



Original Study

Patient-Related Factors Associated With Depressive State in Caregivers of Patients With Dementia at Home

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A B S T R A C T

Keywords:

Activities of daily living
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Objectives: To identify patient-related factors associated with depressive state in caregivers of patients with dementia, we investigated the caregivers' and patients' characteristics in relation to the depressive state in their caregivers.

Design: Prospective hospital-based cohort study.

Setting: Two memory clinics in Japan.

Participants: Outpatients with dementia (n = 135) and their caregivers at home.

Measurements: The outpatients and their caregivers were divided into 2 groups according to the Center for Epidemiologic Studies Depression Scale for caregivers. To identify the patient-related factors that cause depressive state in caregivers, Mini-Mental State Examination (MMSE), the Physical Self-Maintenance Scale for fundamental activities of daily living (ADL), and the instrumental ADL scale (IADL) scores for instrumental ADL and the neuropsychiatric inventory (NPI) subscale score for behavioral and psychological symptoms of dementia were compared between the 2 groups. We used logistic regression to determine the independent predictors of caregiver depressive state.

Results: There was no significant difference in MMSE score between the 2 groups. Logistic regression analysis revealed that the depressive state in caregivers was related with IADL score and delusion in NPI subscale of patients.

Conclusions: Depressive state in caregivers was independent of the decline in cognitive function in patients with dementia but was associated with decline in instrumental ADL and severity of delusion.

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The caregiver burden in patients with dementia has been frequently investigated because of its adverse effect on the mental health of caregivers and on the quality of care provided to the patients. Previous studies demonstrated that the cognitive abilities of patients with dementia do not have a strong influence on caregiver burden,¹ whereas behavioral disturbances in patients contributes the most to family caregiver burden.² In addition, low activities of daily living (ADL) levels in patients with dementia are correlated with caregiver burden.³

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Although caregiver burden and depressive symptoms in caregivers are both rooted in their emotional and psychological reaction to care demands, the relationship between these 2 parameters is unclear. Caregivers with higher levels of burden tend to have higher levels of depressive symptoms; however, caregivers with higher levels of depressive symptoms do not necessarily have higher levels of burden.⁴

Some comprehensive epidemiologic studies have focused on the presence of depressive state in caregivers. A cross-sectional analysis using the Medicare Alzheimer's Disease cohort revealed that 32% of caregivers had significant depressive symptoms.⁵ Several dimensions of the caregiver's personality influences both burden and depressive symptoms in them.⁶ Several studies suggest that caregivers with poor health condition, or fewer financial resources, are at a higher risk for depression. Some evidence also suggests that women and spousal caregivers are at a higher risk for depression.^{7,8} Thus, previous studies on depression in caregivers mainly focused on caregiver

characteristics. However, we have hypothesized that not only factors associated with caregivers, but also patient-related factors, may induce caregiver depressive state.

In this study, we estimated the prevalence of depressive state among family caregivers of patients with dementia, and investigated the caregivers' and patients' characteristics in relation to the depressive state in caregivers.

Methods

Participants

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

We studied 135 outpatients with dementia and their caregivers at the memory clinics of Kumamoto University and Kumamoto Mental Health Hospital. The participants were selected on the basis of inclusion/exclusion criteria from a consecutive series of 232 outpatients who had undergone their first medical examination at the memory clinics from June 2011 to March 2012. All individuals were examined by senior neuropsychiatrists (M.I. and M.H.) using routine laboratory tests, standard neuropsychological examinations, and brain magnetic resonance imaging (MRI) or brain computed tomography (CT). The diagnosis of dementia was based on the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition-revised (DSM-III-R). The following patients were excluded from the current study: (1) those without a reliable informant; (2) those with developmental abnormalities, serious psychiatric diseases, such as major depression, or substance abuse before the onset of dementia; (3) complication of other neurological diseases or unstable medical illnesses such as diabetes mellitus, thyroid disease, vitamin deficiencies, or malignant diseases; (4) those whose caregivers had hearing loss; and (5) inability to provide informed consent. The diagnosis of each dementia was established according to the international consensus criteria. Patients were divided into probable Alzheimer's disease (AD), which was defined according to the criteria of the National Institute for Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association,⁹ probable vascular dementia (VaD), which was defined according to the criteria of the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences,¹⁰ and probable dementia with Lewy bodies (DLB), which was defined according to the Consensus Criteria for the clinical diagnosis of DLB 2005.¹¹ The physical comorbidity (hypertension, diabetes, hyperlipidemia, etc) in patients was confirmed by routine laboratory tests and interviews of their caregivers.

Assessments

Caregiver depressive symptoms were assessed using the Center for Epidemiologic Studies Depression (CES-D) scale.^{12,13} The CES-D score was used as a total summed score, with 16 as a cutoff point for the risk of clinical depressive state. Patients and their caregivers were divided into 2 groups according to the CES-D score for caregivers. Patients and caregivers were classified into the depressive group if the caregiver's CES-D score was ≥ 16 points and into the nondepressive group if it was < 16 points.¹²

The degree of perceived burden was measured using the Zarit Caregiver Burden Interview (ZBI)^{14,15} We also evaluated caregiver burden using the Neuropsychiatric Inventory, Caregiver Distress

(NPI-D) subscale¹⁶; for each symptom domain of the Neuropsychiatric Inventory (NPI), caregivers were asked to rate their emotional or psychological distress on a scale of 0–5.

Mini-Mental State Examination (MMSE)¹⁷ is one of the most widely used cognitive screening tests that quantitatively assess the severity of cognitive functions. The fundamental ADL of patients were evaluated using the Physical Self-Maintenance Scale (PSMS),^{18,19} We also assessed instrumental ADL using the Instrumental Activities of Daily Living scale (IADL).^{18,19}

We evaluated the comprehensive behavioral and psychological symptoms of dementia (BPSD) of patients semiquantitatively through their caregivers using the NPI.^{20,21} Using this inventory, the following 10 BPSD were rated based on the patients' condition during the month that preceded the interviews: delusion, hallucination, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior.

Statistical Analysis

Statistical differences between the depressive caregiver group and the nondepressive caregiver group were assessed using Student's 2-tailed *t*-test for age, education, duration of illness, and MMSE, ZBI, PSMS, IADL, and NPI scores. The χ^2 test of independence was used to compare the parameters: sex, physical comorbidity, relationship of caregiver with the patient, living with patients, and diagnosis. Moreover the NPI and NPI-D subscale scores were compared between the 2 groups using Student's *t*-tests. Significance was set at 0.05 (2-tailed) for all analyses. To determine independent predictors of caregiver depressive state, we used multiple logistic regression analysis with forward selection method (likelihood ratio). We controlled all the factors that were included in the bivariate comparisons. Statistical analyses were performed using SPSS for Windows, v. 17.0.

Results

A total of 135 patients consisted of 86 women and 49 men with mean age 79.5 years (standard deviation = 8.1), mean MMSE score of 16.8 points (standard deviation = 6.1). The level of severity of dementia was Clinical Dementia Rating (CDR) 0.5 in 41 cases, CDR1 in 59, CDR2 in 29, and CDR3 in 6. Among the 135 caregivers of patients with dementia, 44 caregivers (32.6%) presented depressive state. The diagnosis of patients was as follows: AD in 62.2% (84/135), VaD in 16.3% (22/135), DLB in 14.1% (19/135), and other conditions in 7.4% (10/135). The diagnosis of patients was AD in 50.0% (22/44), VaD in 36.4% (16/44), DLB in 9.1% (4/44) of patients in the depressive group, and AD in 68.1% (62/91), VaD in 6.6% (6/91), DLB in 16.5% (15/91) of patients in the nondepressive group. There was a significant difference in each diagnosis between the 2 groups ($P = .001$).

The characteristics of patients and caregivers in each group of depressive and nondepressive are presented in Table 1. The depressive group included 35 female caregivers (79.5%) and the nondepressive group included 57 female caregivers (62.6%); thus, caregivers with depressive state exhibited a significant female predominance compared with those with a nondepressive state ($P = .048$). In addition, the caregivers with depressive state exhibited a higher ZBI score than those without depressive state ($P < .001$).

PSMS and IADL scores were significantly lower in patients in the depressive caregiver group than in the nondepressive caregiver group ($P < .001$). However, there was no significant difference in either of the PSMS and IADL subscale scores between the 2 groups. The total NPI score was significantly higher in patients in the depressive caregiver group than in those in the nondepressive caregiver group ($P = .003$). There was no significant difference between the 2 groups with respect to other demographic variables of patients and caregivers.

Table 1
Characteristics of Patients and Caregivers in Each Group of Depressive and Nondepressive

	Depressive Group (n = 44)	Nondepressive Group (n = 91)	P
Caregivers			
Age, mean (SD)	62.8 (13.3)	62.0 (12.9)	.726
Male/female	9/35	34/57	.048*
Relations, spouse/children/others	13/21/10	37/44/10	.153
Living with patients/separated	34/10	71/20	.922
ZBI total score, mean (SD)	33.0 (14.2)	17.9 (13.5)	<.001*
Patients with dementia			
Age, mean (SD)	80.9 (7.9)	78.8 (8.1)	.165
Male/female	15/29	34/57	.711
Years of education, mean (SD)	9.4 (2.4)	10.0 (2.9)	.249
Duration of illness, mean (SD)	2.3 (2.1)	2.2 (1.9)	.882
Physical comorbidity, having / not having	37/7	63/28	.065
MMSE score, mean (SD) (range 0–30)	15.5 (6.8)	17.5 (5.6)	.095
PSMS, mean (SD) (range 0–6)	2.8 (2.0)	4.4 (1.8)	<.001*
IADL, mean (SD) (range 0–8)	3.0 (2.3)	5.1 (2.3)	<.001*
NPI total scores, mean (SD) (range 0–120)	15.0 (11.5)	9.0 (8.7)	.003*

IADL, Instrumental Activities of Daily Living scale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; PSMS, Physical Self-Maintenance Scale; ZBI, Zarit Caregiver Burden Interview.

*P < .05.

The results of the analysis of the relation between the NPI subscale score of patients and the presence of a depressive state in the caregivers are presented in Table 2. Apathy was found to be the most common symptom, whereas euphoria was the rarest symptom in both groups. Patients in the depressive caregiver group had significantly higher NPI and NPI-D scores in the delusion domain compared with those in the nondepressive caregiver group (P = .006 and P = .005, respectively). There was no significant difference between the 2 groups in other domains.

The result of multiple logistic regression analysis is presented in Table 3. Of caregiver factors, ZBI score was independently associated with depressive state [odds ratio (OR), 1.055; P = .001]. Of patient-related factors, IADL score and delusion in NPI subscale score were independently associated with caregiver depressive state (OR, 0.772; P = .008 and OR, 1.273; P = .018, respectively).

Discussion

In this study, we analyzed the patient-related predictors of depressive state in caregivers of patients with dementia. While several factors have been pointed out as the predictors of caregiver

Table 2
NPI and NPI-D Subscale Scores of Patients and Their Relation to the Depressive State in Caregivers

Subscales	Depressive Group (n = 44)		Nondepressive Group (n = 91)		P			
	n (%)	Mean (SD)	n (%)	Mean (SD)				
		NPI		NPI-D		NPI	NPI-D	
Delusion	19 (43.2%)	1.95 (3.1)	0.95 (1.4)	18 (19.8%)	0.54 (1.4)	0.27 (0.7)	.006*	.005*
Hallucination	20 (45.5%)	1.36 (2.6)	0.68 (1.2)	18 (19.8%)	0.65 (1.7)	0.30 (0.8)	.056	.060
Agitation/aggression	17 (38.6%)	1.25 (2.0)	1.02 (1.4)	31 (34.1%)	0.99 (1.9)	0.60 (1.1)	.465	.087
Depression/dysphoria	23 (52.3%)	1.68 (2.5)	0.93 (1.1)	38 (41.8%)	1.00 (1.7)	0.54 (0.8)	.105	.044*
Anxiety	15 (34.1%)	1.14 (2.1)	0.61 (0.9)	31 (34.1%)	1.04 (2.2)	0.47 (0.9)	.816	.410
Euphoria	4 (9.1%)	0.25 (1.0)	0.07 (0.3)	2 (2.2%)	0.03 (0.2)	0.01 (0.1)	.168	.273
Apathy	33 (75.0%)	4.14 (3.9)	1.13 (1.0)	62 (68.1%)	2.98 (3.1)	0.83 (0.9)	.063	.091
Disinhibition	6 (13.6%)	0.48 (1.4)	0.34 (0.9)	8 (8.8%)	0.22 (0.9)	0.13 (0.5)	.277	.176
Irritability/lability	15 (34.1%)	1.07 (1.8)	0.75 (1.5)	25 (27.4%)	0.80 (1.7)	0.45 (0.9)	.409	.160
Aberrant motor behavior	14 (31.8%)	1.70 (3.2)	0.68 (1.2)	16 (17.6%)	0.78 (2.0)	0.32 (0.8)	.082	.066

NPI, Neuropsychiatric Inventory; NPI-D, Neuropsychiatric Inventory Caregiver Distress; SD, standard deviation.

*P < .05, Analysis by t-test.

Table 3
Predictors of Caregiver Depressive State: Multivariate Analysis

	B	Odds Ratio (95% CI)	P
Caregiver factor			
ZBI score	0.054	1.055 (1.022–1.090)	.001*
Patient-related factors			
IADL score	–0.258	0.772 (0.639–0.934)	.008*
Delusion in NPI subscale	0.241	1.273 (1.043–1.554)	.018*

CI, confidence interval, IADL, Instrumental Activities of Daily Living scale; NPI, Neuropsychiatric Inventory; ZBI, Zarit Caregiver Burden Interview.

*P < .05, Model χ^2 P < .01.

depression in previous studies,^{8,22,23} simultaneous investigations of various patient-related factors was the strength of our study. We comprehensively assessed the association between depressive state in main family caregivers and patient-related factors using the MMSE, PSMS, IADL, and NPI scores. These results suggest that depressive state in caregivers is associated with a decline in ADL and the severity of BPSD rather than with a decline in cognitive function, in patients with dementia. In addition, we also found that instrumental ADL and delusion as patient-related factors were independently associated with caregiver depressive state.

Some studies reported that a lower level of ADL in patients with dementia was associated with higher caregiver burden,^{2,3,8} whereas others reported that caregiver burden was not associated with the level of ADL in patients.^{4,13} In the present study, patients' instrumental ADL independently associated with caregiver depressive state, whereas patients' fundamental ADL did not associate with caregiver depressive state. Therefore, we suggest that even if there is a small subjective care burden, the decline in instrumental ADL may directly induce depressive state in caregivers. In other words, even if caregivers were free from subjective burden, there might be objective burden that induced their depressive state on the caregivers of patients with impaired instrumental ADL. To confirm this hypothesis, it will be necessary to investigate the objective care burden, such as actual care time (the time required for caring for a patient at home). Compared with AD, VaD was generally associated with severe ADL limitations.²⁴ Thus, the caregivers of patients with VaD may have a higher risk of developing depressive state due to the decline in patient's ADL. To compare other types of dementia, patients with VaD were observed more frequently in the depressive caregiver group than the nondepressive caregiver group in this study.

A previous community-based study showed that irritability in patients resulted in the highest caregiver burden as well as the presence of strong associations between caregiver burden and agitation, depressive state, delusion, and hallucinations in patients.¹⁶ Another study indicated that agitation was associated with the highest caregiver burden and that agitation, delusions, apathy,

irritability and aberrant motor behavior were significantly correlated with caregiver burden.²⁵ A clinic-based study revealed that delusions yielded the highest caregiver burden score, followed by agitation, anxiety, irritability, and depressive state.³ Although the relationship between individual BPSD and the caregiver burden for patients with dementia has been investigated in detail, few comprehensive epidemiologic studies have focused on the relationship between individual BPSD and depressive state in caregivers. In the present hospital-based study, patients in the depressive caregiver group had significantly higher NPI and NPI-D scores in the delusion domain than those in the nondepressive caregiver group. Delusions of theft were the most common type of delusion among patients with AD.²⁶ Moreover, these patients complained to neighbors or other family members that principal caregivers were stealing their valuables. They directly criticized the principal caregivers and in some cases attacked them.²⁷ As indicated in previous studies,^{3,16,25} delusions in AD are strongly related to the caregiver burden, which may induce depressive state in the caregivers of these patients.

This study had several limitations. First, the results may have been biased because all patients were recruited from the dementia outpatient clinics. BPSD varies depending on the patient's care settings. Second, we did not perform pathologic confirmation of the dementia subtype in our patients. Third, our sample size was relatively small for analyzing each dementia subtype, although the relatively large cohort used (compared with those of previous studies) was one of the advantages of the present study. A similar investigation should be performed in future using a larger sample size.

Conclusions

In this prospective hospital-based cohort study of patients with dementia and their caregivers at home, depressive state in caregivers was independent of the decline in cognitive function in patients with dementia but was associated with decline in instrumental ADL and severity of delusion. These findings suggest that we should focus on support for instrumental ADL impairments and on the treatment of BPSD (particularly delusions) in the management of patients with dementia before their caregivers develop a depressive state. Focusing not only on caregiver characteristics but also assessing patient-related factors are essential for supporting long-term care of patients with dementia at home.

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ORIGINAL ARTICLE

Is sense of coherence helpful in coping with caregiver burden for dementia?

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Abstract

Background: Sense of coherence (SOC) is associated with a reduced risk of various health problems and is thought to be a major factor related to the ability to cope with stress. In the present study, we examined the association between caregiver burden and SOC among caregivers to persons with dementia.

Methods: Participants included 274 caregivers or family members of community-dwelling elderly dementia patients. To assess the cognitive function of patients, neuropsychological tests (e.g. Mini-Mental State Examination, Clinical Dementia Rating) were conducted by a clinical psychologist who was well trained in interviewing participants; the tests used a semi-structured interview protocol. Senior neurologists and psychiatrists also independently evaluated the dementia status of patients. To assess the SOC and caregiver burden, a social welfare counsellor asked questions from a 13-item version of the SOC scale and the short, eight-item Japanese version of the Zarit Caregiver Burden Interview (ZBI).

Results: Among 78 caregivers of elderly subjects with cognitive impairment due to dementia, the ZBI score was significantly associated with SOC ($r = -0.38$, $P = 0.001$). Multiple regression analyses revealed that SOC scores ($\beta = -0.42$, $P < 0.001$) and Mini-Mental State Examination scores ($\beta = -0.28$, $P = 0.009$) were significantly associated with ZBI scores ($F_{(2, 76)} = 10.51$, $P < 0.001$). SOC was closely associated with personal strain in the ZBI ($\beta = -0.41$, $P < 0.001$; $F_{(3, 75)} = 8.53$, $P < 0.001$).

Conclusion: Caregivers with a strong SOC may be less prone to experiencing personal strain from their burden. These results suggest that reinforcement of SOC would contribute to reducing the personal strain.

Key words: caregiver burden, dementia, resilience, stress coping.

INTRODUCTION

In 2012, the Japanese population included an estimated 30.79 million people 65 years of age and older, accounting for 24.1% of the population.¹ It is therefore predicted that the incidence of age-related diseases will increase along with the growth of the elderly population. Among the diseases associated with ageing, dementia is often accompanied by behavioural and psychological symptoms of dementia (BPSD) and related cognitive impairment, and as a consequence, is associated with an enormous drain on caregivers.^{2–4}

Today, Japan faces an unprecedented situation with respect to its rapidly growing elderly population; therefore, reducing the burden on caregivers for dementia patients is an urgent social objective.

In 1986, George and Gwyther defined caregiver burden as 'the physical, psychological or emotional, social and financial problems that can be experienced by family members caring for impaired older adults'.⁵ Many subsequent studies have suggested that caregiver burden is closely associated with the health and well-being of caregivers.^{6–10} Furthermore,

whether a caregiver feels burdened in a particular situation depends on their ability to cope with stressful situations.^{11,12}

With respect to the ability to cope with stress, Antonovsky proposed sense of coherence (SOC) as an important factor for health enhancement based on the results of research in highly motivated and healthy middle-aged and older people under stressful conditions.¹³ According to Antonovsky's conceptualization, SOC has three components: comprehensibility, manageability and meaningfulness. Comprehensibility refers to people's ability to realize that their situation is understandable and/or predictable. Manageability refers to people's perception of their ability to cope with a difficult situation. Lastly, meaningfulness is the ability to find meaning in everyday events and/or in problems confronted.

Recently, it has been reported that the relationship between strong SOC and better health exists in various countries and ethnic/cultural groups.¹⁴⁻¹⁶ Among caregivers for terminally ill cancer patients, but not for dementia patients, a strong SOC has been shown to mediate the effects of caregiving stressors, appraisals of caregiving confidence, and subjective caregiving burden on caregivers' depressive distress.¹⁷ It is believed that those with a strong SOC are better able to cope with difficult situations as caregivers, which can have a positive impact on dementia patients.¹⁸⁻²⁰

Hospital-based studies may provide a biased representation of caregiver's burden. Because extreme BPSD will motivate caregivers to take their charge to a hospital, the caretaker who visits the hospital would likely feel a greater burden and weakened self-esteem. Therefore, we aimed to explore in this epidemiological study whether a significant relationship exists between caregiver burden and SOC.

METHODS

Participants and procedures

We randomly selected 1000 community residents aged 65 years old and older who lived in Omuta City, Japan, from a nationwide dementia prevalence study. Participants were admitted to the survey between January 2012 and November 2012. Among the 1000 residents selected, 511 elderly participated. And of these 511 participants, 274 who participated in the study with a family member or caregiver were subjected to an investigation. A total of 229 subjects and

their family members/caregivers who did not have missing data values were included in the statistical analyses. The procedure for enrolment of the participants is shown in Figure 1. Caregivers for subjects with mild cognitive impairment and dementia (*n* = 78) were included in the statistical analysis to assess the relationship between burden and SOC.

Participants were sent a study invitation that instructed them to visit a municipal facility to participate in the study and undergo neurocognitive and medical examinations. In cases where the examinee could not visit a study site, a physician and a health-care professional visited the residence and conducted the interview. Interviews and neurocognitive testing were performed by well-trained clinical psychologists, social welfare counsellors, or nurses. A neurologist or psychiatrist then performed a physical examination and were responsible for diagnosing dementia. When it was difficult to reach a diagnosis, several doctors diagnosed the subjects using magnetic resonance imaging.

In order to assess cognitive function, we used the Japanese version of the Mini-Mental State

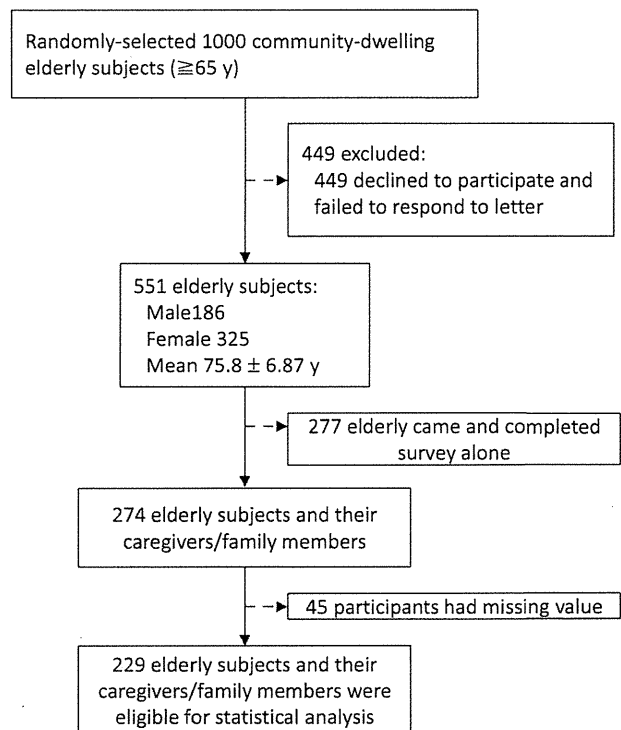


Figure 1 Enrolment of participants. y, years.

Examination (MMSE) and the logical memory scale (I) of the Wechsler Memory Scale-Revised.^{21–24} Among cases in which dementia was suspected based on the results of these two neuropsychological tests, the Geriatric Depression Scale was used to assess depression in the elderly,²⁵ and the Psychogeriatric Assessment Scale was used to assess cognitive impairment due to depression or stroke.²⁶ In cases where a more in-depth examination was necessary, cerebral magnetic resonance imaging was performed to determine the type of dementia.

Caregivers and family members who attended with the study participants were assessed using the Zarit Caregiver Burden Interview (ZBI),^{27–29} the 13-item SOC scale,³⁰ and the Clinical Dementia Rating (CDR),³¹ which is a standardized clinical dementia staging instrument. This study was approved by the Human Ethics Review Committee of Kumamoto University (Number 491) (Kumamoto, Japan). All participants and caregivers provided written informed consent before participating in this study.

Measurements

The MMSE is a one of the most frequently used assessment methods for the estimation of cognitive function, and it has been shown to have adequate reliability and validity.²² The Japanese version of the MMSE, which has a maximum score of 30 points, consists of 10 cognitive function domains. A higher score on the MMSE reflects better cognitive function.

The CDR is a widely used observational method for the assessment of dementia severity. The CDR consists of six domains for cognitive and functional performance in relation to dementia; global severity scoring is classified as non-dementia (CDR 0), mild cognitive impairment or questionable dementia (CDR 0.5), mild dementia (CDR 1), moderate dementia (CDR 2), and severe dementia (CDR 3).

Caregiver burden was assessed using the short, eight-item Japanese version of the ZBI developed by Arai *et al.*²⁷ The eight items were assessed on a 5-point Likert scale, ranging from 0 (never) to 4 (nearly always). The total score for this scale ranged from 0 to 32 points, with higher scores indicating increased caregiver burden. The validity and reliability of this test have been well established in previous studies.^{28,29}

The ability to cope with stress was evaluated using the 13-item SOC scale. For each of the 13 questions, a family member or caregiver was asked to provide an

answer on a 7-point scale with two anchoring phrases, 'very often' (1) and 'very seldom or never' (7). The total SOC score ranged from 13 to 91, with a higher score reflecting a stronger SOC. The 13-item version of the SOC scale has been shown to have adequate reliability and validity.^{30,32}

Statistical analyses

Pearson's correlation and multiple linear regression were used for data analysis. We applied the stepwise procedure to identify related variables for inclusion in regression models ($P < 0.05$). All statistical analyses were performed using SPSS Statistics 20.0.0.1 statistical software (IBM Corporation, Armonk, NY, USA). A two-tailed P -value of less than 0.05 was considered significant.

RESULTS

The characteristics of participants and information regarding dementia are summarized in Table 1. The mean age of the 229 impaired elderly subjects was 74.0 ± 7.0 years, and 94 of the participants were men (41.0%). Of the 229 subjects, 53 (23.1%) were diagnosed with mild cognitive impairment, 16 (7.0%) with Alzheimer's disease, 4 (1.7%) with vascular dementia, 2 (0.9%) with dementia with Lewy bodies, 1 (0.4%) with Parkinson's disease with dementia, and 1 (0.4%) with frontotemporal dementia. The rate of CDR equal to or greater than 0.5 in the sample was 34.1%; the CDR informant was typically the subject's spouse (65.9%).

Table 2 shows Pearson's correlation coefficients for relationships between background information, cognitive function, stress-coping ability, and caregiver burden among the 78 caregivers and/or family members. The ZBI score was significantly associated with the SOC score ($r = -0.38$, $P < 0.001$). Multiple linear regression analysis revealed that the SOC score ($\beta = -0.42$, $P < 0.001$) and MMSE score ($\beta = -0.28$, $P = 0.009$) were significantly associated with the ZBI score ($F_{(2, 76)} = 10.51$, $P < 0.001$) (Table 3).

To more closely examine the association between stress coping ability and caregiver burden, we performed multiple linear regression analysis with the SOC score as the dependent variable and with sex, age, years of education, MMSE score, and ZBI score as independent variables (stepwise method). As shown in Table 4, decreased personal strain in the ZBI was significantly associated with a high SOC score

Table 1 Characteristics of participants

Age, mean \pm SD (years)	74.0 \pm 7.0
Sex (<i>n</i>)	
Men	94 (41.0%)
Women	135 (59.0%)
Condition and diagnosis (<i>n</i>)	
Normal control	154 (67.2%)
Mild cognitive impairment	53 (23.1%)
Alzheimer's disease	16 (7.0%)
Vascular dementia	4 (1.7%)
Dementia with Lewy bodies	2 (0.9%)
Frontotemporal dementia	1 (0.4%)
Parkinson's disease with dementia	1 (0.4%)
Difficulty in diagnosis	1 (0.4%)
Clinical Dementia Rating (<i>n</i>)	
CDR 0	151 (66.0%)
CDR 0.5	54 (23.6%)
CDR 1	9 (3.9%)
CDR 2	7 (3.1%)
CDR 3	8 (3.5%)
Geriatric Depression Scale, mean \pm SD	3.6 \pm 2.9
Mini-Mental State Examination, mean \pm SD	25.9 \pm 5.6
Zarit Caregiver Burden Interview, mean \pm SD [†]	2.3 \pm 4.7
Personal strain	1.7 \pm 3.3
Role strain	0.7 \pm 1.9
Score of sense of coherence, mean \pm SD	72.4 \pm 12.7
Informant about CDR, burden, and SOC (<i>n</i>)	
Spouse	151 (65.9%)
Child (living together)	31 (13.5%)
Child (living separately)	27 (11.8%)
Child's partner (living together)	6 (2.6%)
Child's partner (living separately)	3 (1.3%)
Other	11 (4.8%)

[†]Eight-item version of the test.

CDR, Clinical Dementia Rating; SOC, sense of coherence.

($F_{(3, 75)} = 8.53, P < 0.001$) among elderly subjects after controlling for sex and cognitive function.

DISCUSSION

In this study, we aimed to examine the factors that determine caregiver burden and to identify the association between caregiver burden and stress-coping ability. We found that for elderly subjects, caregiver burden was significantly associated with a lower MMSE score of participants and a weakened SOC. Furthermore, SOC was particularly closely related to personal strain in the ZBI after confounding factors such as sex and cognitive function were controlled.

The ZBI score is based on two subscores: personal strain and role strain. Stress-coping ability is related to personal strain, which is 'how personally stressful the experience is'.²⁹ Reinforcement of SOC might therefore decrease the personal strain of a caregiver's burden. In contrast, role strain, which is 'stress due to

role conflict or overload',²⁹ was not associated with SOC. Therefore, the introduction of formal instrumental support such as respite care would help reduce the role strain of a caregiver's burden rather than enhance stress-coping ability.

To our knowledge, four studies have examined SOC among caregivers for individuals with dementia.^{18–20,33} In 2008, Andr n and Elmst hl revealed that caregivers with a lower caregiver burden had significantly higher SOC scores than those with a higher burden. They proposed that a low SOC might be a hallmark characteristic of a high-risk group of caregivers for whom early interventions to reduce the burden would be warranted.²⁰ Furthermore, Orgeta and Sterzo reported that caregivers with a low SOC are more likely to report high levels of depression and anxiety. They emphasized the need to for psychotherapeutic interventions that target the enhancement of SOC for familial caregivers of people with dementia.¹⁸ In a randomized controlled trial, Langeland *et al.* reported that group talk therapy for community residents with mental health problems enhanced the SOC and life satisfaction of participants.³² It is therefore expected that employing interventions to enhance SOC, such as the nursing care activities for community residents reported by Langeland *et al.*, might be effective in reducing caregiver burden for dementia. The results of that study, however, pertain to European nations, and there is a paucity of data from research involving Japanese caregivers. The similar association regarding Japanese subjects in the present study lends support to these previous findings.

Our study has several notable limitations. First, cause-and-effect relationships could not be determined because of the cross-sectional study design. Second, only a limited amount of caregiver information was collected, and some potentially confounding factors cannot be ruled out. SOC is believed to be nurtured in the process of maturation. Because it is thought that factors such as familial background, life experience, and individual economic conditions can potentially influence SOC, these caregiver factors should be controlled for in future studies. Third, our analysis did not assess or control for the severity of BPSD. Regarding psychosocial factors of caregivers and the BPSD of participants, these should ideally have been, but were not, controlled for statistically by multivariate data analysis in large samples. Fourth, the paucity of data regarding caregivers for dementia

Table 2 Correlations between age, years of education, cognitive function, sense of coherence, and ZBI

	Age		Years of education		MMSE score		SOC score	
	<i>r</i>	<i>P</i> -value	<i>r</i>	<i>P</i> -value	<i>r</i>	<i>P</i> -value	<i>r</i>	<i>P</i> -value
ZBI score	0.21	0.066	-0.05	0.650	-0.21	0.067	-0.38	<0.001***
Age	-	-	-0.24	0.033*	-0.34	0.002**	-0.14	0.233
Years of education	-0.24	0.033*	-	-	0.17	0.145	0.20	0.076
MMSE score	-0.34	0.002**	0.17	0.145	-	-	-0.16	0.154
SOC score	-0.14	0.233	0.20	0.076	-0.16	0.154	-	-

****P* < 0.001, ***P* < 0.01, **P* < 0.05. MMSE, Mini-Mental State Examination; SOC, sense of coherence; ZBI, Zarit Caregivers Burden Interview.

Table 3 Association between caregivers' burden and related factors

	β	<i>t</i>	<i>P</i> -value
Sex (male = 0, female = 1)		n.s	
Age		n.s	
Years of education		n.s	
MMSE score	-0.28	-2.68	0.009**
SOC score	-0.42	-4.10	<0.001***

****P* < 0.001, ***P* < 0.01. MMSE, Mini-Mental State Examination; n.s means not significance; SOC, sense of coherence.

Table 4 Association between sense of coherence and two subscores of Zarit Burden Interview

	β	<i>t</i>	<i>P</i> -value
Sex (male = 0, female = 1)	-0.25	-2.36	0.021*
Age		n.s	
Years of education		n.s	
MMSE score	-0.29	-2.75	0.007**
Zarit Burden Interview			
Personal strain	-0.41	-4.04	<0.001***
Role strain		n.s	

****P* < 0.001, ***P* < 0.01, **P* < 0.05. MMSE, Mini-Mental State Examination; n.s means not significance.

patients with clinically moderate or severe symptoms may limit the generalizability of results in this study.

In summary, this study yielded new evidence regarding the association between caregiver burden and stress-coping ability. The study's limitations notwithstanding, our findings contribute to a better understanding of the concept of SOC in dementia care. Caregiver burden related to the care of dementia patients is a very common problem in Japan. Therefore, further longitudinal or interventional studies would be worthwhile.

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Family history of frontotemporal lobar degeneration in Asia – an international multi-center research

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ABSTRACT

Background: Previous studies in western countries have shown that about 30%–50% of patients with frontotemporal lobar degeneration (FTLD) have a positive family history, whereas the few epidemiological studies on FTLD done in Asia reported much lower frequencies. It is not clear the reason why the frequencies of FTLD with positive family history were lower in Asia. Furthermore, these findings were not from studies focused on family history. Therefore, it is necessary to conduct further studies on the family history of FTLD in Asia. This international multi-center research aims to investigate the family histories in patients with FTLD and related neurodegenerative diseases such as progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), and motor neuron diseases in a larger Asian cohort.

Methods: Participants were collected from five countries: India, Indonesia, Japan, Taiwan, and Philippines. All patients were diagnosed with behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD), progressive non-fluent aphasia (PA), frontotemporal dementia with motor neuron disease (FTD/MND), PSP, and corticobasal degeneration (CBD) according to international consensus criteria. Family histories of FTLD and related neurodegenerative diseases were investigated in each patient.

Results: Ninety-one patients were included in this study. Forty-two patients were diagnosed to have bvFTD, two patients had FTD/MND, 22 had SD, 15 had PA, one had PA/CBS, five had CBS and four patients had PSP. Family history of any FTLD spectrum disorder was reported in 9.5% in bvFTD patients but in none of the SD or PA.

Conclusion: In contrast to patients of the western countries, few Asian FTLD patients have positive family histories of dementia.

Key words: Asia, epidemiology, family history, bvFTD, FTLD

Introduction

Frontotemporal lobar degeneration (FTLD) is the second most common cause of early-onset dementia after Alzheimer's disease (AD; Neary, 1999). FTLD includes three clinical subtypes: frontotemporal dementia (bvFTD or behavioral variant FTD) characterized by a progressive

deterioration of behavior and personality, as well as semantic dementia (SD) and progressive non-fluent aphasia variants of progressive aphasia (PA; Neary *et al.*, 1998). The broader FTLD spectrum also includes FTD with motor neuron disease (FTD/MND) and parkinsonian syndromes such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). While CBD requires a pathological diagnosis, the purely clinical entity is termed corticobasal syndrome (CBS).

Researches in western countries frequently report a strong family history in FTLD patients. In a community-based study by the Cambridge group, almost one-third of the participants (29%) with

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FTLD had a positive family history (Ratnavalli *et al.*, 2002). In a nationwide survey in the Netherlands, 38% of FTLN patients had one or more first-degree relatives with dementia before the age of 80 years, compared with 15% of the control participants (Stevens *et al.*, 1998). In a hospital-based study by the Manchester group (Snowden *et al.*, 1996), a family history was seen in all subtypes of FTLN and 50 % of their bvFTD cases had a positive family history, similar to the findings in a Swedish series (Gustafson, 1987). On the other hand, there are only few studies on heredity in Asian FTLN patients. In the two clinic-based studies from Japan, family history was either absent (Ikeda *et al.*, 2004) or reported in less than 5% of FTLN patients (Wada-Isoe *et al.*, 2012). In a study from India, only 8.3% of bvFTD patients had a first-degree relative affected with a FTLN spectrum disorder (Ghosh *et al.*, 2013). The authors of the study also suggested that there could be distinctive behavioral patterns in Asian patients with bvFTD. Most patients in that study showed florid behavioral symptoms even in the early stages.

As advances in genetics and molecular pathology usher in clinical trials with biologically driven, disease-specific therapies for individual FTLN subtypes, it becomes essential to ensure that cross-cultural clinical and genetic differences in FTLN and its related disorders are clearly recognized. With this in mind, the present study aims to look at the family history in the different FTLN spectrum disorders in Asian countries.

Methods

Patients were recruited for the study from consecutive outpatients who attended the following Asian centers between January 2010 and December 2012: (1) Cognitive Neurology Unit, Department of Neurology, Apollo Gleneagles Hospitals (India), (2) Hasan Sadikin Hospital, Faculty of Medicine, Padjadjaran University (Indonesia), (3) Department of Neuropsychiatry, Faculty of Life Science, Kumamoto University Hospital (Japan), (4) St. Lukes Medical Center (Philippines), and (5) Taipei Veterans General Hospital and Cardinal Tien Hospital (Taiwan). All patients were examined by senior neurologists or psychiatrists and were assessed by a combination of careful medical history, laboratory testing, morphological imaging of brain such as magnetic resonance imaging (MRI) or computed tomography (CT), and functional imaging such as single photon emission computed tomography (SPECT), whenever possible. In some patients with severe behavioral symptoms, it was difficult to perform functional imaging without

sedation. Patients were diagnosed with FTLN (bvFTD, SD, PA), FTD/MND, PSP, and CBS according to recognized diagnostic criteria (Brooks, 1994; Litvan *et al.*, 1996; Neary *et al.*, 1998; Boeve *et al.*, 2003). The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria (McKhann *et al.*, 1984) were used to diagnose Alzheimer's disease. Only those patients who had reliable informants such as their spouses, were included in this study.

Each pedigree was investigated across five generations (first- and second-degree relatives) for any affected family member. Data obtained from interviewing patients and family members were used to make detailed family trees. The affected family members were categorized according to appropriate diagnostic criteria into one of the following disorders: bvFTD, SD, PA, FTD/MND, PSP, CBS, MND, Parkinson's disease, and other dementias. Age at onset and a medical history, whenever possible, were also obtained. When a family had more than one affected member, only a single proband was included to avoid overestimation.

All procedures followed the Clinical Study Guidelines of Ethics Committee of Kumamoto University Hospital, Apollo Gleneagles Hospitals, Taipei Veterans General Hospital, National Yang-Ming University Hospital, Hasan Sadikin Hospital, St. Lukes Medical Center, and Cardinal Tien Hospital, and were approved by the respective internal review boards. A complete description of the study procedures was provided to the patients and their caregivers and written informed consent was obtained from them.

Results

Ninety-one patients were recruited from the five institutes. Demographic data are shown in Table 1. Forty-two patients had a diagnosis of bvFTD, two patients had FTD/MND, 22 had SD, 15 had PA, one had PA/CBS, five had CBS, and four patients had PSP. One of the patients was clinically diagnosed as FTD/MND, who showed FTLN-TDP pathology by brain biopsy. This patient and two others were found to have the C9ORF72 mutation by genetic testing. The Mini-Mental State Examination (MMSE) scores, Clinical Dementia Rating (CDR) scores, average age at onset, and duration of illness at presentation are summarized in Table 2. The MMSE scores were not available in 13 patients because of their severe behavioral and/or language disturbances, while in four patients

Table 1. Demographic data for the 91 patients with frontotemporal lobar degeneration spectrum disorders

	N	M/F	MEAN AGE AT ONSET (YEARS)	MEAN DURATION (YEARS)	NUMBER OF THE EACH DIAGNOSTIC GROUP						
					BVFTD	FTD/ MND	SD	PA	PA/ CBS	CBS	PSP
India	39	29/10	61.4	3.2	23 (15)	1 (1)	5 (4)	3 (2)	0	4 (4)	3 (3)
Indonesia	4	0/4	55.0	5.5	3 (0)	0	0	0	1 (0)	0	0
Japan	18	11/7	62.5	5.7	5 (4)	0	9 (5)	2 (2)	0	1 (0)	1 (0)
Philippines	7	1/6	57.7	3.1	5 (1)	0	0	2 (0)	0	0	0
Taiwan	23	8/15	63.2	2.7	6 (2)	1 (0)	8 (2)	8 (4)	0	0	0
Total	91	49/42	61.5	3.7	42(22)	2 (1)	22 (11)	15 (8)	1 (0)	5 (4)	4(3)

Notes: The numbers within brackets denote the number of male patients.

bvFTD = behavioural variant frontotemporal dementia; FTD/MND = frontotemporal dementia with motor neuron disease; SD = semantic dementia; PA = progressive non-fluent aphasia; PA/CBS = progressive non-fluent dementia and corticobasal syndrome overlap; CBS = corticobasal syndrome; PSP = progressive supranuclear palsy.

Table 2. Age, duration, MMSE scores, and CDR scores by diagnostic group

DIAGNOSIS OF PATIENTS	N	MEAN AGE AT ONSET (YEARS)	MEAN DURATION (YEARS)	MMSE SCORE	DISTRIBUTION OF CDR SCORE (0/0.5/1/2/3) (NUMBERS OF PATIENTS)
bvFTD	42	59.9	3.7	15.4	0/5/14/18/5*
FTD/MND	2	63.5	4.5	21.0	0/1/1/0/0
SD	22	59.5	1.8	14.3	0/4/12/1/3
PA	15	67.1	3.3	15.5	1/4/4/3/2
PA/CBS	1	76.0	5.0	–	0/0/0/1/0
CBS	5	64.0	1.7	18.2	0/1/2/2/0
PSP	4	61.3	3.3	21.5	0/1/2/0/0
Total	91	61.5	3.7	15.7	1/16/35/25/10

Notes: Numeral shows the number of patients in each CDR score.

Data of 13 cases in MMSE and 4 cases in CDR were could not available.

MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating; bvFTD = behavioural variant frontotemporal dementia; FTD/MND = frontotemporal dementia with motor neuron disease; SD = semantic dementia; PA = progressive non-fluent aphasia; PA/CBS = progressive non-fluent dementia and corticobasal syndrome overlap; CBS = corticobasal syndrome; PSP = progressive supranuclear palsy.

CDR scores were not recorded. Sixty-six patients had information of all of their first-degree relatives. They include 35 patients with bvFTD, 14 with SD, seven with PA, one with PA/CBS overlap syndrome, five with CBS and four with PSP. Data on family history in the different FTLD spectrum disorders are shown in Table 3. Family history of any FTLD spectrum disorder was found in 5.5% of all patients, 9.5% of those with bvFTD, 50% of those with FTD/MND (out of only two patients), but in none of those with SD, PA, PA/CBS, CBS, and PSP. Among the four probands with bvFTD and positive family history, two also had family history of bvFTD, one had family history of PA, and one had family history of MND.

One bvFTD proband had three family members with FTD, including first-degree relatives, although neither pathological nor genetic data were available for any of them. Each of the other probands with bvFTD had only one other family member with a

FTLD spectrum disorder. One of two probands with FTD/MND had one family member with MND. Family history of other dementias including AD and undiagnosed dementias was found in 27.5% of all patients, 26.2% of bvFTD, 27.3% of SD, 50% of PA, 75% of PSP, and in the only patient with PA/CBS overlap, but in none with FTD/MND or CBS.

Discussion

To date, family history in FTLD, reported mostly from western European and North American populations, has been seen in up to 40% of patients, with roughly 10% of patients showing an autosomal dominant inheritance pattern (Goldman *et al.*, 2005; 2007; van Swieten and Rosso, 2008). Relevant data from Asia are sparse (Ikeda *et al.*, 2004; Ghosh *et al.*, 2013). Our study is one of the

Table 3. Family history data in each diagnostic group

DIAGNOSIS OF PATIENTS	FAMILY MEMBERS AFFECTED WITH FTLD AND RELATED DISEASES			FAMILY MEMBERS AFFECTED WITH OTHER OR UNDIAGNOSED DEMENTIA	
	N	N	%	N	%
bvFTD	42	4 (including 1 MND)	9.5	11	26.2
FTD/MND	2	1 (MND)	50.0	0	0.0
SD	22	0	0.0	6	27.3
PA	15	0	0.0	4	26.7
PA/CBS	1	0	0.0	1	100.0
CBS	5	0	0.0	0	0.0
PSP	4	0	0.0	3	75.0
Total	91	5	5.5	25	27.5

Notes: FTLD and related diseases included FTLD spectrum disorders and MND. One patient with MND among four affecting family members in bvFTD group; one affected family member with MND in the FTD/MND group. bvFTD = behavioural variant frontotemporal dementia; FTD/MND = frontotemporal dementia with motor neuron disease; SD = semantic dementia; PA = progressive non-fluent aphasia; PA/CBS = progressive non-fluent dementia and corticobasal syndrome overlap; CBS = corticobasal syndrome; PSP = progressive supranuclear palsy.

largest reports of FTLD in an Asian population. A positive family history of FTLD spectrum disorders was found in 5.5% of our patients. Together with the previous Asian studies, our findings, therefore, support the infrequent occurrence of family history in Asian FTLD patients. It might be due to genetic differences between western and Asian populations.

In our patients, only one proband with bvFTD showed a clear autosomal dominant inheritance pattern, whereas none of the SD patients gave a family history of any FTLD spectrum disorder. Goldman *et al.* (2005) reported autosomal dominant inheritance in 18.2% of their patients with bvFTD and 1.9% of their SD patients, while Rohrer *et al.* (2009) described this inheritance pattern in 20% of their bvFTD patients but not in their SD patients. Goldman *et al.* (2005) also showed that familial aggregation, in which there were three or more affected family members, occurred in 8.1% of bvFTD patients but not in SD patients, and that 18.2% of bvFTD patients and 15.1% of SD patients had a single affected first-degree relative. In our study, most of the bvFTD patients had sporadic disease and only 2.4% of patients had a single affected relative. Therefore, in Asia, the occurrence of familial FTLD is undoubtedly lower than that in the western countries.

In recent years, various genetic abnormalities in microtubule-associated protein tau (MAPT), progranulin (GRN), and C9ORF72 have been associated with familial FTLD. In Asia, MAPT

mutations have been reported in familial SD (Ishizuka *et al.*, 2011), although typically in low frequency (Wada-Isoe *et al.*, 2012). These results suggest that genetic factors for the development of FTLD may have a less important role in the Asian population. Rohrer *et al.* (2009) demonstrated that 186 out of the 225 FTLD patients in their study had no mutations in known genes such as MAPT, GRN, valosin-containing protein (VCP), TARDP, chromatin modifying protein 2B (CHMP2B), and fused in sarcoma (FUS), and did not show strong family history. Unknown genetic defects may be associated with the development of many sporadic FTLD cases.

There are several limitations in the current study. First, although diagnosis of each proband was based on comprehensive examination including brain imaging, and followed recognized consensus criteria, the information regarding family histories were obtained by semi-structured interviews of the proband and family members. It was thereby difficult to confirm the diagnosis in many deceased or distant family members. Second, for most of our patients the diagnosis was based on clinical criteria and was not confirmed by definite pathological or genetic tests. However, going by the number of patients with FTLD spectrum disorders recruited for this study, this may be the largest research to date focusing on the family history of these disorders in Asia. This could, therefore, form the basis for future neurogenetic research in Asian countries.

Conclusion

Previous epidemiological studies have suggested that familial FTLD was rare in Asian countries. The current study, by focusing on family history in FTLD patients, demonstrated that, unlike patients from western countries, few Asian FTLD patients have a positive family history of dementia. Future research could explore possible reasons underlying these differences.

Conflict of interest

None.

Description of author's roles

R. Fukuhara participated in the study design, analyzed the data, and wrote the paper. A. Ghosh, J. Fuh, J. Dominguez, and P. A. Ong carried out clinical assessment, collected the data, and edited and revised the paper. A. Dutt and Y. Liu carried out clinical assessment and collected data. H. Tanaka carried out clinical assessment, collected the data, and assisted the analyses. M. Ikeda participated in the study design, and editing and revising the paper. All of the authors contributed to and approved the manuscript.

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Preliminary communication

Item non-response on self-reported depression screening questionnaire among community-dwelling elderly

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ABSTRACT

Background: In responses to self-reported depression screening questionnaires, item non-response, which refers to the absence of answers to specific questions, is problematic. The objective of this study were (1) to clarify the features of respondents with item non-response on a self-reported elderly depression screening questionnaire (15-item geriatric depression scale; GDS-15) as compared to respondents with full responses, and (2) to compare positive depression screening rates calculated using two methods: excluding respondents with item non-response (complete case analysis; CCA) and estimating by multiplying mean scores from valid responses by the total number of GDS-15 items for respondents with item non-response.

Methods: This was a cross-sectional study conducted from 2010 to 2012. Of 4794 elderly subjects (65 years and older) living in one town in Japan 2836 community-dwelling elderly people (59.2%) were included in the analysis.

Results: Item non-response was observed in 25.0% of respondents. Respondents with item non-response had a higher rate of depression and mental and physical problems. Respondents with depression (estimated GDS-15 score ≥ 6) and suicidal ideation both had a 1.6-times higher risk of item non-response on the GDS-15. The positive depression screening rate on GDS-15 by CCA was 16.5%, compared with 18.9% when calculated by the estimated GDS-15 score.

Limitations: Our survey was conducted in one rural area and targeted only elderly people.

Conclusion: The incidence of item non-response among community-dwelling elderly people was associated with depression of the respondent. Excluding subjects with item non-response when calculating positive depression screening rates in elderly individuals causes the rate to be underestimated.

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1. Introduction

Although self-reported survey research is convenient, inexpensive, and places little burden on respondents, item non-response, that is, absence of answers to specific questions, is problematic (Yan and Curtin, 2010). Item non-response occurs for many reasons, including careless mistakes, refusal to respond to questions about private issues, the absence of a "not applicable" option, or use of questions that the respondent does not understand.

The complete case analysis (CCA) method is commonly used to address missing data from survey respondents by excluding

subjects with missing data from analysis. If item non-response occurs at random (referred to as "Missing Completely at Random"), it can be ignored. CCA is convenient for this type of data, although it decreases the number of respondents. However, other types of missing data may also occur. These include "Missing at Random" data, in which the incidence of missing responses depends on some measurable characteristic of the individual but not on the missing value itself, and "Missing not at Random" data, in which the incidence of missing depends on missing itself. For example, people with high or low income might be less likely to report their income. For both "Missing at Random" and "Missing not at Random" data, missing itself has an important meaning and the results determined by complete case analysis are biased.

We had an opportunity to analyze secondary data of depression among community-dwelling elderly assessed by the geriatric depression scale (GDS)-15 Japanese version, a self-reported questionnaire (Niino et al., 1991). We hypothesized that item non-response would

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not occur at random because depression itself affects the incidence of item non-response. For example, depressed people often lack motivation and have difficulty concentrating, which may lead to missing responses. In addition, item non-response may occur in elderly respondents due to decreases in cognitive function. However, little is known about the issue of item non-response on a self-reported elderly depression screening questionnaire. Although Shrive et al. described how to deal with missing data on the Zung Self-reported Depression scale using six different imputation techniques, they carried out random simulations using only the full-response group (Shrive et al., 2006), which does not reflect a real non-response situation.

The aim of this study is to clarify features of respondents with item non-response on the GDS-15 compared with respondents with full-responses and compare positive depression screening rates calculated using CCA with rates determined by GDS-15 estimated by multiplying mean scores from valid responses by the number of total GDS-15 items. Our hypothesis is that rates calculated using CCA will underestimate the true rate of depression.

2. Methods

2.1. Participants and procedures

We used secondary data obtained from an epidemiologic survey study conducted from 2010 to 2012 in Asagiri, Kumamoto, Japan. Asagiri has suffered from depopulation and aging. A detailed description of the survey is available elsewhere (Fukunaga et al., 2012).

In each year, one area of the town was selected and all residents aged 65 years and older received a self-reported questionnaire by postal mail. They were asked to return questionnaires using the return envelope. Returning the questionnaire was assumed to represent informed consent. Of 4794 subjects, 3167 (66.1%) returned the questionnaire. A total of 331 subjects who were in the hospital or nursing home or who could not answer because of dementia or other reasons were excluded. All procedures for the present study followed the 2009 Clinical Study Guidelines of the Ethics Committee of Kumamoto University Hospital (Kumamoto, Japan) and were approved by the Internal Review Board.

2.2. Measures

GDS was used to assess depression. Although a standard 30-item version (Yesavage et al., 1983) and a shortened 15-item version (Sheikh and Yesavage, 1986) are available, this study used the Japanese 15-item version. GDS-15 Japanese version has a sufficient reliability and validity (Watanabe and Imagawa, 2013). For each item, subjects answered "Yes" or "No". Depressive answers were scored 1-point for each item and sum of all items represented the GDS-15 total score (range, 0–15). A score of 6 or more is considered to represent 'possible depression' (Schreiner et al., 2001).

Other variables assessed included age, gender, living alone or not, routine hospital visits, sleep problems (having/not having), appetite (having/not having), serious worries about money (having/not having), suicidal ideation (having [included "sometimes", "often", and "always"]/not having).

2.3. Statistical analysis

For statistical analysis, we calculated the incidence of item non-response on the GDS-15 by counting the number of unanswered items. Respondents who failed to answer one or more questions were defined as the "item non-response group" and those who answered all questions were defined as the "full-response group." We compared sociodemographic characteristics, physical and

mental complaints, and each item of the GDS-15 between the item non-response group and full-response group, excluding cases with item non-response in each analysis. Second, we compared mean GDS-15 scores and the percentage of respondents who scored ≥ 6 between two groups. For item non-response group, we estimated GDS-15 scores by multiplying the mean score from valid responses by the number of GDS-15 items. Logistic regression analysis was conducted to assess the likelihood of item non-response among depressive respondents or respondents with suicidal ideation. In addition, we compared the positive screening rate calculated by CCA with the one determined by GDS-15 estimates (multiplying the mean score from valid responses by the number of GDS-15 all items). All tests were 2-tailed and the significance levels were Bonferroni-corrected. All statistical analyses were performed with SPSS 21.0J for Windows (IBM SPSS Japan, Tokyo, Japan).

3. Results

Of 2836 subjects, 719 (25.0%) were included in the "item non-response group". In this group, 54% did not respond to 1 item, 19% did not respond to 2 items, 15% did not respond to 3 to 5 items, 9% did not respond to 6 to 14 items, and 4% did not respond to any item. Mean age and the percentage of females were significantly higher in the item non-response group than the full-response group. In the item non-response group, the percentage with routine hospital visits, sleep problems, loss of appetite, and having suicidal ideation was significantly higher than in the full-response group. The GDS-15 mean score and the percentage of the respondents who scored cutoff point of 6 or more of GDS-15 were significantly higher in the item non-response group than in the full-response group (Table 1).

Table 2 shows the incidence of item non-response of all respondents for each GDS-15 item and the comparison of the percentage of depressive answers in each item between groups. In 13 of 15 items, the percentage of respondents who selected depressive answers was significantly higher in the item non-response group than in the full-response group.

Logistic regression analysis revealed that the existence of depression (GDS-15 score ≥ 6) and suicidal ideation were risk factors for item non-response after adjusting for age, gender, and routine hospital visits. Odds ratios were 1.6 (95% CI, 1.3–2.0, $p < 0.001$) and 1.6 (95% CI, 1.2–2.0, $p < 0.001$), respectively.

When we calculated the positive depression screening rate on GDS-15 by CCA, that is, excluding the item non-response group, the percentage was 16.5%. When we calculated GDS-15 score in item non-response group by multiplying mean scores from valid responses by the number of total GDS-15 items, the total positive rate was 18.9%, which was remarkably higher than that calculated using CCA.

4. Discussion

The present study was the first to show a correlation between the incidence of item non-response and depression among elderly community-dwelling survey respondents. Respondents with depression and suicidal ideation had a 1.6 times higher risk of item non-response on the GDS-15. In addition, the rate calculated using CCA was lower than GDS-15 estimates determined by multiplying mean scores from valid responses by the number of total GDS-15 items. From these findings, we could conclude that the rate of depression calculated using CCA would be underestimated. Recently, imputation methods such as multiple imputation analysis have been gaining use when dealing with item non-response (Rubin, 1987). However, this technique has some restrictions. For

Table 1
Comparison of demographic and other characteristics between the item non-response and full-response groups.

	Item non-response group (N=719)	Full-response group (N=2117)	t/χ^2 ^c
Mean age ^a	78.0	76.0	$t=6.8^{***}$
Gender ^a (female, %)	66.0	56.8	$\chi^2=18.3^{***}$
Living alone ^a (%)	14.9	12.0	$\chi^2=4.0$
Routine hospital visit ^a (having, %)	85.5	79.8	$\chi^2=10.7^*$
Seep problems ^a (having, %)	32.7	23.2	$\chi^2=24.6^{***}$
Loss of appetite ^a (having, %)	15.2	9.7	$\chi^2=16.0^{**}$
Worries about money ^a (having, %)	13.0	9.7	$\chi^2=6.0$
Suicidal ideation ^a (having, %)	19.8	11.6	$\chi^2=28.0^{***}$
Mean GDS-15 score ^b	4.1	2.8	$t=8.5^{***}$
Cutoff score ≥ 6 ^b (%)	26.1	16.5	$\chi^2=31.7^{***}$

^a Excluded respondents who did not respond to each factor.

^b Excluded 26 respondents with full non-response.

^c * < 0.05, ** < 0.01; Bonferroni-corrected.

Table 2
Incidence rate of item non-response and comparison of the percentage of depressive answers between the item non-response and full-response groups.

GDS-15 items	Incidence rate of item non-response (%)	The percentage of depressive answer		
		Item non-response group (N=719)	Full-response group (N=2117)	χ^2 ^a
Are you basically satisfied with your life? YES/NO	2.6	15.3	12.1	4.7
Have you dropped many of your activities and interests? YES/NO	4.9	32.6	22.2	26.6 ^{***}
Do you feel that your life is empty? YES/NO	4.1	19.0	11.0	23.5 ^{***}
Do you often get bored? YES/NO	6.1	29.3	21.5	14.5 ^{**}
Are you in good spirits most of the time? YES/NO	7.2	24.5	17.9	15.8 ^{***}
Are you afraid that something bad is going to happen to you? YES/NO	3.9	16.9	11.1	14.6 ^{***}
Do you feel happy most of the time? YES/NO	3.7	16.4	9.1	26.6 ^{**}
Do you often feel helpless? YES/NO	7.9	27.5	21.9	7.1
Do you prefer to stay at home, rather than going out and doing new things? YES/NO	3.2	46.8	34.6	30.7 ^{**}
Do you feel you have more problems with memory than most? YES/NO	3.6	41.4	27.5	43.7 ^{**}
Do you think it is wonderful to be alive now? YES/NO	3.4	11.9	7.3	13.6 [*]
Do you feel pretty worthless the way you are now? YES/NO	4.8	20.1	10.6	37.0 ^{***}
Do you feel full of energy? YES/NO	4.0	50.3	36.3	39.0 ^{***}
Do you feel that your situation is hopeless? YES/NO	5.1	12.0	7.1	14.3 ^{**}
Do you think that most people are better off than you are? YES/NO	6.3	42.7	29.2	36.2 ^{***}

Answers in bold indicate depressive answer. One point is scored for each bolded answer.

^a * < 0.05, ** < 0.01; Bonferroni-corrected.

example, multiple imputation analysis cannot be used with “Missing not at Random” data or categorical data. Previous studies suggest that the most suitable way to deal with item non-response differs depending on the research topic (Desai et al., 2011; Ali et al., 2011; Hallgren and Witkiewitz, 2013; Ng et al., 2013). Thus, item non-response should be handled with extreme caution and results interpreted cautiously.

Elderly or depressive respondents are thought to have a higher risk of item non-response (Mody et al., 2008). Elderly people are more likely to miss or skip more items because of cognitive impairment including difficulty in understanding and judgment or physical problems such as vision deficits, whereas depressed patients tend to have low motivation, inability to concentrate, or easy fatigability. Thus, creating a questionnaire that is easy for every respondent to answer is also important (e.g., increasing the size of the text or changing the color for each line). This would be effective not only for elderly or depressive respondents but for all respondents.

Item non-response occurred more frequently in females than in males, which is consistent with a previous study (Ying, 1989). This finding may reflect the fact that female respondents are older than male respondents, as the average lifespan is longer for females than males in Japan and other countries.

4.1. Limitations

Our study has several limitations. First, it is difficult to generalize our results because our survey was conducted in one rural area and targeted only elderly people. Second, we could not distinguish writing from dictation from self-written responses in our survey. For cases of writing from dictation, the incidence of item non-response might be lower. In addition, the issue of “unit non-response” should be determined as well as item non-response. Unit non-response means that an eligible sample unit fails to participate in a survey because of failure to establish contact or refusal to cooperate. Some studies reported worse health status among the unit non-response group, although others reported opposite findings (Volken, 2013). Further studies about item and unit non-response among patients diagnosed with depression and the correlation between item non-response and severity of depression are needed to support our results.

4.2. Conclusions and clinical implications

Our study revealed that the incidence of item non-response among community-dwelling elderly people was associated with depression of the respondent. When calculating positive

depression screening rates in elderly individuals, to reduce item non-response and not to exclude subjects with item non-response would be important.

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Conflict of interest

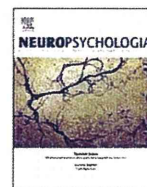
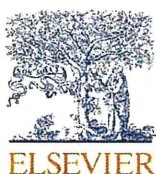
None of the authors has a conflict of interest to disclose.

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Hallucinators find meaning in noises: Pareidolic illusions in dementia with Lewy bodies



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ABSTRACT

By definition, visual illusions and hallucinations differ in whether the perceived objects exist in reality. A recent study challenged this dichotomy, in which pareidolias, a type of complex visual illusion involving ambiguous forms being perceived as meaningful objects, are very common and phenomenologically similar to visual hallucinations in dementia with Lewy bodies (DLB). We hypothesise that a common psychological mechanism exists between pareidolias and visual hallucinations in DLB that confers meaning upon meaningless visual information. Furthermore, we believe that these two types of visual misperceptions have a common underlying neural mechanism, namely, cholinergic insufficiency. The current study investigated pareidolic illusions using meaningless visual noise stimuli (the noise pareidolia test) in 34 patients with DLB, 34 patients with Alzheimer's disease and 28 healthy controls. Fifteen patients with DLB were administered the noise pareidolia test twice, before and after donepezil treatment. Three major findings were discovered: (1) DLB patients saw meaningful illusory images (pareidolias) in meaningless visual stimuli, (2) the number of pareidolic responses correlated with the severity of visual hallucinations, and (3) cholinergic enhancement reduced both the number of pareidolias and the severity of visual hallucinations in patients with DLB. These findings suggest that a common underlying psychological and neural mechanism exists between pareidolias and visual hallucinations in DLB.

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1. Introduction

In our everyday life, we believe that we instantaneously recognise the physical features of objects in the external world through vision. However, psychologists and neuroscientists have demonstrated that our instantaneous visions are often unreliable and that object recognition depends on context, prediction and proactive inference (Bar, 2007; Friston, 2005; Kersten, Mamassian, & Yuille, 2004). Misperceptions associated with a variety of neurological and psychiatric diseases, e.g., hallucinations and illusions, are classic examples of what occurs when these types of active aspects of perception do not work. For example, patients with schizophrenia would believe hallucinatory voices to be tricks and be less annoyed if the underlying context or premise that no

one possesses the ability to transfer his/her voices through electrical waves was not corrupted (Frith & Done, 1988; Kapur, 2003).

Dementia with Lewy bodies (DLB) is presumably one of the most common disorders that causes visual misperceptions. Approximately 80% of patients with DLB reportedly experience visual hallucinations (Luis et al., 1999; McKeith et al., 1996). Uchiyama et al. (2012) recently showed that pareidolias, which are complex visual illusions involving ambiguous forms perceived as meaningful objects, are quite common in DLB and are even observed in DLB patients not experiencing visual hallucinations. What is the difference between a visual hallucination and a pareidolia? By definition, visual hallucinations are perceptions without real perceptual objects. In contrast, the pareidolias observed in the previous study (Uchiyama et al., 2012) arose from pictures containing visual scenes with contexts or meanings. Therefore, these conditions differ regarding whether the perceptual objects exist in reality (Ey, 1973). Based on this point of view,

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