role in the development of muscle loss, leading to frailty in elderly individuals.[44,45] It seems likely that diabetic patients with higher HbA1c are more prone to have muscle weakness and impaired life function, compared with those in patients with HbA1c <7.0%.

Apo E4 carriage is the strongest genetic risk factor for AD so far identified. It has been reported that the Apo E4 allele is highly prevalent among individuals with AD, with 64% of all patients with sporadic AD carrying at least one copy of the Apo E4 allele.[46] In contrast, the presence of an AD pattern on SPECT has 87% sensitivity and 90% specificity for discriminating AD from other dementias.[47] The lowered incidence of Apo E4 carriage and AD-pattern in diabetic patients with HbA1c <7% implies the possible involvement of non-AD dementia disorders. It should be noted that subcortical WML were unchanged in this group of diabetic patients.

In this respect, it is interesting to note the report of Fukazawa *et al.* where the frequency of Apo E4 carriers was 30~40% in a subgroup of diabetic patients with AD.[48] As for the pathological background, age-associated tauopathies, such as argyrophilic grain disease (AGD) and neurofibrillary tangle-predominant dementia, have been suggested. AGD is characterized by progressive amnesia, with other cognitive functions being relatively spared.[49] Because there are no specific criteria for the clinical diagnosis of AGD, it is still difficult to discriminate AGD from AD.[50,51] The metabolic effects of diabetes and invisible microinfarctions could affect cognitive function in some subtypes of dementia in diabetic older adults.[48]

To date, several organizations for the management of diabetes in the USA, Europe, Canada and Japan have introduced their guidelines for the treatment of older diabetes patients.[52–55] These guidelines share the concept that glycemic targets should be determined individually, with a targeted range of 6.5~7.5% for HbA1c in robust diabetic older adults, versus 7.5~8.5% for HbA1c in frail older adults. However, there is still no convincing data on which to base a target for glycemic control to maintain brain function in older adults, particularly for individuals with dementia. In this respect, the present study shows that patients in the lower HbA1c group had fewer BPSD. A positive correlation of BPSD with HbA1c was shown for inappropriate dressing, hoarding and urinary incontinence. Conversely, the present results showed that diabetic participants with mild AD had several properties of physical frailty and ADL impairment, and suggested that diabetic patients with more advanced stages of dementia should be treated less stringently, if we consider the guidelines described here. To address these controversies, prospective studies will be required to clarify the glycemic control levels for prevention of physical and psychological complications of dementia in diabetic older adults.

The present study had several limitations. It was a cross-sectional study, and therefore no causality can be inferred between HbA1c and the several clinical manifestations studied. Identification of non-AD dementia disorders in diabetic patients with HbA1c <7.0% should be investigated in future. Second, the impact of hypoglycemia on brain function was not directly examined. Because hypoglycemic episodes are often atypical or absent in older adults, it is difficult to obtain reliable information on hypoglycemia from patients with dementia and their caregivers.[56] We hypothesize that hypoglycemic episodes might occur more frequently in diabetic patients with HbA1c <7.0%, because all diabetic participants were receiving antihyperglycemic agents and/or insulin. However, fewer clinical problems were observed in patients with lower HbA1c.

Based on the present findings, it can be stated conclusively that there are subtypes of diabetic patients with AD from the viewpoint of clinical features and brain pathophysiology. Physical and psychological complications of dementia are largely dependent on glucose control levels. Although these distinctions require further corroboration, it seems clear that a comprehensive approach to diabetes and dementia will be needed in order to achieve reasonable control in older diabetic patients with AD.

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Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Effect of cerumen impaction on hearing and cognitive functions in Japanese older adults with cognitive impairment

Saiko Sugiura,[1] Minori Yasue,[1] Takashi Sakurai,[2] Chieko Sumigaki,[2] Yasue Uchida,[1,3] Tsutomu Nakashima[4] and Kenji Toba[5]

[1]Department of Otorhinolaryngology, [2]Center for Comprehensive Care and Research on Memory Disorders, National Institute for Longevity Science, [5]National Institute for Longevity Science, National Center for Geriatrics and Gerontology, Obu, [3]Department of Otorhinolaryngology, Aichi Medical University, Nagakute, and [4]Department of Otorhinolaryngology, Graduate School of Medicine, Nagoya University, Nagoya, Japan

Aim: To assess the effect of cerumen impaction and its removal on hearing ability and cognitive function in elderly patients with memory disorders in Japan.

Methods: Pure tone audiometry (PTA) and the Mini-Mental State Examination (MMSE) were administered to participants before and after cerumen removal. Participants who had cerumen impaction in the better-hearing ear comprised the case group; the control group consisted of participants who either did not have cerumen impaction or had it in the worse hearing ear. Hearing and cognition changes were compared between the groups after cerumen removal.

Results: A total of 55 patients who completed all examinations were assigned to the case group (29 patients) or the control group (26 patients). The average hearing change was 4.6 ± 7.4 in the case group and 0.9 ± 0.9 in the control group ($P = 0.029$). The average change in MMSE score was 0.7 ± 2.5 in the case group and −1.0 ± 4.1 in the control group ($P = 0.068$). The case group showed a significant improvement in MMSE scores after age adjustment compared with the control group ($P = 0.049$).

Conclusion: Hearing improved significantly in the case group relative to controls after cerumen removal. A significant cognitive improvement in the case group relative to controls was additionally observed after cerumen removal with age adjustment. Thus, the present results suggest routine ear canal examinations might benefit elderly individuals with memory disorders. **Geriatr Gerontol Int 2014; 14 (Suppl. 2): 56–61.**

Keywords: cognitive impairment, dementia, hearing impairment, Mini-Mental State Examination, pure tone audiometry.

Introduction

Cerumen is a complex of ceruminous and sebaceous gland secretions, and various other substances in the ear canal. Dry and wet variations of cerumen are found in humans, and the presence of either is different among the ethnic groups.[1] The wet variation is present in over 90% of white and black people. A combination of wet and dry variations is seen in populations of certain parts of the Middle East and Southeast Asia. The dry variation is major in North China, Korea and Japan, and is present in approximately 70–80% of Japanese people.

Cerumen impaction is more common in children, the elderly and individuals with an intellectual disability.[1] Indeed, the prevalence of cerumen impaction appears to increase with age in adults; in the geriatric population (those aged 65 years and older), the incidence of cerumen impaction is reportedly 19–34%.[2–4] Furthermore, studies have shown that people with an intellectual disability have a higher prevalence (24–25%) of cerumen impaction, regardless of age.[5,6] Cerumen impaction is also more likely to occur in people with wet type cerumen.[1] Cerumen impaction leads to itching, pain, hearing loss, tinnitus, vertigo and choronic otitis externa. Hearing loss caused by cerumen impaction is up to 40 dB.[7] The prevention of hearing loss is advantageous, because hearing loss has been implicated as an independent risk factor for cognitive impairment and

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Correspondence: Dr Saiko Sugiura MD, Department of Otorhinolaryngology, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka, Obu, Aichi 474-8511, Japan. Email: saikos@ncgg.go.jp

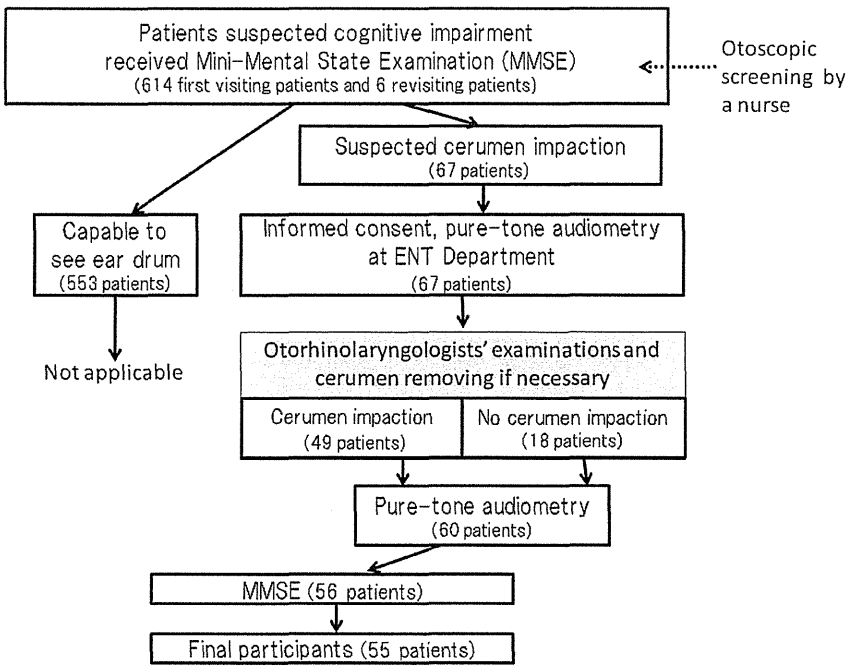

Figure 1 Study protocol.

dementia.[8,9] Moore *et al.* studied the influence of cerumen impaction clearance on Mini-Mental State Examination (MMSE) performance.[10] In their study, 65.5% of the participants had cerumen in at least one ear, and hearing and the MMSE score improved significantly in participants with impacted cerumen after cerumen removal. In an earlier study, we reported that cerumen impaction of the better-hearing ear (BHE) was observed in 10.7% of community-dwelling Japanese older adults aged older than 60 years.[11] Cerumen was significantly associated with poorer hearing and a lower MMSE score.

The aim of the present study was to investigate the potential contribution of cerumen impaction and cerumen removal on hearing and cognitive function in Japanese patients with memory disorder.

Methods

Participants

The participants were 67 patients (28 males, 39 females; mean age 81.7 ± 5.6 years) who visited the Center for Comprehensive Care and Research on Memory Disorders (CCCRMD), National Institute for Longevity Science, National Center for Geriatrics and Gerontology between 9 July to 30 November in 2012. The study protocol was approved in advance by the Committee of the Ethics of Human Research of the National Center for Geriatrics and Gerontology (NCGG). The study protocol is shown in Figure 1. The patients who visited the center because of a memory disorder were first asked to complete the MMSE and were then given an otoscopic screening by a nurse. If cerumen impaction was suspected, it was recommended to the patients that they visit the Ear, Nose and Throat (ENT) Department, and detailed information regarding the present study was provided to them at the ENT department. Written informed consent was obtained from each patient who agreed to participate in the study. The initial audiometric test was carried out before evaluation of the ear by otorhinolaryngologists. After the pure tone audiometry (PTA) assessment, the participants were given ear canal examinations by an otorhinolaryngologist and cerumen removal was carried out, if necessary. Regardless of whether significant cerumen impaction was observed, the PTA assessment was administered to participants. The second MMSE was administered weeks to months later at the center. Participants who could not complete the PTA or MMSE were excluded from the present study. Seven participants could not complete the PTA because of poor reproducibility. Four participants refused to complete the second MMSE. One participant was excluded from the study because she began memantine hydrochloride regimen between the first and the second MMSE. Thus, the total number of participants was 55 (25 male, 30 female; mean age 81.3 ± 5.8 years, range 68–93 years). A total of 33 of the participants were not taking medications to treat dementia at any time during the study. The remaining 12 patients were taking medication for memory disorders during the study period (memantine hydrochloride: 2 patients, donepezil hydrochloride: 8 patients, memantine and donepezil: 2 patients); however, these

patients did not begin, end or change medications during the course of the study.

Functional assessment

The MMSE[12] was administered to participants by clinical psychologists both before and after the otological examination. Functional assessment was also administered using the Barthel Index[13] before the otological examination.

The PTA measurement was carried out by a clinical laboratory technician using a diagnostic audiometer (AA-75; RION, Tokyo, Japan) that was calibrated according to Japanese Industrial Standards T 1201. The air-conduction pure tone average of hearing thresholds (AHT) of the right and left ears were calculated as the average of 0.5, 1, 2 and 4 kHz for each ear before and after the otological examination. The BHE was decided by the AHT after cerumen removal.

Ceruman removal was carried out under a microscope using irrigation and suction procedures. Cerumen impaction was diagnosed if the volume of cerumen exceeded one-third of the ear canal.

The MMSE-administering psychologist and the audiometric examiner were uninformed about the presence or absence of cerumen impaction.

A questionnaire assessing participants' frequency of ear cleaning, cerumen type, and incidence of itching within the ear canal was also administered to the participants and their family. Ear cleaning less than once a month was defined as no ear cleaning.

Statistical analysis

The participants who completed the entire process were divided into two groups. The case group consisted of participants who had cerumen impaction in the BHE, whereas the control group included participants who either did not have cerumen impaction both or had it only in the worse hearing ear.

Statistical analyses were carried out using the statistical analysis system (SAS) version 9.3 (SAS Institute, Cary, NC, USA). Unless otherwise stated, all values are presented as the mean ± SD. The χ^2-test for categorical variables and the Student's *t*-test for continuous variables were used to assess differences in characteristics between the two groups. A general linear model for assessment of correlation between changes in MMSE score and changes in the AHT of the BHE was carried out in the case group. Then, a general linear model adjusted by age, sex, baseline MMSE score and changes in the AHT of the BHE was used to assess differences in the changes in MMSE score between the case and control groups. A value of $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the characteristics of participants with and without cerumen impaction. There were no significant differences in age, sex, Barthel Index score, AHT of the BHE, baseline MMSE score or duration of the first and the second MMSE between the two groups. There

Table 1 Participant characteristics and changes in pure tone audiometry and MMSE scores after cerumen removal

	All participants	Cerumen impaction of BHE	No cerumen impaction of BHE	*P*-value†
n	55	29	26	
Age	81.3 ± 5.8	79.9 ± 5.4	82.8 ± 5.8	0.055
Male, *n* (%)	25 (45.5%)	15 (51.7%)	10 (38.5%)	0.324
No ear cleaning, *n* (%)	23 (41.8%)	15 (51.7%)	8 (30.8%)	0.222
Wet type earwax, *n* (%)	14 (25.5%)	7 (24.1%)	7 (26.9%)	0.735
Ear canal itching, *n* (%)	16 (29.1%)	6 (20.7%)	10 (38.5%)	0.274
Baseline AHT of BHE (dB)	42.6 ± 15.5	43.2 ± 15.4	41.9 ± 15.8	0.748
Barthel Index‡	90.4 ± 13.8	89.0 ± 14.4	91.8 ± 13.3	0.483
AHT of BHE after cerumen removal (dB)	39.8 ± 14.1	38.6 ± 12.5	41.0 ± 15.9	0.535
Change in AHT (dB)	2.8 ± 6.4	4.6 ± 7.4	0.9 ± 0.9	0.029
Baseline MMSE score	18.0 ± 6.3	17.6 ± 6.6	18.5 ± 6.0	0.61
MMSE score after cerumen removal	17.9 ± 6.7	18.3 ± 6.8	17.5 ± 6.7	0.657
Change in MMSE score	−0.1 ± 3.4	0.7 ± 2.5	−1.0 ± 4.1	0.068
Time between MMSE (days)	41.0 ± 28.4	43.2 ± 34.2	38.4 ± 19.6	0.549

Data presented as mean ± standard deviation. †The *t*-test for continuous data, χ^2-test for categorical data. ‡One participant in the no cerumen impaction of best hearing ear (BHE) group and two participants in cerumen impaction of BHE group did not have the Barthel Index estimated. AHT, air-conduction pure-tone average of hearing thresholds; MMSE, Mini-Mental State Examination; PTA, pure tone audiometry.

Table 2 Results of the general linear model

Adjustment	Change in MMSE score in case group	Change in MMSE score in control group	*P*-value
	0.7 ± 0.6	−1.0 ± 0.7	0.068
Age	0.8 ± 0.7	−1.1 ± 0.7	0.049
Sex	0.7 ± 0.6	−1.2 ± 0.7	0.05
Baseline MMSE	0.6 ± 0.6	−1.0 ± 0.7	0.079
Changes in AHT of BHE	0.7 ± 0.6	−1.1 ± 0.7	0.065
All of above	0.8 ± 0.7	−1.3 ± 0.7	0.043

Data presented as least mean square ± standard error. AHT, air-conduction pure-tone average of hearing thresholds; BHE, best hearing ear; MMSE, Mini-Mental State Examination.

was a non-significant trend in the case group towards a lower incidence of ear cleaning and ear canal itching. There were no significant differences in the prevalence of wet type cerumen between the case group (24.1%) and the control group (26.9%). Changes in AHT were significantly larger in the case group than in the control group. Differences in MMSE score before and after otorhinolaryngological intervention differed with marginal significance between the case group and control group ($P = 0.068$).

Two participants classified as having severe hearing loss before cerumen removal (an AHT of 70 dB or greater) were reclassified as having moderate hearing loss (an AHT of 40–69d B) after cerumen removal. Two participants classified as having moderate hearing loss before cerumen removal were reclassified as having mild hearing loss (an AHT of less than 40 dB) after cerumen removal. There was a marginal significant correlation between hearing improvement and differences in the MMSE scores ($R^2 = 0.166$, $P = 0.079$).

Table 2 shows the results of the general linear analysis. There was a significant improvement in MMSE score in the case group after cerumen removal compared with the control group, after adjusting for age; however, adjusting for sex, baseline MMSE score or AHT change rendered this improvement non-significant. Nevertheless, a significant effect of BHE cerumen impaction on the change in MMSE score was observable even after the addition of all adjustments. Furthermore, the only measured variables that significantly affected the changes in MMSE scores after cerumen removal was BHE cerumen impaction ($P = 0.043$; age: $P = 0.297$, sex: $P = 0.300$, baseline MMSE score: $P = 0.323$, change of AHT: $P = 0.894$).

Discussion

In the present study, hearing improved significantly in participants who had BTE cerumen impaction after cerumen removal, and a significant cognitive improvement in the case group relative to controls was observed after cerumen removal with age adjustment.

The cognitively impaired older adults are suggested to have high rates of cerumen impaction, because older adults and people with an intellectual disability have been found to show high prevalence rates of this condition.[2–6] Moore *et al.* reported that 65.6% of residents in a skilled nursing facility had cerumen impaction in at least one ear.[10] The reason for a higher prevalence of cerumen impaction in people with an intellectual disability is still unknown. Several possibilities include poor hygiene and anatomical abnormalities of the ear canal, such as stenosis with Down syndrome, were suggested as possible causes. The reason for a higher prevalence of cerumen impaction in older adults is more clearly accounted. As the skin in the ear canal ages, the surface epithelium thins, the subcutaneous tissue atrophies, the ceruminous glands and the sebaceous glands produce less oil, and the hair in the ear canal lengthens.[1] All of these changes inhibit the excretion of cerumen. Furthermore, the tendency of aging ear canal skin to bleed easily renders cerumen removal aversive and consequently less frequent. Previous reports about the prevalence of cerumen impaction have been from countries where the wet variation of cerumen is present in 90% of the population. In Japan, an estimated 70–80% of the population has the dry variation of cerumen. In a previous study, we reported that cerumen impaction of the BHE was suspected in 10.7% of community-dwelling Japanese older adults above the age of 60 years.[11] However, we only examined the ear canal by otoscopy in that previous study, and thus could not confirm the degree of impaction. In the present study, in which we were limited to first-visit patients at the CCCRMD, 7.0% (43 of 614) of participants had cerumen impaction that exceeded one-third of the ear canal. This frequency was quite low compared with Western countries.[2–4,10] The prevalence of wet type

cerumen in the present study was 25.5%, and the incidence of wet cerumen with impaction and wet cerumen without impaction was not significantly different. The cause of a non-significant incidence of wet cerumen impaction in the present study might be due to the low participants. Furthermore, that genetic diagnosis of wet cerumen was not carried out was a limitation of the present study.

Hearing loss has been reported as an independent risk factor for cognitive impairment and dementia.[8,9] Moore *et al.* reported significant improvement of hearing and MMSE score after cerumen removal.[10] Similarly, Oron *et al.* reported a significant difference in participants' Raven's Standard Progressive Matrices Test scores before and after cerumen removal.[14] In the present study, the change in MMSE score during 40 days in the case group was 0.7, whereas the change in MMSE score in the control group was −1.0. Uhlmann *et al.* reported that a decline in MMSE score in hearing impaired senile dementia of the Alzheimer's type was nearly double that of normal hearing patients.[15] The means of AHT of BTE in the participants of the present study were over 40 dB, thus moderate hearing loss might accelerate the decline of MMSE score, whereas the improvement of hearing partially improved the MMSE score during 40 days. It is possible that hearing improvement is directly or indirectly associated with cognitive function. In the present study, the change in AHT showed a marginal association with the change in MMSE score. Thus, the improvement in MMSE score might result from the direct and the indirect effect of hearing, such as stimulation from environmental sounds and improved speech recognition. The medical sequelae of cerumen impaction include tinnitus, a feeling of fullness in the ear, pain, hearing loss, vertigo, cough and external otitis.[1] Elimination of these peripheral symptoms of cerumen impaction might also contribute to cognitive improvement. Further investigations that clarify the effect of ear canal hygiene on hearing and cognitive function for longer period are necessary.

Although the prevalence of cerumen impaction is low in Japan compared with Western countries, cerumen removal can have similar effects on hearing and cognition. Thus, routine ear canal examinations and cleaning could benefit older adults in Japan. Although methods for wet type cerumen removal have been investigated,[16] there is minimal information regarding the removal of dry type cerumen. The use of ear picks sometimes causes severe injury of the ear.[17] It has also been warned that the use of a cotton tip increases the risk of cerumen impaction and otitis externa.[18] Therefore, the development and assessment of effective methods for removal are imperative.

The present study found that 7.0% of new patients with memory disorders had cerumen impaction. Evaluation of hearing after cerumen removal resulted in a statistically significant improvement. Improvement in cognition relative to controls was also significant after adjustment for age. Thus, routine ear canal examinations can benefit older adults with memory disorders.

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Disclosure statement

The authors declare no conflict of interest.

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

Masaki Kamiya,[1,2] Takashi Sakurai,[1] Noriko Ogama,[1] Yohko Maki[3] and Kenji Toba[1]

[1]Center for Comprehensive Care and Research on Memory Disorders, [2]Department of Rehabilitation, National Center for Geriatrics and Gerontology, Obu, and [3]Graduate School of Health Sciences, Gunma University, Gunma, Japan

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; 14 (Suppl. 2): 45–55.**

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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Correspondence: Dr Takashi Sakurai MD PhD, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka-cho, Obu, Aichi 474–8511, Japan. Email: tsakurai@ncgg.go.jp

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.

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

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.

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%.

Caregivers of patients with urinary incontinence have higher levels of stress and depression than those caring for people with other conditions, and incontinence leads to early institutionalization.[33–35]

Regarding IADL, deficits in handling domestic finances and transportation were common factors associated with CB in men and women. It is time-consuming and often stressful for caregivers to take over the financial responsibilities of the household.[29,36] Non-compliance with medication in women would cause caregivers mental stress. Regarding BADL, dressing was a candidate factor for CB in AD patients with more severe cognitive dysfunction. AD patients might often refuse to be helped with personal care including changing their clothes, which causes stress to their caregivers.

In cognitive stage of AD17–12, BPSD, IADL and geriatric syndrome were also associated with CB. BPSD were worse and care burden became more severe. Regarding IADL, caregivers were annoyed with the patients' deficits in their own personal tasks, such as in the use of transportation (in men and women) and in self-medication (men). Deficit in handling finances was still shown to be an associated factor in women. This could have been related to a lack of awareness by patients of a deficit.[36] Patients who are unaware of functional deficits often overestimate their ability and believe they are capable of activities beyond their capabilities, which can cause problems and stress in caregivers. As comorbidity, falls indicate further deterioration of motor function, and fatigue might reflect and accelerate passiveness.

In AD11–0, prominent factors for CB were BPSD, including Motor aggressiveness and Behavior disturbance. The frequency of BPSD related to CB markedly increased at this stage. For instance, agitation is a symptom related to frontal lobe dysfunction, with a prevalence of nearly 50% in AD.[37,38] It can be triggered by physical problems, such as pain and lack of sleep; psychiatric problems, such as anger, aggressiveness, anxiety and depression; environmental stresses, such as noisiness and inadequate temperature; and as a side-effect of medication. Agitation can also be a single determinant of early institutionalization.[25–28]

Although sleep disturbance and ringing in the ears could be associated with CB in this stage, the contribution of geriatric syndrome to CB was not obvious (Table 3). In this connection, it should be noted that participants in the present study were outpatients without serious physical complications. Alternatively, the increment of BPSD might have obscured the role of geriatric syndrome as a burden factor in the analysis with a relatively small number of participants ($n = 87$).

This study clearly indicated that various differential factors were cognitive stage-dependently associated with CB. It should be stressed that the higher prevalence of BPSD, geriatric syndrome and impairment of life function in particular cognitive stages was not always a burden factor. For instance, symptoms of Behavior disturbance in AD29–24 were not as frequent as in AD11–0, but were factors responsible for CB. Urinary incontinence was markedly increased in cognitive stages of AD11–0, but was associated with CB even in AD23–18. It seems likely that caregivers are surprised and embarrassed by their first experience of problematic symptoms of dementia in patients who have moderate cognitive dysfunction. It is therefore important to know and predict these burden factors in advance. Second, even if certain factors showed an association with CB in one cognitive stage, they did not always remain burden factors in subsequent cognitive stages. Different activities of IADL were shown to be burden factors in particular cognitive stages.

The results of the present study suggested that prevention of BPSD and comorbidity of geriatric syndrome is an essential consideration in the management of AD. At the same time, life care support for deteriorated IADL should be considered even for patients belonging to AD29–24. Treatment of BPSD and comorbidity could be beneficial in ameliorating CB, as comorbidity can cause various BPSD, and BPSD increase the risk of geriatric syndrome, such as falls and muscle weakness, and vice versa. It was reported that half of BPSD were caused by comorbidity and medication; in AD, 23% of BPSD are caused by medication, 18.3% by comorbidity and 6.7% by a combination of the two.[39] It is well established that physical rehabilitation is effective for not only the prevention of falls/motor disturbance, but also improvement of mood, apathy and day–night reversal.

Previous studies have shown that individualized educational and support programs for caregivers are effective to ameliorate CB.[40,41] Educational programs should provide prognostic information on the disease of dementia, as well as factors associated with CB. In this respect, the findings of the present study might be informative for caregiver education.

The present study had several limitations. It was a cross-sectional study. A second limitation was selection bias of the study participants, although the participants were composed of a large number of patients consecutively selected in the Medical Center for Dementia at the NCGG. All data were obtained from outpatients, and inpatients suffering from various physical complications, such as recurrent pneumonia and fractures, were not included. Finally, CB is comprised of multidimensional factors including patient factors, such as the severity of disease, premorbid characteristics, and financial and social status, caregiver factors, and other environmental factors, all of which are highly individualized.[42] The present study mainly analyzed burden factors on the patients' side. To clarify the multifactorial mechanisms of CB, more detailed information on

demographics, socioeconomic conditions and use of several care services need to be analyzed. However, our observation provides important information on CB, which might reflect general attitudes of caregivers to demented older adults, when they first attended a medical center for consultation on dementia. Longitudinal follow-up studies of demented older adults with detailed information on CB are required.

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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 Prevalence of Dementia Behavior Disturbance Scale (DBD) subitems in subjects with normal cognition (NC), amnestic Mild cognitive impairment (aMCI) and Alzheimer's disease (AD)29–24, AD23–18, AD17–12, and AD11–0.
Figure S2 Prevalence of symptoms of geriatric syndrome in participants with normal cognition (NC), amnestic mild cognitive impairment (aMCI) and varying stages of Alzheimer's disease (AD).