In this study, there are some methodological issues. Firstly, there is a possibility that results were affected by the peculiarity of an university hospital (population bias by institution). Secondly, age at onset was ascertained by an interview with the primary caregiver and then patients are classified into EO-AD and LO-AD groups in many studies. However, in some cases, caregivers' memories may have been inaccurate (Oppenheim, 1994), making it difficult to obtain an accurate medical history. Therefore, in this study, we decide to classify subjects by age at first assessment. This method can strictly identify EO-AD patients, whereas there is possibility that a few EO-AD patients may be put into the LO-AD group.

In this study, we used standardized test batteries to evaluate BPSD and compared between EO-AD and LO-AD groups. It became clear that significant differences were found between these two groups in terms of BPSD, especially delusions and hallucinations, although the levels of cognitive function and severity of dementia are not different. In the EO-AD group, prevalence of BPSD is relatively lower compared with the LO-AD group. Several functional imaging studies and our results show the possibility of the existence of biological subtypes of AD.

To confirm our assumption, further community based surveys with generally low bias and imaging studies with strictly controlled experimental designs are needed.

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Caregiver Burden Associated with Behavioral and Psychological Symptoms of Dementia in Elderly People in the Local Community

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Key Words

Neuropsychiatric Inventory · Neuropsychiatric Inventory Caregiver Distress Scale · Caregiver's burden · Behavioral and psychological symptoms of dementia · Nakayama study

Abstract

Background: Despite many studies about the association between caregiver burden and behavioral and psychological symptoms of dementia (BPSD), there have been no population-based studies to evaluate caregiver burden associated with each BPSD. ***Objective:*** To evaluate caregiver burden associated with the individual BPSD in elderly people living in the community. ***Methods:*** The subjects were 67 participants with dementia living with their caregivers (diagnosed in the third Nakayama study): 51 Alzheimer's disease, 5 vascular dementia and 11 other. The Neuropsychiatric Inventory (NPI) and NPI Caregiver Distress Scale (NPI-D) were used to assess subjects' BPSD and related caregiver distress, respectively. ***Results:*** In the subjects exhibiting BPSD, aberrant motor behavior had the highest mean NPI score, and depression/dysphoria had the lowest. Agitation/aggression had the highest mean NPI-D score, and euphoria/elation had the lowest. Delusion, agitation/aggression, apathy/indifference, irritability/lability and aberrant motor behavior showed a correlation between the NPI and NPI-D scores. ***Conclusion:*** The burden associated with BPSD is different for each symptom and does not always depend on frequency and severity of BPSD. These findings suggest that some symptoms, such as agitation/aggression and irritability/lability, may affect the caregivers significantly, although their frequency and severity are low.

Introduction

Behavioral and psychological symptoms of dementia (BPSD) are distressing to patients and caregivers [1, 2] and often lead to institutionalization [3–5]. However, appropriate management of BPSD lessens the burden of caregivers [6]. Thus, BPSD have important diagnostic, prognostic and management implications.

Caregiver burden is a multilayered phenomenon involving various factors on both sides (care recipients and caregivers) [7]. The structure of the care recipients' side consists of various factors such as their activities of daily living, severity of dementia, and BPSD. The correlation of caregiver burden with the recipient's activities of daily

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Table 1. Subjects' and caregivers' data

Subjects (M:F)	67 (29:38)
Mean age ± SD, years	80.8 ± 7.0 (66–97)
Diagnosis (AD/VaD/others)	51/5/11
Mean education ± SD, years	8.1 ± 2.5 (0–13)
Mean MMSE score ± SD	20.1 ± 5.2 (1–28)
CDR (0.5/1/2/3)	24/22/13/8
Caregivers (M:F)	15:52
Caregivers' mean age ± SD, years	63.5 ± 10.9 (39–81)
Caregivers' relationship (spouse/child/child-in-law)	28/13/26
Mean ZBI score ± SD	19.6 ± 14.8 (0–66)
Mean NPI score ± SD	13.3 ± 13.9 (0–58)
Mean NPI-D score ± SD	4.6 ± 5.6 (0–24)

Figures in parentheses are ranges.

living and severity of dementia is still controversial [8]. Meanwhile, numerous studies have claimed that the recipient's BPSD may be the most important care recipient variable in terms of their adverse impact on caregiver burden [9].

Other previous studies have demonstrated a strong association between caregiver burden and the care recipient's BPSD such as wandering, agitation or depression [10–13]. Almost all relevant studies, however, evaluate the correlation between the general burden of caregivers and BPSD. Evaluation of the correlation between caregiver burden and individual BPSD will make clear which symptoms require intervention and will be useful in reducing the burden of the caregiver.

The Neuropsychiatric Inventory Caregiver Distress Scale (NPI-D) [11, 14] is an instrument that provides a quantitative measure of the distress experienced by caregivers in relation to the individual symptom domains assessed by the Neuropsychiatric Inventory (NPI) [15–17], which is a comprehensive instrument of BPSD.

Although there are some studies using the NPI-D [11, 12], these studies have come from clinic-derived samples such as patients in Alzheimer's disease research centers. These sources are subject to referral bias. There are few population-based studies investigating the relationship between BPSD and burden. Pot et al. [18] evaluated caregivers' distress and their stressor. However, they used their original assessment scale for BPSD and burden. To our knowledge, there have been no population-based studies to evaluate caregiver burden associated with each BPSD with comprehensive assessment scales.

The aim of the present investigation is to evaluate caregiver burden associated with each BPSD of elderly patients with dementia living in the Japanese community.

Methods

Subjects

The study was conducted on all people aged 65 years and older residing in Nakayama town [19]. The first study was done in 1997 and the second study in 2001. The third study was carried out among 1,521 residents aged 65 years and older between April 2004 and April 2006. In the present study, we analyzed the data from the third study.

The diagnosis of dementia was established according to DSM-III-R criteria [20]. Alzheimer's disease (AD) was defined according to the NINCDS-ADRDA criteria [21], vascular dementia according to the NINDS-AIREN criteria [22] and other dementia according to the standard criteria of each dementia.

Ninety-two participants fulfilled the diagnostic criteria of dementia. Among these, 67 participants living with a caregiver were selected for this study: 51 probable AD, 5 vascular dementia, and 11 other (2 dementia resulting from normal-pressure hydrocephalus, 2 progressive supranuclear palsy, 1 dementia with Lewy bodies, 1 dementia resulting from subdural hematoma, 1 dementia resulting from alcoholism, 1 Parkinson's disease with dementia, 1 dementia resulting from head trauma, 1 dementia resulting from anoxia and 1 dementia resulting from organic phosphorus toxicosis).

The demographic information of the subjects and caregivers is summarized in table 1.

Written informed consent was obtained from all participants (or relatives when necessary), with a full explanation of the procedures.

General Assessment for Dementia

Senior neuropsychiatrists administered the Mini-Mental State Examination (MMSE) [23], and standard physical and neurological examination to the subjects. The severity of dementia was evaluated using the Clinical Dementia Rating (CDR) [24]. All subjects were asked to undergo a cranial computed tomography (CT), and some of them were checked with a blood test and/or a brain single photon emission computed tomography (SPECT) when necessary.

BPSD and Caregiver Distress Scale

The NPI [15–17] and the NPI-D [11, 14] were used to assess subjects' BPSD and related caregiver distress, respectively. The general caregiver burden was assessed by the Zarit Caregiver Burden Interview (ZBI) [7]. All of these were administered by senior neuropsychiatrists. The NPI is a validated caregiver-based clinical instrument that evaluates 10 domains of neuropsychiatric symptoms: delusion, hallucination, agitation/aggression, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability and aberrant motor behavior. The informant was asked if the behavior represented a change from that shown by the participant before the onset of dementia and had been present during the previous month. If a positive re-

Table 2. NPI component scores and their relationship to the NPI-D score

Symptom scale	Patients	ZBI	Distress	Frequency		Severity		Product	
		mean ± SD	mean ± SD	mean ± SD	rD	mean ± SD	rD	mean ± SD	rD
Delusions	21 (31)	24.5 ± 14.6	2.1 ± 1.6	2.1 ± 1.3	0.35 (NS)	2.1 ± 0.9	0.55*	5.0 ± 4.4	0.53*
Hallucinations	7 (10)	28.0 ± 16.8	1.4 ± 1.1	2.1 ± 1.2	0.55 (NS)	1.7 ± 1.0	0.65 (NS)	4.6 ± 4.5	0.51 (NS)
Agitation/aggression	26 (39)	29.4 ± 15.9	2.3 ± 1.4	2.5 ± 1.1	0.56**	1.5 ± 0.7	0.78**	3.9 ± 1.4	0.76**
Dysphoria/depression	14 (21)	24.4 ± 13.1	0.7 ± 0.6	1.8 ± 0.9	0.44 (NS)	1.1 ± 0.4	0.49 (NS)	2.1 ± 1.5	0.52 (NS)
Anxiety	10 (15)	26.2 ± 15.6	1.4 ± 1.1	2.5 ± 1.4	0.09 (NS)	1.4 ± 0.7	0.17 (NS)	4.1 ± 3.9	0.16 (NS)
Euphoria/elation	2 (3)	23.5 ± 16.5	0.0 ± 0.0	2.5 ± 2.1	0.50 (NS)	1.0 ± 0.0	1.0 (NS)	2.5 ± 2.1	0.50 (NS)
Apathy/indifference	47 (70)	21.0 ± 14.0	1.4 ± 1.2	3.6 ± 0.9	0.22 (NS)	1.8 ± 0.7	0.34*	6.7 ± 3.4	0.36*
Disinhibition	12 (18)	25.6 ± 14.0	2.1 ± 1.2	2.0 ± 1.0	−0.12 (NS)	1.5 ± 0.7	0.46 (NS)	3.1 ± 2.4	0.13 (NS)
Irritability/lability	23 (34)	28.3 ± 16.7	2.1 ± 1.4	2.8 ± 1.0	0.46*	1.6 ± 0.7	0.67**	4.6 ± 3.0	0.75**
Aberrant motor behavior	16 (24)	24.2 ± 9.5	1.9 ± 1.1	3.0 ± 1.1	0.37 (NS)	2.3 ± 0.8	0.81**	7.1 ± 3.5	0.72**
Median	15 (22)	25.1	1.7	2.5	0.44	1.6	0.55	4.4	0.51
Total	62 (93)	19.6 ± 14.8	5.0 ± 5.6					14.3 ± 13.9	0.70**

Figures in parentheses are percentages. The total score of distress shows a mean score of the total NPI-D of 62 subjects who presented >1 symptom. The mean scores of individual NPI and NPI-D show the mean score of the subjects who presented each symptom. rD: Spearman rank correlation coefficients between NPI frequency, severity and NPI-D scale score. NS = Not significant; * $p < 0.05$; ** $p < 0.01$.

sponse was obtained from the screening questions, the behavioral domain was explored with scripted questions that focused on specific features of the behavioral disturbance. The informant then rated the behaviors. Scores from 1 to 4 were obtained for the frequency, and 1–3 for the severity of each behavior. The NPI score for each domain was the product of the frequency and severity subscores, maximum 12. The maximum total NPI score for the 10 domains is 120. The NPI-D is an instrument that provides a quantitative measure of the distress experienced by caregivers in relation to the individual symptom domains assessed by the NPI. After rating each symptom domain of the NPI, caregivers were asked to rate the emotional or psychological distress that they experienced in relation to the symptom on a 6-point scale: 0 (not at all distressing), 1 (minimally distressing), 2 (mildly distressing), 3 (moderately distressing), 4 (severely distressing) and 5 (extremely distressing). The maximum total NPI-D score for the 10 domains is 50. Both the reliability and the validity of the Japanese version of the NPI and NPI-D, like those of the original version, have been shown to be high [14, 16].

To examine how much variability in ZBI score the total NPI-D score explains, we calculated the Spearman rank correlation coefficient between these 2 scores.

For all analyses, $p < 0.05$ was considered to be the criterion for significance.

Results

The mean age of the subjects was 80.8 ± 7.0 years. The mean MMSE score was 20.1 ± 5.2. The level of dementia was graded as very mild (CDR = 0.5) in 35.8% (n = 24), mild (CDR = 1) in 32.8% (n = 22), moderate (CDR = 2) in 19.4% (n = 13),and severe (CDR = 3) in 11.9% (n = 8). The mean age of the caregivers was 63.5 ± 10.9 years. Most caregivers were female (n = 52, compared with 15 males) and spouses (n = 28, compared with 26 children-in-law and 13 children), and the mean ZBI score was 19.6 ± 14.8.

In all subjects, total NPI-D score was significantly correlated with ZBI score ($rs = 0.51$, $p < 0.01$). In the subjects exhibiting BPSD, total NPI-D score was similarly correlated with ZBI score ($rs = 0.51$, $p < 0.01$). This fact indicates that almost 25% of variability in ZBI score is explained by total NPI-D score.

Table 2 shows the NPI component scores and theirrelationship to the NPI-D scores. Sixty-two of the subjects (93%) had shown 1 or more BPSD in the previous month. The most common symptom was apathy/indifference (70%), followed by agitation/aggression (39%) and irritability/lability (34%). Euphoria/elation (3%) was the most uncommon symptom. In the subjects exhibiting BPSD, aberrant motor behavior had the highest mean NPI score (7.1 ± 3.5), followed by apathy/indifference (6.7 ± 3.4), delusions (5.0 ± 4.4), hallucinations (4.6 ± 4.5) and irritability (4.6 ± 3.8). Dysphoria/depression had the lowest mean NPI score (2.1 ± 1.5), followed by euphoria/elation (2.5 ± 2.1) and disinhibition (3.1 ± 2.4). Agitation/aggression had the highest mean NPI-D score (2.3 ± 1.4), followed by irritability/lability (2.1 ± 1.4), disinhibition (2.1 ± 1.2), delusions (2.1 ± 1.6) and aberrant motor behavior (1.9 ± 1.1). Euphoria/elation had the lowest mean NPI-D score (0.0 ± 0.0), followed by dysphoria/depres-

Table 3. Frequency distribution of NPI distress ratings for NPI symptom domains

Symptom scale	Patients	Low distress		Medium distress		High distress		Total %
		n	%	n	%	n	%	
Delusions	21	9	43	7	33	5	24	7
Hallucinations	7	3	43	4	57	0	0	0
Agitation/aggression	26	11	42	8	31	7	27	10
Dysphoria/depression	14	13	93	1	7	0	0	0
Anxiety	10	7	70	2	20	1	10	1
Euphoria/elation	2	2	100	0	0	0	0	0
Apathy/indifference	47	29	62	16	34	2	4	3
Disinhibition	12	5	42	4	33	3	25	4
Irritability/lability	23	10	43	9	39	4	17	6
Aberrant motor behavior	16	6	38	8	50	2	13	3
Median	15.0	8.0	43.0	5.5	33.0	2.0	11.5	3.0

Distress: low = NPI-D score 0–1, medium = NPI-D score 2–3, high = NPI-D score 4–5.
Total: percent of total subject sample with NPI-D score 4–5 (high distress) in relation to symptom (n = 67).

sion (0.7 ± 0.6). Delusion, agitation/aggression, apathy/indifference, irritability/lability and aberrant motor behavior showed a significant correlation between the NPI and NPI-D scores.

Furthermore, according to the study by Kaufer et al. [11], we divided NPI-D ratings into 3 categories (low = NPI-D score 0–1, medium = NPI-D score 2–3, and high = NPI-D score 4–5) to examine the severity of caregiver distress in relation to individual NPI symptom domains (table 3). Overall, about 2 fifths (43%) of NPI symptoms were associated with low distress, about 1 third (33%) were reported to cause a medium amount of distress, and only 11.5% of symptoms elicited caregiver reports of high distress. In individual NPI symptom domains, delusion, hallucination, agitation/aggression, disinhibition, irritability/lability and aberrant motor behavior had high or medium distress scores for half of the caregivers. The symptoms distress ratings for dysphoria/depression, anxiety and euphoria/elation were generally lower than those of other symptoms. Dysphoria/depression and euphoria/elation were not reported by any caregiver to be severely distressing. Though apathy/indifference was the most common symptom, over 1 half of caregivers reported low distress ratings. Across all subjects, the symptoms most frequently reported to be severely distressing to caregivers were agitation/aggression, delusion and irritability/lability.

In the next place, we divided NPI ratings into 3 categories (low = NPI score 1–4, medium = NPI score 5–8 and high = NPI score 9–12; table 4). Delusion, agitation/aggression, irritability/lability and aberrant motor behavior had the highest NPI-D score in the high NPI score group. Apathy/indifference had the same NPI-D score in the medium NPI score and high NPI score groups. In hallucination, dysphoria/depression, anxiety and disinhibition, the mean NPI-D scores of the medium NPI score group were higher than those of the other 2 groups.

Discussion

This is the first population-based study to evaluate caregiver burden associated with individual BPSD of elderly people living in the community.

Although the ZBI is a validated and comprehensive instrument measuring caregiver burden and has been used in numerous studies, it cannot be used to evaluate the burden associated with individual BPSD.

Using the NPI-D, however, this study was able to demonstrate that the caregiver burden of BPSD is different depending on individual BPSD.

Most caregivers felt high or medium distress dealing with delusions, hallucination, agitation/aggression, disinhibition, irritability/lability and aberrant motor behavior of the patients and felt low distress dealing with dysphoria/depression, anxiety and euphoria/elation of the patients. Though agitation/aggression had the highest mean NPI-D score (2.3 ± 1.4), its mean NPI score was

Table 4. Frequency distribution of NPI score ratings for NPI symptom domains

Symptom scale	Patients	Low NPI score		Medium NPI score		High NPI score	
		n	NPI-D score mean ± SD	n	NPI-D score mean ± SD	n	NPI-D score mean ± SD
Delusions	21	13 (62)	1.8 ± 1.6	3 (14)	2.0 ± 0.8	5 (24)	2.8 ± 1.5
Hallucinations	7	4 (57)	0.8 ± 0.8	1 (14)	3	2 (29)	2.0 ± 0.0
Agitation/aggression	26	18 (69)	1.6 ± 1.0	5 (19)	3.8 ± 0.4	3 (12)	4.0 ± 0.8
Dysphoria/depression	14	13 (93)	0.6 ± 0.5	1 (7)	2	0 (0)	0
Anxiety	10	7 (70)	1.1 ± 0.6	2 (20)	2.5 ± 1.5	1 (10)	1
Euphoria/elation	2	2 (100)	0	0 (0)	0	0 (0)	0
Apathy/indifference	47	19 (40)	0.8 ± 0.7	19 (40)	1.8 ± 1.0	9 (19)	1.8 ± 1.5
Disinhibition	12	10 (83)	1.8 ± 1.2	1 (8)	4	1 (8)	3
Irritability/lability	23	15 (65)	1.3 ± 1.0	5 (22)	3.2 ± 0.7	3 (13)	4.0 ± 0.8
Aberrant motor behavior	16	3 (19)	0.7 ± 0.5	7 (44)	1.6 ± 0.5	6 (38)	2.8 ± 0.9
Median	15.0	11.5 (67.0)	1.0	2.5 (16.5)	2.3	2.5 (12.5)	2.4

Figures in parentheses are percentages. NPI score: low = 1–4, medium = 5–8, high = 9–12.

only 3.9 ± 1.4, which is the fourth smallest among the 10 BPSD. Moreover, this study demonstrated that only delusion, agitation/aggression, apathy/indifference, irritability/lability and aberrant motor behavior showed a significant correlation between the NPI and NPI-D scores.

Based upon the foregoing, the current study suggests that (1) the burden associated with BPSD is different by individual BPSD, (2) it does not depend on frequency and severity of BPSD, and (3) even if the frequency and severity of the exhibiting symptoms are low, some symptoms may inflict a heavy burden on the caregiver. The other way round, however high the frequency and severity of the exhibiting symptoms are, some symptoms may not place a heavy burden on the caregiver, such as anxiety and apathy/indifference.

There are other studies that used NPI-D. Kaufer et al. [11] evaluated 85 AD patients enrolled in university memory disorder clinics. They showed that there was a strong association between burden and irritability/lability, agitation/aggression, dysphoria/depression, delusion and hallucination. Craig et al. [12] did a cross-sectional study of 435 AD patients enrolled in university memory disorder clinics. They also reported that the average NPI-D scores of agitation/aggression and dysphoria/depression were higher than other symptoms. The results of our study had partially replicated findings (such as agitation/aggression and irritability/lability), but disinhibition and aberrant motor behavior had a high distress score, and the dysphoria/depression distress rating was generally lower than those of other symptoms. This may be because the subjects of this study are chosen from population-based study and are not biased (i.e. by consulting a doctor). As mentioned above, BPSD is one of the factors of in-home care failure and it can become the caregiver's motivation to consult a medical specialist. On this account, in a clinic-based study, BPSD and burden associated with it may be reported to be severer than they are in fact. On the other hand, dysphoria/depression may precipitate a memory clinic referral only if severe and not if only mild.

Several limitations may be identified with respect to the current study. First, our study contains a relatively small sample size. Second, the present study did not sufficiently investigate factors related to the caregivers' mental status (such as depression or other psychiatric symptoms). Third, our study investigates various dementing illnesses. Hirono et al. [25] reported that BPSD may correspond to different patterns of cerebral involvement characteristic of each dementing illness and frequency of BPSD was different in each disease. This suggested that the burden associated with BPSD may be different for each dementia. Fourth, theoretically the NPI-D and frequency and severity should be rated independently. However, the original version of the NPI-D was standardized by the same method in our study. Therefore, we think there is no substantial influence. Fifth, our conclusions may only pertain to Japan. However, to our knowledge, there have been no population-based studies using estab-

lished comprehensive scales such as the NPI-D. In the future, population-based studies about caregiver burden associated with BPSD should be done in many countries using the same methods.

Despite these limitations, we think that our findings are quite reliable because they are based on community-dwelling elderly patients with dementia, which was diagnosed carefully with widely accepted clinical criteria and an established comprehensive tool for the assessment of BPSD and the burden of BPSD.

Nowadays, the diagnostic techniques of dementia are progressing, and several forms of dementia have become treatable. Moreover, the spread of knowledge of dementia enables people to consult a medical specialist earlier and/or to apply for public service earlier. However, many caregivers are still standing alone in the community. The burden of the caregiver causes caregivers' depression [9] and leads to abuse [26]. Therefore, the burden is a social issue and it is important to evaluate BPSD precisely.

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Correlation of visual hallucinations with occipital rCBF changes by donepezil in DLB

Abstract—The authors explored the neural substrate of visual hallucinations in dementia with Lewy bodies (DLB) by investigating changes in regional cerebral blood flow (rCBF) and psychiatric symptoms, before and after cholinesterase inhibitor treatment. Twenty subjects with DLB were treated with donepezil for a 12-week period. Hallucinations attenuated while receiving therapy, whereas occipital rCBF focally increased, suggesting that functional visual association cortex deficits may cause visual hallucinations in patients with DLB.

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Dementia with Lewy bodies (DLB) is characterized by recurrent visual hallucinations, fluctuating cognitive impairment, and parkinsonism.[1] There is consistent evidence that cholinesterase inhibitors are effective in DLB, with visual hallucinations being particularly responsive to treatment.[2]

In contrast to Alzheimer disease (AD), which shows bilateral parietotemporal dysfunction, DLB is associated with severe occipital hypometabolism and hypoperfusion on fluorodeoxyglucose positron emission tomography (FDG-PET)[3] and SPECT.[4] No previous studies have addressed the possible relationships between changes in regional cerebral blood flow (rCBF) and psychiatric symptoms in DLB during cholinesterase inhibitor treatment. We hypothesized that the observed improvement in visual hallucinations with cholinesterase inhibitor medication could be associated with changes in rCBF, thus offering an insight into the neural substrate of visual hallucinations in patients with DLB.

Methods. Participants were recruited from a university hospital outpatient clinic. Twenty patients (age 77.4 ± 5.3 years; 10 women) with probable DLB, according to consensus guidelines[1] who were living with a responsible caregiver were selected. Cases met consensus criteria, but, because of the nature of this study, a history of visual hallucinations was a mandatory inclusion criterion. Furthermore, 18 cases had reported visual hallucinations in the month before scanning. Exclusion criteria included 1) Hoehn and Yahr score >3, 2) MRI evidence of focal brain lesions, 3) neuroleptic or antiparkinsonian therapy. Written informed consent was obtained from all subjects or their relatives.

Patients were treated for 12 weeks with donepezil according to Japanese dosing guidelines for AD. Donepezil was commenced at 3 mg/day. After 2 weeks, patients were reassessed for adverse effects. Patients who were tolerating therapy then had their dose titrated up to 5 mg/day for the remaining 10 weeks.

The Neuropsychiatric Inventory (NPI)[5] and the Mini-Mental State Examination (MMSE) were administered at baseline and 12 weeks. The NPI is a validated, caregiver-based instrument for measuring behavioral changes in dementia, such as delusions and hallucinations. The two-tailed Wilcoxon signed-rank test for paired samples was used for statistical analysis of the total NPI and MMSE scores, and the cutoff for significance between baseline and 12-week assessments was set at $p < 0.05$. We also made use of the two-tailed Wilcoxon signed-rank test to examine changes in the NPI subscales: the significance was set at $p < 0.05$ after Bonferroni correction (nominal α of 0.05/10 = 0.005). All SPECT scans were carried out under identical conditions using 740 MBq technetium-99m hexamethyl-propyleneamine oxine (^{99m}Tc-HMPAO) with patients' eyes closed (monitored through the procedure by a radiologist) in a quiet, dimly lit room. The SPECT system used a four-head rotating gamma camera equipped with high-resolution low-energy collimators, providing an in-plane spatial resolution of 7.5 mm full width at half maximum (FWHM). Data were obtained from the 140-keV photo peak (10% window) over a 360-degree rotation and 128 × 128 matrix. The slice thickness and axial resolution of SPECT images were 2.0 mm. The step-and-shoot format was used (acquisition time: 20 s/step; zoom factor: 1.33). Transaxial images of ^{99m}Tc-HMPAO SPECT were reconstructed by filtered back projection using Butterworth and Ramp filters (cutoff frequency 0.12 cycle/cm) with attenuation correction (Chang, 0.08/cm).

Data were analyzed using MATLAB 6.5 (The MathWorks. Inc.) and SPM99 (Wellcome Department of Cognitive Neurology, London, UK).[6] Raw images were spatially transformed to the SPM99 SPECT template. The spatially normalized images were resliced to a 2 × 2 × 2-mm voxel size and then smoothed with an isotropic 16-mm FWHM Gaussian filter.

The SPM analysis used the one scan per subject, paired t test model between scans at baseline and 12 weeks. Each individual image was normalized by proportional scaling across the entire data set to a mean of 50 mL/100 mL/min. The threshold images show voxels, which are different using $p < 0.001$ (uncorrected).

Results. The mean scores (± SD) at baseline for the MMSE and total NPI were 17.2 ± 5.8 and 30.0 ± 20.0 (table 1). At 12 weeks, there was improvement in both MMSE (20.5 ± 5.8; $z = -2.613$, $p = 0.009$) and total NPI score (8.2 ± 7.6; $z = -3.465$, $p = 0.0006$). Among the NPI subscales, the most improvement was in hallucinations ($z = -3.724$, $p = 0.0002$). All hallucinations were visual in type.

The figure and table 2 show the voxels of increased rCBF compared with baseline ($p < 0.001$ uncorrected). All significant changes were restricted to the occipital lobes. The statistical peaks in the right occipital region (p corrected = 0.144, $k = 741$, $t = 5.55$, $Z = 4.23$, peak coordinates $x = 38$, $y = -84$, $z = -8$) and the left occipital region

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Table 1 *Changes in the scores of MMSE, total scores of NPI and NPI subscales for patients with DLB using cholinesterase inhibitor medication (N = 20)*

	Baseline		12 Wk			
	Mean	SD	Mean	SD	z*	p
MMSE	17.2	5.8	20.5	5.8	−2.613	0.0090†
NPI total score	30.0	20.0	8.2	7.6	−3.465	0.0006‡
Delusions	6.0	4.5	2.3	2.7	−2.755	0.0058
Hallucinations	6.4	4.0	1.4	1.8	−3.724	0.0002§
Agitation/aggression	2.9	4.5	0.8	1.8	−1.956	0.0505
Depression/dysphoria	1.7	2.4	0.8	2.0	−1.423	0.1549
Anxiety	2.8	4.0	0.6	1.7	−1.988	0.0461
Euphoria/elation	0.0	0.0	0.0	0.0		
Apathy/indifference	3.1	3.6	0.8	1.7	−2.267	0.0229
Disinhibition	0.8	2.3	0.2	0.9	−1.069	0.2850
Irritability/lability	1.8	3.1	0.9	1.9	−1.125	0.2604
Aberrant motor behavior	2.0	3.3	1.0	2.8	−0.980	0.3270

* Wilcoxon signed-rank tests.
† Greater change at 12 weeks than that at baseline ($z = -2.613$, $p = 0.0090$).
‡ Less change at 12 weeks than that at baseline ($z = -3.465$, $p = 0.0006$).
§ Less change at 12 weeks than that at baseline ($z = -3.724$, $p = 0.0002$).

MMSE = Mini-Mental State examination; NPI = Neuropsychiatric Inventory; DLB = dementia with Lewy bodies.

(p corrected = 0.220, k = 825, t = 5.28, Z = 4.09, peak coordinates $x = -36$, $y = -84$, $z = -8$) corresponded to visual association cortices.

Discussion. We demonstrated that cognitive function and psychiatric symptoms, particularly visual hallucinations, improved and that occipital rCBF increased with donepezil therapy in DLB. Previous SPECT and FDG-PET studies in patients with DLB reported dysfunction in the occipital area compared with AD patients and controls.[3,4] Some reports have suggested that visual hallucinations are specifically associated with occipital dysfunction[7]; furthermore, occipital cholinergic deficits have been reported in the brains of patients with DLB.[8] The current results suggest that occipital cholinergic deficits, occipital hypoperfusion, and visual hallucinations may be directly interrelated.

While clinicopathologic studies in DLB have demonstrated extensive neocortical cholinergic deficits that correlate with clinical symptoms,[9] cortical Lewy bodies are found in the anterior frontal, temporal, insular, and cingulate cortices, but rarely in occipital cortex. Furthermore, reports have also suggested that there are no structural changes in gray matter on MRI in the occipital lobe of patients with DLB.[10] Functional imaging changes caused by DLB in the occipital area may not therefore be the result of underlying structural changes in the gray matter but

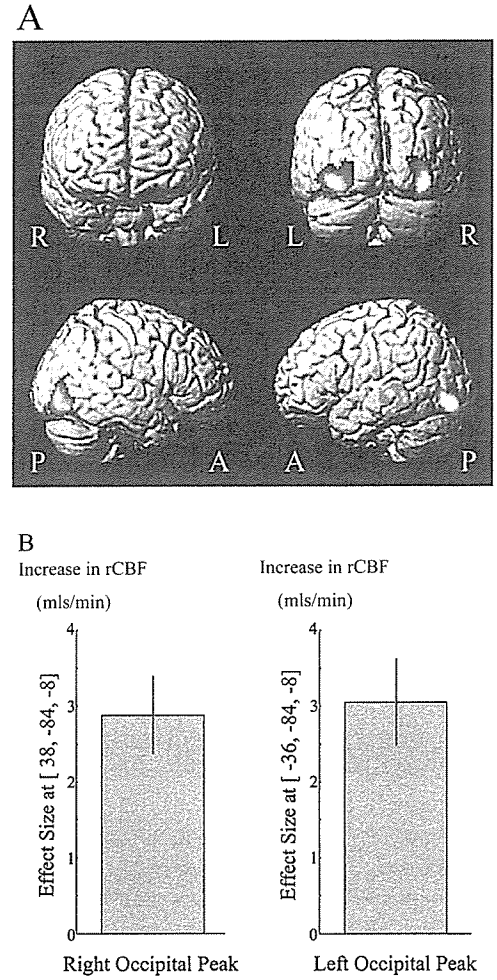

Figure. (A) Significant perfusion increases in regional cerebral blood flow in patients with dementia with Lewy bodies at 12 weeks compared with at baseline using cholinesterase inhibitor medication (N = 20) (statistical parametric mapping analysis [paired t test, $p < 0.001$ uncorrected]). (B) The magnitude of the effect at baseline and with donepezil for the right and left occipital peaks.

instead may be caused by a lack of acetylcholine from presynaptic neurons originating in the forebrain or brainstem. In other words, we speculate that a significant component of the occipital perfusion defect previously described in DLB is physiologic. Patients with the posterior cortical atrophy variant of AD also have marked occipital cortex deficits seen on SPECT or PET but rarely hallucinate and have pathologic evidence of local neurodegeneration. Taken together, we propose that a specific lack of cholinergic inputs from the forebrain or brainstem, rather than a local destructive process, may therefore be a key to the genesis of visual hallucinations in DLB. This imbalance can be restored with cholinesterase inhibitors, suggesting that postsynaptic muscarinic receptors are relatively preserved, leading to an increase in occipital neuronal activity as indicated by improvement in cerebral perfusion.

Cholinergic transmission is also implicated in maintaining alertness, and it has been reported that

Table 2 Significant increase in regional cerebral blood flow in patients with dementia with Lewy bodies at 12 weeks compared with at baseline using cholinesterase inhibitor medication (N = 20)

					Peak coordinates*			
p Corrected	*k*	*t*	*Z* Score	*p* Uncorrected	*x*	*y*	*z*	Anatomic region
0.144	741	5.55	4.23	<0.000	38	−84	−8	Right inferior occipital lobe
0.220	825	5.28	4.09	<0.000	−36	−84	−8	Left inferior occipital lobe

* Coordinates in Talairach space and statistical parametric mapping analysis (paired *t* test, $p < 0.001$ uncorrected).

an increased level of alertness would be expected in order to reduce patients' tendencies to hallucinate. We cannot exclude a possible relationship between alertness and hallucinations in DLB. However, if improving visual hallucinations is purely a function of alertness, the association between a focal rCBF increase in occipital areas and improving visual hallucinations is difficult to reconcile. Therefore, it seems appropriate to speculate that the bilateral increase in occipital rCBF is specifically associated with improvement of visual hallucinations.

There are a few limitations in the present study. The first is sample size. It is difficult to recruit suitable patients with DLB for two SPECT scans in 12 weeks; however, it should be noted that this DLB cohort is larger than most previously studied by SPECT. Second, the absence of controls raises the possibility that occipital SPECT changes were nonspecific; nevertheless, the focal nature of the rCBF increase, in a highly plausible locus for visual hallucination, makes this interpretation seem less likely. Finally, we could not confirm the presence of visual hallucinations or control for the effects of fluctuating cognitive impairment during SPECT acquisition, but neither could most previous studies. Future studies assessing cognitive status and probing for the presence of hallucination immediately after image acquisition may offer further insights.

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原　著

日本語版 NPI-D と NPI-Q の妥当性と信頼性の検討

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要旨　目的：Neuropsychiatric Inventory (NPI) に対応した介護負担尺度 NPI-Caregiver Distress Scale (NPI-D) と NPI のアンケート版 NPI-Brief Questionnaire Form (NPI-Q) を邦訳し妥当性と信頼性を検討した。方法：対象は認知症患者 152 名。対象者に MMSE，主介護者に NPI-Q，NPI，NPI-D，Zarit 介護負担尺度 (ZBI) を施行し，ZBI・MMSE と NPI-D を比較し NPI-D の妥当性を，NPI・NPI-D と NPI-Q を比較し NPI-Q の妥当性を検討した。30 名に別の評価者が NPI-D を再評価し NPI-D の信頼性を，27 名に NPI-Q を再施行し NPI-Q の信頼性を検討した。結果・結論：日本語版 NPI-D，NPI-Q は原著版とほぼ同等の妥当性と信頼性を有し，認知症患者の精神症状と介護者の負担度の評価に有用である。

Key words：dementia, Neuropsychiatric Inventory, NPI-brief questionnaire form, NPI-caregiver distress scale

I. はじめに

認知症患者は認知機能障害に加えて，しばしば多様な精神症状と行動障害を呈し，そのことは介護者の負担を増加させ[4,16]，在宅介護が困難となる主な原因となっている[7,14]。また，精神症状の中には多くの認知機能障害と異なり，適切な投薬により改善しうるものもある[8]。このことから，精神症状を客観的に把握することは認知症患者の適切な治療やケアに必要不可欠である。精神症状の評価尺度には種々のものがあるが，国際的に広く用いられている数少ない包括的な評価尺度の 1 つに 1994 年に Cummings らによって開発された Neuropsychiatric Inventory (以下 NPI)[1] がある。

NPI は認知症患者でよく認められる精神症状である妄想，幻覚，興奮，うつ，不安，多幸，無為，脱抑制，易刺激性，異常行動の 10 項目からなる。検査形式はそれぞれの項目に，主質問と下位質問が設定されており，主質問により当該精神症状が疑われる場合には，下位質問を行ってその有無を確認し，存在する場合にはその重症度と頻度を，各項目に用意された診断基準に従って判定する。重症度は 0 ～ 4 点，頻度は 0 ～ 3 点で評価し，点数は重症度と頻度の積の合計で評価され，総点は 0 ～ 120 点となっている。本邦でも認知症患者の精神症状の評価尺度として NPI の有用性が確認されており[5]，日本語版の評価時間は 15 ～ 20 分程度である。

NPI はその後，1998 年に NPI の各精神症状項目の介護者に与える負担 (distress) の程度を評価する項目を付け加えた NPI-Caregiver Distress Scale (以下 NPI-D) が発表された[6,9]。NPI-D は NPI の各項目に関して介護者の負担度を評価するもので，負担度は 0 ～ 5 の 6 段階で評価され，点数が高いほど負担の程度が大きいことを示す。2000 年には介護者を情報提供者として日記式の質問紙で精神症状の重症度と負担度を評価する NPI-Brief Questionnaire Form (以下 NPI-Q)[10] が発表された。NPI-Q は NPI に睡眠異常・食行動異常の 2 項目を加えた 12 項目の精神症状に対して，介護者自身が質問を読み，当該精神症状の有無と，存在する場合は重症度を 1 ～ 3 の 3 段階，負担度を 0 ～ 5 の 6 段階で評価するもので，通常の NPI が 15 分以上

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Table 1 Patient's and caregiver's data
Mean±SD (Range) or N

N (M : F)	152 (76 : 76)
Diagnosis (AD/VaD/DLB/FTLD/Other)	82/9/36/6/19
Age	73.9±7.8 (49-93)
MMSE score	18.5±6.9 (0-30)
CDR (0.5/1/2/3)	2/81/51/18
ZBI	29.0±17.6 (0-84)
Caregivers (M : F)	46 : 106
Caregiver's Age	65.0±11.4 (35-90)
Family Relationship (Spouse/Child/Child-in-laws /Other)	109/29/12/2

AD : Alzheimer's Disease, VaD : Vascular Dementia, DLB : Dementia with Lewy Bodies, FTLD : Fronto-Temporal Lober Degeneration, M : male, F : female, MMSE : Mini-mental State Examination, ZBI : Zarit 介護負担尺度

の時間を要するのに対し，ほとんどが5分以内に評価できることが報告されている[10]。

先にも述べたとおり，精神症状は介護負担を増大させることが知られているが，精神症状そのものによる介護負担を評価する尺度は本邦にはまだない。そこで今回，精神症状の負担度を症状別に評価できるNPI-Dと，通常のNPIよりも短時間に施行することができ，精神症状に対する負担度も評価できるNPI-Qの日本語版を作成し，それぞれの信頼性と妥当性を検討した。

II. 研究方法

NPI-QおよびNPI-DはCummings博士から入手し，原著者の許可を得て邦訳したものを用いた。翻訳に当っては，原著に忠実に訳することを原則とし，一部日本語として不適切な部分は原意を損なわないように留意した。また，今回の翻訳では，NPI-D，NPI-Qで使用されている英文がほぼNPIに使用されているものと同様であり，NPIの英訳自体はすでに長く使用され，妥当性・有用性が確立していることからback translationは行わなかった。

NPI-Qの妥当性の検討のため，まず主介護者にNPI-Qを，続いて通常のNPIおよびNPI-Dを施行し，NPI-Qの評価結果とNPIおよびNPI-Dの評価結果を比較することにより検討した。NPI-Dの妥当性は原著における検討方法と同様に，同時に行った介護負担の評価尺度であるZarit介護負担尺度(以下ZBI)[18]，認知機能の評価尺度であるMini-mental State Examination (以下MMSE)[3]と比較することにより検討した。なお，原著においては介護負担の評価尺度としてはRelative's Stress Scale (RSS)[4]が使用されているが，本邦においては標準化されていないため，ZBIを使用した。

NPI-Dの検査再検査信頼性は30名の対象を無作為に選択し，初回の評価者とは別の評価者が1度目の施行から約1カ月の期間をおいて評価することにより検討した。NPI-Qの検査再検査信頼性は27名の対象を無作為に選択し，NPI試行翌日に再度施行し検討した。妥当性はPearsonの相関係数，もしくはSpearmanの順位相関係数，検査再検査信頼性は級内相関係数を用い検討した。

対象は2003年1月から2005年5月までに，愛媛大学医学部附属病院精神科神経科高次脳機能外来を受診した認知症患者の主介護者のうち，患者と同居している者とした。対象となった主介護者に対し，主治医より口頭および書面で研究目的について説明し，口頭または書面による同意を得た上で調査を行った。対象患者および介護者の背景データをTable 1に示す。Alzheimer病 (Alzheimer's Disease : AD) の診断には，NINCDS-ADRDAの診断基準[12]を，血管性認知症 (Vascular Dementia : VaD) の診断にはNINDS-AIRENの診断基準[15]を，Lewy小体型認知症 (Dementia with Lewy Bodies : DLB) の診断にはDLB international workshopの診断基準[11]を，前頭側頭葉変性症(Fronto-Temporal Lobar Degeneration : FTLD)の診断には国際ワーキンググループの臨床診断基準[13]をそれぞれ用い，診断にあたっては，全例に頭部MRIもしくはCTを，さらに一部の症例を除いてHMPAO-SPECTを施行した。

III. 結 果

1. NPI-Dの妥当性と信頼性の検討

NPI-Dの妥当性の検討のため，NPI-D総得点とMMSE，ZBIの成績を比較した。NPI-D総得点とMMSEは有意に逆相関($rs = -0.27$, $p < 0.01$)した。NPI-D総得点とZBIは有意な正の相関($rs = 0.59$, $p < 0.01$)を示し，その相関はMMSEとの相関よりも強かった。NPI-Dの総得点とMMSEおよびZBIとのSpearman相関係数はKaufer らの報告[9]における原著版NPI-Dの総得点とMMSEのSpearman相関係数($rs = -0.32$, $p < 0.01$)およびRSSとのSpearman相関係数($rs = 0.60$, $p < 0.01$)とそれぞれほぼ同等であった。NPI-Dの総得点の評価者間級内相関は，0.47($p < 0.01$)と有意な正の相関を認めた。

2. NPIの下位項目とNPI-Dの関係

NPIの下位項目の出現頻度，およびNPIの下位項

Table 2 NPI component scores and their relationship to the NPI-distress score

Symptom scale	n(%)	Distress	Frequency		Severity	
		Mean±SD (original[9])	Mean±SD (original[9])	rD※ (original[9])	Mean±SD (original[9])	rD※ (original[9])
Delusions	66 (43)	2.3±1.6 (2.4±1.3)	2.8±1.1 (2.9±1.1)	0.90‡ (0.51)	2.0±0.8 (1.6±0.8)	0.91‡ (0.57)
Hallucinations	42 (28)	1.9±1.4 (1.9±1.5)	2.7±1.1 (2.5±1.4)	0.93‡ (−0.01)	0.7±0.7 (1.4±0.7)	0.92‡ (0.54)
Agitation/Aggression	75 (49)	2.4±1.4 (2.3±1.5)	2.4±1.2 (2.5±1.1)	0.49‡ (0.22)	1.7±0.7 (1.5±0.6)	0.67‡ (0.45)
Dysphoria/Depression	59 (39)	1.6±1.2 (2.5±1.3)	2.3±1.1 (2.5±1.2)	0.90‡ (0.46)	1.5±0.6 (1.4±0.6)	0.88‡ (0.28)
Anxiety	50 (33)	1.9±1.3 (2.2±1.3)	2.7±1.2 (2.6±1.2)	0.53‡ (0.24)	1.5±0.6 (1.4±0.6)	0.44† (0.24)
Euphoria/Elation	12 (8)	0.5±0.6 (0.7±1.2)	2.4±1.2 (2.3±1.2)	0.54 (0.50)	1.2±0.4 (1)	0.53 (1.0)
Apathy/Indifference	109 (72)	1.3±1.1 (2.2±1.3)	3.7±0.6 (3.3±1.0)	0.67‡ (0.39)	1.7±0.6 (1.6±0.8)	0.70‡ (0.44)
Disinhibition	32 (21)	2.3±1.5 (1.8±1.1)	2.5±1.1 (2.3±0.9)	0.55‡ (−0.55)	1.8±0.7 (1.3±0.5)	0.67‡ (0.49)
Irritability/Lability	57 (38)	2.0±1.4 (2.5±1.4)	2.7±1.2 (2.6±1.0)	0.91‡ (0.50)	1.7±0.7 (1.5±0.7)	0.92‡ (0.45)
Aberrant motor behavior	46 (30)	1.4±1.3 (1.5±1.3)	3.5±0.8 (3.2±1.0)	0.41‡ (0.40)	1.9±0.7 (1.5±0.8)	0.52‡ (0.45)

※ : Spearman rank correlation coefficients between NPI frequency, severity and NPI-distress scale score
† : $p<0.05$, ‡ : $p<0.01$

目の頻度，重症度とNPI-Dの相関をTable 2に示す。無為，ついで興奮，妄想の出現が多く，多幸の出現が最も少なかった．負担度の平均点が最も高い下位項目は興奮で，最も低い下位項目は多幸であり，これはKaufer らの報告[9]でも同様の傾向であった。NPIの総得点と負担度の総得点は有意に相関しており（rs = 0.83，$p < 0.01$），Kaufer らの報告[9]における相関（rs = 0.83，$p < 0.01$）と同等であった。

3. NPI-Qの妥当性と信頼性の検討

NPI-Qの妥当性の検討の結果をTable 3に示す。NPI-Qの重症度の総得点は，NPIの総得点と有意な正の相関（r = 0.77，$p < 0.01$）を，MMSEとは有意な負の相関（r = −0.33，$p < 0.01$）を示した。NPI-Qの重症度とNPIの総得点との相関係数（r = 0.77）はKaufer らの報告[10]における相関（r = 0.91）に比べやや低かった。NPI-Qの負担度の総得点は，NPI-Dの総得点と有意な正の相関（r = 0.80，$p < 0.01$）を示し，その相関係数（r = 0.80）はKaufer らの報告[10]の成績（r = 0.92）と大きな差はなかった。重症度および負担度総得点の検査-再検査成績間の級内相関係数はそれぞれri = 0.81（$p < 0.01$）とri = 0.80（$p < 0.01$）で有意な正の相関を示していた。重症度の総得点の級内相関係数はKaufer らの報告[10]における相関（ri = 0.80）とほぼ同様だったが，負担度の級内相関係数はKaufer らの報告[10]の相関（ri = 0.94）に比べやや低かった。

4. NPIの下位項目とNPI-Qの下位項目の比較

NPIの下位項目とNPI-Qの下位項目の出現頻度の比較をTable 4に示す。NPI-Qの方がNPIに比べ多くの精神症状を捉える傾向があり，Kaufer らの報告[10]でも同様の傾向が指摘されていた。

IV. 考 察

NPIは，患者の介護者に質問を行うことにより認知症患者で認められる広範な精神症状の頻度と重症度を評価することを目的として作成され，詳細な研究によりその信頼性，妥当性が検討されている。

今回邦訳したNPI-Dは原著版と同様の方法で検討した結果，原著版と同様に認知機能検査よりも介護負担尺度と強い相関があり，その相関はKaufer らの報告[9]で示されていた相関とほぼ同等であった。今回の研究では，原著版と異なりNPI-D信頼性の検討として最も一致しにくいと考えられる，異なる検者による異なる時期の2回の評価間の相関を検討したが，有意な再現性が示された。以上のことから日本語版NPI-Dは原著版と同様に十分な妥当性，信頼性を有していると考えられた。

また，NPI-Dは多幸以外のNPIのすべての下位項目の重症度，頻度と有意に相関していた。このことから，NPIで測定可能な多幸以外の精神症状の存在は介護負担に強く影響を与える可能性が示唆された。

NPI-Qの重症度の総得点はNPIの総得点と，NPI-Qの負担度総得点はNPI-Dとそれぞれ有意な相関を示し，これらの相関係数はKaufer らの報告[10]と大差がなかった。このことから，日本語版NPI-Qは原著版と同様の妥当性があると考えられた。NPI-Qの検査再検査信頼性は，重症度はKaufer らの報告[10]の相関係数とほぼ同等の成績であったが，負担度の相関係数はKaufer らの報告[10]に比べ低い値であった。これは，原著での再評価が平均6.9時間後に行われていたのに対し，今回の研究では翌日に再施行している違いによる影響と考えられた。

さらにNPI-Qの下位項目の検討から，NPI-Qは

Table 3 Intrascale correlation among the NPI, NPI-Q, and MMSE

Variables	ALL (N=152)		High MMSE (>18) (N=84)		Low MMSE (≦18) (N=68)	
	Present study	Original[10]	Present study	Original[10]	Present study	Original[10]
NPI-Q Severity to NPI total	0.77‡	0.91	0.76‡	0.90	0.73‡	0.95
NPI-Q distress to NPI-D	0.80‡	0.92	0.74‡	0.94	0.81‡	0.92
NPI-Q Severity to NPI-Q distress	0.93‡	0.93	0.88‡	0.92	0.94‡	0.94
NPI total to NPI distress	0.84‡	0.90	0.80‡	0.90	0.85‡	0.90
NPI-Q Severity to MMSE	−0.33‡	−0.41	−0.11 (N.S)	−0.12	−0.12 (N.S)	−0.44
NPI total to MMSE	−0.32‡	−0.32	−0.11 (N.S)	0.04	−0.19 (N.S)	−0.44

Note : Pearson correlation coefficient, † : $p<0.05$, ‡ : $p<0.01$, N.S : not significant

Table 4 Comparison of individual symptoms

Symptom scale	Number (percentage) of subjects with symptom					
	NPI	NPI-Q	Difference NPI-Q to NPI	NPI Moderate-Severe※	NPI-Q Moderate-Severe※	Mod.-Sev.※ Difference NPI-Q to NPI
Delusions	66 (43)	52 (34)	−14 (9)	42 (28)	31 (20)	−11 (7)
Hallucinations	42 (28)	58 (38)	+16 (11)	24 (16)	34 (22)	+10 (6)
Agitation/Aggression	75 (49)	73 (48)	−2 (1)	39 (26)	39 (26)	0 (0)
Dysphoria/Depression	59 (39)	65 (43)	+6 (4)	24 (16)	34 (22)	+10 (6)
Anxiety	50 (33)	87 (57)	+37 (24)	22 (14)	45 (30)	+23 (15)
Euphoria/Elation	12 (8)	32 (21)	+20 (13)	2 (1)	12 (18)	+10 (6)
Apathy/Indifference	109 (72)	93 (61)	−16 (11)	63 (41)	55 (36)	−8 (5)
Disinhibition	32 (21)	29 (19)	−3 (2)	21 (14)	12 (8)	−9 (6)
Irritability/Lability	57 (38)	81 (53)	+24 (16)	31 (20)	46 (30)	+15 (10)
Aberrant motor behavior	46 (30)	39 (26)	−7 (5)	31 (20)	27 (18)	−4 (3)
Nighttime disturbance	−	57 (38)	−	−	38 (25)	−
Appetite/Eating disturbances	−	38 (25)	−	−	18 (12)	−

※symptom severity ratings of either 2 (moderate) or 3 (severe)

Kaufer らの報告[10]と同様に NPI に比べ多くの精神症状を捉える可能性が示唆され，精神症状に関する情報を簡便に把握するために有用であると考えられた。

NPI-D は介護負担に大きな影響を与える精神症状おのおのに関する負担度を評価できるため，介護負担の評価と治療介入によるその軽減の評価に有用であると考えられた。NPI-Q は精神症状の評価に関して NPI と同等の信頼性を有しており，NPI に比べ簡便に施行することが可能なことから，地域疫学調査など多数例での精神症状の検討の際に有用であると考えられる。

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