

Ⅲ．研究成果の刊行に関する一覧表

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書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書 籍 名	出版社名	出版地	出版年	ページ
池田 学	失認, 失行, 失語	樋口輝彦ら編	今日の精神疾患治療指針	医学書院	東京	2016	18-21
橋本 衛、 池田 学	認知症の新しい診断基準について	武田克彦、 村井俊哉	高次脳機能障害の考え方と画像診断	中外医学社	東京	2016	269-279
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橋本 衛	抗認知症薬	橋本洋一郎監修	ブレインナーシング2016夏季増刊号	メディカ出版	大阪	2016	90-95

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Koyama A, Matsushita M, Hashimoto M, Fujise N, Ishikawa T, Tanaka H, Hatada Y, Miyagawa Y, Hotta M, Ikeda M	Mental health among younger and older caregivers of dementia patients.	Psychogeriatrics	17(2)	108-114	2017
Koyama A, Hashimoto M, Tanaka H, Fujise N, Matsushita M, Miyagawa Y, Hatada Y, Fukuhara R, Hasegawa N, Totsukuni S, Matsukuma K, Kawano M, Ikeda M.	Malnutrition in Alzheimer's disease, dementia with Lewy bodies, and frontotemporal lobar degeneration: comparison using serum albumin, total protein, and hemoglobin level.	PLoS One	11(6)	e0157053	2016
Matsushita M, Yatabe Y, Koyama A, Ueno Y, Ijichi D, Ikezaki H, Hashimoto M, Furukawa N, Ikeda M.	Why do people with dementia pretend to know the correct answer? A qualitative study on the behaviour of toritsukuroi to keep up appearances.	Psychogeriatrics	doi: 10.1111/psyg.12553. [Epub ahead of print]		2017

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Ⅳ．研究成果の刊行物・別刷

ORIGINAL ARTICLE

Why do people with dementia pretend to know the correct answer? A qualitative study on the behaviour of *toritsukuroi* to keep up appearances

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Key words: content analysis, dementia, keeping up appearances, shame, symptomatology, *toritsukuroi*.

INTRODUCTION

People often try to suppress negative information and conceal their culpability. The Japanese word *toritsukuroi* is used to describe the glossing over a mistake or problem. The *toritsukuroi* response of a person with dementia is a behaviour intended to preserve appearances or save face in a troubling or confusing situation by saying, for example, 'I'm doing alright' or 'I don't have much difficulty', despite the fact that the person's social life has already been disrupted in a variety of ways. In other instances, some patients attempt to justify a failure on a neuropsychological examination by saying 'I'm not good at writing

Abstract

Background: *Toritsukuroi* is a particular type of behaviour intended to save face or preserve appearances. Clinicians often observe *toritsukuroi* in people with dementia, but current knowledge about this behaviour is based on clinicians' empirical knowledge rather than on observational studies. This study was designed to clarify which behaviours are related to *toritsukuroi* based on neuropsychological examinations.

Methods: The subjects were 91 outpatients with dementia. Verbal responses, with the exceptions of 'I don't know' and erroneous answers, were recorded by certificated clinical psychologists and analyzed by qualitative study procedures. A qualitative study was separately conducted by two researchers to identify themes and types of reactions. The themes found through content analysis were organized and labelled by a senior psychiatrist.

Results: Among the patients, 41.8% verbally responded in way to 'keep up appearances'. Six distinct thematic categories were identified through conventional content analysis: (i) refuting sudden questions; (ii) disclosing trait; (iii) disclosing experience; (iv) demonstrating slight hesitation; (v) appealing to indifference; and (vi) other.

Conclusions: All the responses that we defined as being *toritsukuroi* reflect a denial of acquired cognitive impairment. Further study is needed to clarify the association between *toritsukuroi* and either cognitive function or disease specificity.

sentences', whereas others may make a plausible excuse about an incorrect answer on a cognitive function examination. Until now, the *toritsukuroi* response has been discussed in association with Alzheimer's disease (AD) from a perspective of symptomatology.¹ Tanabe *et al.* indicated that in the overall behavioural changes of dementia, Pick's disease is characterized by a 'going my own way' type of behavioural pattern, whereas AD is characterized by keeping up appearances or faking one's way through a situation.^{2,3} Meguro also described *toritsukuroi* as a behavioural attempt to cover up memory lapses and smooth things over by

becoming talkative and changing the topic of conversation.⁴ The *toritsukuroi* response sometimes makes early diagnosis and treatment difficult. Furthermore, the severity of dementia could be underestimated because of this behaviour. However, the *toritsukuroi* response may be an early clinical symptom of dementia, so it is important to describe how people with dementia pretend to know the correct answer.

Toritsukuroi responses are regarded as typical behaviours found in people with AD. They are commonly observed in clinical experience and by individual clinicians. Despite such responses being commonplace, there are no reports in which *toritsukuroi* responses have been systematically observed and described. Therefore, it is necessary to examine *toritsukuroi* responses through an observational study.

Matsuda wrote that *toritsukuroi* responses differ depending on the situation and the person interacting with the patient.⁵ In some cases, obvious *toritsukuroi* responses observed at the initial consultation are not repeated in subsequent consultations, when patients start complaining about their symptoms. In other cases, patients who give few *toritsukuroi* responses during the doctor's initial consultation make various excuses for what they cannot do in examinations conducted by clinical psychologists.⁵ Because *toritsukuroi* responses occur depending on a given situation, this study aimed to systematize *toritsukuroi* responses. All oral responses of dementia patients in a semi-structured examination setting were observed, recorded, and then categorized. Incorrect answers and those meaning 'I don't know' were excluded.

METHODS

Participants

The subjects were 91 outpatients who visited the Memory Clinic at Kumamoto University Hospital between April and October 2015. The mean age of the patients was 77.5 ± 7.5 years, and 69.9% of the patients were women. The mean Mini-Mental State Examination (MMSE) and Frontal Assessment Battery scores were 18.7 ± 7.24 and 10.5 ± 4.5 , respectively. Fifty-nine patients had a diagnosis of AD, including 7 with AD with cerebrovascular disease,

20 with mild cognitive impairment, 7 with dementia with Lewy bodies, 2 with vascular dementia, 2 with idiopathic normal pressure hydrocephalus, and 1 with Parkinson's disease with dementia.

Procedures

The ethics and research committees of Kumamoto University approved this study. We obtained written informed consent from all patients and their primary caregivers before starting the study.

All patients were diagnosed by neuropsychiatrists. To diagnose the patients, neuropsychological tests, including the MMSE, Frontal Assessment Battery, brain magnetic resonance imaging, and single-photon emission computed tomography, were used. We diagnosed patients with AD according to the criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.⁶ To make other diagnoses, we used the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria for vascular dementia⁷; the general criteria from the International Working Group on Mild Cognitive Impairment for mild cognitive impairment⁸; and the consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies.⁹ To diagnose idiopathic normal pressure hydrocephalus and Parkinson's disease dementia, we followed criteria set forth by previous studies.^{10,11}

Three well-experienced clinical psychologists conducted the MMSE and recorded patients' verbal responses on paper. Recorded verbal responses did not include erroneous answers or those meaning 'I don't know'. However, answers that indicated why a patient could not respond correctly were also recorded. These descriptions were used for qualitative content analysis.

Content analysis

Responses recorded on paper were converted into digital data on a personal computer. Two researchers then separately classified the responses according to similarity. With regard to mismatched responses, we discussed the meanings of the responses and then categorized them. The correspondence rate for classification between the two researchers was 97.9%.

Finally, the categories identified in this study were labelled by a senior psychiatrist.

RESULTS

We obtained verbal responses from 44 of 91 patients (48.3%). We excluded erroneous answers and replies such as 'I don't know'. The reactions of six patients were also excluded because they were determined not to be *toritsukuroi* responses based on discussion. The excluded responses were 'Did you say such a thing?', 'It's not easy to remember as I get old', 'I have little recollection and only fragmentary memories', and 'It (memory) disappears soon'. Because the patients realized their memory deficit on their own, we excluded these verbal responses. After these verbal responses were excluded, 41.8% of respondents were observed to have given *toritsukuroi* responses.

In the qualitative content analysis, verbal responses were identified and placed into six main categories: (i) 'I can't answer a sudden question'; (ii) responses indicating a dislike or expressing a weakness; (iii) 'I wouldn't do/I've never done such a thing'; (iv) 'I've just forgotten'; (v) 'I don't care' or 'I am not aware of it'; and (vi) other (Table 1).

In the first category—'I can't answer such a sudden question'—similar responses included 'I can't answer because you asked me unexpectedly', 'I just came in on a whim today', and 'I can't answer right away.' We called these reactions 'refuting sudden questions'.

The second category—responses indicating a dislike or expressing a weakness—included 'Because I don't like it', 'I'm not good at it', 'I'm lousy at math', 'I have always been bad at arts and crafts', 'I'm clumsy', and 'I easily get nervous'. These responses seem intended to emphasize that failure or ineptness was caused by nature rather than by an acquired cognitive impairment. Therefore, this category was called 'disclosing traits'.

In the third category—'I wouldn't do/I've never done such a thing'—responses included 'I usually don't do such a thing', 'I don't use such words', 'I don't look at the calendar', 'I don't spend my life keeping up with the Heisei years' (Heisei is the current era in Japan and is used in Japanese calendars), 'I don't talk much with others', and 'I never do this [writing]'. These responses seem intended to

emphasize a lack of experience rather than pathological decline as the cause of inability. Therefore, this category was called 'disclosing experiences'.

The fourth category—'I've just forgotten'—included responses such as 'I could remember until just a while ago', 'I came up with the words just before', 'It just slipped my mind', and 'I was doing those things just recently'. These responses attempt to express a person's slight hesitation by insisting that he or she could remember until just recently. We called these reactions 'demonstrating slight hesitation'.

The fifth category—'I don't care' or 'I'm not aware of it'—included 'I'm not particularly aware of it', 'I don't think about it much because I don't really care', 'I feel that anytime will be fine', 'I was absent-minded and didn't take a good look at it', 'I really don't care about the number of years', 'My husband did that sort of thing', and 'I usually come here on a whim'. These reactions seem designed to show one's flexible attitude and that one does not fuss over details. Difficulty in achieving goals was attributed to one's own indifference. We called these reactions 'appealing to indifference'.

The sixth category included reactions that did not fit neatly into any of the other categories. Such responses included 'I can't describe it without knowing what kind of format is used', 'I can't write it because my given name is unusual', and 'I can look it up in my diary because I keep a diary'.

From the first to sixth categories, the percentage of people who gave a *toritsukuroi* response was 34.2%, 36.8%, 21.1%, 13.2%, 39.5%, and 21.1%, respectively. Of the 38 people with *toritsukuroi* responses, 14 people (36.8%) offered two or more *toritsukuroi* responses in a single examination.

DISCUSSION

In this study, we described the verbal responses of patients during the MMSE and conducted qualitative content analysis to conceptualize *toritsukuroi*. *Toritsukuroi* responses observed in this study were all regarded as reactions intended to deny acquired cognitive impairment. To negate the acquired impairment, patients reacted by 'refuting sudden questions' in an attempt to blame situations, 'disclosing traits', 'disclosing experience', or 'appealing to indifference' and then falling back on an inherent predisposition.

Table 1 Qualitative content analysis of *toritsukuroi* in individuals with dementia

Meaning-carrying unit	Condensed meaning-carrying unit	Code	Subcategory
'I can't answer because you asked me unexpectedly' 'I just came on a whim today' 'I can't answer when I'm asked suddenly' 'I can't answer right away'	I can't answer such a sudden question	Sudden question	Refuting sudden question
'Because I don't like it' 'I'm not good at it' 'I'm lousy at math' 'I have always been bad at arts and crafts' 'I'm clumsy' 'I easily get nervous'	Response indicating dislike or expressing a weakness about something	Dislike or weakness	Disclosing traits
'I usually don't do such a thing' 'I don't use such words' 'I don't look at the calendar' 'I don't spend my life keeping up with the Heisei years' 'I don't have talk much with others' 'I never do this thing [writing]'	I wouldn't do/I've never done such a thing	A lack of experience	Disclosing experiences
'I could remember until just a while ago' 'I came up with the words just before' 'It just slipped my mind' 'I was doing those things just recently'	I've just forgotten	Until just a while ago	Demonstrating slight hesitation
'I don't think much about it because I really don't care' 'I don't care about the number of years' 'I'm not particularly conscious of it' 'I feel that anytime will be fine' 'I was absent-minded and didn't take a good look at it' 'My husband did that sort of thing' 'I usually come here on a whim'	I don't care. I am not aware of it	Does not fuss over details	Appealing to indifference
'I can't describe it without knowing what kind of format is used' 'I can look it up in my diary because I keep a diary' 'I can't write it because my given name is unusual'	Others	—	—

Alternatively, patients reacted by 'demonstrating slight hesitation' in an attempt to achieve at least partial success. 'Demonstrating slight hesitation' by saying things such as 'I've just forgotten' stresses that the patient remembered until just before the question was asked; it implies that patient has the ability to recall information. In the third category, responses such as 'I wouldn't do such a thing' also deny the memory deficit and act as an excuse for why the patient cannot answer a question.

The content analysis in this study was separately conducted by two researchers and classified into six

categories depending on similarities. All verbal responses were assessed to fit the definition of a *toritsukuroi* response, and we believe they were classified reasonably. Based on the analysis, it seems that a patients' desire to be on equal footing with the others is behind the *toritsukuroi* responses observed in this study. Such sentiments seem to be attempts to eliminate gaps when patients become aware of their declining cognitive abilities.

It is necessary to consider *toritsukuroi* responses in relation to denial of disease. In a previous report, Ishikawa and Ikeda stated that 'patients with

Alzheimer's disease are not likely to be conscious of their condition and therefore attempt to keep up appearances'.¹² In contrast, we suggest the possibility patients are aware of their cognitive decline and therefore try to keep up appearances. However, *toritsukuroi* responses may not be directly related to whether patients are conscious of their condition. *Toritsukuroi* should be carefully differentiated from awareness of disease from the viewpoint of symptomatology.

Our results demonstrate that *toritsukuroi* was present in about 40% of patients with dementia in the present study. However, reports about *toritsukuroi* are limited to Japan, and we were unable to find reports about *toritsukuroi* from any foreign research institutes. Japan is well known for its social culture of 'shame',¹³ and Japanese people are also known to be particularly conscious of what others think of their actions.¹⁴ *Toritsukuroi* has been described as 'a behaviour to cover one's shortcomings or weaknesses, and an attempt to navigate a situation without feeling shame'.⁵ It is considered to be a socially conscious behaviour in association with feeling shame and trying not to be left behind or excluded by others. Because such reactions may possibly be observed more often in Japanese people, a cultural comparative study might reveal interesting findings in the future. It will be necessary to establish a validated method of assessing *toritsukuroi* behaviour in order to conduct a cross-cultural comparative study. In addition, a patient's premorbid personality or self-esteem should also be considered in association with *toritsukuroi* responses. Although *toritsukuroi* responses have been observed in people with AD, further study is needed to evaluate *toritsukuroi* responses in a larger group of patients to clarify the association of *toritsukuroi* with disease-specificity. The association between the each type of *toritsukuroi* and the severity or behavioural and psychological symptoms of dementia should also be examined in the future study.

It should be noted that this study was limited to verbal *toritsukuroi* responses. However, *toritsukuroi* manifests in non-verbal response, such as gestures and mood, as well as in verbal behaviour. For example, Japanese people sometimes hide their embarrassment behind a smile. We therefore must examine the non-verbal *toritsukuroi* response in future studies.

In this study, we analyzed the content of *toritsukuroi* responses observed during the administration

of the MMSE. We found that responses could be classified into six categories, and all responses implied a denial of acquired cognitive impairment. We believe that future quantitative research is needed and will require the preparation of an evaluation form designed to clarify the association between the frequency of *toritsukuroi* responses and the disease.

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ORIGINAL ARTICLE

Comparing the driving behaviours of individuals with frontotemporal lobar degeneration and those with Alzheimer's disease

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Key words: dementia, driving behaviour, frontotemporal lobar degeneration, traffic accidents.

INTRODUCTION

With the increased interest in dementia patients, there has also been an increased interest in their driving skills. Dementia patients at the wheel is an issue directly related to public safety, but there is no established medical gold standard for evaluating their driving aptitude.^{1,2} There are various causes for dementia, with markedly varying clinical symptoms and behaviours, but driving behaviour assessment according to disease entities seems to be scarce. Most previous studies concerning dementia and driving have reported an association with cognitive functions, such as visual function, visual attention,

Abstract

Background: Assessing driving aptitude in dementia patients is critically important for both patient and public safety. However, there have been only a few reports on the driving behaviours and accident risk of patients with dementia, especially frontotemporal lobar degeneration (FTLD). Therefore, we compared the characteristics of driving behaviours in patients with FTLD and those with Alzheimer's disease (AD).

Methods: The subjects were 28 FTLD and 67 AD patients who visited the Department of Psychiatry, Kochi Medical School Hospital. We conducted semi-structured interviews with their families and caregivers about traffic accident history and changes in patient driving behaviours after dementia onset and then compared the findings between the two groups.

Results: Overall changes in driving behaviours were reported in 89% (25/28) and 76% (51/67) of the FTLD and AD patients, respectively ($P = 0.17$). In the FTLD group, difficulty in judging inter-vehicle distances, ignoring road signs and traffic signals, and distraction were reported in 50% (14/28), 61% (17/28), and 50% (14/28) of patients, respectively, and 75% (21/28) patients had caused a traffic accident after dementia onset. The risk of causing an accident was higher in the FTLD group than in the AD group (odds ratio = 10.4, 95% confidence interval = 3.7–29.1). In addition, the mean duration between dementia onset and a traffic accident was 1.35 years in the FTLD group compared with 3.0 years in the AD group ($P < 0.01$).

Conclusions: Patients with FTLD were more likely to show dangerous driving behaviours than those with AD, and the risk of causing a traffic accident may be higher in patients with FTLD from an early disease stage.

and executive function,^{3–8} and have focused on patients with Alzheimer's disease (AD), whereas only few systematic studies for driving behaviours of patients with frontotemporal lobar degeneration (FTLD) have been conducted.

FTLD is the umbrella term for degenerative dementia with predominant symptoms involving personality/behaviour changes and language impairment with lesions in the frontal and/or temporal lobes.⁹ Clinically, FTLD is divided into frontotemporal dementia (FTD or behavioural variant FTD), semantic dementia, and progressive non-fluent aphasia. Ikeda *et al.* and Ratnavalli *et al.* reported that FTLD was the second

most common cause of primary dementia among the presenile dementias,^{10,11} and FTLN has become an increasingly recognized cause of dementia. Characteristic clinical symptoms of FTLN include disinhibition, stereotypic behaviour, eating disorders, and semantic memory loss; these are markedly different from the symptoms of AD.^{12–17} In FTLN, the posterior regions of the brain remain intact, unlike in AD, and the memory and visuospatial skills are relatively preserved in the initial stages. Therefore, it is reasonable to assume that the driving behaviours of patients with FTLN and AD will be completely different from one another.

To the best of our knowledge, there have been few reports regarding driving behaviour in patients with FTLN and its relation to traffic accidents. A review article by Turk and Dugan on FTD and driving identified only four reports from several electronic databases.¹⁸ Although specific driving issues have been related to antisocial behaviours in FTD, the risk of such patients causing traffic accidents has not been studied yet.

The aim of this study was to compare the characteristics of driving behaviours and traffic accident history between patients with FTLN and AD. We hypothesized that patients with FTLN would show characteristic driving behaviours that differ from those shown by patients with AD, and they would be at a higher risk of causing traffic accidents than patients with AD.

METHODS

Subjects

This study was conducted after approval by the Ethics Committee of Kochi Medical School. We explained the aim of this study to the subjects or their legally authorized representatives, and obtained written consent.

We enrolled consecutive patients who had visited the Department of Psychiatry of Kochi Medical School Hospital between September 1995 and December 2012. Subjects who fulfilled the clinical diagnostic criteria of FTLN and met the definition of one of its types as established by Neary *et al.* were enrolled.⁹ The FTLN group included 28 patients (18 men and 10 women; mean age $\pm$ SD: 67.9 $\pm$ 9.2 years) who had retained their driving licence and drove a car at the time of the first examination. The clinical subtype was FTD in 13 patients, semantic dementia in 13, and

progressive non-fluent aphasia in 2. Patients with AD who met the diagnostic criteria established by the National Institute of Neurological and Communicative Disease and Stroke and Alzheimer's Disease and Related Disorders Association for probable AD were selected.¹⁹ The AD group included 67 patients (42 men and 25 women; mean age $\pm$ SD: 69.8 $\pm$ 10.2 years) who had retained their driving licence and drove a car at the time of the first examination.

No patient had any physical problem, marked visual disturbance, or motor impairment that interfered with driving. Patients who had been followed for less than 1 year after clinical diagnosis were excluded from this study.

Clinical assessment

The age at first examination, sex, age at onset, and disease duration were evaluated at first examination along with the scores for the Mini-Mental State Examination (MMSE),²⁰ instrumental activities of daily living (IADL) scale,²¹ and Clinical Dementia Rating (CDR).²² Based on interviews with the main caregiver or a family member at the first visit, we estimated the onset of dementia and disease duration. For the IADL scale, men and women were evaluated on 5-point and 8-point scales, respectively, and the score was presented as a percentage.

Driving interviews

Semi-structured interviews for evaluating driving behaviours were conducted by senior neuropsychiatrists or clinical psychologists familiar with geriatric psychiatry. The main caregiver or a family member living with the patient was interviewed about the patient's driving behaviours after dementia onset. The questionnaire included items about whether the patient did the following: (i) forgot the destination; (ii) failed to get the car in/out of the garage; (iii) had difficulty judging inter-vehicle distances; (iv) ignored road signs and traffic signals; (v) was distracted (e.g. took their eyes off the road); and (vi) showed overall changes in driving behaviour. We also identified patients' history of traffic accidents, characteristics, and time to first accident from dementia onset. Only traffic accidents caused by a patient were considered. Accidents processed through legal administrative procedures by the police and self-inflicted accidents recognized by family members were included.

Table 1 Characteristics of subjects

	FTLD (<i>n</i> = 28)	AD (<i>n</i> = 67)	<i>P</i> -value
Sex, men (<i>n</i>)	18 (64%)	42 (63%)	0.88
Age, mean $\pm$ SD (years)	67.9 $\pm$ 9.2	69.8 $\pm$ 10.2	0.15
MMSE, mean $\pm$ SD	19.6 $\pm$ 7.6	19.5 $\pm$ 5.8	0.54
CDR (<i>n</i>)			0.06
0.5	16 (57.1%)	21 (31.3%)	
1	9 (32.1%)	32 (47.8%)	
2	3 (10.7%)	14 (20.9%)	
IADL, mean $\pm$ SD (%) [†]	67.4 $\pm$ 35.2	64.1 $\pm$ 23.4	0.65
Disease duration, mean $\pm$ SD (years)	2.0 $\pm$ 1.9	1.7 $\pm$ 1.5	0.37

[†]For the IADL scale, men were evaluated on a 5-point scale and women on an 8-point scale. AD, Alzheimer's disease; CDR, Clinical Dementia Rating; FTLT, frontotemporal lobar degeneration; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination.

Statistical analysis

Continuous variables were expressed as mean $\pm$ SD. Categorical variables were expressed as numbers and percentages. For analyzing continuous variables, *t*-test or Mann–Whitney *U*-test was used. For analyzing categorical variables, χ^2 test was used, and Fisher's exact test was selected when expected frequencies were less than five. The time to first accident from dementia onset was compared between the FTLT and AD groups with the Mann–Whitney *U*-test. Two-sided *P*-values <0.05 were considered significant. All analyses were carried out using SPSS version 21.0 (IBM, Armonk, NY, USA).

RESULTS

Table 1 shows the characteristics of the subjects. There were no significant differences in sex ratio, age, MMSE score, CDR score, IADL score, or disease duration between the two groups.

Figure 1 shows the driving behaviours and traffic accident history after dementia onset based on the driving-related interviews with caregivers and family members. An overall change in driving behaviours was reported at a high frequency in both the groups with no significant difference (*P* = 0.17). Among the characteristics of driving behaviour, the frequency of difficulty in judging inter-vehicle distances, ignoring traffic signals, and distraction were significantly higher in the FTLT group than in the AD group (*P* < 0.001 for all). No significant difference was observed in the frequencies of failure to get the car in/out of the garage between the two groups (*P* = 0.17), and the frequency of forgetting the destination was higher in the AD

group than in the FTLT group (*P* < 0.001). The risk of causing an accident was higher in the FTLT group than in the AD group (odds ratio = 10.4, 95% confidence interval = 3.7–29.1).

With regard to the characteristics of traffic accidents in the FTLT group, rear-end collision was the most frequent type of accident; among the subjects involved rear-end collisions were one in a hit-and-run accident and one involving injury. In contrast, in the AD group, minor accidents due to a failure to get the car in/out of the garage were frequent, but there were no serious accidents resulting in injury or death. Thirteen patients (FTLT: 12, AD: 1) showed difficulties in both judging inter-vehicle distances and distraction, and all had caused a traffic accident.

Table 2 shows the difference between individuals in the FTLT group who had caused accidents and those who had not. No significant differences were observed in sex, age, MMSE score, CDR score, or IADL score between these groups within the FTLT group. Among the characteristics of driving behaviour, only distraction was significantly more frequent in the patients who had caused accidents.

Table 3 shows the difference between individuals in the AD group who had caused accidents and those who had not. No significant differences were observed in sex, age, MMSE score, CDR score, or IADL score between these groups within the AD group. Among the characteristics of driving behaviour, failure to get the car in/and out of the garage and difficulty in judging inter-vehicle distances were significantly more frequent in the patients who had caused accidents.

The mean time between dementia onset and the first traffic accident was 1.35 $\pm$ 0.83 years in the FTLT group and 3.0 $\pm$ 1.36 years in the AD group (*P* < 0.01).

DISCUSSION

Our results indicated that driving behaviours were remarkably different between the two groups, and the risk of causing a traffic accident was much higher in the FTLT group than in the AD group. Difficulty in judging inter-vehicle distances, ignoring traffic signals, and distraction were significantly more frequent in the FTLT group. These driving behaviours may be related to neuropsychiatric manifestations and behavioural changes, such as aggression, impulsivity, restlessness, disinhibition, and environmental dependency syndrome, which can be characteristics

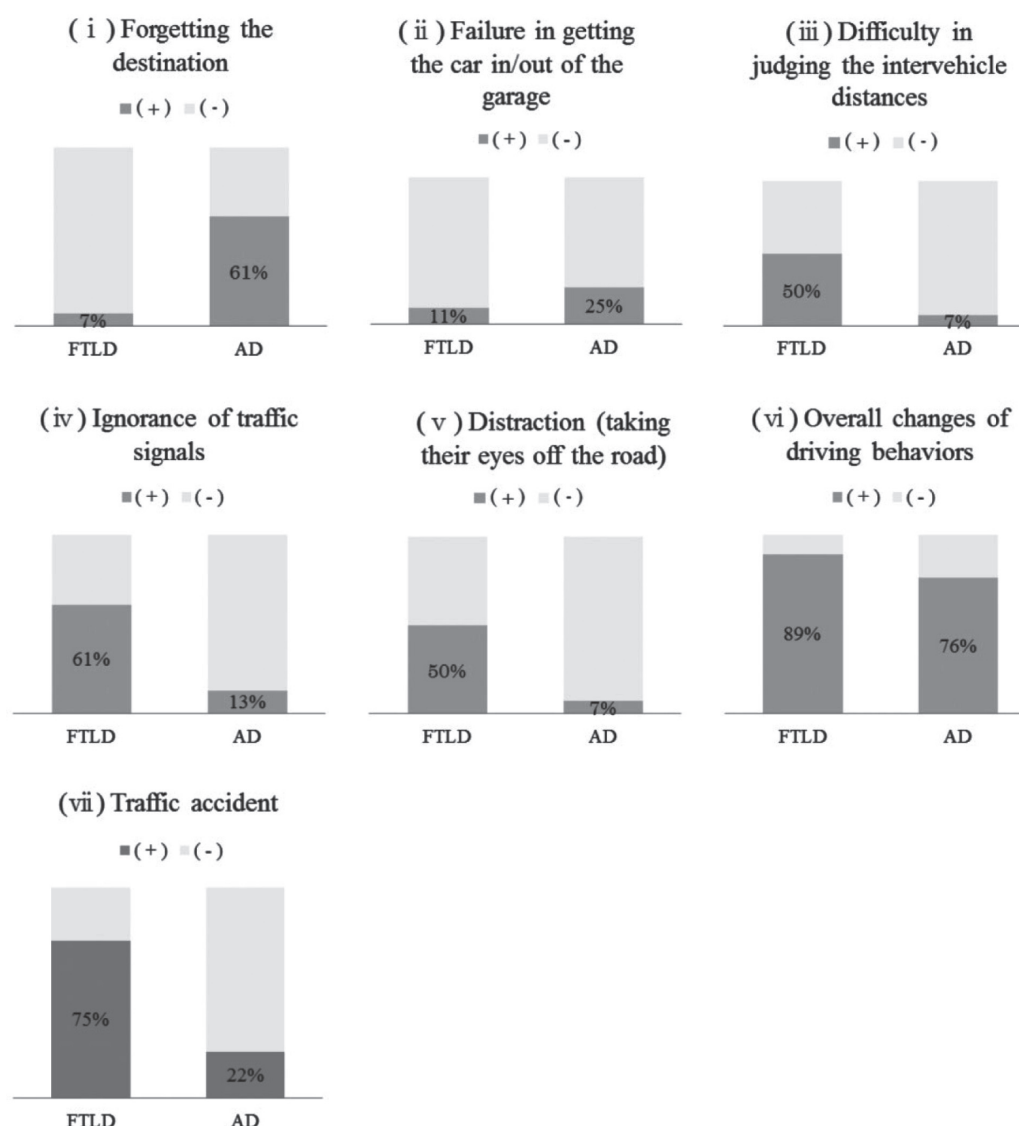


Figure 1 Data concerning the driving behaviours and traffic accident history after dementia onset are shown. Overall changes in driving behaviours were reported at a high frequency in both the FTLD and AD groups. Driving behaviours, difficulty judging inter-vehicle distances, ignoring traffic signals, and taking eyes off the road were significantly more frequent in the FTLD group than in the AD group. No significant difference between the two groups was observed with regard to getting the car in/out of the garage, but forgetting the destination was more frequent in the AD group than in the FTLD group. The frequency of traffic accidents was significantly higher in the FTLD group than in the AD group. AD, Alzheimer's disease; FTLD, frontotemporal lobar degeneration.

of FTLD. Only distraction was shown to have statistically significant difference for increasing the risk of traffic accidents in FTLD. Other driving behaviours did not show statistically significant differences for increasing the risk of traffic accidents in the FTLD group, probably because of the relatively small sample size. Difficulty in judging inter-vehicle distances and ignoring traffic signals were shown to have a tendency to increase the risk of traffic accidents.

The frequency of forgetting the destination was lower in the FTLD group, which may have been due to a lower incidence of memory deficit and visuospatial impairment. All patients who had difficulty with both judging inter-vehicle distances and distraction had caused traffic accidents. Therefore, this result suggests that physicians may be able to identify patients with a higher risk of causing traffic accidents by confirming these two items in any type of dementia.

Table 2 Differences between individuals in the FTLD group who had caused accidents and those who had not

Accident	(+)	(-)	P-value
	<i>n</i> = 21	<i>n</i> = 7	
Sex, men (<i>n</i>)	15 (71%)	3 (75%)	0.17
Age, mean $\pm$ SD (years)	67.1 $\pm$ 9.4	68.1 $\pm$ 9.3	0.80
MMSE, mean $\pm$ SD	19.9 $\pm$ 7.6	18.6 $\pm$ 8.2	0.69
CDR (<i>n</i>)			0.19
0.5	10	6	
1	8	1	
2	3	0	
IADL, mean $\pm$ SD (%)	64.5 $\pm$ 38.7	75.1 $\pm$ 21.7	0.83
Forgetting the destination (<i>n</i>)	1 (4.7%)	1 (14.3%)	0.44
Failure to get the car in/out of the garage (<i>n</i>)	2 (9.5%)	1 (14.3%)	1.0
Difficulty judging inter-vehicle distances (<i>n</i>)	13 (61.9%)	1 (14.3%)	0.07
Ignoring traffic signals (<i>n</i>)	15 (71.4%)	2 (28.6%)	0.07
Distraction (<i>n</i>)	14 (66.7%)	0 (0%)	0.006
Overall changes in driving behaviours (<i>n</i>)	20 (95.2%)	5 (71.4%)	0.14

CDR, Clinical Dementia Rating; FTLD, frontotemporal lobar degeneration; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination.

Table 3 Differences between individuals in the AD group who had caused accidents and those who had not

Accident	(+)	(-)	P-value
	<i>n</i> = 15	<i>n</i> = 52	
Sex, men (<i>n</i>)	11 (73%)	31 (60%)	0.33
Age, mean $\pm$ SD (years)	69.9 $\pm$ 12.1	69.8 $\pm$ 9.8	0.96
MMSE, mean $\pm$ SD	18.5 $\pm$ 6.3	19.8 $\pm$ 5.6	0.46
CDR (<i>n</i>)			0.05
0.5	1	20	
1	9	23	
2	5	9	
IADL, mean $\pm$ SD (%)	62.1 $\pm$ 21.2	64.6 $\pm$ 24.1	0.71
Forgetting the destination (<i>n</i>)	9 (60%)	32 (61.5%)	0.91
Failure to get the car in/out of the garage (<i>n</i>)	8 (53.3%)	9 (17.3%)	0.01
Difficulty judging inter-vehicle distances (<i>n</i>)	4 (26.6%)	1 (1.9%)	0.008
Ignoring traffic signals (<i>n</i>)	4 (26.6%)	5 (9.6%)	0.10
Distraction (<i>n</i>)	3 (20.0%)	2 (3.9%)	0.07
Overall changes in driving behaviours (<i>n</i>)	13 (86.7%)	38 (73.1%)	0.49

AD, Alzheimer's disease; CDR, Clinical Dementia Rating; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination.

The clinical characteristics of FTD include disinhibition, stereotypic behaviour, loss of social awareness and insight, aggression, impulsivity, restlessness, asponaneity, environmental dependency syndrome, and distractibility.^{12,17,23} Although semantic memory impairment, such as loss of word meaning

and impaired object recognition, is a striking facet of semantic dementia, patients with semantic dementia also showed behavioural changes.²⁴ All these neuropsychiatric and neuropsychological symptoms influence compliance with traffic rules and understanding of road signs, and they may interfere with the driving ability of patients with FTLD. Lack of insight into one's own impairment may also lead to dangerous driving.⁹ In a previous study, an association between a reduced ability to drive and lack of insight had been reported in patients with AD.²⁵

A previous study reported a strong correlation between MMSE scores and driving behaviours in elderly drivers.²⁶ However, it is generally difficult to evaluate driving ability in dementia patients based on neuropsychological test batteries alone.^{27–30} de Simone *et al.* reported that there was no correlation between a general measure of cognitive functioning and driving performance in patients with FTD.³¹ We also observed no correlation between MMSE scores and the occurrence of traffic accidents in either group, suggesting that MMSE alone may not be useful in predicting traffic accidents caused by patients with dementia.

CDR is a generally used tool to assess dementia severity that can clinically be very useful. However, no correlation was observed between CDR scores and traffic accidents in the current study. CDR mainly evaluates disturbances of memory, orientation, and judgement. Thus, CDR alone may be inappropriate for evaluating the driving ability of patients with FTLD because they mainly develop changes in personality and behaviour in the early stage. In contrast, in the AD group, only one patient who had caused an accident had a CDR score of 0.5, and the other 14 patients who had caused an accident had a CDR score of ≥ 1 . Our findings showed that some patients in the very early stage of AD could drive safely and that AD patients with a CDR score of ≥ 1 could pose a significant problem in safe driving, which is consistent with the results of previous studies.^{32–35}

IADL is an appropriate instrument to assess independent living skills in the elderly, but no correlation with traffic accidents was observed in this study. Thus, the use of IADL as an index to predict traffic accidents caused by dementia patients may be limited.

In agreement with previous studies,^{31,36,37} we believe that it is dangerous for patients with FTLD to

drive. However, to the best of our knowledge, this is the first report that compared the characteristics of driving behaviours and time until the first accident after disease onset between patients with FTLT and AD. The mean time to the first traffic accident after dementia onset in the FTLT group was 1.35 years, which was shorter than that in the AD group (3 years). Of particular note in this study is that the mean time between disease onset and first accident was shorter than the mean disease duration in patients with FTLT. Therefore, it may be necessary to pay careful attention to the driving behaviours of patients with FTLT and to instruct families to consider the accident risk from a very early stage.

In previous reports, driving was investigated mainly in association with AD. According to a meta-analysis reported by Reger *et al.*, visuospatial skills were the only neuropsychological tasks that correlated with driving ability.³⁸ This correlation probably explains why individuals who had caused an accident in the AD group were significantly more likely to have difficulty parking in a garage and judging inter-vehicle distances in the present study. However, patients with FTLT have little or no visuospatial dysfunction in the early stage. Impaired driving ability in FTLT appears more likely to relate to personality and behavioural changes, such as an increase in aggressiveness, impulsivity, and disinhibition. Thus, apart from dementia severity, physicians should be aware of marked variation in driving behaviours among different types of dementia.

Several limitations should be noted in this study. First, this study did not include assessments for the behavioural and psychological symptoms of dementia. Earlier studies have suggested that agitated and aggressive behaviours measured by the Neurobehavioural Rating Scale are related to speeding and collisions in patients with FTD.³³ Second, changes in driving behaviours were not based on an on-road assessment but on the evaluation of caregivers. However, the main caregiver or a family member living with the patient could closely observe changes in driving; thus, their impressions were considered to be suitable for assessing on-road driving behaviours. Third, factors such as psychosocial background, including place of residence, and medication use were not considered. These factors may affect the risk of traffic accidents, although all subjects were from the same catchment area near one university hospital.

Fourth, we did not measure driving mileage. However, the subjects drove several times a week, and professional drivers were not included as subjects. Therefore, the driving mileage of the subjects can be regarded as the average of their Japanese contemporaries. Finally, there were a small number of patients with FTLT who were evaluated in this study; therefore, future studies will need to increase the number of subjects and evaluate driving behaviours according to the FTLT clinical subtypes.

The results of present study have clarified that patients with FTLT show characteristic driving behaviours that are clearly different from patients with AD, and the risk of causing a traffic accident is much higher among patients with FTLT. Moreover, this risk was high in patients with early-stage FTLT. Physicians need to recognize that the characteristics of driving behaviours of patients with FTLT differ from those with AD, and for both patient and public safety, these patients should cease driving as soon as possible after FTLT has been diagnosed.

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□ CASE REPORT □

Callosal Disconnection Syndrome Associated with Relapsing Polychondritis

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Abstract

Relapsing polychondritis (RP) is a rare inflammatory disorder of the cartilagenous structures, and it sometimes involves the central nervous system. Encephalitis associated with RP causes a wide variety of symptoms according to the affected sites. We herein report the first case of 72-year-old right-handed man who developed acute meningoencephalitis associated with RP involving the corpus callosum. After immunosuppressive therapy, his symptoms dramatically improved, but difficulty in performing bimanual movements with occasional diagnostic dyspraxia in his right hand remained. Because callosal signs are easily missed, especially in acute settings, it would be useful to know that RP can sometimes cause callosal disconnection syndrome.

Key words: relapsing polychondritis, callosal disconnection syndrome, diagnostic dyspraxia

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Introduction

Relapsing polychondritis (RP) is a rare relapsing and remitting inflammatory disorder of the cartilagenous structures (1). RP has been reported to cause central nervous system vasculitis in rare cases, thus leading to various neurological symptoms, such as meningitis, encephalitis (2), parkinsonism (3) and dementia (4), according to the site of lesions. We herein describe, for the first time, that RP may sometimes cause callosal disconnection syndrome.

Case Report

A 72-year old right-handed man with 16 years of education was found lying drowsy on the floor and thereafter was brought to the nearest hospital by ambulance. His past medical history included diabetes mellitus, hypertension, postoperative thoracic aortic aneurysm and cured gastric MALT (mucosa-associated lymphatic tissue) lymphoma. Two years before this presentation, at 70 years of age, he presented

with eruptions over his body and extremities. He was given 60 mg/day oral prednisolone and the eruptions thereafter disappeared, however he developed pain and swelling in his left ear while tapering prednisolone to 5 mg/day. A biopsy of the auricular cartilage showed perichondral inflammation with lymphocytic infiltration. A diagnosis of RP was thus made and oral prednisolone was increased to 10 mg/day with a complete recovery of the symptoms. He then remained in good health until 72 years of age, when he developed a high fever and drowsiness two days before admission.

On admission, the patient was febrile and somnolent. Dysarthria and neck stiffness were evident. Blood tests revealed an elevated white blood cell count and C-reactive protein concentration. A cerebrospinal fluid (CSF) examination showed pleocytosis of 781/mm³ white blood cells with 87% polymorpholeucocytes, a glucose level of 38 mg/dL (blood glucose 149 mg/dL), and a total protein of 582 mg/dL. A computed tomography scan of the brain showed no obvious abnormalities. With the presumptive diagnosis of acute bacterial meningitis, he was treated with dexametha-

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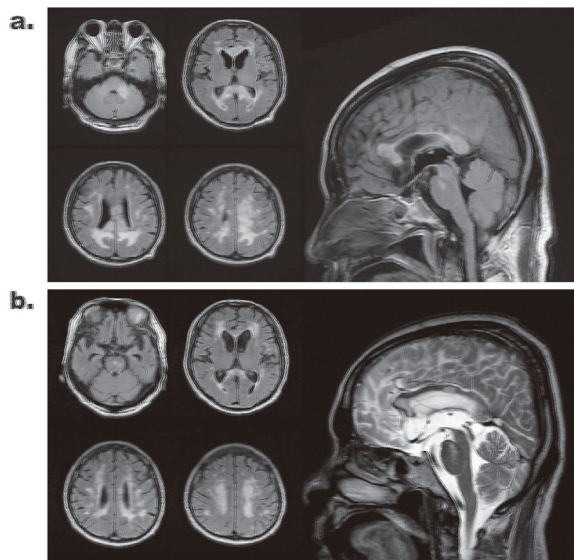


Figure 1. Axial and sagittal fluid attenuation inversion recovery (FLAIR) and T2-weighted sequences in brain MRI. **a:** At presentation: lesions are observed in the corpus callosum and in the left inferior cerebellar peduncle in addition to diffuse subcortical white matter abnormalities. **b:** After 4 months of treatment: the subcortical white matter hyperintense lesions became less remarkable, but the lesions in the genu and splenium of the corpus callosum persisted.

sone 32 mg/day for 4 days and antibiotics. Three days later, the patient demonstrated a dramatic improvement of his CSF abnormalities. Brain magnetic resonance imaging (MRI) showed diffuse subcortical white matter abnormalities without contrast-enhancement including the corpus callosum (Fig. 1a). There was no involvement of the medial frontal cortex. All CSF specimens were negative for bacteria, virus, and fungi or abnormal cells. Acute bacterial meningitis was thought to be unlikely, and alternatively meningoencephalitis associated with RP was highly suspected. All antibiotics were discontinued and oral prednisolone at a dose of 60 mg/day was started, and thereafter his condition improved gradually.

One month after admission, he was transferred to our hospital and oral prednisolone was gradually tapered to 10 mg/day and pulsed intravenous cyclophosphamide (500 mg monthly for 4 months) was administered. At that time, he complained of speech difficulty and sometimes reported that his left hand would not respond as intended. The results of a neurological examination were not remarkable, except for the observed neurocognitive deficits. He was alert but disoriented as to the time and place, and he achieved a score of 13 on the Mini-Mental State Examination (MMSE). His speech was slow and often stopped due to occasional stuttering, but his articulation and prosody were adequate. Circumlocutions and semantic paraphasias were sometimes noted in his spontaneous speech. The abilities of comprehension, repetition, and reading were preserved, but he had difficulty in writing especially with his left hand (Fig. 2a, b). He

could not perform pentagon copy, cube copy and clock drawing in either hand, thus indicating a visuospatial impairment (Fig. 2e). Furthermore, mild left-sided hemispatial neglect was observed when copying line drawings with his right-hand (Fig. 2c, d). Ideomotor apraxia of both hands was observed on verbal command and on imitation. He could not identify his left hand fingers or objects placed in his left hand with his eyes closed, but he was able to do so under visual observation.

After a rehabilitation period of 4 months in our hospital, his cognitive status improved significantly and his MMSE score improved to 21. His speech became faster and more fluent except for some stuttering. He became able to write with his right hand proficiently. Visuospatial impairment also improved remarkably, but he could not copy a double-pentagon or perform clock drawing (Fig. 2f). Apraxia of both hands was markedly diminished. Despite the significant improvement, he still had difficulty in performing bimanual movements, such as tying a string, lacing up shoes and fastening a button, as the right hand would not help the left and at times even tried to interfere with the action of the left hand (diagonistic dyspraxia), even though he often felt a loss of control of his left hand. On repeated MRI, subcortical white matter lesions became less remarkable and the lesions in the corpus callosum shrunk (Fig. 1b).

Discussion

Corpus callosum involvement associated with RP has been inferred on MRIs in a previous report, although callosal disconnection syndrome has never been previously described (5). Because callosal signs and symptoms are prone to be missed, especially in acute settings (6) which can lead to a misestimation of the disease severity, it would therefore be useful to know that RP can sometimes cause callosal disconnection syndrome accompanied by encephalitis.

It is noteworthy that the diagonistic dyspraxia in the present case was in the right hand, although it generally occurs in the left (non-dominant) hand in right-handed individuals (7, 8). This reversed lateralization can be explained by the possibility that our patient had a mixed cortical dominance. In general, dysgraphia and ideomotor apraxia emerge in one's non-dominant hand in callosal disconnection syndrome (9, 10), but these were observed in both hands at the initial stage, which also suggests an altered cortical lateralization in this patient. Nevertheless, tactile anomia (or astereognosia) of the left hand suggests that the left hemisphere dominance of language function (10).

Another peculiar thing to be noted in this case is a discrepancy between the affected-sides of diagonistic dyspraxia and the loss of the sense of agency. It is possible that the left hemisphere accounts for the verbal expression of a feeling of the loss of control over his left hand, even if the left hand actually manifested the patient's intention.

In the current study, we describe a patient who presented with right-sided diagonistic dyspraxia due to callosal discon-

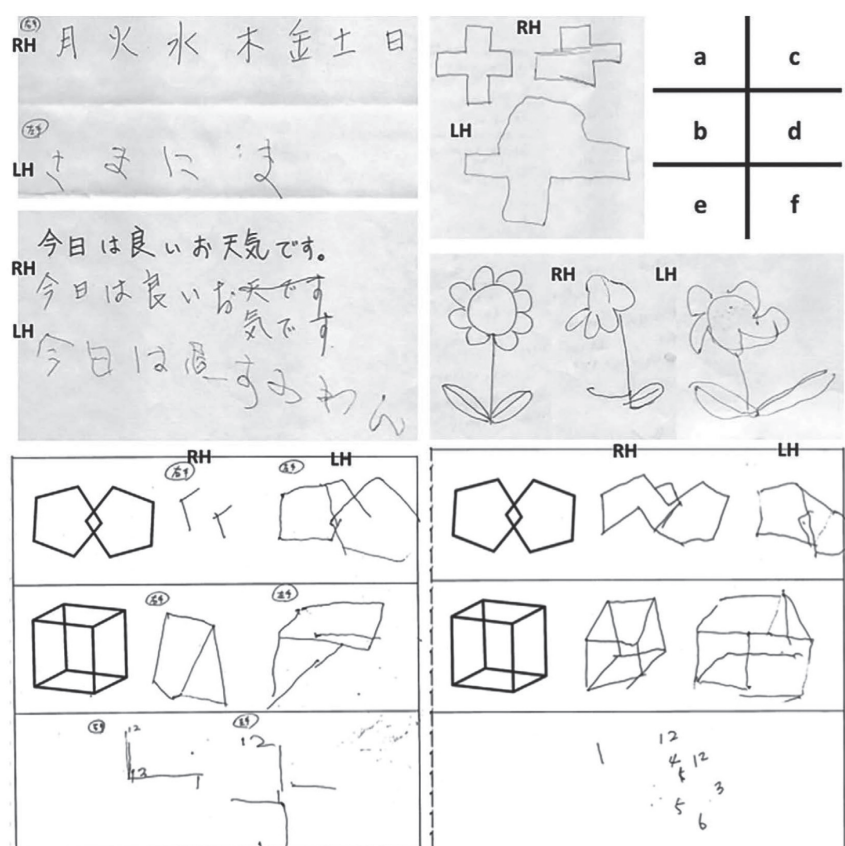


Figure 2. Samples of patient's writing, figure copying and clock drawing. a: When instructed to recite the days of the week, the patient made only a minor error with his right-hand, but he could only write meaningless characters with his left-hand. b: When asked to copy a simple sentence, the patient made only a minor mistake with the right-hand, but he could write only a nonsensical phrase with the left-hand. c and d: Mild left-sided hemispatial neglect was observed when copying line drawings with his right-hand. e: He could not copy line drawings or draw a clock at presentation. f: After 4 months of treatment, he became able to copy a cube with his right hand, but he remained unable to copy a double-pentagon or draw a clock.

nection secondary to RP. The present report adds an additional case of callosal disconnection syndrome in a RP patient. RP should therefore be considered as a rare cause of alien hand syndrome.

The authors state that they have no Conflict of Interest (COI).

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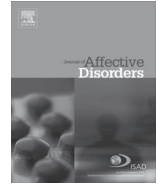
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Short communication

Comparisons of prevalence and related factors of depression in middle-aged adults between urban and rural populations in Japan

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ABSTRACT

Background: Findings of urban–rural differences in the prevalence of depression have been controversial, and few reports have directly compared the related factors of depression between urban and rural areas. The present study aimed to investigate differences between urban and rural areas in Japan with regards to the prevalence of and related factors of depression in middle-aged adults, in order to further understanding of the features of depression in this demographic.

Methods: We used a multistage, random sampling procedure and mailing method. In total, 5000 participants were recruited from urban and rural areas in Kumamoto Prefecture (2500 in each area). Participants were aged from 40 to 64 years. Depression was assessed using the Center for Epidemiologic Studies Depression scale (CES-D).

Results: The prevalence of middle-aged depression was not different between the urban and rural areas. Logistic regression analysis found that being female, living alone, and having a chronic illness were significantly associated with depression in urban-dwelling middle-aged adults. Younger age, sleep disturbance, and financial strain were significantly associated with depression in both urban and rural areas. **Limitations:** The definition of depression was based on CES-D scores, without corroborating clinical evaluation.

Conclusions: We found no marked differences in the prevalence of middle-aged depression between the urban and rural areas. Some related factors of depression in middle-aged adults differed between urban and rural areas in Japan. Effective intervention programs for middle-aged adults with depression should consider regional differences.

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1. Introduction

Population movement from rural to urban areas has occurred world-wide in the 20th century. It is anticipated that two-thirds of the world's population will be living in urban areas by 2030 (Galea, 2011; Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, 2010). This urbanization is characterized by factors such as higher rates of criminality, social isolation, air pollution and noise (Inaba, 2013). The possibility of urban and rural differences in mental disorders is of interest to researchers, and there is ongoing discussion about the association of urbanization with a greater risk of morbidity and mortality, including for psychiatric disorders (Crowell et al., 1986;

Judd et al., 2002; Peen et al., 2010).

Studies investigating urban and rural differences in depression are important, as disparity in public health services between urban and rural areas is focal concern. The results of these studies are critical in planning mental health services and in building our understanding of the etiology of depression (Wang, 2004). However, studies of urban–rural differences in the prevalence of non-psychotic psychiatric disorders have yielded contradictory results, with some studies finding higher rates in urban areas and others finding no difference between urban and rural areas (Romans et al., 2011).

In developed countries, research has focused on differences in depression between urban and rural areas, whereas few studies have made this comparison in an Asian context. In Japan, there has been one study reported the difference in depression in older adults between urban and rural areas (Sarai, 1983), and some studies have found the suicide rate in rural areas to be higher than

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in urban areas in Japan (Watanabe et al., 1995). However, few reports have directly compared the related factors of depression between urban and rural areas. In particular, there is a paucity of research comparing related factors of depression in urban- and rural-dwelling middle-aged adults, although this comparison has been explored in older adults. In a previous study, we reported regional differences in the prevalence of and related factors of depression in older adults between urban and rural populations in Japan (Abe et al., 2012); this investigation was conducted concomitantly with this present study. Furthermore, there has been little research comparing related factors of depression between middle-aged and older adults.

The present study aimed to investigate the differences between urban and rural populations in the prevalence of and related factors of depression in middle-aged adults in Japan. We also discuss differences in the related factors of depression between middle-aged and older adults.

2. Methods

2.1. Study population

The present study was conducted in urban and rural areas of Japan's Kumamoto Prefecture. Data collection for the urban area was conducted in Kumamoto City, the biggest city in South Kyushu, with a population of approximately 730,000 people. The rural area investigated was in Aso District, with a population of approximately 70,000 people. Aso District is located in a mountainous area of Kumamoto Prefecture; economically active populations are generally employed within the agriculture and forestry industry, and have the typical characteristics of rural areas in Japan.

2.2. Data collection

Data were collected in a multistage, random sampling procedure. The census tracts for Kumamoto City and Aso District between November 2010 and December 2010 were chosen. A total of 2500 participants were recruited from among the middle-aged residents (those aged between 40 and 64 years) in each area. Based on approximate age and gender distribution of the population in Kumamoto city, we selected 1,000 residents aged 40–49 (500 male and 500 female), 1,000 residents aged 50–59 (500 male and 500 female), and 500 residents aged 60–64 (250 male and 250 female) in each area.

Self-administered questionnaires were mailed to the participants. The questionnaires covered socio-demographic variables, sleep status and symptoms of depression. Socio-demographic variables included age, sex, living status ("living alone" or "living with someone"), work status ("employed or housewife/househusband or "unemployment"), financial strain ("present" or "absent" of strong financial worry), suicidal ideation ("every time", "often", "sometimes" or "never"; "every time", "often" and "sometimes" were reclassified as present, and "never" as absent. We didn't ask the plan or attempt of suicide.), drinking habits ("do not drink", "less than once a month", "2–4 times a month", "2–3 times per week", "4 or more times per week"; classified only "do not drink" was reclassified as absent and all other answers as present), and history of medical disease ("heart disease," "hypertension," "brain infarction," "diabetes," "cataract," and "others"; responses were reclassified as present if any of these was indicated and absent if none were noted). We used specific statements to assess the state of sleep; with response options of "good," "trouble with sleep," "taking longer than 30 min to fall asleep," "abrupt awakening," and "early morning awakening". Any response other

than "good" was considered as indicating sleep disturbance. The questionnaires were returned using an addressed, reply-paid envelope, along with the participant's written, informed consent. All procedures in the present study strictly followed the 2009 Clinical Study Guidelines of the Ethics Committee of Kumamoto University Hospital and were approved by the Internal Review Board.

2.3. Measurements

We used the Center for Epidemiologic Studies Depression Scale (CES-D) to measure depression. The CES-D was developed for use in studies on the epidemiology of depressive symptomatology in the general population (Radloff, 1977), and has been used extensively in the fields of psychiatry and public health. The reliability and validity of the Japanese version has been demonstrated by Shima et al. (Shima et al., 1985). Participants who scored 16 points or more were considered to be "possibly depressed" as in previous studies.

2.4. Statistical analyses

After excluding incomplete responses, the valid responses on each item were scored. The means and standard deviations (SD) were calculated for age, sleeping hours and CES-D scores. To clarify factors associated with depression in urban and rural areas, the chi-square tests were used for categorical variables (sex, living alone, work status, financial strain, suicidal ideation, drinking habits, chronic illness, sleep disturbance and the prevalence of depression), and a Student's t-test for non-categorical variables (age, number of people living together, sleeping hours and CES-D score). Finally, logistic regression analyses were conducted to identify additional factors related to depression and to calculate odds ratios (OR) for each factor in both urban and rural areas. Suicidal ideation was not used in this analysis as it was not an independent variable. A two-sided *P* value of 0.05 or less was defined as statistically significant. Tolerance and variation inflation factor (VIF) were both examined and it was determined that multicollinearity was not an issue for the independent variables. All exploratory and formal statistical analyses were performed with SPSS Version 21.0 (IBM SPSS, Tokyo, Japan) for Windows.

3. Results

3.1. Participant characteristics

The characteristics of the participants are presented Table 1. In total, 1739 questionnaires were valid after incomplete responses were excluded. The return rates were 41.2% for Kumamoto City (urban area) and 41.6% for Aso District (rural area). Valid response rate tended to be higher in older residents and female (around 40%). Valid response rate in male aged 40–49 was the lowest (22.0% in Kumamoto City; 23.8% in Aso District). There were no significant differences in the sex ratio and mean ages between the urban and rural areas. There was no significant difference in the average CES-D scores between the urban and rural areas. The prevalence of depression, that is, subjects with CES-D scores of 16 points or more, was almost the same for both areas (Kumamoto City, 22.8%; Aso District, 23.5%).

3.2. Univariate associations with clinically relevant depressive symptoms

In the urban area (Kumamoto City), depression in middle-aged adults was significantly associated with sex (female), age, living alone, work status, chronic illness, sleep disturbance, sleeping

Table 1
Characteristics of participants in each area.

	Kumamoto city (urban)	Aso district (rural)	P
Total group: N	878	861	
Sex: N (%)			0.699
M	383 (43.6)	367 (42.6)	
F	495 (56.4)	494 (57.4)	
Age (years) #: mean (s.d.)	53.2 (6.95)	52.8 (7.02)	0.272 0.931
Living alone: N (%)	74 (8.4)	71 (8.2)	
Living with someone: N (%)	804 (91.6)	790 (91.8)	
Numbers of people living together#: mean (s.d.)	3.13 (1.42)	3.55 (1.79)	< 0.001
Work status: N (%)			0.105
Employed or housewife (househusband)	761 (86.7)	769 (89.3)	
Unemployment	117 (13.3)	92 (10.7)	
Chronic illness: N (%)			0.725
present	310 (35.3)	297 (34.5)	
absent	568 (64.7)	564 (65.5)	
Sleep disturbance: N (%)			0.460
absent	617 (70.3)	619 (71.9)	
present	261 (29.7)	242 (28.1)	
Sleeping hours# (hours): mean (s.d.)	6.37 (1.11)	6.53 (1.08)	0.003
Suicidal ideation: N (%)			0.909
present	199 (22.7)	193 (22.4)	
absent	679 (77.3)	668 (77.6)	
Drinking habits: N (%)			0.920
present	566 (64.5)	553 (64.2)	
absent	312 (35.5)	308 (35.8)	
Financial strain: N (%)			0.728
present	188 (21.4)	191 (22.2)	
absent	690 (78.6)	670 (77.7)	
CES-D score#: mean (s.d.)	11.6 (8.9)	12.3 (8.7)	0.116
Nondepressed subjects: N (%)	678 (77.2)	659 (76.5)	0.776
Depressed subjects: N (%)	200 (22.8)	202 (23.5)	

#: Student's *t*-test, others: chi-square test

CES-D: The Center for Epidemiologic Studies Depression Scale.

SD: standard deviation.

hours, suicidal ideation, and financial strain (Table 2). For rural-dwelling middle-aged adults (Aso District), age, living alone, work status, chronic illness, sleep disturbance, sleeping hours, suicidal ideation and financial strain were significantly associated with depression (Table 2). The variables significantly associated with depression in middle-aged adults common to both areas were age, living alone, work status, chronic illness, sleep disturbance, sleeping hours, suicidal ideation and financial strain, while sex (female) was significantly associated with depression only in the urban area.

3.3. Logistic regression model

Table 3 shows the variables independently associated with depression in middle-aged adults in each area following logistic regression analysis. In the urban area, six variables (sex [female], younger age, living alone, chronic illness, sleep disturbance, financial strain) were significantly associated with depression in middle-aged adults, while in the rural area, a significant association was found for only three variables (younger age, sleep disturbance, financial strain). Variables associated with depression differed between the urban and the rural areas; for urban-dwelling middle-aged adults, being female, living alone and having a chronic illness were characteristic related factors of depression.

4. Discussion

In the present study, the prevalence of depression in middle-aged adults in Japan was investigated, and the related factors of

urban and rural areas were compared. We found no marked differences in the prevalence of middle-aged depression between the urban (22.8%) and rural areas (23.5%). Romans et al. (Romans et al., 2011) compared geographic variability in rates of depression and three anxiety disorders in Canadians aged 15 years and older, and found a lower prevalence of depression in those living in rural areas. Similarly, Wang reported a lower prevalence of 12-month major depressive episodes in rural areas than those in urban areas in Canada (Wang, 2004). Conversely, the United States (US) National Comorbidity Study found no difference between rural and urban areas when the current (30 days) and 12-month prevalence of major depression was compared in metropolitan areas, smaller cities, and rural areas (Blazer et al., 1994; Kessler et al., 2003). In addition, Wang (Wang, 2004) noted that no significant difference between urban and rural areas in the prevalence of major depression in various countries (Hwu et al., 1989; Lee et al., 1990; Parikh et al., 1996). However, Probst et al. (Probst et al., 2006) reported that the prevalence of depression was significantly higher in residents of rural areas compared with urban areas in adult populations in the US. Breslau et al. (Breslau et al., 2014) compared the prevalence of major depression across four categories of urbanicity such as large metropolitan areas, small metropolitan areas, semi-rural areas and rural areas in the US, and found a slightly higher prevalence in small urban and semi-rural areas relative to large urban areas. In Japan, previous national survey didn't report urban–rural difference in common mental disorders (Kawakami et al., 2004, 2005).

As mentioned, findings of urban–rural differences in the prevalence of depression have been controversial. Peen et al. (Peen et al., 2010) attributed the inconsistency of these findings to a number of associated factors: first, a variety of definitions for “urban” and “rural” have been used; second, there were cultural differences between studies and countries; and third, there was considerable heterogeneity in the methods used in the available literature, for example, outcome measures and adjustment for different types of confounders. They concluded that urban rates of depression may be somewhat higher than rate of depression in rural areas. Furthermore, some researchers have hypothesized that there are biological differences such as neurodevelopmental (Lederbogen et al., 2011) and epigenetic features (Galea, 2011) between urban and rural areas.

In general, the prevalence of depression is high in people with lower social status; although Japan's epidemiological survey did not indicate a clear association between depression and lower social status (Kawakami et al., 2004, 2005; Kessler et al., 2003). Previous studies have reported that both sex (female) and younger age are associated with depression (Andrade et al., 2003; Kawakami et al., 2005). Kessler et al. (Kessler et al., 2003) found that being unemployed or disabled, being previously married and having a low income were factors associated with severe major depressive disorders in the US.

Socio-demographic related factors of depression and the prevalence of depression in urban and rural populations have been the focus of previous research; however, few studies have compared extensive related factors of depression between urban and rural populations. We could not find any studies investigating urban–rural differences in related factors of depression in younger or middle-aged adults, while two studies reported urban–rural differences in related factors of depression in older adults (Abe et al., 2012; Kim et al., 2002).

In the present study, common related factors of depression in middle-aged adults in both urban and rural areas were younger age, sleep disturbance, and financial strain, while sex (female), chronic illness, and living alone were related factors of depression in urban-dwelling middle-aged adults. Being female, having a chronic illness, and living alone are considered to present social

Table 2

Relationships between depression and possible related factors in each area.

	Kumamoto city				Aso district			
	N	Depressed subjects: N (%)	Nondepressed subjects: N (%)	P	N	Depressed subjects: N (%)	Nondepressed subjects: N (%)	P
Total group: N (%)	878	200(22.8)	678(77.2)	0.015	861	202(23.5)	659(76.5)	0.464
Sex: N (%)								
Male	383	72 (36.0)	311 (45.9)		367	91 (45.0)	276 (41.9)	
Female	495	128 (64.0)	367 (54.1)	0.001	494	111 (55.0)	383 (58.1)	0.010
Age (years) #: mean (s.d.)		51.7 (7.2)	53.6 (6.8)			51.7 (6.8)	53.1 (7.05)	
Living alone: N (%)	74	31 (15.5)	43 (6.3)	0.001	71	28 (13.9)	43 (6.5)	0.002
Living with someone: N (%)	804	169 (84.5)	635 (93.7)		790	174 (86.1)	616 (93.5)	
Numbers of people living together#: mean (s.d.)		3.02 (1.42)	3.16 (1.41)			3.38 (1.76)	3.60 (1.79)	
Work status: N (%)				0.018				0.019
Employed or housewife (househusband)	761	163 (81.5)	598 (88.2)		769	171 (84.7)	598 (90.7)	
Unemployment	117	37 (18.5)	80 (11.8)		92	31 (15.3)	61 (9.3)	
Chronic illness: N (%)				0.004				0.042
present	568	88 (44.0)	222 (32.7)		297	82 (40.6)	215 (32.6)	
absent	310	112 (56.0)	456 (67.3)		564	120 (59.4)	444 (67.4)	
Sleep disturbance: N (%)				< 0.001				< 0.001
absent	617	82 (41.0)	535 (78.9)		619	83 (41.1)	536 (81.3)	
present	261	118 (59.0)	143 (21.1)		242	119 (58.9)	123 (18.7)	
Sleeping hours# (hours): mean (s.d.)		6.00 (1.41)	6.48 (0.98)	< 0.001		6.18 (1.18)	6.63 (1.03)	< 0.001
Suicidal ideation: N (%)								
present	199	119 (59.5)	80 (11.8)		193	122 (60.4)	71 (10.8)	
absent	679	81 (40.5)	598 (88.2)	0.053	668	80 (39.6)	588 (89.2)	0.801
Drinking habits: N (%)								
present	566	117 (58.5)	449 (66.2)		553	128 (63.4)	425 (64.5)	
absent	312	83 (41.5)	229 (33.8)	< 0.001	308	74 (36.6)	234 (35.5)	< 0.001
Financial strain: N (%)								
present	188	93 (46.5)	95 (14.0)		191	92 (45.5)	99 (15.0)	
absent	690	107(53.5)	583 (86.0)		670	110 (54.5)	560 (85.0)	

#: Student's *t*-test, others: chi-square test

SD: standard deviation.

vulnerability: the social position of women may be still unstable (especially in workplace) in Japan despite the progression of women's social advancement; having a chronic illness is general disadvantage in health and society; and, living alone suggests poor or limited social support. From the perspective of social support, we previously found an association between living alone and depression in older adults living in a rural community in Japan (Fukunaga et al., 2012). In our another study (Abe et al., 2012) reported regional differences in related factors of depression in older adults using the same two study areas, being female, having a chronic illness and living alone were not related factors of depression in older adults in either urban or rural areas; a finding that contrasts with the results of the present study targeting middle-aged adults. While the self-rating scales for used to assess depression were different for the middle-aged (CES-D) and older

adults (Geriatric Depression Scale) in these two studies, middle-aged, urban residents with social vulnerability were found to have a higher risk for depression than rural residents. In Japan, it was reported that social participation decreased in middle-aged adults and increased in elderly adults (Inaba, 2013). The different results for older adults in our previous study might indicate an aspect of urbanization.

Financial strain was a common risk factor for middle-aged and older adults in both urban and rural areas; further, in urban-dwelling middle-aged adults, financial strain showed a remarkably high OR in relation to depression. This suggest financial strain may be especially stressful for middle-aged people in urban areas. Our finding that unemployment was not risk factor for depression in middle-aged adults in either urban or rural areas was surprising, particularly as our previous study found unemployment was

Table 3

Logistic regression analyses of the relationship between participant's depressive state and multivariate factors in urban and rural areas.

Variables	Kumamoto city (urban)			Aso district (rural)		
	OR	95%CI	P	OR	95%CI	P
Female	1.580	1.067–2.340	0.022	0.939	0.643–1.371	0.744
Age	0.932	0.906–0.958	< 0.001	0.950	0.924–0.976	< 0.001
Living alone	2.621	1.465–4.689	0.001	1.494	0.813–2.745	0.196
Unemployment	1.144	0.668–1.960	0.623	1.781	0.999–3.174	0.0503
Chronic illness	1.637	1.096–2.446	0.016	1.066	0.718–1.583	0.751
Sleep disturbance	4.568	3.129–6.669	< 0.001	5.524	3.792–8.048	< 0.001
Drinking habits	0.745	0.504–1.101	0.140	0.912	0.616–1.350	0.646
Financial strain	3.987	2.698–5.890	< 0.001	3.756	2.554–5.522	< 0.001

Model chi-square; Kumamoto City: 197.5, Aso District: 181.2

OR: odds ratio, CI: confidence interval.

common risk factor for depression for urban and rural older adults (Abe et al., 2012). As unemployment is often perceived as more serious for middle-aged than older adults, this discrepancy may be related to the diversification of life-styles and values for urban and rural middle-aged adults in the present study. Sleep disturbance was common related factor in middle-aged adults in both urban and rural areas, but also can be one of the symptoms of depression. In our previous study, sleep disturbance was only a related factor of depression in older adults living in urban areas (Abe et al., 2012). This feature suggests that there has been some urbanization of the life-styles of middle-aged people, even those living in rural areas.

4.1. Limitations

The results of the present study should be considered within the context of some limitations. First, the definition of depression was based on CES-D scores, without corroborating clinical evaluation. However, the CES-D is a well-validated instrument for assessing depression, and it has widespread use in epidemiological studies. Second, other related factors, such as personality and important life events in the few months before the assessment were not investigated. Third, as different self-rating scales for depression were used, we could not compare the differences in related factors of depression between middle-aged and older people in detail. Fourth, the response rates were low in both areas, especially in younger male, so we need to interpret results with considering the selection bias in this study.

4.2. Conclusions and clinical implications

In conclusion, we found no marked differences in the prevalence of middle-aged depression between the urban and rural areas. Variables associated with depression differed between the urban and the rural areas; for urban-dwelling middle-aged adults, being female, living alone and having a chronic illness were characteristic related factors of depression. Effective intervention programs for middle-aged adults with depression should consider regional differences.

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Contributors

NF and YA collected the data and analyzed with support by AK. NF wrote the paper. AK, RF, YN and MI provided valuable help on this study. All authors discussed the results and commented on the manuscripts.

Declaration of interest

None.

Conflict of interest

None.

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ORIGINAL ARTICLE

Mental health among younger and older caregivers of dementia patients

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Key words: activities of daily living (ADL), behavioural and psychological symptoms of dementia (BPSD), carers, depression, quality of life (QOL).

INTRODUCTION

Dementia is a worldwide problem that affects 44.4 million people.¹ As dementia progresses, cognitive dysfunction, impairment of activities of daily living

Abstract

Aim: Caregiver burden in dementia is an important issue, but few studies have examined the mental health of younger and older family caregivers by comparing them with age- and gender-matched community residents. We aimed to compare the mental health of dementia caregivers with that of community residents and to clarify factors related to mental health problems in younger and older caregivers.

Methods: We studied 104 dementia caregivers; 46 were younger (<65 years) and 58 were older (≥65 years). A total of 104 community residents who were matched for age and gender were selected. We compared depression (Center for Epidemiologic Studies Depression Scale for younger participants; Geriatric Depression Scale for older participants), health-related quality of life (QOL) short-form health survey (SF-8), sleep problems, and suicidal ideation between the caregivers and community residents by age. Behavioural and psychological symptoms of dementia, activities of daily living (ADL), and instrumental ADL were assessed among patients with dementia using the Neuropsychiatric Inventory, Physical Self-Maintenance Scale, and Lawton Instrumental ADL Scale, respectively.

Results: According to SF-8 results, both younger and older caregivers had significantly worse mental QOL than community residents (younger caregivers: 46.3 vs community residents: 49.7, $P = 0.017$; older caregivers: 48.2 vs community residents: 51.1, $P = 0.024$) but were not more depressive. Sleep problems were significantly more frequent in younger caregivers (39.1%) than in community residents (17.0%) ($P = 0.017$). Multiple regression analysis revealed that caregivers' deteriorated mental QOL was associated with patients' behavioural and psychological symptoms of dementia in younger caregivers and with dementia patients' instrumental ADL and female gender in older caregivers.

Conclusions: Dementia caregivers had a lower mental QOL than community residents. To maintain caregivers' mental QOL, it is necessary to provide younger caregivers with skills or professional interventions for dealing with behavioural and psychological symptoms of dementia, and older caregivers must be offered adequate care support.

(ADL) and instrumental ADL (IADL), and the behavioural and psychological symptoms of dementia (BPSD) appear. Previous studies have indicated that the burdens of caregiving deteriorate caregivers'

mental health. Caregivers have higher rates of depressive and anxiety disorders,^{2–5} lower quality of life (QOL),⁶ higher risk of hypertension and heart disease, decreased immunity, and greater mortality than non-caregivers.⁷

Some interventions targeting caregivers' mental health or QOL have been developed and assessed. However, the effects of these interventions are limited.^{8,9} Jensen *et al.* reviewed the effectiveness of educational interventions for dementia caregivers and concluded that they had a small effect on caregivers' depression and that the effect on caregivers' QOL was unclear.⁸ Caregivers' mental health or QOL has been reported to be influenced by complex factors such as patient's dementia severity, BPSD, ADL, and IADL.¹⁰ However, factors related to mental health problems vary depending on the caregiver's age because of differences in social roles, care environment, and physical conditions. To improve the effects of intervention, we must clarify the types of mental problems that caregivers experience as well as the factors that lead to deterioration of mental health in younger and older caregivers.

In Japan, an elderly care insurance system was launched in 2000 with the aim of providing various services to elderly individuals in need of long-term care and supporting caregivers. This system has made a modest contribution to alleviate caregiver burden,¹¹ but the mental, physical, and economic burdens on caregivers remain high.

Therefore, the aims of this study were as follows: (i) to compare mental health among dementia caregivers with age- and gender-matched community residents in Japan, and (ii) to clarify factors related to mental health problems that have been observed more frequently in caregivers than in community residents. In both analyses, we divided participants into two groups based on age: younger (<65 years) and older (≥65 years).

METHODS

Participants

This study was approved by the Human Ethics Review Committee of Kumamoto University. After a complete description of all study procedures was provided, written informed consent was obtained from all patients and their family caregivers.

Participants in this study were the main family caregivers of consecutive dementia outpatients in the outpatient clinic of the Department of Neuropsychiatry, Kumamoto University Hospital, from January to April 2015. Family caregivers who provided daily support for dementia patients were asked to participate in this study; those who cared for patients living in nursing homes were excluded. We studied 104 dementia caregivers (43 men, 61 women); 46 were younger (aged <65 years) and 58 were older (aged ≥65 years). The relationships of caregivers to patients were spouses ($n = 57$), adult children ($n = 38$), daughters-in-law ($n = 5$), and other relatives ($n = 4$). The mean age $\pm$ SD of the caregivers was 65.2 ± 11.8 . The diagnoses of the patients were Alzheimer's disease ($n = 58$), vascular dementia ($n = 7$), Alzheimer's disease and cerebrovascular disease ($n = 9$), dementia with Lewy bodies ($n = 10$), mild cognitive impairment ($n = 11$), and other types of dementia ($n = 9$). Dementia was diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, third edition (text revision). Alzheimer's disease, vascular dementia, dementia with Lewy bodies, and mild cognitive impairment were diagnosed according to the National Institute for Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association,¹² the National Institute for Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria,¹³ the consensus criteria for the clinical diagnosis of dementia with Lewy bodies,¹⁴ and the National Institute on Aging Alzheimer's Association (NIA-AA) diagnostic criteria,¹⁵ respectively.

Community residents were selected from a community survey conducted in a town in Kumamoto Prefecture in October 2014. Data for age- and gender-matched community residents ($n = 104$) who were confirmed to not be caring for family members were used (matched pair method).

Measures

Assessment for caregivers and community residents

To assess mental health among dementia caregivers and community residents, we used self-reported questionnaires that consisted of multiple scales. All scales used in this study have sufficient reliability and validity.

Depression

For younger participants, the Japanese version of the Center for Epidemiologic Studies Depression Scale was used.^{16,17} This scale consists of 20 items answered on a 4-point Likert scale from 0 (rarely or none of the time) to 3 (most or all of the time); a score ≥ 16 was regarded as representing depression.

For older participants, the Japanese version of the 15-item Geriatric Depression Scale was used.^{18,19} For each item, participants answered yes or no. Depressive answers were scored with 1 point for each item, and the sum of all items represented the Geriatric Depression Scale total score (range: 0–15). A score ≥ 6 was considered to represent possible depression.²⁰

Health-related QOL

Health-related QOL was measured with the Japanese version of SF-8,^{21,22} which consists of eight domains: (i) physical functioning; (ii) physical role functioning; (iii) bodily pain; (iv) general health perception; (v) vitality; (vi) social functioning; (vii) emotional role functioning; and (viii) mental health. The SF-8 yields two summary scores from those domains: the Physical Component Summary score and the Mental Component Summary (MCS) score. Higher scores indicate better QOL.

Other variables

Other variables assessed included age, gender, sleep problems over the previous 2 weeks (present/absent), and suicidal ideation (present (i.e. sometimes, often, or always)/absent). For caregivers, employment status (employed/unemployed) was also assessed.

Assessment of patient functioning and caregiver burden

The assessments of patient functioning and caregiver burden were conducted as part of the usual clinical assessment. Mini Mental State Examination (MMSE) was conducted on patients. The Neuropsychiatric Inventory, Physical Self-Maintenance Scale, Lawton IADL, and Zarit Caregiver Burden Interview (ZBI) were administered by interview to caregivers.

Cognitive function

The MMSE, one of the most frequently used cognitive screening questionnaires, was used to assess the cognitive function of patients.^{23,24} MMSE scores

range from 0 to 30, with higher scores indicating better cognitive function.

BPSD

The Japanese version of the 12-item NPI was used to assess BPSD.^{25,26} The NPI consists of 12 neuropsychiatric symptoms (i.e. hallucinations, delusions, agitation/aggression, dysphoria/depression, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor behaviour, sleep and night-time behaviour disorders, and appetite and eating disorders). The score of each domain was calculated by frequency (1: less than once a week; 2: once a week; 3: a few times a week; 4: once a day or more) $\times$ severity (1: mild; 2: moderate; 3: severe). We regarded the sum of all scores of each domain as the NPI total score (range: 0–156), with higher scores indicating worse conditions.

ADL

The Physical Self-Maintenance Scale was used to evaluate patients' ability to perform basic ADL.^{27,28} Six domains (i.e. toileting, feeding, dressing, grooming, physical ambulation, and bathing) were assessed. The scores range from 0 to 6, with higher scores indicating better functioning.

IADL

The Lawton IADL Scale was used.^{27,28} Eight domains (i.e. using the telephone, shopping, preparing food, housekeeping, doing laundry, using transportation, handling medications, and handling finances) were assessed. The scores range from 0 to 8, with higher scores indicating better functioning.

Caregiver burden

The Japanese version of the ZBI was used.^{29,30} The ZBI consists of 22 questions on the impact of the patient's disabilities on the lifestyle of the caregiver. It assesses various problems caused by caregiving, including caregiver health, psychological well-being, finances, social life, and the relationship between the caregiver and care recipient. For each item, caregivers indicate how often they feel a certain way (never: 0; rarely: 1; sometimes: 2; quite frequently: 3; nearly always: 4). The sum of the scores ranges from 0 to 88, with higher scores indicating higher burden.

Statistical analysis

We compared mental health problems (depression, health-related QOL, sleep problems, and suicidal ideation) between dementia caregivers and community residents by age group (<65 years and ≥65 years), using the paired *t*-test and McNemar's test. Next, we conducted a multiple regression analysis to clarify clinical and sociodemographic factors related to mental health problems that were seen significantly more frequently in caregivers than in community residents by age group. Third, the correlation between mental health problems and caregiver burden was examined in both younger and older caregivers. All tests were two-tailed, and the significance levels were set at $P < 0.05$. All statistical analyses were performed with SPSS 23.0J for Windows (IBM SPSS Japan, Tokyo, Japan).

RESULTS

Women accounted for 76% of younger caregivers and 45% of older caregivers. The most common diagnosis of the patients being cared for was Alzheimer disease in both younger and older caregivers. About 80% of the younger caregivers were patients' children, whereas more than 90% of the older caregivers were patients' spouses. Caregivers who lived with patients were about 60% among younger caregivers and about 95% among older caregivers. The mean MMSE score $\pm$ SD was 17.0 ± 6.8 in patients who were cared for by younger caregivers and 18.1 ± 6.6 in patients who were cared for by older caregivers (Table 1).

Table 2 shows the comparison of mental health problems between caregivers and community residents. Younger caregivers scored lower than age- and gender-matched community residents on the MCS (caregivers: 46.3, community residents: 49.7, $P = 0.017$) and had a significantly higher rate of sleep problems (caregivers: 39.1%, community residents: 13.0%, $P = 0.017$). The mean Center for Epidemiologic Studies Depression Scale score tended to be higher in caregivers than in community residents, but the difference was not significant (caregivers: 12.7, community residents: 10.0, $P = 0.061$). Older caregivers scored lower than age- and gender-matched community residents on the MCS (caregivers: 48.2, community residents: 51.1, $P = 0.024$). There was no

significant difference in depression between caregivers and community residents in either age group.

Given that both younger and older caregivers had lower MCS scores than community residents, multiple regression analysis was conducted to clarify the factors related to caregivers' MCS score in each age group. The predictors of MCS score were drawn from the scores for MMSE, NPI, Physical Self-Maintenance Scale, and Lawton IADL; patient age and gender; caregiver gender; and caregiver employment status and then determined with univariate analysis. Only statistically significant variables were selected as dependent variables (NPI score and caregiver employment status in younger caregivers; IADL score and caregiver gender in older caregivers). As a result of multiple regression analysis, high NPI scores in patients were significantly related to low MCS scores in younger caregivers ($\beta = -0.355$, $P = 0.019$). Low Lawton IADL scores in patients ($\beta = 0.280$, $P = 0.027$) and female caregivers ($\beta = -0.288$, $P = 0.023$) were significantly related to low MCS scores in older caregivers (Table 3). We checked the variance inflation factor and found that there was no collinearity among variables.

Table 1 Patient and caregiver characteristics

	Younger caregivers (<i>n</i> = 46)	Older caregivers (<i>n</i> = 58)
Gender (<i>n</i>)		
Male	11	32
Female	35	26
Relationship to patient (<i>n</i>)		
Spouse	4	53
Child	36	2
Daughter-in-law	5	0
Other	1	3
Living situation (<i>n</i>)		
Living with patient	27	55
Not living with patient	19	3
Diagnosis of patient (<i>n</i>)		
Alzheimer's disease	30	28
Vascular dementia	1	6
Dementia with Lewy bodies	4	6
Alzheimer's disease + vascular dementia	3	6
Mild cognitive impairment	5	6
Other	3	6
Patients' mean MMSE score	17.0	18.1

MMSE, Mini-Mental State Examination.

Table 2 Comparisons of mental health between caregivers and controls

Younger caregivers	Caregiver group (n = 46)	Control group (n = 46)	t/χ^2	P-value
Mean CES-D score	12.7	10.0	1.921	0.061
CES-D cut-off score ≥ 16 (%)	23.9	19.6	0.256	0.791
Mean PCS score	45.6	47.7	1.318	0.194
Mean MCS score	46.3	49.7	2.485	0.017
Sleep problems (%)	39.1	13.0	8.118	0.017
Suicidal ideation (%)	10.9	15.2	0.383	0.754
Older caregivers	Caregiver group (n = 58)	Control group (n = 58)	t/χ^2	P-value
GDS mean score	3.4	2.6	1.399	0.167
GDS cut-off score ≥ 6 (%)	19.0	13.8	0.566	0.629
PCS mean score	46.4	44.8	1.127	0.265
MCS mean score	48.2	51.1	2.322	0.024
Sleep problems (%)	27.6	17.2	1.785	0.263
Suicidal ideation (%)	10.3	8.6	0.100	1.000

CES-D, Center for Epidemiologic Studies Depression Scale; GDS, Geriatric Depression Scale; MCS, Mental Component Summary of SF-8; PCS, Physical Component Summary of SF-8; SF-8.

Table 3 Multiple regression analysis of predictors of mental quality of life (Mental Component Summary of SF-8) among caregivers (forced entry method)

Younger caregivers	β	t	P-value
NPI score	-0.355	2.431	0.019
Employment (Reference = unemployment)	-0.192	1.318	0.195
Adjusted $R^2 = 0.172$			
Older caregivers	β	t	P-value
Gender (Reference = female)	-0.288	2.341	0.023
Lawton IADL score	0.280	2.280	0.027
Adjusted $R^2 = 0.145$			

Lawton IADL, Lawton Instrumental Activities of Daily Living Scale; NPI, Neuropsychiatric Inventory; SF-8.

MCS score significantly correlated with ZBI score in both younger and older caregivers, and a stronger correlation was seen in older caregivers (younger caregivers: $r = -0.37$, $P = 0.01$; older caregivers: $r = -0.53$, $P < 0.01$).

DISCUSSION

In the present study, we clarified the effects of caring for patients with dementia on caregivers' mental health by comparing caregivers with age- and gender-matched community dwelling residents who did not care for family members. One of the important findings was the lower mental QOL among the dementia caregivers. Although deteriorated QOL among caregivers has already been reported,⁶ our results indicated that dementia caregiving interfered with only the mental aspects of QOL. In addition, 40% of younger caregivers had sleep problems. In

our research, some caregivers answered that they had no sleep problems because they were taking hypnotic agents. We did not count them as having sleep problems, so the percentage of sleep problems among caregivers might be underestimated. It was not clear whether sleep problems were caused by caregiving stress or night-time behaviour disturbance, and it was also unclear why younger caregivers have sleep problems more frequently than older caregivers; more research on these topics is needed.

Although previous studies reported higher rates of depression among dementia caregivers,²⁻⁵ our results indicated that dementia caregivers are not more depressive than community residents. This inconsistency might be due to differences in the method of assessing depression; we did not deal with clinical depression as diagnosed by criteria for depressive disorder but rather with caregivers' subjective feelings of depression.

It has already been pointed out that cognitive function, ADL, IADL and BPSD affect caregivers' QOL.¹⁰ In our study, factors related to deteriorated mental QOL among caregivers differed according to their age; the most relevant factor for younger caregivers was patients' severe BPSD, while patients' decreased IADL was the most relevant for older caregivers. This result indicates that, to improve caregivers' mental health, it is necessary to provide opportunities for younger caregivers to gain skills or professional support in managing the behavioural problems of patients and to offer sufficient social support (e.g. day care and home help services) for older caregivers. However, caution is needed when interpreting this result because we could not clarify whether the difference in related factors between younger and older caregivers was caused only by their age. The results may have been affected by the fact that older caregivers were more likely than younger caregivers to be patients' spouses and living with patients.

Although Thomas *et al.* reported lower QOL in female caregivers than in male caregivers,¹⁰ our study suggested that lower mental QOL was seen only in older female caregivers. Adequate support for older female caregivers might therefore be especially needed.

In our study, patients' cognitive function was not strongly related to caregivers' mental QOL. This was consistent with previous studies indicating that the relationship between caregivers' QOL or depression and patients' declining cognitive function is weak compared to the relationship between caregivers' QOL and patients' BPSD, ADL, and IADL.^{10,31}

Mental QOL was correlated with caregiver burden, which indicates that dementia caregiving affects the entirety of the caregiver's life. The correlation was particularly strong in older caregivers. In contrast with younger caregivers who are physically healthy, likely engage in many social activities and hobbies, and have social roles other than caregiving, older caregivers may take on caring for their family member alone and feel that care comprises a large part of their lives. Caregiver burden includes not only objective aspects but also subjective feeling, and therefore the relation between caregiver burden and mental QOL is complex and interactive. Further research is required to clarify the effect of subjective and objective burden on caregivers' mental QOL.

There are some limitations to the present study. First, we could not compare the mental health of younger caregivers with that of older caregivers directly because we used a different measurement for each group. Instead, we aimed to clarify caregivers' mental health within age groups and used the Center for Epidemiologic Studies Depression Scale for younger caregivers and Geriatric Depression Scale for older ones. It is generally thought that younger and older people exhibit different types of depressive symptoms, so we thought that the simple comparison of depression was difficult. Second, although caregivers and community residents were age- and gender- matched, other socio-demographic factors were not considered. Third, because our data were collected in an outpatient clinic at the university hospital, the sample might be biased. Fourth, we could not assess some factors reported to be related to caregiver burden, such as care environment (e.g. length of caregiving and social support for caregivers) and personal factors (physical or economic problems, personality traits or sense of coherence).^{32–34}

Further studies are needed to identify the effects of these factors and to obtain suggestions for improving the mental health of caregivers.

Despite these limitations, the present study has important implications for supporting caregivers of dementia patients. We should pay close attention to caregivers' mental QOL rather than depressive moods, although a few caregivers were diagnosed with depressive disorder and some may require medical treatment. Our finding that the factors related to lower mental QOL among caregivers differ by caregiver age may also be useful in establishing effective support or interventions for dementia caregivers.

In conclusion, when considering the mental health of caregivers, we should pay attention to their mental QOL and sleep problems. In addition, to maintain caregivers' mental QOL, it is necessary to provide younger caregivers with skills or professional interventions to address patients' BPSD and to provide older caregivers with adequate care support.

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RESEARCH ARTICLE

Malnutrition in Alzheimer's Disease, Dementia with Lewy Bodies, and Frontotemporal Lobar Degeneration: Comparison Using Serum Albumin, Total Protein, and Hemoglobin Level

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Abstract

Malnutrition among dementia patients is an important issue. However, the biochemical markers of malnutrition have not been well studied in this population. The purpose of this study was to compare biochemical blood markers among patients with Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and frontotemporal lobar degeneration (FTLD). A total of 339 dementia outpatients and their family caregivers participated in this study. Low serum albumin was 7.2 times more prevalent among patients with DLB and 10.1 times more prevalent among those with FTLD than among those with AD, with adjustment for age. Low hemoglobin was 9.1 times more common in female DLB patients than in female AD patients, with adjustment for age. The levels of biochemical markers were not significantly correlated with cognitive function. Family caregivers of patients with low total protein, low albumin, or low hemoglobin were asked if the patients had loss of weight or appetite; 96.4% reported no loss of weight or appetite. In conclusion, nutritional status was worse in patients with DLB and FTLD than in those with AD. A multidimensional approach, including blood testing, is needed to assess malnutrition in patients with dementia.

Introduction

Cognitive function and nutrition are thought to have strong correlations. In general, weight loss associated with malnutrition often precedes the onset of dementia and then increases in pace with progression of the disease [1]. Longitudinal cohort studies have reported that malnutrition itself is a risk factor for cognitive decline [2]. A possible correlation has also been found between deficiency in specific nutrients (e.g., vitamin B12 and folate) and decreased cognitive function [3,4].

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People with cognitive decline have various eating and swallowing problems. Eating and swallowing problems, along with the behavioral and psychological symptoms of dementia, can strongly affect nutritional status. Kai et al. reported that more than 80% of patients with Alzheimer's disease (AD) have eating and swallowing disturbances [5]. Other forms of dementia are also associated with several types of eating problems. In frontotemporal lobar degeneration (FTLD), changes in eating behavior (e.g., changes in appetite, food preferences, eating habits, and other oral behaviors) are frequently seen [6]. In dementia with Lewy bodies (DLB), eating and swallowing problems result from various factors, including Parkinsonism [7]. The reported prevalence of swallowing problems among dementia patients is 13%–57% [8].

Eating and swallowing problems increase the risk of malnutrition. Droogsma et al. reported that about 14% of community-dwelling people with dementia were at risk of malnutrition [9]. Among the dementia diagnostic groups, DLB patients have an especially high reported rate of malnutrition [10]. These previous studies assessed malnutrition with the Mini Nutritional Assessment [11], which consists of six aspects: decreased food intake, weight loss, mobility, psychological stress or acute disease, presence of dementia or depression, and Body Mass Index. This tool is convenient and reliable, but it lacks information about biochemical marker levels. To our knowledge, no studies have used biological blood markers to examine nutritional status in different types of dementia.

It is important to detect malnutrition in dementia patients as early as possible. In the usual clinical setting, some clinicians may judge patients' nutritional status only by asking family caregivers about appetite and weight change in patients. However, it is unknown whether information provided by family caregivers about nutritional status agrees with biochemical marker levels.

The purpose of this study was i) to compare biochemical blood marker levels in three types of neurodegenerative dementia: AD, DLB, and FTLD; and ii) to examine the relationship between patient malnutrition and caregiver awareness of the patient's appetite and weight change.

Methods

Participants

This study was approved by the Human Ethics Review Committee of Kumamoto University. After a complete description of all study procedures was provided, written informed consent was obtained from patients and their family caregivers.

Consecutive outpatients at the Dementia Clinic of the Department of Neuropsychiatry, Kumamoto University Hospital and their family caregivers participated in this study. Inclusion criteria were 1) diagnosis of AD, DLB, or FTLD; 2) living at home; 3) age under 90 years; 4) no physical illness which would affect biochemical blood values, such as hepatic or kidney dysfunction or severe inflammation. First-visit patients with AD were recruited from April 2010 to November 2014, and those with DLB and FTLD from June 2007 to November 2014. This difference of the survey period is due to the difference of prevalence of each diagnosis, that is, DLB and FTLD is rare diagnoses compared with AD.

Patients who fulfilled the above criteria ($n = 339$) were examined by senior neuropsychiatrists who have adequate experience with dementia patients. All patients underwent routine laboratory tests, neuroimaging studies such as magnetic resonance imaging and single-photon emission computed tomography, and standard neuropsychological examinations. Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised [12]. Patients were diagnosed with probable AD, defined according to the National Institute for Neurological and Communicative Disorders and Stroke and the

Alzheimer's Disease and Related Disorders Association [13]; probable DLB, defined according to the Consensus Criteria for the clinical diagnosis of DLB, 2005 [14]; or probable FTLT, defined according to the Consensus Criteria for the clinical diagnosis of FTLT [15].

Measures

Total protein, albumin, and hemoglobin were assessed as biological blood markers related to malnutrition. Malnutrition was defined as total protein level <6.5 g/dL and serum albumin <3.5 g/dL [16, 17]. For hemoglobin, we set abnormal levels according to sex (<12 g/dL for men; <11 g/dL for women) because men and women have different hemoglobin levels [18].

Other variables assessed were age, sex, years of education, duration of illness, cognitive function, and appetite/weight change. Cognitive function was assessed with the Mini-Mental State Examination (MMSE) [19]. The MMSE is a widely used cognitive screening test that assesses the severity of cognitive impairment. Scores range from 0 to 30, with higher scores indicating better cognitive functioning. To assess changes in appetite and weight, we used a part of the Japanese version of the 12-item Neuropsychiatric Inventory [20, 21]. The Neuropsychiatric Inventory, a semi-structured interview with a caregiver, is used to assess the behavioral and psychological symptoms of dementia. We used a subquestion in the domain of "Appetite and eating change." Patients with "loss of appetite" or "weight loss" during the past month were regarded as "having loss of appetite or weight."

Statistical analysis

First, we compared the prevalence of low total protein, serum albumin, and hemoglobin among AD, DLB, and FTLT groups with the chi-square test and Z-test for comparison of column proportions. Next, we conducted polytomous logistic regression analysis to clarify the likelihood of low total protein, serum albumin, and hemoglobin among the three groups after adjusting for age. Then, the Pearson's correlation coefficients were calculated between biochemical markers and demographic and clinical factors. Finally, we examined the perception of patients' nutritional status among caregivers of patients with biochemical indications of malnutrition.

All tests were two-tailed and the significance levels were set at $p < 0.05$. All statistical analyses were performed with SPSS 23.0J for Windows (IBM SPSS Japan, Tokyo, Japan).

Results

Demographic and clinical characteristics of the patients are shown in Table 1. Mean patient age was lower in the FTLT group than in the AD and DLB groups. There were no significant differences among the three diagnostic groups in sex, years of education, duration of illness, or MMSE scores.

There were significant differences in total protein among the three diagnostic groups, but in post hoc testing, the differences were not significant. The prevalence of low albumin was significantly higher among patients with DLB (6.2%) than among those with AD (0.8%) ($p < 0.05$). Among female patients, the prevalence of low hemoglobin was significantly higher in the DLB group (10.3%) than in the AD group (1.2%) ($p < 0.05$). There were no significant differences in hemoglobin levels among male patients (Table 2).

Polytomous logistic regression analysis adjusting for age among the three diagnostic groups showed that DLB and FTLT patients were 7.2 times and 10.1 times more likely, respectively, to have low serum albumin than AD patients (DLB: Wald = 4.983, $p = 0.026$; FTLT: Wald = 4.014, $p = 0.045$). Female DLB patients were also 9.1 times more likely to have low hemoglobin (Wald = 6.208, $p = 0.013$) than female AD patients. There were no significant

Table 1. Demographic and other characteristics of the three diagnostic groups.

	AD (n = 238)	DLB (n = 65)	FTLD (n = 36)	F/ χ^2	p
Mean age, years ^a	77.3	78.4	68.1	23.5	<0.001
Sex, M/F (n)	69/169	26/39	12/24	2.923	0.232
Mean years of education	10.7	10.2	10.9	1.465	0.233
Mean duration of illness, years	2.5	2.4	2.8	0.623	0.537
Mean MMSE score	19.3	18.6	17.7	1.441	0.238

AD, Alzheimer's disease; DLB, Dementia with Lewy bodies; FTLD, Frontotemporal lobar degeneration; MMSE, Mini-Mental State Examination

^a AD, DLB > FTLD (p<0.001)

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differences among the three diagnostic groups in total protein or in hemoglobin among the men (Table 3).

We calculated the Pearson's correlation coefficient between each biochemical marker and demographic and clinical factors. Age was significantly correlated with albumin level in AD ($r = -0.343$, $p < 0.01$) (Bonferroni-corrected p-value). There were no significant correlations between biochemical markers and other factors (duration of illness, years of education, and MMSE).

We examined the association between biochemical levels and caregivers' perceptions of patients' loss of appetite or weight. Of the 28 patients who were diagnosed with malnutrition based on total protein, serum albumin, or hemoglobin level, all but one family caregiver (96.4%) answered that the patient had neither loss of appetite nor weight loss.

Discussion

This study is the first to clarify malnutrition according to type of dementia by assessing biochemical blood markers of nutritional status. In our study, the biochemical indicators of malnutrition were at lower levels in DLB and FTLD patients than in AD patients. In one of the few studies that have compared nutritional status by type of dementia, Roque et al. reported that malnutrition was more frequently seen in patients with DLB [10], which is consistent with our results. The prevalence of malnutrition among patients with FTLD was not higher than among those with AD and DLB in simple comparison. However, after adjusting for age among types of dementia, the prevalence of malnutrition was higher in the FTLD group than in the AD group. It would be generally natural to think that malnutrition in FTLD is rare, because eating problems such as preference for certain foods and overeating are frequently seen in FTLD. In fact, a previous study reported higher Body Mass Index in FTLD than in other types of

Table 2. Prevalence of abnormal blood marker values (%).

	AD (n = 238)	DLB (n = 65)	FTLD (n = 36)	χ^2	p	
Total protein <6.5 g/dL	3.4	9.2	11.1	6.194	0.045	
Albumin <3.5 g/dL	0.8	6.2	5.6	8.041	0.018	AD<DLB
Hemoglobin <12 g/dL (males)	5.8	7.7	0	0.931	0.628	
Hemoglobin <11 g/dL (females)	1.2	10.3	4.2	0.035	0.011	AD<DLB

Chi-square test and Z-test were used to compare column proportions.

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Table 3. Odds ratio of abnormal levels of biochemical blood markers (reference = AD).

		Odds ratio (95% CI)	
	AD (n = 238)	DLB (n = 65)	FTLD (n = 36)
Total protein <6.5 g/dL	1	2.8 (0.9–8.5)	3.2 (0.7–14.0)
Albumin <3.5 g/dL	1	7.2 (1.3–40.4)*	10.1 (1.1–97.7)*
Hemoglobin <12 g/dL (male)	1	1.3 (0.2–7.5)	-
Hemoglobin <11 g/dL (female)	1	9.1 (1.6–52.1)*	6.3 (0.5–77.5)

*p<0.05

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dementia [22], although that study did not adjust for age among dementia diagnostic groups. However, because the onset of FTLD is generally earlier than that of other types of dementia and because nutritional status worsens with age, comparison with adjustment for age is more appropriate. FTLD patients have many types of eating problems and often want to eat only certain foods [6], which might lead to unbalanced dietary intake and malnutrition [23].

Older people are generally more likely to develop malnutrition as they age, so our finding that albumin level correlated with patient age in AD was reasonable. Meanwhile, biochemical levels were not correlated with cognitive function, which was inconsistent with a previous study [24]. On the other hand, it is reported that loss of appetite is seen regardless of the stage of dementia [5]. This difference could result in part from selection bias: previous studies have evaluated patients with more severe dementia living in hospitals or nursing homes, whereas our data are from patients with milder dementia. Our result suggests that malnutrition can occur at any stage of dementia among dementia outpatients.

Most of the family caregivers of dementia patients with malnutrition reported that their patients did not have loss of appetite or weight. This result suggests that interviews with family caregivers might not be an accurate method of assessing nutritional status. A previous study that found that the nutritional status of dementia patients was associated with their caregivers' nutritional status [25], suggesting that family caregivers of patients with malnutrition might not be aware of the patients' nutritional status. Therefore, to assess the nutritional status of dementia patients, it is necessary not only to interview family caregivers but also to use objective indicators such as biochemical markers or body weight.

Although this is the first study to use biochemical blood markers to compare nutritional status among different types of dementia, there are some limitations to be addressed. The first and most important is that there is controversy regarding the validity of using biomarkers to assess nutritional status. To examine nutritional status precisely, it would be important to assess more various and broader aspects of nutritional state (e.g., other biochemical markers such as folate, vitamin B and D, BMI, meal surveys). Nonetheless, we think it is worth measuring core nutritional biomarkers, because some studies clarified that biochemical marker (total protein, albumin, and hemoglobin) and the Mini Nutritional Assessment was relatively correlated [24, 26]. The finding that feeding intervention for dementia patients improved albumin and hemoglobin levels [27] also supports the validity of assessing biochemical markers. Next, the sample size in FTLD and DLB is not enough because these are considerably rare diseases compared with AD [28]. A larger sample size would yield more reliable results. Third, it is also impossible to know whether differences in nutritional status among dementia diagnostic groups results from eating behavior that are typical for each diagnostic group, or if malnutrition itself causes certain types of dementia. The fourth limitation is that the participants were all outpatients and therefore their dementia was relatively mild and their level of nutrition was generally good. Our research should be viewed as preliminary for these important limitations,

and further researches are needed that examine the possibility of malnutrition multidimensionally in DLB and FTLD using larger sample sizes.

In conclusion, serum albumin and hemoglobin were lower among patients with DLB and FTLD than among those with AD when adjusting for age. This is a preliminary study; more substantive research is needed to clarify the factors that cause differences in albumin and hemoglobin levels among dementia diagnostic groups. Also, family caregivers of dementia patients with biochemical markers of malnutrition did not recognize patients' loss of appetite or weight loss. It is important to understand the discrepancy between biomarkers and caregivers' impression of nutritional status in the clinical setting. Multidimensional nutritional assessment in patients with dementia (e.g., BMI, meal survey, and more extensive nutritional markers such as folate, vitamin B and D) would be needed in future studies.

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Author Contributions

Conceived and designed the experiments: AK MH HT NF MM YM YH RF NH ST KM MK MI. Performed the experiments: AK MM. Analyzed the data: AK MH MM. Wrote the paper: AK MH MI.

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