addition, counseling for dementia patients' family members enabled prolonged home care.[6,7] However, all of these studies have methodological shortcomings. For example, when selecting study subjects from the population of dementia patients requiring care, these studies categorized symptoms too broadly, ranging from slight to severe. In addition, study program providers (interveners) were only chosen from the paramedic profession rather than from an interdisciplinary group.

In order to address some of these issues, the Center for Comprehensive Care and Research on Memory Disorders (Monowasure-Center) of the National Center for Geriatrics and Gerontology (NCGG) embarked on an interdisciplinary program of educational support for dementia patients and their families immediately after the definitive diagnosis of dementia. We examined the learning needs and post-learning attitude changes of patients and their families in order to assess the effectiveness of this interdisciplinary program of educational support.

Methods

Operational definition

First, the interdisciplinary research team set up two operational definitions. We defined the first few months after a definitive dementia diagnosis as the "early stage." Next, we set up a program offered through an interdisciplinary collaboration as "early-stage educational support."

Psycho-educational program

We divided the program structure broadly into two domains: the "cure domain" concerned with diagnosis, treatment and medication for dementia, and the "care domain" concerned with care methods and social support for dementia patients. Furthermore, the cure domain consisted of medical care content and medication content, the care domain consisted of nursing care content and welfare content. We then set up four content categories for each domain (Table 1), and assigned physicians, pharmacists, nurses and psychiatric social workers as interveners.

Participants

The study protocol was approved by the institutional review board of the NCGG of Japan. Candidate patients and their family caregivers submitted informed consent before participating in the study. The total number of participants was 170. This research included several cases in which there were two or more family participants to one patient. In these cases, all participating family members in the household were counted in the number of participants. Following are the details of the 170 study participants (Fig. S1).

The study participants were 51 dementia patients (henceforth referred to as "patients") who had been given a definitive dementia diagnosis only a few months before participation in the program (August 2012 to August 2013). The 51 patients targeted in the study comprised 41 patients who participated in both the cure and the care domains, and 10 patients who participated in only the care domain. Furthermore, the study also targeted 119 family members of patients, raising the total number of participants to 170. These 119 family members comprised 53 who participated in both the cure and the care domains, and 66 who participated in only one domain. Of these 66 single-domain participants, 27 participated in the cure domain, and 39

Table 1 Structure of educational program

Domain	Program content	Intervener	Time provided (min)	No. times	Theme
Cure	Medical care	Physician	15	One time/one month	Basic knowledge about dementia
	Medication	Pharmacist	15	One time/one month	Pharmacological treatment and management through medication
Care	Nursing care	Nurse	15	One time/one month	Understanding dementia patients as "people with dementia" and coping methods
	Welfare	Psychiatric social worker	15	One time/one month	Provision of information concerning social resources that help patients and their caregivers in the community

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participated in the care domain. Participation in each domain was based on request rather than random allocation.

Assessment and questionnaires

The items of type of dementia, Barthel Index (BI),[8] Mini-Mental State Examination (MMSE),[9] Dementia Behavior Disturbance Scale (DBD)[10] and Zarit Burden Interview (ZBI)[11] were collected through patients' electronic health records, and descriptive questionnaires issued before and after each program. The questionnaire items administered before attending the program inquired about personal attributes and what the participant desired to learn. After completion of the program, we examined participants' learning needs and attitude changes for each domain, using four items: (i) degree of usefulness for future life and caregiving; (ii) degree to which anxieties about life and care are resolved; (iii) degree of improvement in future life and increase in incentive for care; and (iv) degree to which understanding of dementia is promoted. For the responses, we used a five-point Likert scale with possible answers to each question being: (i) completely disagree; (ii) disagree somewhat; (iii) cannot say either way; (iv) agree considerably; and (v) agree very much.

Statistical analysis

We carried out a statistical analysis of the quantitative data and categorized the qualitative data. For the data analysis of χ^2-test, we used the SPSS windows version 21.0 program (SPSS, Chicago, IL, USA).

Results

Characteristics of patients and family members

Characteristics of both patients and family member participants were analyzed (Table 2). Patients' clinical characteristics were analyzed according to sex, age, type of dementia, the BI, the MMSE score and the DBD. Among the clinical characteristics, Alzheimer's disease was the most common type of dementia (88.2%). In addition, some participating patients showed early-stage dementia with MMSE (mean ± SD) scores of 19.9 ± 4.5.

The family member characteristics analyzed were sex, age group, family relationship to patient, living with patients and the ZBI. Approximately 70.0% of family member participants were females, and approximately 50.0% of family member participants were in the old age group. In the family member's relationship to patient group, "spouse" accounted for the highest proportion of responses (47.9%).

Learning needs according to program contents and change in participant attitude

Cure domain (program content: Medical care/ Medication).

Table 2 Baseline characteristics of patients and family members

The items	*n* (%)	Mean ± SD
Patients characteristics (*n* = 51)		
Sex (female)	30 (58.8)	
Age (years)		78.8 ± 6.6
Types of dementia		
Alzheimer's disease	45 (88.2)	
Vascular dementia	5 (9.8)	
Dementia with Lewy bodies	1 (2.0)	
Barthel Index		94.5 ± 15.9
MMSE (total score)		19.9 ± 4.5
DBD scale (total score)		13.1 ± 8.1
Living with family members (at home)	47 (92.1)	
Family members' characteristics (*n* = 119)		
Sex (female)	83 (69.7)	
Older age group (from 60s to 80s)	59 (49.5)	
Patient's spouse	57 (47.9)	
Patient's daughter or son	41 (34.5)	
Patient's daughter or son-in-law	14 (11.8)	
Living with patients (at home)	114 (95.8)	
ZBI (total score)		19.6 ± 4.5

DBD, Dementia Behavior Disturbance Scale; MMSE, Mini-Mental State Examination; ZBI, Zarit Burden Interview.

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Learning needs

A total of 27 patients and 80 family members gave complete answers regarding learning needs (Table 3). The majority of the patients' answers were categorized as "Understand how the advance of dementia can be prevented" and "Gained a general understanding of dementia." Many patients expressed a desire to know how to slow down the progress of dementia, as well as general things to keep in mind when going about their daily lives. Patients also stated their desire to confirm whether their current disease and symptoms were real.

With regard to family members, the majority of answers were in the categories "Gain understanding about dementia" and "How to cope with dementia and the patient."

Attitude change

With regard to program 1, "Leads to understanding of dementia" and "Useful for future care and living methods" had high values of more than 80.0% for patients, and more than 70.0% for family members (Table 4). We did not find a statistical difference, but more than 70.0% of the patients answered "Leads to increased motivation to live," and similarly, more than 70.0% of family members answered that it "Leads to a resolution of anxiety about life and care."

For program 2, results for "Led to a resolution of anxiety about life and care" were approximately 70.0% for both patients and family members. In this program, family members' attitudes appeared to change, with 72.5% of family members, a markedly high result, answering that the program is "Useful for future care and living methods" and "Leads to increased motivation to live."

Care domain (Program content: Nursing care/ Welfare).

Learning needs

On the topic of learning needs, 30 patients and 92 family members gave complete answers (Table 3). An extremely high proportion of patients (90.0%) answered that the program helped them to "Gain a general understanding of dementia." This result showed patients'

Table 3 Learning needs according to program contents

Domain	Content	Category	Patients $n = 27$	Family members $n = 80$
Cure	Medical care/Medication	†Gain a general understanding of dementia	8 (29.6%)	35 (43.8%)
		†Learn how to prevent dementia from progressing	10 (37.0%)	5 (6.3%)
		Gain knowledge on the treatment methods for dementia	5 (18.5%)	16 (20.0%)
		Learn how to approach dementia	0 (0.0%)	18 (22.5%)
		†Resolution of psychological anxiety and conflict	4 (14.8%)	3 (3.8%)
		Find fellow dementia patients and caregivers	0 (0.0%)	2 (2.5%)
		Examine ways in which to announce dementia	0 (0.0%)	1 (1.3%)
			Patients $n = 30$	Family members $n = 92$
Care	Nursing care/Welfare	Learn care methods	0 (0.0%)	56 (60.8%)
		†Gain a general understanding of dementia	27 (90.0%)	17 (18.5%)
		†Learn how to prevent dementia from progressing	12 (40.0%)	0 (0.0%)
		Learn living methods	0 (0.0%)	5 (5.4%)
		Learn theories of coping with dementia patients	1 (3.3%)	6 (6.5%)
		Acquire information on the various types of social support	0 (0.0%)	4 (4.3%)
		Connection with community and whether or not to announce dementia	0 (0.0%)	2 (2.2%)
		†Resolution of psychological anxiety and conflict	1 (3.3%)	2 (2.2%)
		Learn ways to make use of social resources	0 (0.0%)	1 (1.1%)
		Other	4 (13.3%)	0 (0.0%)

†Categories raised (as needs) in both categories.

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Table 4 Cure domain: Change in participants' attitude according to program contents

Program content	Questions inquiring about	Responses†	Patients (n = 27)	Family members (n = 80)	P-value (χ^2-test)
1. Medical care	Q1: Program content is useful for future care and living methods	Agree	21 (77.7%)	60 (75.0%)	$P = 0.97$
		Disagree	6 (22.3%)	20 (25.0%)	
	Q2: Program content linked to a resolution of anxiety concerning life and care	Agree	19 (70.3%)	58 (72.5%)	$P = 0.85$
		Disagree	8 (29.7%)	22 (27.5%)	
	Q3: Program content linked to improvement in future life and increase in motivation to live	Agree	19 (70.4%)	54 (67.5%)	$P = 0.95$
		Disagree	8 (29.6%)	26 (32.5%)	
	Q4: Program content linked to understanding of dementia	Agree	22 (81.5%)	66 (82.5%)	$P = 0.78$
		Disagree	5 (18.5%)	14 (17.5%)	
2. Medication	Q1: Program content is useful for future care and living methods	Agree	17 (62.9%)	58 (72.5%)	$P = 0.09$
		Disagree	10 (37.1%)	22 (27.5%)	
	Q2: Program content linked to a resolution of anxiety concerning life and care	Agree	18 (66.6%)	59 (73.7%)	$P = 0.42$
		Disagree	9 (33.4%)	21 (26.3%)	
	Q3: Program content linked to improvement in future life and increase in motivation to live	Agree	16 (59.2%)	58 (72.5%)	$P = 0.06$
		Disagree	11 (40.8%)	22 (27.5%)	
	Q4: Program content linked to understanding of dementia	Agree	16 (59.2%)	55 (68.7%)	$P = 0.30$
		Disagree	11 (40.8%)	25 (31.3%)	

†For each question, we calculated the answers by using a five-point Likert scale whereby we combined the number of participants who selected "Agree very much" and "Agree considerably" as those who selected "Agree"; we counted those who selected "Completely disagree," "Disagree somewhat" and "Cannot say either way" as "Disagree." We additionally used a χ^2-test.

desires to learn the means to prevent their dementia from worsening. In other words, patients wanted to learn about treatments and living methods that could stop the progression of their dementia.

As for family members, 60.8% showed a desire to "Learn care methods." Family members desired to know more about the ways to approach problem behaviors in dementia patients.

Attitude change

In program 3, the degree of attitude change among patients was polarized at approximately 60.0% (Table 5). Those whose degree of attitude change was 60.0% or above answered that it was "Useful for future living methods" and "Leads to increased motivation to live." As for the degree of attitude change among family members, the results were high (70.0%) on all four items. The highest items were "Leads to a resolution of anxiety about life and care," and "Leads to understanding of dementia," at 76.1% and 78.3% respectively. A significant difference was observed in the latter (χ^2-test, $P < 0.05$).

With regard to program 4, the degree of attitude change among patients remained at approximately 60.0% for all four items, with the highest of these, at 66.6%, being "Leads to increased motivation to live." As for family members, no significant difference was observed, but "Useful for future life and care" and "Leads to a resolution of anxiety about life and care" were high at 72.8% and 71.7%, respectively.

Discussion

Although educational support programs typically target family caregivers,[12] the present study was unique in that it targeted patients as well. As very little time had passed since the definitive dementia diagnosis, both patients and family members might have been confused or anxious,[13,14] but they showed high expectations for learning. In considering these concerns and expectations, it is important to examine the learning needs and attitude changes throughout the program.

As shown in Table 2, both patients and family members were aging. We reasoned that there was elderly care by the elderly because of the high rate of "spouse" in the family relationship to patient. Dementia conditions will worsen little by little from diagnosis, even if patients have early-stage dementia. Therefore, the necessity for learning about the cure and care of dementia was suggested as preparation for preventing care burden and care breakdown.

Many patients and their family members showed learning needs for medical care content in the cure

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Table 5 Care domain: Change in participants' attitude according to program contents

Program content	Questions inquiring about	Responses†	Patients (n = 30)	Family members (n = 92)	P-value (χ^2-test)
3. Nursing care	Q1: Program content is useful for future care and living methods	Agree	19 (63.3%)	65 (70.7%)	$P = 0.82$
		Disagree	11 (36.7%)	27 (29.3%)	
	Q2: Program content linked to a resolution of anxiety concerning life and care	Agree	18 (60.0%)	70 (76.1%)	$P = 0.17$
		Disagree	12 (40.0%)	22 (23.9%)	
	Q3: Program content linked to improvement in future life and increase in motivation to live	Agree	19 (63.3%)	67 (72.8%)	$P = 0.59$
		Disagree	11 (36.7%)	25 (27.2%)	
	Q4: Program content linked to understanding of dementia	Agree	17 (56.6%)	72 (78.3%)	$P = 0.40$
		Disagree	13 (43.4%)	20 (21.7%)	
4. Welfare	Q1: Program content is useful for future care and living methods	Agree	19 (63.3%)	67 (72.8%)	$P = 0.21$
		Disagree	11 (36.7%)	25 (27.2%)	
	Q2: Program content linked to a resolution of anxiety concerning life and care	Agree	19 (63.3%)	66 (71.7%)	$P = 0.73$
		Disagree	11 (36.7%)	26 (28.3%)	
	Q3: Program content linked to improvement in future life and increase in motivation to live	Agree	20 (66.6%)	62 (67.4%)	$P = 0.72$
		Disagree	10 (33.4%)	30 (32.6%)	
	Q4: Program content linked to understanding of dementia	Agree	19 (63.3%)	63 (68.4%)	$P = 0.96$
		Disagree	11 (36.7%)	29 (31.6%)	

†For each question, we calculated the answers by using a five-point Likert scale whereby we combined the number of participants who selected "Agree very much" and "Agree considerably" as those who selected "Agree"; we counted those who selected "Completely disagree," "Disagree somewhat" and "Cannot say either way" as "Disagree." We additionally used a χ^2-test.

domain, including dementia progression, symptoms and ways to prevent progression. Family members tended to desire information about the progression of dementia and treatment methods appropriate for stopping it, as well as the symptoms that appear. Such results support the demand for a program with continuity between cure and care.

When we attempted to verify the efficacy of each program according to attitudinal change, we found that the results were different depending on participants' attributes. The most notable results among patients were in the medical care content (program 1) "Degree of usefulness for future life," "Degree of increased motivation to live" and "Degree to which the program helped participants understand dementia." Many patients felt this program helped to them seek a way of life that prevents dementia from worsening.

With regard to family members, "Degree of resolution of anxiety about life and care" was markedly high across all the programs. Examining the programs individually, "Degree to which understanding of dementia was promoted" was markedly high for medical care content (program 1) and nursing care content (program 3), and "Degree of usefulness for future life and care" was markedly high for medication content (program 2) and welfare content (program 4). We could infer that, in each case, cure and care were shown to be effective as one unit, with "gaining understanding of dementia patients and their symptoms" in the former, and "learning methods for sustainable care" in the latter. Interdisciplinary educational support, consisting of both cure and care content, can provide appropriate psychological care. Another benefit of interdisciplinary educational support is that, through learning the knowledge and skills necessary for living with dementia, patients and their family members spontaneously involved themselves in medical consultations and treatment. This benefits healthcare providers by facilitating medical consultations, and empowers patients and family members about cure and care.

The present study provides evidence for three assertions:

1 Both patients and family members feel a need to learn medical care content including dementia progression, symptoms and methods to prevent progression.
2 Learning medical care content would lead to their use of knowledge and an increased motivation to live.
3 Learning medical care content is effective in helping family members understand dementia, and leads to the acquisition of skills for coping with dementia patients and their symptoms.

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Following these three points, we suggest that medical care content was the core of interdisciplinary educational support for early-stage dementia patients and their family members. Finally, there is a need to continue research to verify this program's effectiveness.

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Disclosure statement

The authors declare no conflict of interest.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 Flow chart of the study protocol.

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ORIGINAL ARTICLE

Left ventricular diastolic dysfunction is associated with cerebral white matter lesions (leukoaraiosis) in elderly patients without ischemic heart disease and stroke

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Aim: Cerebral white matter lesions (WML) are known to increase with age, as is left ventricular (LV) diastolic dysfunction with normal contraction. Although aging is a common risk factor, the link between these diseases is not fully understood. The aim was to clarify this relationship, using the ratio between early diastolic mitral inflow and early diastolic mitral annular tissue velocity (E/E'). E/E' measured by tissue Doppler echocardiography offers an indicator of the severity of LV diastolic dysfunction, reflecting both diastolic LV stiffness and diastolic LV filling pressure.

Methods: Participants comprised 75 patients aged between 65 and 75 years with normal LV contraction and no signs or history of symptomatic heart failure, ischemic heart diseases, atrial fibrillation, stroke, or cognitive dysfunction. The volume of WML was quantified on brain magnetic resonance imaging.

Results: The participants were classified into three groups: Low E/E', E/E' ≤ 8; Middle E/E', 8 < E/E' < 15; and High E/E', E/E' ≥ 15. WML volume was 3.6 ± 3.0 mL in Low E/E', 5.4 ± 6.5 mL in Middle E/E' and 12.0 ± 11.0 mL in High E/E', increasing significantly with increased diastolic LV stiffness (Low *vs* High, $P = 0.034$; Middle *vs* High, $P = 0.016$). Linear regression analysis showed the positive association between the volume of WML and E/E' ratio ($r = 0.377$, $P = 0.0009$).

Conclusions: This investigation identified an association between LV diastolic dysfunction and WML. Further investigations are required to clarify whether there is a direct association between the two diseases. **Geriatr Gerontol Int 2014; 14 (Suppl. 2): 71–76.**

Keywords: cerebral white matter lesions, left ventricular diastolic dysfunction, ratio of early diastolic mitral inflow to early diastolic mitral annular tissue velocity.

Introduction

Cerebral white matter lesions (WML) on magnetic resonance imaging (MRI) consisting of nerve axons or glia have been shown to exist in older adults. Cerebral WML have been established to increase with age, and are associated with heightened risks of stroke,[1,2] cognitive decline[3,4] and depressive disorder.[5]

Left ventricular (LV) diastolic dysfunction with normal contraction also increases with age.[6,7] This dysfunction is characterized by increased stiffness of the left ventricle caused by proliferation of the extracellular matrix and progression of myocardial fibrosis, and by decreased elasticity of cardiomyocytes as a result of abnormalities in calcium dynamics, energy metabolism or the cytoskeleton of cardiomyocytes.[8]

Although studies have not reached consistent conclusions, some studies have suggested an association between LV systolic dysfunction and brain abnormalities, such as WML[9] and cognitive decline.[10] At present, cerebral hypoperfusion resulting from LV systolic dysfunction is speculated to contribute to the brain abnormalities.[11] In contrast, no reports have described the relationship between LV diastolic dysfunction with

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normal contraction and brain abnormalities. The purpose of the present study was thus to clarify this relationship by focusing on WML and brain function.

We applied the ratio between early diastolic mitral inflow and early diastolic mitral annular tissue velocity (E/E') as an indicator of the severity of LV diastolic dysfunction, and evaluated the relationship between E/E' ratio and cerebral WML volume among elderly patients with normal LV contraction and without symptomatic heart failure.

Methods

Participants

Outpatients aged 65–75 years (mean age 69.3 ± 3.4 years) treated by the Department of Cardiology at the National Center for Geriatrics and Gerontology were enrolled. Among these, patients with symptomatic heart failure, ischemic heart disease, valvular heart disease, atrial fibrillation, stroke, neurodegenerative disorder or clinically diagnosed dementia were excluded. To exclude patients with prior myocardial infarction, angina or stroke, prespecified criteria were used to define those diseases using a combination of self-report of a doctor diagnosis, World Health Organization chest pain questionnaire and 12-lead exercise electrocardiography.[12] We also excluded those patients with ejection fraction (EF) < 50% or LV end-diastolic volume index (LVEDVI) ≥ 97 mL/m^2 on echocardiography, major brain infarction resulting from major cerebral artery lesions detected on brain MRI, ≥50% stenosis in the carotid arteries on ultrasonography with 2-D and Doppler analysis, or cognitive dysfunction (Mini-Mental State Examination score [MMSE] <24). The study protocol was approved by the ethics/conflict of interest committee at the National Center for Geriatrics and Gerontology. Written informed consent was obtained from all participants before participation.

Study design

The registration period was from April 2010 to August 2012. In the present study, WML volume, E/E', left ventricular EF (LVEF) and cognitive functions (MMSE, Logical Memory 1 and 2 of the revised Wechsler Memory Scale test, Trail-Making Test [TMT] [A] and [B], Raven's Colored Progressive Matrices [RCPM], and Geriatric Depression Scale [GDS]) were evaluated within 1 month of enrolment. In addition, blood pressure, body mass index (BMI), pulse wave velocity (PWV), carotid intimal media thickness (IMT), and levels of plasma B-type natriuretic peptide (BNP) and hemoglobin (Hb) A1c were also determined. Tests of cognitive functions were carried out by two clinical psychologists. A total of 82 patients were initially registered, but seven patients were excluded because of atrial fibrillation in three patients, cerebral infarction resulting from a major cerebral artery lesion in one patient, valvular disease (mitral valve stenosis) in one patient and systolic impairment shown by EF < 50% on echocardiography in two patients. The number of participants in the final analysis was therefore 75.

Neuroimaging studies

Brain MRI was used for the quantification of WML volume. A standard series of axial T1-weighted (repetition time [TR], 485 ms; echo time [TE], 11 ms), T2-weighted (TR, 3800 ms; TE, 93 ms) and fluid-attenuated inversion recovery (TR, 8000 ms; TE, 101 ms; inversion time, 2500 ms; matrix, 256 × 256) MRI sequences were carried out using a 1.5-T MR system (Siemens Avanto, Muenchen, Germany). Scans were carried out parallel with the anterior commissure-posterior commissure line, with 6-mm thick slices and an interslice gap of 1.2 mm. MRI data were processed to measure total volumes of the intracranial space, parenchyma, ventricles and WML using a fully automatic segmentation program (Software for Neuro-Image Processing in Experimental Research: SNIPER) developed in the Department of Radiology at Leiden University Medical Center (Leiden, the Netherlands). Detailed procedures for MRI post-processing using SNIPER have been described elsewhere.[13]

Echocardiographic examination

Echocardiography was carried out using an ACUSON SC2000 volume imaging ultrasound system (Siemens Medical Solutions, Tokyo, Japan). LVEF was estimated using Teichholz's method. To determine E/E', pulse wave tissue Doppler echocardiography was applied to the apical four-chamber view at both septal and lateral mitral annuli by two experienced cardiosonographers.[14]

Criteria for analysis

Hypertensive patients were defined as patients already undergoing regular antihypertensive treatment, patients with blood pressure in the examination room exceeding 140/90 mmHg on two separate occasions during outpatient visits or patients with mean blood pressure exceeding 135/85 mmHg on 24-h ambulatory blood pressure monitoring. Diabetic patients were defined as patients who were already undergoing regular treatment for diabetes or with HbA1c ≥ 6.5%.

Statistical analysis

Values are shown as mean ± standard deviation unless otherwise stated. When patients were stratified

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according to E/E', differences among the three groups were analyzed using analysis of variance, followed by the Tukey–Kramer multiple comparison test or Kruskal–Wallis multiple comparison test, and differences among the two groups were analyzed using χ^2-square test or Fisher's exact test, Student's *t*-test and Welch's test. Values of $P < 0.05$ were considered significant. Data were analyzed using SPSS version 17.0 software (SPSS, Chicago, IL, USA).

Results

Three-group comparison of age, sex, hypertension or diabetes based on E/E' ratio

The ratio between early diastolic mitral inflow (E) and early diastolic mitral annular tissue velocity (E') as estimated by echocardiography has recently been identified as a useful indicator of the severity of LV diastolic dysfunction. E/E' has been shown to reflect both diastolic LV stiffness and diastolic LV filling pressure. More precisely, E/E' > 8 has been identified as a marker of elevated diastolic LV stiffness,[15] whereas E/E' ≥ 15 also shows a diastolic LV filling pressure is definitely elevated.[16] For classification based on the severity of LV diastolic dysfunction, we used E/E' from echocardiography and classified participants into three groups: E/E' ≤ 8 (Low E/E'); 8 < E/E' < 15 (Middle E/E'); and E/E' ≥ 15 (High E/E'). This classification was established based on the European Heart Journal Guideline 2007.[17] Differences in background factors between the three groups are presented in Table 1. Importantly, no significant differences were detected between groups in terms of age, sex, hypertension or diabetes.

Cerebral WML volume increases with severity of LV diastolic dysfunction

In the present study, WML were classified as periventricular WML (PVL) and deep WML (DWML). Table 2 summarizes cerebral WML volume, PVL volume and DWML volume. All cerebral WML were found to increase in volume as E/E' increased. Although no significant differences were seen between Low E/E' and Middle E/E', significant differences were found in comparisons between each of these groups and High E/E'. Then, we carried out linear regression analysis to clarify the relationship between WML volume and E/E' ratio. As a result, we confirmed a positive association between WML volume and E/E' ratio ($r = 0.377$, $P = 0.0009$) (Fig. 1).

Table 1 Patients' characteristics

	Total	E/E' ≤ 8	8 < E/E' < 15	15 ≤ E/E'
n	75	10	51	14
Males	36	8	22	6
Age (years)	69.3 ± 3.4	69.1 ± 2.1	69.2 ± 3.6	69.6 ± 3.3
Hypertension (*n*)	55	6	37	12
Diabetes mellitus (*n*)	10	0	6	4
IMT (mm)	0.67 ± 0.11	0.65 ± 0.11	0.66 ± 0.10	0.73 ± 0.15
PWV (cm/s)	1816 ± 307	1665 ± 267	1835 ± 308	1853 ± 319
BMI (kg/m^2)	23.4 ± 3.9	22.3 ± 2.3	23.2 ± 3.4	24.6 ± 3.9
Echocardiographic data				
EF (%)	65.7 ± 4.3	64.2 ± 1.6	65.6 ± 4.8	67.1 ± 3.4
E/E'	11.8 ± 3.5	7.1 ± 0.4*	11.1 ± 1.9*	17.4 ± 2.2*
BNP (pg/mL)	29.9 ± 36.0	23.1 ± 20.2	26.2 ± 29.7	47.7 ± 57.1

*$P < 0.01$. BMI, body mass index; BNP, plasma B-type natriuretic peptide; E/E', ratio of early diastolic mitral inflow (E) to early diastolic mitral annular tissue velocity (E'); EF, ejection fraction; IMT, carotid intimal media thickness; PWV, pulse wave velocity.

Table 2 The relationship between LV diastolic dysfunction and lesion volume

	Total	E/E' ≤ 8	8 < E/E' < 15	15 ≤ E/E'
WML (mL)	6.4 ± 7.6	3.6 ± 3.0*	5.4 ± 6.5*	12.1 ± 11.0*
PVL (mL)	5.6 ± 6.8	3.4 ± 2.7*	4.8 ± 5.8*	10.2 ± 10.1*
DWML (mL)	0.8 ± 1.4	0.2 ± 0.3*	0.6 ± 1.0*	1.9 ± 2.2*

*$P < 0.05$. DWML, deep subcortical white matter lesions; PVL, periventricular white matter lesions; WML, white matter lesions.

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Relationship between LV diastolic dysfunction and brain function

As shown in Table 3, although performance of brain functional tests worsened with the severity of LV diastolic dysfunction, no significant differences were seen among the three groups except for GDS. We then re-divided the studied population into two groups based on the presence of LV diastolic dysfunction ($E/E' \leq 8$ and $8 < E/E'$) and re-analyzed. As results, significant differences were identified between the severity of LV diastolic dysfunction and MMSE (29.0 ± 0.9, 28.2 ± 2.0, respectively; $P = 0.040$) or GDS (1.2 ± 0.9, 3.6 ± 2.6, respectively; $P < 0.001$), and associated tendencies were also found between severity of LV diastolic dysfunction and TMT (B) data (96.5 ± 27.8, 119.6 ± 48.9, respectively; $P = 0.151$), TMT (B–A) data (51.9 ± 26.7, 71.6 ± 41.5, respectively; $P = 0.151$) and RCPM (29.7 ± 2.4, 28.0 ± 4.6, respectively; $P = 0.091$). No significant differences were detected between the two groups in terms of age, sex, hypertension or diabetes. In addition, we carried out regression analysis between WML volume and scores from brain function tests, but no significant relationships were observed (data not shown).

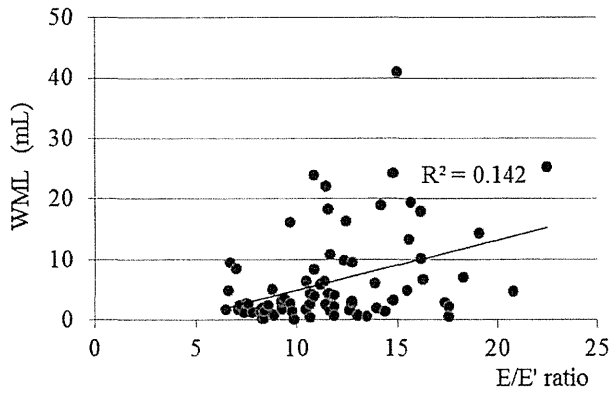

Figure 1 Linear regression analysis of cerebral white matter lesions (WML volume and the ratio between early diastolic mitral inflow and early diastolic mitral annular tissue velocity (E/E'). A positive correlation is apparent between WML volume and E/E' ratio ($r = 0.377$, $P = 0.0009$).

Discussion

The present study investigated the relationship between severity of LV diastolic dysfunction and the volume of WML in elderly patients, showing a clear association between the two. Importantly, the present results were obtained from analyses of elderly patients with neither ischemic heart disease nor symptomatic stroke. In addition, the present results were obtained from analyses of groups showing no significant differences statistically in age, hypertension or diabetes mellitus, all of which represent common risk factors for the development and progression of both WML[18] and LV diastolic dysfunction. Considering this background, there might be a mechanism that directly connects WML and LV diastolic dysfunction. Further prospective investigations are required to clarify it.

Theoretically, LV diastolic dysfunction causes systemic hypoperfusion as a result of the reduction of LV stroke volume, which is caused by decreased LV end-diastolic volume and decreased LV inflow from the left atrium as a result of the increased LV stiffness. LV diastolic dysfunction with normal contraction thus also causes systemic hypoperfusion the same as LV systolic dysfunction. Considering the common effect to systemic perfusion of LV systolic and diastolic dysfunction, the relationships between brain abnormalities and LV systolic or diastolic dysfunction might be therefore expected to be the same.

The relationship between LV systolic dysfunction and brain abnormalities has been discussed, but remains unclear. The present findings suggest that the severity of LV diastolic dysfunction is associated with WML development and progression. Such results are consistent with previous studies that investigated

Table 3 The relationship between LV diastolic dysfunction and brain function

	Total	$E/E' \leq 8$	$8 < E/E' < 15$	$15 \leq E/E'$
MMSE	28.3 ± 1.9	29.0 ± 0.9	28.2 ± 1.8	27.9 ± 2.7
Logical memory (1)	21.4 ± 7.0	22.0 ± 5.2	21.8 ± 6.8	19.0 ± 8.6
Logical memory (2)	20.0 ± 7.6	20.8 ± 6.5	20.6 ± 7.4	17.1 ± 9.1
RCPM	28.3 ± 4.4	29.7 ± 2.4	28.4 ± 4.5	26.5 ± 4.7
TMT-A (s)	47.4 ± 14.4	44.6 ± 10.8	47.1 ± 14.8	51.3 ± 15.7
TMT-B (s)	116.3 ± 47.0	96.5 ± 27.8	117.7 ± 48.9	126.6 ± 50.6
TMT(B-A)(s)	69.0 ± 40.2	51.9 ± 26.7	70.6 ± 42.4	75.3 ± 39.0
GDS	3.2 ± 2.6	1.2 ± 0.9*	3.4 ± 2.5*	4.2 ± 3.0*

*$P < 0.01$. GDS, Geriatric Depression Scale; Logical Memory, logical memory in the revised Wechsler Memory Scale test; MMSE, Mini-Mental State Examination; RCPM, Raven's Colored Progressive Matrices; TMT, Trail-Making Test.

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associations between LV systolic dysfunction and WML volume,[9,19] but are inconsistent with the others.[20,21] One of the reasons why the results of previous studies have been controversial could be the study populations investigated. Participants in previous studies have comprised patients with LV systolic dysfunction, and, as a result, a large number of ischemic heart disease patients were included as study participants. Needless to say, ischemic heart disease is known to be associated with a high risk of cerebrovascular complications. Therefore, these patients might have impacted the results of previous studies and prevented consistent results. The present study excluded patients with ischemic heart disease from participating in the study as much as possible, which might have facilitated the identification of a clear association between LV diastolic dysfunction and WML.

The most important, but difficult question is how LV diastolic dysfunction is associated with WML development and progression. We cannot answer this question based only on the results of the present cross-sectional study. However, considering that LV diastolic dysfunction itself reduces systemic perfusion in the same manner as LV systolic dysfunction, systemic hypoperfusion as a result of the progression of LV diastolic dysfunction might impair the system for the autoregulation of cerebral blood flow, disrupt cerebral perfusion, and cause WML development and progression, as previously speculated.[22] Further studies are required to clarify these issues.

It has been postulated that WML are associated with cognitive dysfunction and depressive mood.[23,24] In the present study, we could not show a significant association between severity of LV diastolic dysfunction and cognitive decline in three-group comparisons, whereas a clear association was shown for GDS. When we carried out two-group comparison analysis between $E/E' \leq 8$ and $8 < E/E'$ to test the association of LV diastolic capacity with cognition, a significant difference in global brain function (MMSE) was identified.

In this connection, most previous studies that detected clear associations between WML and cognitive decline comprised a study population of at least 100 participants, including patients with cognitive decline.[25,26] The present sample was thus thought to be relatively small to detect the association between LV diastolic function and cognitive function, even if an association was actually present. Regarding the effect of WML on physical functions or cognition, a "threshold effect" has been suggested.[27–29] Recent studies show that regional distribution of WML, rather than total volume of WML, seems more important to manifest functional implication of WML.[24,30] In addition, WML are known to be one of the risk factors for cognitive impairment, but other factors, such as years of education, medication and smoking status, are also known to affect cognitive function. Other factors might to thus obscure the association between the two diseases in the present study.

We therefore believe that the present results do not preclude an association between the diseases, but rather fail to confirm one. Further detailed and prospective analysis is required to settle this matter.

Previous studies have already shown that increases in WML volume are associated with the development of dementia and stroke, and with increased mortality. At present, no effective treatments for WML have been established. Suppression of the development and progression of WML is therefore crucial. From this perspective, the finding that the progress of LV diastolic dysfunction is associated with the development and progression of WML is important. Further investigations are required to clarify whether there is a direct association between LV diastolic dysfunction and WML.

The number of participants in the present study was small, at just 75. Therefore, even though an association between WML volume and severity of LV diastolic dysfunction was able to be confirmed, we could not identify an association between cognitive function and LV diastolic function or WML volume. In addition, because the present study represented a cross-sectional analysis, the mechanism by which WML develop in patients with LV diastolic dysfunction could not be clarified. Further investigation with a larger number of patients is therefore warranted.

The present results suggest the possibility that LV diastolic dysfunction is associated with the development and progression of WML. Future studies will need to investigate in a greater number of patients whether LV diastolic dysfunction directly associates with the progression of WML.

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Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Factors associated with increased caregivers' burden in several cognitive stages of Alzheimer's disease

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Aim: To investigate factors associated with caregiver burden (CB) in persons caring for older adults with various cognitive stages of Alzheimer's disease (AD).

Methods: Participants were 1127 outpatients and their caregivers. Participants comprised 120 older adults with normal cognition (NC), 126 with amnestic mild cognitive impairment (aMCI) and 881 with AD. AD patients were subclassified into four groups by Mini-Mental State Examination (MMSE) score: AD29–24 (n = 117), AD23–18 (n = 423), AD17–12 (n = 254) and AD11–0 (n = 87). Participants and their caregivers underwent comprehensive geriatric assessment batteries including Zarit Burden Interview (ZBI) Barthel Index, Lawton Index, Dementia Behavior Disturbance Scale (DBD) to evaluate CB, Instrumental and Basic Activity of Daily Living (IADL/BADL), and Behavioral and Psychological Symptoms of Dementia (BPSD). The comorbidity of geriatric syndrome and the living situation of the patient/caregiver were also assessed.

Results: ZBI score was higher in patients with lower MMSE score. Multivariate regression analysis identified that DBD was consistently associated with CB in all patients; symptoms related to memory deficit were related to CB in aMCI; differential IADL, such as inability to use a telephone, use transportation, manage finances, shop, cook and take responsibility for own medication, were related to CB in AD29–24, AD23–18 and AD17–12, and geriatric syndrome including falls and motor disturbance, sleep problems, urinary incontinence, and fatigue was related to CB in AD23–18 and AD17–12.

Conclusions: Multiple factors including BPSD, impaired life function and geriatric syndrome were cognitive stage-dependently associated with CB. Preventive treatment of BPSD and comorbidity, and effective assistance for IADL deficits could contribute to alleviation of CB. **Geriatr Gerontol Int 2014; ••: ••–••.**

Keywords: activity of daily living, Alzheimer's disease, behavioral and psychological symptoms of dementia, caregivers' burden, geriatric syndrome.

Introduction

Dementia is characterized by cognitive deficit and a loss of functional independence.[1] Because of the growing dependency associated with progression of dementia, caregivers bear an ever increasing burden of care and management of patients with dementia. As caregiving for patients with dementia is physically, emotionally and financially demanding, the burden has significant implications for caregivers' physical and mental health, personal and social life, and overall well being.[2–8] Furthermore, it is assumed that the chronic mental and physical burden on caregivers could result in reduced quality of care for patients with dementia, which might worsen the patients' health status, and cause behavioral and psychological symptoms of dementia (BPSD).

There is wide variation in the psychological symptoms and physical complications of dementia, depending on the severity of dementia, the population and differences among several diseases manifesting dementia.[9,10] Multifactorial mechanisms might underlie the increase in caregiver burden (CB).[11,12] However, little is known about factors associated with CB according to the progression of dementia. To date, comprehensive research has not been well carried out to clarify such factors in demented individuals. Therefore, in the present study, we aimed to identify the factors associated with CB according to the stage of cognitive decline

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in older adults with Alzheimer's disease (AD), which is the causative disease in more than 50% of all dementia. Previous studies showed that BPSD of individuals with dementia is one of the largest factors contributing to CB,[11,12] and individuals with AD require increased assistance in daily living as dementia progresses. Furthermore, patients might suffer from various comorbid conditions, which impose an additional burden on caregivers. We hypothesized that BPSD and activities of daily living (ADL), as well as comorbid diseases of geriatric syndrome, could be candidates for factors associated with CB. Understanding the factors associated with CB in each stage of cognitive decline should be informative not only for caregivers in order to alleviate CB, but also for medical and healthcare professionals for effective dementia treatment in daily practice.

Methods

Study participants

The study protocol was approved by the Ethical Review Board of Japan's National Center for Geriatrics and Gerontology (NCGG), and the patients and their caregivers provided informed consent before participation in the study. The participants were 1127 outpatients (362 male, 799 female; aged 78.5 ± 6.2 years) and their families, who attended the Medical Center for Dementia at Japan's NCGG during the period from September 2010 to August 2012. They were composed of 120 with normal cognition (NC), 126 with amnestic mild cognitive impairment (aMCI) and 881 with AD. NC, who visited NCGG with suspicion of dementia, were diagnosed as having normal cognitive function. aMCI was diagnosed based on the criteria defined by Petersen *et al.*,[13] and AD was diagnosed as probable AD or possible AD based on the criteria published by the U.S. National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association.[14] The AD patients were subclassified into four groups by their total scores of the Mini-Mental State Examination (MMSE):[15] AD29–24 (MMSE score range 24–29; $n = 117$), AD23–18 (18–23; $n = 423$), AD17–12 (12–17; $n = 254$) and AD11–0 (0–11; $n = 87$). Patients with severe conditions, such as cardiac failure, renal disorder, liver dysfunction, neurological and psychiatric disorders such as depression, and alcohol abuse were excluded from the present study.

Assessment

On the first day when study participants attended the Medical Center for Dementia for consultation on the disease causing dementia, comprehensive geriatric assessment batteries were carried out to evaluate disability, mood and cognitive function of the patients, and to measure CB of the caregivers. Global cognitive status was tested using the MMSE, and depressive mood was estimated by the self-rated Geriatric Depression Scale (GDS; 15 items).[16] The patients' basic/instrumental activities of daily living (BADL/IADL) were assessed by the Barthel Index (BI)[17] and Lawton Index (LI),[18] respectively. LI is composed of five questions for men (telephone use, shopping, transportation, medication, handling finances) and three additional questions for women (food preparation, housekeeping, laundry). BPSD were assessed using the Dementia Behavior Disturbance Scale (DBD),[19] and CB using the Zarit Burden Interview (ZBI).[20]

Comorbid conditions of geriatric syndrome and the living situation of the patient/caregiver were assessed by questionnaires administered to the patients and their caregivers. The following were assessed as comorbid conditions: presence or absence of geriatric syndrome symptoms including hearing disturbance, visual disturbance, pollakiuria, lumbago, falls, leg pain, diarrhea/constipation, fatigue, cough/sputum, edema, upper limb pain, itching, sleep disturbance, headache, ringing in the ear, numbness, palsy, palpitation, dysphasia, speech disturbance, urinary disturbance, back pain, tremor, chest pain, dyspnea, mastication disorder, syncope, abdominal pain, nausea/vomiting, fever and decubitus ulcer.

Statistical analysis

Analysis of covariance (ANCOVA) with covariates of age and sex was applied to compare six groups of NC, aMCI, AD29–24, AD23–18, AD17–12 and AD11–0, followed by post-hoc analysis (Scheffe) to detect statistically significant differences.

Factor analysis (principal factor method and promax rotation) was carried out on 28 subitems of DBD in patients with AD. Items with a factor loading of <0.4 were deleted, and six factors were extracted as shown in Table 1. These factors were interpreted as "Behavioral disturbance" (factor 1), "Verbal aggressiveness" (factor 2), "Memory impairment" (factor 3), "Motor aggressiveness" (factor 4), "Incontinence" (factor 5) and "Apathy" (factor 6).

The factors associated with CB were analyzed using multiple linear regression analyses in six groups. The dependent variables were summed scores of ZBI, and the candidates for associated factors were total scores of BI, LI, DBD, number of conditions of geriatric syndrome with age and sex, which were entered in a stepwise fashion into multiple linear regression analyses. For analysis of DBD, we entered factors 1–6 identified by factor analysis as independent variables. We carried out similar analyses for BI, LI and comorbid conditions of geriatric syndrome, but symptoms whose frequency were 10% or lower were excluded from the analysis.

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Table 1 Factor loading for Dementia Behavior Disturbance Scale subitems in Alzheimer's disease

	Factor 1 Behavior disturbance	Factor 2 Verbal aggressiveness	Factor 3 Memory impairment	Factor 4 Motor aggressiveness	Factor 5 Incontinence	Factor 6 Apathy
21. Wanders aimlessly in or outside house during day	**1.006**	−0.105	−0.072	−0.012	0.081	−0.213
17. Gets lost outside	**0.790**	−0.109	−0.035	0.085	−0.049	−0.002
07. Paces up and down	**0.786**	0.012	0.078	−0.102	−0.015	−0.075
16. Wanders in house at night	**0.784**	−0.002	−0.069	0.079	−0.063	0.019
14. Moves arms or legs in restless or agitated way	**0.494**	0.305	−0.144	−0.041	0.061	0.022
04. Wakes up at night for no obvious reason	**0.471**	0.023	−0.006	0.027	−0.013	0.267
08. Repeats the same action over and over	0.395	0.188	0.193	−0.122	−0.055	0.044
09. Is verbally abusive, swears	−0.130	**0.897**	0.007	−0.029	−0.033	0.016
05. Makes unwarranted accusations	−0.019	**0.690**	0.070	−0.006	−0.017	−0.004
23. Screams for no reason	0.059	**0.604**	−0.136	0.267	−0.090	−0.050
11. Cries or laughs inappropriately	0.199	**0.484**	0.042	−0.062	0.044	−0.024
12. Refuses to be helped with personal care	0.128	0.290	0.186	0.041	0.052	0.020
19. Overeats	0.098	0.245	−0.015	−0.076	0.150	0.239
02. Loses, misplaces, or hides things	−0.111	0.024	**0.877**	0.030	0.009	−0.167
01. Asks the same question repeatedly	−0.036	−0.060	**0.515**	0.051	−0.090	0.043
13. Hoards things for no obvious reason	0.067	0.099	**0.452**	−0.048	−0.049	0.109
15. Empties drawers or closets	0.255	0.091	0.294	0.027	0.077	−0.054
28. Throws food	0.018	−0.114	0.048	**0.741**	0.137	−0.069
26. Destroys property or clothing	0.015	0.034	0.024	**0.733**	−0.172	0.167
22. Makes physical attacks (hits, bites, scratches, kicks, spits)	−0.051	0.301	0.018	**0.466**	0.197	−0.149
27. Is incontinent of feces	0.024	−0.077	−0.016	0.116	**0.709**	0.007
20. Is incontinent of urine	−0.033	0.031	−0.077	−0.067	**0.689**	0.184
06. Sleeps excessively during day	−0.173	0.032	−0.124	−0.003	0.081	**0.718**
03. Lack of interest in daily activities	0.068	−0.109	0.152	0.007	0.056	**0.490**
10. Dresses inappropriately	0.177	−0.094	0.264	0.047	0.117	0.302
18. Refuses to eat	0.198	0.103	0.006	0.153	−0.087	0.217

Factor analysis: principal factor method and promax rotation. Items with significant loading (≥0.4) are shown in bold.

Interfactor correlations

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
Factor 1	1.000					
Factor 2	0.646	1.000				
Factor 3	0.563	0.544	1.000			
Factor 4	0.305	0.447	0.096	1.000		
Factor 5	0.472	0.429	0.307	0.215	1.000	
Factor 6	0.578	0.514	0.549	0.197	0.500	1.000

All analyses were carried out using the Japanese version of SPSS for Windows version 19.0 (IBM Corporation, Armonk, NY, USA), and statistical significance was set as $P < 0.05$.

Results

Demographics

The clinical profiles of the patients and their social conditions are shown in Table 2. Total scores of DBD and ZBI increased (indicating worsening), and those of BI and LI decreased (indicating worsening) in patients with worse performance of the MMSE. Social conditions were not different among the six groups. The frequencies of DBD subitems and conditions of the geriatric syndrome are shown in Supporting Information Figs S1 and S2, respectively.

Factors associated with ZBI

First, we carried out comprehensive analysis to identify the impact of BPSD, life function and number of conditions of geriatric syndrome on ZBI (Table 3). Because there was no difference in ZBI score according to the presence or absence of family members at their house, subsequent regression analyses to investigate the association with ZBI were adjusted for age and sex. Total score of DBD was consistently associated with ZBI in all groups ($P < 0.001$ for all). LI total score was associated with aMCI and cognitive stages from AD29–24 to AD17–12, whereas total BI score was not. Geriatric syndrome had an effect on ZBI in AD23–18 and AD17–12.

To precisely show which DBD factors contribute to increment of ZBI, we carried out regression analyses using the six DBD factors detected by factor analysis (Table 4). Factor 1 (Behavioral disturbance) was associated with ZBI in all stages of AD. In AD29–24, frequency of #4 (Wakes up at night for no obvious reason) was 24.3%, #7 (Paces up and down) 20.6%, and #14, #16, #17 and #21 < 20%. In AD23–18, the frequency of #4 was 35.8%, #7 26.6% and #14 (Moves arms or legs in a restless or agitated way) 23.7%. In AD17–12 and AD11–0, all subitems of factor 1 were present in more than 30% of cases. Factor 2 (Verbal aggressiveness) was associated with ZBI in aMCI and cognitive stages of AD23–18 and AD17–12. In aMCI, the frequency of #5 (Unwarranted accusations) was 28.4% and of #9 (Verbally abusive, swears) was 28.4%. In AD23–18, the frequency of #5 was 37.2%, #9 37.1% and #11 (Cries or laughs inappropriately) 26.1%. In AD17–12, all subitems of factor 2 were observed at a frequency of 20~42%. Factor 3 (Memory impairment) was associated with ZBI in aMCI. The frequency of #1 (Asks same question repeatedly) was 46.8%, #2 (Loses, misplaces or hides things) 47.8% and #13 (Hoards things for no obvious reason) 30.6%. Factor 4 (Motor aggressiveness) was associated with ZBI in AD29–24 and AD11–0. In AD29–24, the frequency of #26 (Destroys property or clothing) was 13.1%. In AD11–0, the frequency of #22 (Makes physical attacks) was 35.2%, and of #26 and #28 (Throws food) was 23.7%. Factor 5 (Incontinence) was associated with ZBI in AD23–18. The frequency of #20 (Urine) 35.8% and #27 (Feces) was 18.0%. Factor 6 (Apathy) was associated with ZBI in aMCI and all stages of AD except AD11–0. The frequency of #3 (Lack of interest) and #6 (Sleeps excessively during the day) was approximately 50% of patients in all subclasses.

Regarding IADL, impaired function of telephone use, transportation, finance handling and responsibility for own medication were associated with CB in men. In women, transportation, shopping, food preparation, medication and finance were important functions for their caregivers (Table 5). Although BADL was not associated with CB in comprehensive analysis (Table 3), we explored possible factors associated with CB by using subitems of BI. As a result, deficit related to motor disturbance (Climbing stairs) was an associated factor in aMCI, impaired bathing and grooming in AD29–24, and inability to dress in AD23–18, AD17–12 and AD11–0 (Table 5).

Regarding geriatric syndrome, comorbidity-related motor function (Falls and palsy), urinary disturbance, sleep disturbance, and fatigue were associated factors in AD23-18 and AD17-12 (Table 6).

Discussion

The present study clearly showed that ZBI score is higher in patients with more severe cognitive decline, and that multiple factors, including BPSD, impaired life function and geriatric syndrome, are independently associated with CB. A variety of positive and passive BPSD were consistent burden factors in aMCI or all patients with AD. Symptoms related to memory deficit were factors related to CB in aMCI. Differential IADL, such as inability to use a telephone, transportation, finance handling, shopping, cooking and responsibility for own medication, and geriatric syndrome were also associated with CB in individual cognitive groups of AD. As components of geriatric syndrome, falls and motor disturbance, sleep disturbance, urinary incontinence, and fatigue were related to CB in AD. Thus, the present study carried out a comprehensive analysis to clarify the factors for CB in several cognitive stages of AD. This information could be important for caregivers to lessen CB, but also for medical professionals for successful management of AD.

aMCI is characterized by memory disturbance without substantial interference with work, usual social activities or other ADL.[13] Therefore, BPSD related to memory deficit was the prominent factor associated

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Table 2 Clinical profiles and social conditions of study participants

	NC	aMCI	AD29–24	AD23–18	AD17–12	AD11–0	All
n	120	126	117	423	254	87	1127
Sex (male/female)	50/70	44/82	42/75	121/302	67/187	25/62	362/799
Age (years)	73.6 ± 5.7	77.0 ± 5.7[a]	77.7 ± 5.7[a]	78.8 ± 5.8[a]	80.6 ± 5.9[a,b,c,d]	80.6 ± 7.2[a,b,c]	78.5 ± 6.2
Education (years)	11.5 ± 2.6	11.1 ± 2.6	10.8 ± 2.5	10.3 ± 2.6[a]	9.4 ± 2.4[a,b,c,d]	8.6 ± 2.2[a,b,c,d]	10.2 ± 2.6
Comprehensive geriatric assessment batteries							
Mini-Mental State Examination	27.8 ± 2.2	26.0 ± 1.8[a]	25.4 ± 1.5[a]	20.5 ± 1.6[a,b,c]	15.0 ± 1.6[a,b,c,d]	7.8 ± 3.2[a,b,c,d,e]	20.2 ± 5.8
Geriatric Depression Scale	4.1 ± 2.9	4.2 ± 2.7	4.2 ± 2.6	4.4 ± 2.8	4.9 ± 3.2	5.3 ± 2.9	4.5 ± 2.9
Dementia Behavior Disturbance scale	6.4 ± 6.2	8.6 ± 7.2	12.8 ± 8.5[a]	15.6 ± 9.7[a,b]	20.6 ± 13.4[a,b,c,d]	31.8 ± 17.9[a,b,c,d,e]	15.9 ± 12.6
Zarit Burden Interview	9.0 ± 10.5	9.4 ± 8.0	15.7 ± 13.5[a]	20.8 ± 15.2[a,b]	25.5 ± 16.3[a,b,c,d]	32.3 ± 18.8[a,b,c,d,e]	19.8 ± 16.0
Barthel index	99.0 ± 3.9	98.8 ± 4.8	98.2 ± 5.2	96.2 ± 9.0	91.7 ± 14.1[a,b,c,d]	75.9 ± 23.5[a,b,c,d,e]	94.4 ± 12.7
Lawton Index							
Male	4.9 ± 0.6	4.3 ± 1.0	3.7 ± 1.1[a]	3.2 ± 1.4[a,b]	2.6 ± 1.4[a,b,c]	1.2 ± 1.2[a,b,c,d,e]	3.4 ± 1.5
Female	7.7 ± 0.8	7.1 ± 1.4	6.7 ± 1.4[a]	5.7 ± 1.8[a,b,c]	4.3 ± 1.9[a,b,c,d]	2.3 ± 1.9[a,b,c,d,e]	5.5 ± 2.2
Social condition: Living with							
Children (%)	33.0	39.2	31.3	46.1	51.4	51.7	44.1
Spouse (%)	56.5	43.2	53.0	34.1	31.9	25.3	38.2
Others (%)	2.6	2.4	0.8	5.5	2.8	10.3	4.1
None (%)	7.8	15.2	14.8	14.3	13.9	12.6	13.6

The patients were divided into six groups: normal cognition (NC), amnestic mild cognitive impairment (aMCI), Alzheimer's disease (AD) 29–24, AD23–18, AD17–12 and AD11–0 (AD patients were subclassified into four groups by Mini-Mental State Examination score). Data are shown as mean ± SD. [a]$P < 0.05$; comparison versus NC, [b]$P < 0.05$; comparison versus aMCI, [c]$P < 0.05$; comparison versus AD29–24; [d]$P < 0.05$; comparison versus AD23–18, [e]$P < 0.05$, comparison versus AD17–12 (ANCOVA, age- and sex-adjusted, Scheffe).

Table 3 Factors associated with caregiver burden regarding behavioral and psychological symptoms of dementia, instrumental/basic activities of daily living, total number of geriatric syndrome conditions, age, and sex

	NC		aMCI		AD29–24		AD23–18		AD17–12		AD11–0	
	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
DBD total score	0.466	<0.001	0.53	<0.001	0.489	<0.001	0.491	<0.001	0.394	<0.001	0.701	<0.001
Barthel Index total score												
Lawton Index total score	−0.208	0.018			−0.263	0.002	−0.25	<0.001	−0.172	0.007		
No. conditions of geriatric syndrome							0.093	0.017	0.123	0.039		
Age												
Sex (male)							0.082	0.035				

The patients were divided into six groups: normal cognition (NC), amnestic mild cognitive impairment (aMCI), Alzheimer's disease (AD) 29–24, AD23–18, AD17–12 and AD11–0 (AD patients were subclassified into four groups by Mini-Mental State Examination score). Behavioral and psychological symptoms of dementia, and instrumental/basic activities of daily living were evaluated using the Dementia Behavior Disturbance Scale (DBD), Lawton Index, and Barthel Index, respectively. Lawton Index scores were calibrated to a full score of 8 to show the mean of the total participants including men. Dependent variables were summed scores of Zarit Burden Interview, and independent variables were total scores of DBD, Lawton Index, and Barthel Index, and number of conditions of geriatric syndrome, which were entered in a stepwise fashion into multiple linear regression analyses. Standardized β-values and *P*-values are shown.

Table 4 Factors associated with caregiver burden regarding behavioral and psychological symptoms of dementia, age and sex

		NC		aMCI		AD29–24		AD23–18		AD17–12		AD11–0	
		β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
Factor 1	Behavior disturbance					0.238	0.009	0.194	<0.001	0.216	0.001	0.484	<0.001
Factor 2	Verbal aggressiveness			0.471	<0.001			0.328	<0.001	0.26	<0.001		
Factor 3	Memory impairment			0.166	0.029								
Factor 4	Motor aggressiveness					0.211	0.018					0.229	0.022
Factor 5	Incontinence							0.209	<0.001				
Factor 6	Apathy	0.336	<0.001	0.271	<0.001	0.329	<0.001	0.134	0.002	0.168	0.006		
	Age							0.104	0.014				
	Sex (male)							0.105	0.012				

The patients were divided into six groups: normal cognition (NC), amnestic mild cognitive impairment (aMCI), Alzheimer's disease (AD) 29–24, AD23–18, AD17–12 and AD11–0 (AD patients were subclassified into four groups by Mini-Mental State Examination score). Behavioral and psychological symptoms of dementia were evaluated using the Dementia Behavior Disturbance Scale (DBD). Factors associated with care burden were analyzed using multiple linear regression analyses in six groups. Dependent variables were summed scores of Zarit Burden Interview, and dependent variables were factors 1–6 identified by factor analysis, which were entered in a stepwise fashion into multiple linear regression analyses. Standardized β-values and *P*-values are shown.

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Table 5 Factors associated with caregiver burden regarding instrumental/basic activities of daily living, age and sex

	NC		aMCI		AD29–24		AD23–18		AD17–12		AD11–0	
	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
IADL men												
Ability to use telephone	−0.322	0.026	−0.390	0.009	−0.499	0.001					−0.390	0.009
Mode of transportation					−0.290	0.033	−0.300	0.001	−0.263	0.032		
Ability to handle finances							−0.329	<0.001				
Responsibility for own medication									−0.287	0.020		
Age			−0.324	0.028							−0.324	0.028
IADL women												
Mode of transportation	−0.305	0.013					−0.187	0.001	−0.173	0.019		
Shopping			−0.386	0.001	−0.258	0.033						
Food preparation					−0.305	0.012	−0.220	<0.001				
Responsibility for own medication							−0.219	<0.001				
Ability to handle finances							−0.125	0.022	−0.245	0.001	−0.400	<0.001
BADL												
Fecal incontinence	−0.219	0.018										
Transfers (bed to chair and back)	−0.202	0.029										
Climbing stairs			−0.219	0.014								
Bathing					−0.769	<0.001						
Grooming					0.535	0.002						
Urinary incontinence							−0.251	<0.001				
Dressing							−0.196	<0.001	−0.297	<0.001	−0.276	0.011
Age			−0.204	0.023			0.136	0.003				
Gender (male)			0.204	0.023	0.213	0.013						

The patients were divided into six groups: normal cognition (NC), amnestic mild cognitive impairment (aMCI), Alzheimer's disease (AD) 29–24, AD23–18, AD17–12 and AD11–0 (AD patients were subclassified into four groups by Mini-Mental State Examination score). Instrumental activities of daily living (IADL) were evaluated using the Lawton Index (LI), and basic activities of daily living using the Barthel Index (BI). Dependent variables were summed scores of Zarit Burden Interview, and dependent variables were subitems of LI or BI, which were entered in a stepwise fashion into multiple linear regression analyses. Standardized β-values and *P*-values are shown.

Table 6 Factors associated with caregiver burden regarding presence or absence of comorbid conditions of geriatric syndrome

Geriatric syndrome	NC		aMCI		AD29–24		AD23–18		AD17–12		AD11–0	
	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
Falls					0.190	0.035			0.162	0.008		
Cough/sputum					0.185	0.038						
Diarrhea/constipation					0.209	0.020						
Palsy							0.209	<0.001				
Sleep disturbance							0.119	0.012			0.230	0.035
Urinary disturbance									0.182	0.003		
Fatigue									0.162	0.010		
Ringing in the ear											0.217	0.047
Age							0.178	<0.001				
Sex (male)					0.243	0.007	0.133	0.004				

The patients were divided into six groups: normal cognition (NC), amnestic mild cognitive impairment (aMCI), Alzheimer's disease (AD) 29–24, AD23–18, AD17–12 and AD11–0 (AD patients were subclassified into four groups by Mini-Mental State Examination score). Dependent variables were summed scores of Zarit Burden Interview, and dependent variables were comorbid general symptoms (presence or absence), which were entered in a stepwise fashion into multiple linear regression analyses. Standardized β-values and *P*-values are shown.

with CB. At the same time, Verbal aggressiveness, such as unwarranted accusations and swearing, and Apathy were other prominent factors associated with CB. Individuals with aMCI might tend to be easily upset, with a lack of control over their impulses when their errors are pointed out, as they might feel distressed by difficulty coping with things they had previously been able to do easily, because of cognitive decline. In contrast, awareness of cognitive decline might exert influences on negative symptoms including apathy, as patients tend to lose motivation as it gradually becomes difficult for them to maintain social interaction, enjoy hobbies and even deal with daily activities.

Although total LI score was not changed in our patients with aMCI (Table 2), recent research has shown that individuals with aMCI have slight functional impairment.[21] Among IADL, functions related to social roles and engagements deteriorated first, followed by those related to domestic roles, and finally those related to personal tasks.[22] Deficits in telephone use in men and shopping in women could be candidate factors for CB. It seems likely that the inability to use a telephone disturbs the family caregivers' social life through miscommunication, and impairment of shopping has to be supported by other family members.[23]

In cognitive stage of AD29–24, positive and passive symptoms of BPSD and impaired IADL were prominent in CB. Motor aggressiveness including destructive behavior was a burden factor. In AD, aggressiveness is one of the most frequent BPSD, with a prevalence of over 70% in AD,[24] and aggressiveness can be a single determinant of caregiver burden and early institutionalization.[25–28] Behavior disturbance, such as Waking up at night and Pacing up and down, were also factors associated with CB. Mobility of an AD patient might increase CB, as such patients require extra attention and supervision, which might in turn cause a more stressful situation for caregivers.[29] Apathy, a syndrome of decreased initiation and motivation, is one of the most common BPSD, with a prevalence of over 70% in AD.[30] In the course of AD progression, apathy becomes more severe as degeneration of frontosubcortical circuits develops.[31] It is also problematic that apathy is associated with deterioration of ADL because of the patient's indolence and inactivation of goal-directed cognitive activity, which increases the workload and stress of their caregivers.[32]

Regarding IADL, in addition to factors related to social roles (telephone use and transportation in men) and those related to domestic roles (shopping and food preparation in women), those related to personal tasks were associated with CB in this stage. Deficit in using transport might trigger withdrawal and accelerate passiveness. Regarding BADL, impaired grooming and bathing could contribute to CB.

In stage of AD23–18, BPSD, IADL and geriatric syndrome were associated with CB. Verbal aggressiveness and Behavior disturbance, as well as Apathy, were important factors. Daytime sleepiness and comorbidity of sleep disturbance were associated with CB, both of which could have a severe negative impact on the physical and mental health of both patients and caregivers. Day–night reversal and sleep disturbance might trigger BPSD, such as agitation, irritability and apathy, resulting in the breakdown of community-based care. Furthermore, incontinence (mostly urinary incontinence) was also associated with CB, although the prevalence of urinary incontinence in this stage was 15.0%.

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