Table 4. Step-wise multiple linear regression of care recipients' and caregivers' variables on ZBI score

	B	SE	β	p
Caregiver GDS-15	1.899	0.143	0.420	<0.001
Level of severity of dementia	3.151	0.482	0.201	<0.001
Basic ADL score	−0.374	0.091	−0.128	<0.001
Fall experience	3.511	1.069	0.098	0.001
Recipient GDS-15	0.462	0.151	0.097	0.002

$R^2 = 0.334$, adjusted $R^2 = 0.329$.
The following variables were added to the analysis: care recipient's age and gender, fall history in the past 6 months, GDS-15 and bADL scores, Carlson comorbidity index, level of severity of dementia, the presence of COPD, age and gender of caregiver, caregiver's GDS-15 score, type of caregiver–care receiver relationship (spouse or child), and the physical health status of caregiver.

presence of COPD, as well as the age and gender of the caregiver, caregiver's GDS-15 score, type of caregiver-care receiver relationship (spouse or child), and the physical health status of the caregiver were entered into the regression analyses. The best set of predictors of burden, identified by stepwise linear regression, was the caregiver's GDS-15 score, level of severity of dementia, bADL score, fall history in the past 6 months, and care recipient's GDS-15 score. These variables accounted for 33% of the total variance in burden. When the presence of dementia and behavioral disturbance, rather than the level of severity of dementia, were entered into the analysis, the predictors of caregiver's GDS-15 score, presence of behavioral disturbance, bADL score of the care recipient, presence of dementia, fall history, and GDS-15 score of the care recipient were identified (adjusted $R^2 = 0.33$).

DISCUSSION

The present study demonstrated that previous fall history is associated with caregivers' burden. This association persists even when controlling for various possible confounding factors such as ADL status and the presence of chronic diseases including dementia. Although the exact reasons for this association are unknown, it is possible that the majority of caregivers are frightened about their family member falling, and that fall history leads to the psychological distress in the caregiver, which may be related to the caregiver's burden.

Consistent with previous reports (Colerick and George, 1986; Vedhara *et al.*, 1999; Yaffe *et al.*, 2002; Pinquart and Sorensen, 2003), the presence of dementia and behavioral disturbance, physical impairment, and caregiver depressive mood are independent predictors of caregiver burden in the present study. Numerous studies have demonstrated the burden of caregivers of chronic psychiatrically ill elderly, and most are caregivers of demented elderly. It has been reported that depressive symptoms in elderly persons are independently associated with significantly higher levels of informal care-giving, even after adjustment for the effects of major coexisting chronic conditions (Langa *et al.*, 2004). Patient depression was also associated with poor caregiver quality of life (Sewitch *et al.*, 2004). However, few studies had been conducted to examine the association between caregiver burden and recipient depressive mood. One study using a small sample size from outpatient mental clinics reported that patients' behavior and mood disturbance are associated with caregiver burden (Scazufca *et al.*, 2002). In the present study it was clearly demonstrated that care recipient depressive mood is associated with caregiver burden. Although depression is known to be frequently associated with cognitive and physical impairment, this association persists even when adjusting for these factors. Although in this study the level of care-giving was not estimated, it appears that higher levels of care-giving to the depressed elderly reflect the caregiver's burden. It has been reported that depressive mood might be one of the risk factors of falls (Cesari *et al.*, 2002), although we still do not know if depression is a consequence of falls or if depression triggers the fall. Therefore, it is possible that the care recipient depressive mood associated with falls may affect caregiver burden.

Several potential limitations of this study are noted. First, the participants, although a community-based sample, were frail elderly eligible for the LTCI program and, therefore, it may not be possible to generalize the results to healthy elderly. Second, other factors that have been demonstrated to be related to the caregiver's burden, including incontinence of the care recipient (Flaherty *et al.*, 1992) and durations of care-giving (McConaghy and Caltabiano, 2005), were not incorporated into this analysis. Therefore, the possibility exists that a variable omitted from the analysis may contribute to the burden of the caregiver. Economic status and perceived social support may also be related to caregiver burden (Murray *et al.*, 1999). However, the economic status, which was classified into three subjective categories, as well as the number of formal services used, did not correlate with caregiver burden in this study's population (data not shown). Third, the number of falls in the past 6 months was not available in the baseline data of the participants of the NLS-FE. Therefore, the effect of the fall frequency on caregiver burden has not been evaluated.

KEY POINTS

- Little attention has been paid to the impact on caregivers who provide care to a family member who has falls.
- We demonstrated that the fall history in the past 6 months of the frail elderly living in the community, as well as care recipient depressive mood, was associated with caregiver burden.
- Preventing falls is important, not only for the frail elderly but also for their caregivers, to reduce care burden.

In the present study it was demonstrated that fall history in the past 6 months, as well as care recipient depressive mood, is associated with caregiver burden. It appears that preventing falls is important, not only for the frail elderly but also for their caregivers, to reduce care burden. In addition, health care professionals should inquire about the adequacy of social support for their elderly patients with depressive symptoms and should also be alert to potential caregiver burden among the family members who provide care.

ACKNOWLEDGEMENTS

This study was supported by a Grant-in Aid for the Comprehensive Research on Aging and Health from the Ministry of Health, Labor, and Welfare of Japan, and a grant from Mitsui Sumitomo Insurance Welfare Foundation. The authors wish to thank all the patients, caregivers and the many nurses participating in the study, and the Nagoya City Health Care Service Foundation for Older People for their vigorous cooperation.

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Underuse of Medications for Chronic Diseases in the Oldest of Community-Dwelling Older Frail Japanese

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OBJECTIVES: To test the following hypotheses: (1) the rate of polypharmacy, defined as six or more prescribing medications, is lower in the oldest old (≥85) than in younger older people (65–84); (2) beneficial medication use is lower in the oldest old; (3) the underuse of these medications in the oldest old is associated with physical or cognitive impairment or comorbid conditions.

DESIGN: A cross-sectional study of the baseline data from the Nagoya Longitudinal Study for Frail Elderly.

SETTING: Community-based.

PARTICIPANTS: One thousand eight hundred seventy-five community-dwelling older people (632 men, 1,243 women).

MEASUREMENTS: The data, which were collected at the patients' homes or from care-managing center records, included the clients' demographic characteristics, depression status as assessed using the short version of the Geriatric Depression Scale, a rating for basic activities of daily living (ADLs), prescribed medications, and physician-diagnosed chronic diseases.

RESULTS: The oldest old had less polypharmacy even after controlling for ADLs and comorbid conditions. The underuse of beneficial medications for the oldest old was observed after adjusting for ADLs, cognitive impairment, comorbid conditions, antithrombotic agents for subjects with a history of cardiovascular diseases, acetylcholinesterase inhibitors for those with dementia, and antidepressants for those with depression. However, being aged 85 and older was not associated with the underuse of hypoglycemic and antihypertensive agents by those with diabetes mellitus and hypertension, respectively.

CONCLUSION: Among community-dwelling frail older people, the rate of polypharmacy is lower in the oldest members than in the younger ones. The underuse of prescribed medications for chronic diseases/conditions of frail older people is common but not for all conditions. J Am Geriatr Soc 54:598–605, 2006.

Key words: polypharmacy; undertreatment; elderly

It has been reported that the underuse of medications, defined as the omission of drug therapy that is indicated for the treatment or prevention of a disease or condition, is an important and increasingly recognized problem in older people.[1,2] The underprescribing of drugs seems to have a negative effect on health outcomes for older people,[3,4] but apart from concern about the risks of the excess prescribing of inappropriate or unnecessary drug therapy for older people,[5,6] there is still insufficient knowledge about the adverse consequences associated with the underprescribing of beneficial drug therapies. It is not known whether all kinds of medications are underused in older people or whether specific medications for specific chronic diseases or conditions are selectively underused in older people. In addition, knowledge about the factors that influence the underuse of medications for the common chronic diseases of older people is sparse. There is also a lack of knowledge about how functional and psychological factors influence the use of medication by physicians or how frailty and comorbidity affect drug use by older people.

The national policy in not only Japan but also Western countries is to enable elderly people to retain their independence as long as possible, to have a high quality of life, and to continue living at home as long as they can. It is essential to prevent frail older people from suffering from recurrent diseases and additional illnesses that would require them to receive care in an acute setting or to be admitted to a nursing home or to cause mortality. Therefore, preventive medication for chronic diseases/conditions is important for frail older people living in a community setting.

In the present study targeting frail, community-dwelling elderly persons (≥65), the following hypotheses were tested: (1) the rate of multiple medication use is lower in the oldest people (≥85) than in younger ones (65–84); (2) beneficial medication use for common chronic conditions such as cardiovascular disease (CVD), dementia, depression,

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DOI: 10.1111/j.1532-5415.2006.00659.x

0002-8614/06/$15.00

diabetes mellitus, and hypertension is lower in the oldest people than in younger ones; and (3) the underuse of these medications in the oldest old is associated with physical impairment, cognitive impairment, or comorbid conditions.

METHODS

Study Design and Subjects

The present study consisted of a cross-sectional analysis of 1,875 elderly persons (632 men, 1,243 women) who participated in the Nagoya Longitudinal Study for Frail Elderly (NLS-FE). The study population was community-dwelling older people (≥65) eligible for long-term care insurance (LTCI) who lived in Nagoya City, Japan, and were provided various home care services from the Nagoya City Health Care Service Foundation for Older People, which has 17 visiting nursing stations associated with care-managing centers. Japan introduced a universal-coverage LTCI program in April 2000[7,8] that covers care for people aged 65 and older and people aged 40 and older with 15 specific diseases such as cerebrovascular disease and presenile dementia. Under the LTCI program, care levels (Level 0 to Level 5) are determined according to eligibility criteria. Older people in the community who are eligible for LTCI are frail and chronically ill, have physical and mental problems, and are easy to admit to an acute hospital or institute setting. During the registration period for the NLS-FE (November 1, 2003, to December 31, 2003), 1,875 of 3,630 elderly clients agreed to participate in this study. The NLS-FE participants were scheduled to undergo comprehensive in-home assessments at baseline and 6, 12, and 24 months by trained nurses. In the present study, the cross-sectional data from the baseline assessment were used. Informed consent for participation was obtained verbally from the patients or, for those with substantial cognitive impairment, from a surrogate (usually the closest relative or legal guardian), as well as from caregivers, according to procedures approved by the institutional review board of Nagoya University Graduate School of Medicine.

Data Collection

Three hundred twenty-eight nurses visited the clients' homes and collected the data using standardized interviews with patients or surrogates and caregivers and from care-managing center records. The data included clients' demographic characteristics, depressive symptoms as assessed using the short version of the Geriatric Depression Scale (GDS-15),[9] and a rating for seven basic activities of daily living (ADLs) (feeding, bathing, grooming, dressing, toileting, walking, and transferring), with summary scores ranging from 0 (total disability) to 20 (no disability).[10]

Information obtained from care-managing center records included the following physician-diagnosed chronic conditions: ischemic heart disease, congestive heart failure, liver diseases, cerebrovascular disease, diabetes mellitus, dementia, chronic obstructive pulmonary disease, renal disease, cancer, hypertension, pressure ulcer, depression, and diseases constituting the Charlson Comorbidity Index,[11] which represent the sum of a weighted index that takes into account the number and seriousness of preexisting comorbid conditions. In the present study, only a limited number of subjects diagnosed for depression by a physician according to the care-managing center records were observed. Therefore, the participants were considered to be depressed if their GDS-15 score was 6 or higher.

The data also included the number of prescribed medications and their corresponding therapeutic classes, including antihypertensive drugs, antiplatelets, anticoagulants, antipsychotic medications (including antidepressants), hypoglycemics, nonsteroidal antiinflammatory drugs and acetaminophen, anti-Alzheimer's disease drugs (acetylcholinesterase inhibitors), gastrointestinal medications, and insulin. The information about regular prescribed medications was recorded in interviews with patients and caregivers and taken from prescription records and classified by nurses using standard instruments. Clients eligible for LTCI have their own primary care physicians, who submit a report on their clinical status every 6 months.

Statistical Analysis

Analysis of variance with a Bonferroni correction for multiple comparisons was used to determine differences between age groups (65–74, 75–84, and ≥85) for continuous variables, and the Kruskal-Wallis test was used to test categorical variables. The chi-square test was used to compare the presence of chronic diseases/conditions or the number of prescription medications used between age groups. Univariate and multivariate logistic regression was used to determine which characteristics of older people predicted multiple medication use or the underuse of beneficial medication. For the logistic regression analysis, the ADL score (range 0–20) was categorized into three groups with approximately equal number of participants in each group: high function (≥18), mid function (12–17), and low function (≤11). The number of prescribed medications was also categorized into four groups (0, 1–2, 3–5, and ≥6). All analyses were performed using SPSS version 11.0 (SPSS, Inc., Chicago, IL).

RESULTS

Table 1 shows the characteristics of the participants according to age group. ADL score was lowest in the oldest old (≥85). The prevalence of a history of coronary heart disease, hypertension, and dementia increased, and the prevalence of diabetes mellitus decreased, with age. Polypharmacy, defined as six or more prescribed medications, decreased with age. To identify the factors influencing polypharmacy in frail older people in the community, logistic regression analysis was conducted (Table 2). Participants with congestive heart failure (odds ratio (OR) = 1.66, 95% confidence interval (CI) = 1.09–2.55), coronary heart disease (OR = 3.05, 95% CI = 2.16–4.31), and diabetes mellitus (OR = 1.51, 95% CI = 1.06–2.15) were more likely to be receiving multiple medications according to multivariate analysis. In contrast, participants with dementia were less likely to have been prescribed multiple medications (OR = 0.64, 95% CI = 0.48–0.84). The oldest old had less polypharmacy using univariate analysis (OR = 0.64, 95% CI = 0.49–0.82) and multivariate analysis (OR = 0.55, 95% CI = 0.39–0.77) controlled for sex, ADL dependency, and the presence of common chronic diseases.

Table 1. Characteristics of Community-Dwelling Frail Older People Stratified by Age

Characteristic	Total (N = 1,875)	Age 65–74 (n = 433)	Age 75–84 (n = 827)	Age ≥85 (n = 615)	*P*-value
Men/women (% of men/total)	632/1,243 (33.7)	191/242 (44.1)	275/552 (33.3)	166/449 (27.0)	<.001
Age, mean ± SD*	80.6 ± 7.7	70.5 ± 2.7	79.4 ± 2.8	89.3 ± 3.6	<.001
Activity of daily living score, mean ± SD (range 0–20)†	12.8 ± 6.6	12.6 ± 6.8	13.6 ± 6.3	11.8 ± 6.7	<.001‡
Charlson Comorbidity Index, mean ± SD†	2.0 ± 1.6	2.2 ± 1.7	1.9 ± 1.5	2.0 ± 1.5	.003§
GDS-15 score, mean ± SD (range 0–15)†	6.6 ± 3.6	6.8 ± 3.8	6.5 ± 3.6	6.5 ± 3.6	.38
Chronic diseases (% of total)					
Congestive heart failure	8.5	1.8	6.5	15.7	<.001
Coronary heart disease	12.2	7.0	12.5	15.2	<.001
Cerebrovascular disease	34.3	40.1	32.4	33.1	.03
Diabetes mellitus	12.0	16.1	12.3	8.9	.003
Dementia	34.4	24.8	31.0	45.7	<.001
Hypertension	24.3	19.4	24.5	27.3	.01
Depression (GDS-15 score ≥6)	57.2	58.4	56.7	57.1	.27
Cancer	9.1	9.1	8.8	9.6	.90
Use of medications (% of total)					
0	5.1	3.3	3.3	8.9	<.001
1–2	16.8	14.0	15.7	20.3	
3–5	41.9	41.9	43.2	40.2	
≥6	36.2	40.9	37.8	30.6	

*Analysis of variance or †Kruskal-Wallis was used for analysis; chi-square test was used for others.
‡Aged 65–74 vs 75–84, $P = .007$; 65–74 vs ≥85, $P = .003$; 75–84 vs ≥85, $P < .001$.
§Aged 65–74 vs 75–84, $P < .001$; 65–74 vs ≥85, $P = .02$; 75–84 vs ≥85, $P = .08$.
SD = standard deviation; GDS-15 = 15-item Geriatric Depression Scale.

Logistic regressions were conducted to evaluate the extent to which age group and the characteristics of older people were independent predictors of being prescribed essential medications. Univariate analysis showed the rates of prescription of antithrombotic agents (antiplatelet or warfarin), acetylcholinesterase inhibitors, and antidepressants in older people with a history of CVD (including coronary heart disease and stroke), dementia, and depressive symptoms, respectively, declined substantially with age (Table 3), but in participants with diabetes mellitus or hypertension, age did not influence hypoglycemic (oral hypoglycemic drugs or insulin) or antihypertension use. Being female was associated with the underuse of antithrombotic agents in older people with a history of CVD (male: OR = 1.80, 95%

Table 2. Logistic Regression Analysis for Polypharmacy

Characteristic	Univariate Odds Ratio (95% Confidence Interval)	Multivariate Odds Ratio (95% Confidence Interval)
Age (reference: 65–74)		
75–84	0.88 (0.69–1.11)	0.71 (0.53–0.95)
≥85	0.64 (0.49–0.82)	0.55 (0.39–0.77)
Male (reference: female)	1.26 (1.03–1.53)	1.05 (0.82–1.35)
Activity of daily living score (range 0–20) (reference: high function (≥18))		
Mid function (12–17)	1.26 (0.99–1.59)	1.35 (1.03–1.79)
Low function (≤11)	0.94 (0.74–1.19)	1.38 (0.99–1.89)
Presence of chronic diseases (reference: absence)		
Congestive heart failure	1.91 (1.36–2.68)	1.66 (1.09–2.55)
Coronary heart disease	2.65 (1.98–3.54)	3.05 (2.16–4.31)
Cerebrovascular disease	0.96 (0.78–1.18)	1.10 (0.84–1.43)
Dementia	0.59 (0.47–0.73)	0.64 (0.48–0.84)
Diabetes mellitus	1.59 (1.19–2.13)	1.51 (1.06–2.15)
Depression (Geriatric Depression Scale-15 score ≥6)	1.27 (1.02–1.58)	1.26 (0.99–1.59)
Hypertension	0.87 (0.69–1.08)	0.82 (0.62–1.08)

Table 3. Univariate Analysis of Characteristics Associated with Participants Receiving Medication

Characteristic	Antithrombotic Agent Use for History of CVD		Acetylcholinesterase Inhibitor Use for Dementia		Antidepressant Use for Depression		Hypoglycemic Use for Diabetes Mellitus		Antihypertensive Use for Hypertension	
	n, Odds Ratio (95% Confidence Interval)									
Age										
65–74	163,	1.00 —	83,	1.00 —	173,	1.00 —	60,	1.00 —	83,	1.00 —
75–84	290,	0.75 (0.51–1.10)	205,	1.00 (0.51–1.94)	348,	0.68 (0.34–1.35)	94,	1.56 (0.73–3.32)	196,	2.05 (0.99–4.27)
≥85	219,	0.48 (0.32–0.73)	202,	0.44 (0.21–0.93)	220,	0.40 (0.16–0.96)	48,	0.55 (0.25–1.26)	155,	1.92 (0.89–4.11)
Sex										
Female	391,	1.00 —	336,	1.00 —	465,	1.00 —	129,	1.00 —	302,	1.00 —
Male	281,	1.80 (1.32–2.46)	154,	0.79 (0.45–1.38)	276,	0.69 (0.36–1.35)	73,	0.75 (0.40–1.41)	132,	0.56 (0.31–1.03)
Activity of daily living score (range 0–20)										
High function (≥18)	167,	1.00 —	74,	1.00 —	237,	1.00 —	59,	1.00 —	160,	1.00 —
Mid function (12–17)	238,	1.14 (0.77–1.70)	180,	0.50 (0.27–0.93)	272,	0.93 (0.45–1.91)	71,	1.27 (0.56–2.88)	143,	0.88 (0.42–1.88)
Low function (≤11)	265,	0.81 (0.54–1.20)	233,	0.13 (0.06–0.28)	232,	0.88 (0.41–1.89)	72,	0.60 (0.28–1.29)	130,	0.57 (0.28–1.16)
Chronic diseases										
Congestive heart failure										
Absence	613,	1.00 —	438,	1.00 —	624,	1.00 —	189,	1.00 —	363,	1.00 —
Presence	59,	0.89 (0.52–1.54)	51,	0.22 (0.05–0.94)	63,	0.51 (0.12–2.15)	13,	0.30 (0.10–0.94)	42,	2.75 (0.64–11.78)
CVD										
Absence			221,	1.00 —	390,	1.00 —	110,	1.00 —	201,	1.00 —
Presence			268,	0.28 (0.16–0.48)	297,	0.48 (0.23–0.97)	92,	0.71 (0.38–1.31)	204,	1.12 (0.61–2.07)
Dementia										
Absence	380,	1.00 —			507,	1.00 —	130,	1.00 —	236,	1.00 —
Presence	268,	0.67 (0.49–0.93)			161,	1.49 (0.73–3.02)	65,	0.48 (0.25–0.91)	154,	0.62 (0.33–1.14)
Depression										
Absence	198,	1.00 —	120,	1.00 —			67,	1.00 —	154,	1.00 —
Presence	297,	1.26 (0.87–1.81)	161,	1.06 (0.54–2.08)			90,	0.65 (0.31–1.37)	184,	1.30 (0.64–2.62)
Diabetes mellitus										
Absence	580,	1.00 —	424,	1.00 —	597,	1.00 —			328,	1.00 —
Presence	92,	0.89 (0.57–1.40)	65,	0.96 (0.45–2.03)	90,	1.18 (0.48–2.90)			77,	0.72 (0.35–1.48)
Hypertension										
Absence	468,	1.00 —	336,	1.00 —	557,	1.00 —	125,	1.00 —		
Presence	204,	0.54 (0.38–0.76)	154,	0.50 (0.27–0.93)	184,	1.14 (0.58–2.27)	77,	1.15 (0.61–2.19)		

CVD = cardiovascular disease.

Table 4. Multivariate Analysis of Characteristics Associated with Participants Receiving Medication

Characteristic	Antithrombotic Agent Use for History of CVD (n = 480)	Acetylcholinesterase Inhibitor Use for Dementia (n = 280)	Antidepressant Use for Depression (n = 668)	Hypoglycemic Use for Diabetes Mellitus (n = 154)	Antihypertensive Use for Hypertension (n = 302)
	Odds Ratio (95% Confidence Interval)				
Age (reference 65–74)					
75–84	0.90 (0.56–1.42)	0.67 (0.25–1.82)	0.59 (0.28–1.26)	1.39 (0.54–3.54)	1.98 (0.75–5.19)
≥85	0.53 (0.32–0.90)	0.21 (0.06–0.71)	0.33 (0.12–0.91)	0.53 (0.19–1.49)	1.48 (0.55–3.98)
Sex (reference female)					
Male	1.57 (1.08–2.30)	1.20 (0.54–2.68)	0.74 (0.35–1.57)	0.93 (041–2.13)	0.79 (0.34–1.80)
Activity of daily living score (reference high function (≥18))					
Mid function (12–17)	1.17 (0.74–1.84)	0.56 (0.24–1.29)	0.91 (0.40–2.03)	1.73 (0.66–4.53)	0.94 (0.39–2.27)
Low function (≤11)	0.94 (0.58–1.54)	0.07 (0.02–0.26)	0.96 (0.40–2.31)	1.28 (0.49–3.58)	0.80 (0.29–2.20)
Presence of chronic disease (reference absence)					
Congestive heart failure	1.18 (0.61–2.27)	0.29 (0.03–2.46)	0.63 (0.14–2.82)	0.26 (0.06–1.01)	1.93 (0.41–9.14)
CVD		0.26 (0.12–0.57)	0.45 (0.21–0.97)	0.95 (0.43–2.10)	1.70 (0.75–3.86)
Dementia	0.92 (0.61–1.39)		1.88 (0.87–4.05)	0.68 (0.28–1.66)	0.73 (0.32–1.65)
Depression	1.25 (0.85–1.84)	1.75 (0.80–3.82)		0.62 (0.27–1.39)	1.54 (0.72–3.29)
Diabetes mellitus	0.56 (0.32–0.99)	0.73 (0.23–2.34)	0.85 (0.31–2.29)		0.77 (0.30–1.97)
Hypertension	0.69 (0.45–1.05)	0.37 (0.15–0.92)	1.40 (065–2.99)	1.28 (0.54–3.03)	

CVD = cardiovascular disease.

CI = 1.32–2.46), and having a higher ADL dependency was associated with the underuse of acetylcholinesterase inhibitors in those with dementia (low ADL function: OR = 0.13, 95% CI = 0.06–0.28). In older people with dementia or diabetes mellitus, those with heart failure were less likely to be prescribed acetylcholinesterase inhibitors (OR = 0.22, 95% CI = 0.05–0.94) and hypoglycemics (OR = 0.30, 95% CI = 0.10–0.94). In older people with dementia or depression, those with a history of CVD were less likely to be prescribed acetylcholinesterase inhibitors (OR = 0.67, 95% CI = 0.49–0.93) and antidepressants (OR = 0.48, 95% CI = 0.23–0.97). The presence of dementia was associated with the underuse of antithrombotic agents and hypoglycemic drugs in older people with a history of CVD (OR = 0.67, 95% CI, 0.49–0.93) and those with diabetes mellitus (OR = 0.48, 95% CI = 0.25–0.91).

Multivariable analysis showed that the oldest age group received fewer antithrombotic agents (OR = 0.53, 95% CI = 0.32–0.90), acetylcholinesterase inhibitors (OR = 0.21, 95% CI = 0.06–0.71), and antidepressants (OR = 0.33, 95% CI = 0.12–0.91) among older people with a history of CVD and those diagnosed with dementia and with depressive symptoms, respectively (Table 4). When a separate analysis was conducted of the participants with a history of stroke and those with a history of coronary heart disease, the oldest age group was less likely to be prescribed antithrombotic agents in subjects with a history of coronary heart disease (OR = 0.29, 95% CI = 0.09–0.91) but not with stroke (OR = 0.66, 95% CI = 0.37–1.19). Analysis also showed that women with a history of CVD were less likely than men with CVD to be prescribed antithrombotic agents (male: OR = 1.57, 95% CI = 1.08–2.30) and that having a low ADL function was associated with the underprescription of acetylcholinesterase inhibitors (low ADL function: OR = 0.07, 95% CI = 0.02–0.26) in older people with dementia. In older people with hypertension or diabetes mellitus, none of the factors studied were associated with the underprescription of antihypertensive or hypoglycemic drugs, respectively. In older people with depressive symptoms, those with a history of CVD were less likely to be prescribed antidepressants (OR = 0.45, 95% CI = 0.21–0.97).

DISCUSSION

In the present study, the presence of various chronic diseases, including congestive heart failure, coronary heart disease, and diabetes mellitus, was demonstrated to influence multiple medication use in community-dwelling frail older people. In contrast, participants with dementia were less likely to be prescribed multiple medications. Whether doctors prescribe differently for patients with cognitive impairment is a controversial issue. Some studies have shown that fewer drugs are prescribed for patients with dementia than for those without,[12,13] but other studies have demonstrated no significant difference between patients with and without dementia in the average number of medications prescribed.[14,15] Nevertheless, it is more important to know the influence of the presence of cognitive impairment on the use of beneficial medication for specific chronic diseases than that on the total number of prescribed medications. This study also showed, using a multivariate logistic regression model controlling for other confounding factors, that the oldest age group (≥85) is less likely to be prescribed multiple medications. It is possible that these oldest patients do not see their primary care physician, even if they have chronic diseases or conditions, but this was found not to be true, because the number of visits they made to their primary physician per month was not a predictor of underuse of medication for chronic diseases and conditions (data not shown). These results prove the hypothesis that the rate of multiple medication use is lower in the oldest community-dwelling frail older people (≥85) than in the younger old.

Previous studies have showed that nursing home residents aged 85 and older are less likely to be treated than those aged 65 to 74 for stroke secondary prevention[16] and that there is a marked underuse of aspirin in the treatment of older patients with documented prior myocardial infarction at the time of admission to a nursing home.[17] In agreement with these studies based at the nursing home, the present study targeting community-dwelling older people demonstrated that the oldest subjects with a history of CVD were less likely to be prescribed antithrombotic agents for secondary prevention. Nevertheless, when a separate analysis was conducted of the participants with a history of stroke and those with a history of coronary heart disease, older age was still a predictor of nonuse of antithrombotic agents in subjects with a history of coronary heart disease but not with stroke. In the present survey, hemorrhagic and ischemic stroke were not differentiated between in the stroke diagnosis. Although ischemic strokes account for 85% of all strokes of persons aged 65 and older according to the Japanese national survey, it is possible the inclusion of hemorrhagic stroke affected the analysis.

In the present study, the oldest group univariate and multivariate analyses indicated underuse of acetylcholinesterase inhibitors by older people with dementia. It is possible that a higher proportion of the oldest elderly might have a severe form of Alzheimer's disease and therefore not be eligible for treatment with acetylcholinesterase inhibitors. Few published studies on the use of antidepressants have focused on the older population, even though the prevalence of depression is high in community-dwelling elderly persons. In the present study, 57.2% of the participants had a GDS-15 score of 6 or higher, although only 2% of the subjects were diagnosed with depression in primary care settings, consistent with reports from other countries that the majority of older people with depression are not diagnosed in primary care.[18,19] Alternatively, potentially effective antidepressant medications are also used inadequately in older populations. According to the data from a national survey in Canada, the rate of antidepressant use was 3.1% in older people in the community. Of those who were depressed, 4.2% were taking an antidepressant.[20] In the current survey, only 5.9% of subjects who had depressive symptoms received antidepressants, and univariate analysis showed that the oldest old with depression were less likely to use antidepressants than those who were younger. The multivariate analysis confirmed this association.

Only several reports on the rate of drug treatment for diabetes mellitus in older people have been found. One cross-sectional study demonstrated that the likelihood of drug treatment for people with diabetes with insulin or oral

hypoglycemics declined substantially with increasing age.[21] In the present study, the use of hypoglycemic agents by older people diagnosed with diabetes mellitus was the lowest in the oldest persons, and in comparison with persons aged 65 to 74, the OR of hypoglycemic use in the oldest old was 0.53 using multivariable logistic regression analysis, although the *P*-value did not reach statistical significance ($P = .23$).

In this population of frail older people living at home, the nonuse of antihypertensive medication was relatively low in older people with hypertension, and no difference in the ratio of the prescription of antihypertensive drugs between age categories was found. Furthermore, no association was detected between the nonuse of antihypertensive medication and any factors tested, not only in the univariate analysis but also in the multivariate analysis. This is in contrast to previous studies showing that older people were likely to be undertreated for hypertension.[22,23]

It has been suggested that ADL impairment, cognitive impairment, and comorbid conditions are factors influencing the underprescription of beneficial agents in older people associated with chronic diseases: the underuse of antithrombotic agents by stroke patients with severe cognitive or physical impairment,[16,24] hypoglycemic agents underuse by older people with diabetes mellitus with higher levels of comorbidity,[21] and the underuse of antihypertensive medication by older people with cognitive impairment or comorbidity.[22,23] Nevertheless, in the current study, even after controlling for ADL dependency and the presence of dementia, age was still a significant predictor of the nonuse of antithrombotic agents by older people with a history of CVD, acetylcholinesterase inhibitors by older people with dementia, and antidepressants by older people with depression. In addition, the present study suggests that the influence of ADL dependency, cognitive impairment, and comorbid conditions on the underuse of beneficial medications was also dependent on each chronic disease/condition. The lowest category of ADL function was only associated with the nonuse of acetylcholinesterase inhibitors by the demented elderly using multivariable logistic regression analysis. The presence of dementia was associated with the nonuse of antithrombotic agents by the participants with a history of CVD in univariate analysis, but multivariate analysis did not confirm this association. Furthermore, no association was detected between the nonuse of antihypertensive medication and the presence of dementia in univariate and multivariate analysis. It is possible that, to avoid the risk of adverse drug reactions, physicians decide not to use beneficial medications for the oldest old, although multiple medication use may not always be a disadvantage for older people with comorbid conditions when drugs with proven efficacy in elderly patients are available. These results suggest again that it is not easy to predict the underuse of prescribed beneficial medication in older persons but is instead complex and dependent on each chronic disease/condition. The history of CVD was associated with the nonuse of acetylcholinesterase inhibitors by older people with dementia using univariate and multivariate logistic regression analysis. It is possible that the origin of dementia for most of them might be vascular.

There are many factors that contribute to the underuse of beneficial medications in the oldest old. The use of age as an indicator of benefit of care is imprecise, in that elderly persons differ appreciably in physical, mental, and cognitive status and in life expectancy. It is of concern that the very population that receives the most medications may not always have a favorable risk/benefit ratio. Physicians may decide not to use a medication, because patients may not benefit from treatment (e.g., the low use of acetylcholinesterase inhibitors by demented older people with the lowest ADL function). In fact, geriatric therapeutics must also take into account specific geriatric diseases (e.g., dementia, CVD) and syndromes (e.g., falls, gait and balance disturbances, incontinence, ADL impairment). As proposed by others,[25] the lack of high-quality evidence derived from clinical studies with relevance to treating older patients with multiple chronic medical conditions may be one of the factors that contribute to the underuse of beneficial medications in the oldest old. In fact, clinical evidence often does not provide a definitive answer on the benefits or risks of many drug therapies in older people, especially in those aged 75 and older.[26] Of a number of chronic diseases common in older people, the evidence for drug therapy has been accumulating in the field of hypertension faster than with other diseases. This may be one of the reasons that the highest prescription rate is for antihypertensive medication and the reason there is no restriction of treatment in the oldest patients.

A recent study indicated that the cost of prescription drugs is another problem contributing to the undertreatment of diseases in older people.[27] These cost-related problems seem to be dependent on health insurance systems, which vary between countries. In Japan, universal mandatory health insurance, which covers nearly all regular health care, including prescription drugs, covers the entire population. Elderly health insurance for people aged 75 and older or aged 65 and older with some impairments covers health care, including prescription drugs, with a 10% copayment. Therefore, it is unlikely that cost problems influenced these results or that their influence, if any, was great.

The major limitation of this study was that diagnoses of chronic diseases were based solely on information available in the care-managing centers' records, which were based on the data provided by primary care physicians every 6 months. The accuracy of the diagnosis of chronic diseases by these physicians was not evaluated. It was also not discovered how severe these chronic conditions, which included dementia, diabetes mellitus, and hypertension, were. The results may not be representative of frail older Japanese in the community as a whole, because the subjects in this study represented an urban population. In addition, these findings may not be generalizable to other populations given that health practices, ethnic attitudes about treating very old people, and cost/access to medications may influence these results. Because of the small numbers of participants with each chronic condition, these observations cannot be commented on conclusively. The findings of this study need to be reproduced in a larger sample of practices.

In summary, it was demonstrated that, among community-dwelling frail older people, the rate of multiple medication use is lower in the oldest persons than in the younger ones. In addition, the underuse of beneficial medication for the oldest persons in this group was observed: antithrombotic agents by subjects with a history of CVD,

acetylcholinesterase inhibitors by subjects with dementia, and antidepressants by subjects with depression. Nevertheless, the oldest persons with diabetes mellitus and hypertension were not associated with the underuse of hypoglycemic and antihypertensive agents, respectively. Thus, the underuse of prescribing medication for chronic diseases/conditions of frail older people living in the community is common but not for all conditions.

ACKNOWLEDGMENTS

Financial Disclosure: This study was supported by a Grant-in-Aid for Comprehensive Research on Aging and Health from the Ministry of Health, Labor, and Welfare of Japan and a grant from Mitsui Sumitomo Insurance Welfare Foundation. The authors have no conflicts of interest with the manufacturers of any drug evaluated in this paper.

Author Contributions: Masafumi Kuzuya: study concept, design, conduct of study, interpretation of data, and preparation of manuscript. Yuichiro Masuda and Yoshihisa Hirakawa: conduct of study, interpretation of data. Mitsunaga Iwata: analysis and interpretation of data. Hiromi Enoki: statistical analysis and interpretation of data. Jun Hasegawa and Xian Wu Cheng: acquisition of data. Akihisa Iguchi: study concept and study supervision.

Sponsor's Role: The sponsor had no role in the design, methods, subject recruitment, data collection, analysis, or manuscript preparation.

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WAIS-R のプロフィールを用いた Mild Cognitive Impairment とアルツハイマー型痴呆の比較

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認知神経科学

Vol. 8　No. 1　2006 年 3 月発行

原　著

WAIS-Rのプロフィールを用いたMild Cognitive Impairmentとアルツハイマー型痴呆の比較†

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Key words: MCI, AD, WAIS-R, ADAS, プロフィール、数唱

【要旨】 痴呆性疾患の前駆状態を表す概念として、軽度認知障害（MCI: Mild Cognitive Impairment）が提唱されている。本研究ではMCIとADの高次脳機能障害の特徴を検討するために、WAIS-Rを用いてIQ、下位検査とプロフィール得点を検討した。Petersen（1995）の基準を満たすMCI患者9名とAD患者3名を対象とし、ADASとWAIS-Rを実施した。なお、WAIS-Rのプロフィール得点は、下位検査評価点から言語性ないし動作性評価点の平均点を引いた値とした。ADASとWAIS-Rの関連を検討するためにスピアマンの順位相関を算出した結果、ADASとWAIS-RのPIQ、「類似」、「絵画配列」で負の相関が見られた。プロフィール得点では、ADASと「類似－言語性評価点」、「絵画配列－動作性評価点」と負の相関が、「数唱－言語性評価点」と正の相関が見られた。以上の結果から、認知障害が進行するにつれ「数唱」は維持されるが、PIQ、「類似」、「絵画配列」で測定される機能は低下することが示された。MCIとADの認知障害の質的な違いが示され、プロフィールの詳細な検討の必要性が示唆された。

はじめに

痴呆性疾患の前駆状態を表す概念として、軽度認知障害（MCI: Mild Cognitive Impairment）が提唱されている。MCIはアルツハイマー型痴呆（以下AD）になるリスクが高く[1)]、痴呆性疾患に対しての早期の予防、治療的介入のために関心が高まっている。MCIについて、Petersenら（1995）は、MMSEなどのスクリーニング検査やWechsler Adult Intelligence Scale-Revised（WAIS-R）などの認知機能検査では正常範囲だが、認知機能の中でも記憶に関する訴えがあり、Wechsler Memory Scale-Revised（WMS-R）などの記憶検査では同年齢者に対し1.5 SD以上の低下[1)]を示す記憶障害のみが見られる状態と提唱している。本研究では、このPetersenのMCIの概念（1995）[1)]をMCIの操作的定義とし、MCIとAD患者を対象として高次脳機能の検討を行った。比較検討の指標として、本研究ではWAIS-Rを使用した。WAIS-RのIQと下位検査に加え、プロフィールによりMCIとADの高次脳機能障害の特徴を示し、MCIとADの認知障害の質的な違いを明らかにすることを本研究の目的とした。

I. 方法

対象者　京都府立医科大学附属病院の神経内科外来を受診し、自覚・他覚的に記憶障害のエピソードを有し、PetersenのMCIの基準[1)]を満たすMCI患者9名（男性2名、女性7名。平均年齢は75.78歳、SD=7.07）とAD患者3名（男性2名、女性1名。平均年齢は70.67歳、SD=7.57）を本研究の対象とした。またMCI患者の中で、ADASの得点が10点未満の者を軽度障害MCI（Mild MCI）、10点以上の者を中等度障害MCI（Moderate MCI）とした[2)]。

測度　記憶を中心とする認知機能検査としてAlzheimer's Disease Assessment Scale（ADAS）の日本版（ADAS-Jcog.）[2)]を使用した。この検査は11の下位検査から構成されており、得点が高くなるほど認知機能が低下していることを示す。またWAIS-R成人知能検査[3)]の日本版を様々な認知機能の指標として使用した。WAIS-Rは「知識」、「数唱」、「単語」、「算数」、「理解」、「類似」の6種類の言語性検査と、「絵画完成」、「絵画配列」、「積木模様」、「組合せ」、「符号」の5種類の動作性検査から構成されており、得点が高くなるほど遂行が高くなることを示す。ただし、WAIS-Rの適用年齢以上の者の得点については、70-74歳の年齢群の換算表を使用し、下位検査評価点とIQを算出した。以上の検査は検査入院時に実施され、同一検査者によって評定された。

手続き　ADASの得点とWAIS-Rの下位検査評価

† 本研究は、第10回認知神経科学会（2005年、京都）において発表されたデータの一部を再分析、再構成したものである。

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Table 1. 軽度障害 MCI と中等度障害 MCI と AD 患者の ADAS、WAIS-R の得点の基礎統計量

	ADAS	FSIQ	VIQ	PIQ
Mild MCI	6.40±0.99 (5.0～ 7.6)	102.60± 7.37 (93～110)	98.40± 7.02 (88～107)	107.00±7.48 (100～117)
Moderate MCI	13.00±1.43 (11.3～14.7)	98.00± 5.89 (92～104)	97.00±14.10 (84～112)	100.00±4.83 (96～107)
AD	15.87±3.16 (12.3～18.3)	85.33±13.65 (73～100)	87.00±15.72 (76～105)	88.67±7.10 (81～ 95)

軽度障害・中等度障害 MCI と AD 患者群の ADAS、WAIS-R の FSIQ、VIQ、PIQ の平均値と標準偏差を、( ) 内には範囲を示した。なお、MCI の群分けには ADAS の得点を使用し、10 点未満を軽度障害 MCI 群、10 点以上を中等度障害 MCI 群とした。

点・プロフィール得点・IQ のそれぞれとのスピアマンの順位相関係数を算出し、ADAS と WAIS-R の各指標間の関連性について検討した。その際に $p<.05$ を有意な相関とした。プロフィール得点は、対象者ごとに言語性、動作性それぞれの各下位検査の評価点から、その対象者の言語性あるいは動作性評価点の平均点を引いた値とした。

(プロフィール得点)＝(下位検査評価点)－(言語性ないし動作性評価点の平均点)

II. 結果

軽度障害・中等度障害の MCI 患者、AD 患者のそれぞれの ADAS、IQ(全検査 IQ: FSIQ、言語性 IQ: VIQ、動作性 IQ: PIQ) の平均値と標準偏差を Table 1 に示した。AD 群は、ADAS の得点から比較的軽度の AD であった。

ADAS の得点と WAIS-R の下位検査・プロフィール得点・IQ との相関係数を検討したところ、ADAS と下位検査の間では「類似」($r=-.70$, $p<.05$)、「絵画配列」($r=-.69$, $p<.05$) と負の相関が見られた。ADAS とプロフィール得点の検討では「数唱－言語性評価点」と正の相関が見られ($r=.66$, $p<.05$)、「類似－言語性評価点」($r=-.71$, $p<.05$) と「絵画配列－動作性評価点」($r=-.75$, $p<.01$) とは比較的高い負の相関が見られた。また ADAS と IQ の検討では、PIQ と比較的高い負の相関が見られた ($r=-.75$, $p<.01$) (Table 2)。

Figure 1 は ADAS とプロフィール得点で有意な相関が見られた「数唱－言語性評価点」、「類似－言語性評価点」、「絵画配列－動作性評価点」について、ADAS の得点とプロフィール得点との散布図を表した。「数唱－言語性評価点」は ADAS の得点が上がるにつれプロフィール得点は負の値から正の値になっているのに対し、「類似－言語性評価点」、「絵画配列－動作性評価点」はプロフィール得点が正の値から負の値へと変化していた。

また、軽度障害と中等度障害の MCI と AD 患者の

Table 2. ADAS と WAIS-R の下位検査、プロフィール得点、IQ との相関係数

	ADAS
下位検査	
知識	.01
数唱	.26
単語	－.38
算数	－.21
理解	－.46
類似	－.70*
絵画完成	－.49
絵画配列	－.69*
積木模様	－.21
組合せ	－.31
符号	－.42
プロフィール得点	
知識－言語性平均	.52
数唱－言語性平均	.66*
単語－言語性平均	－.20
算数－言語性平均	.47
理解－言語性平均	－.49
類似－言語性平均	－.71*
絵画完成－動作性平均	－.11
絵画配列－動作性平均	－.75**
積木模様－動作性平均	.33
組合せ－動作性平均	.37
符号－動作性平均	－.18
FSIQ	－.34
VIQ	－.20
PIQ	－.75**

a) *$p<.05$, **$p<.01$

軽度障害・中等度障害 MCI と AD 患者における ADAS と WAIS-R の下位検査、プロフィール得点、IQ とのスピアマンの順位相関係数を示した。* は $p<.05$ の有意水準を、** は $p<.01$ の有意水準を示した。

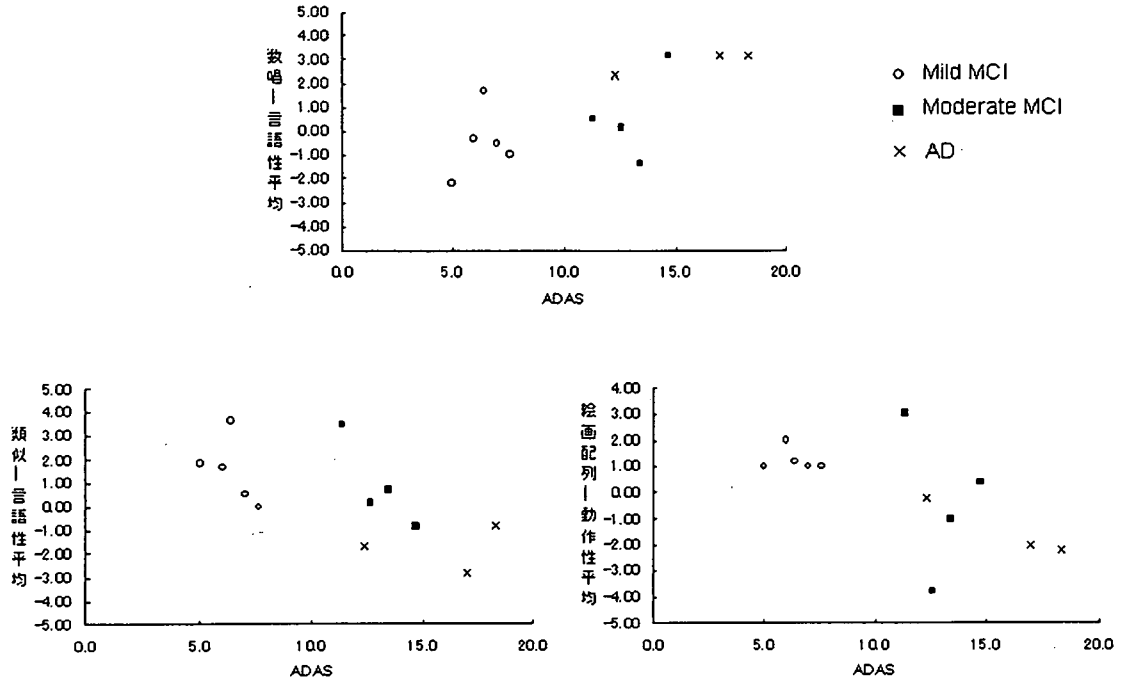

Figure 1. ADAS と WAIS−R のプロフィール得点の散布図
図中の○は軽度障害の MCI で、■は中等度障害の MCI、×は AD を表す。

WAIS-R の下位検査評価点の各群の平均値をプロットしたプロフィールを Figure 2 に表した。MCI と AD ではプロフィールで異なる特徴が示されていた。各群の下位検査評価点の平均は、MCI の軽度障害では 7.80 点から 12.40 点の範囲にあり、中等度障害では 7.50 点から 11.50 点の範囲にあった。AD では「数唱」の 10.67 点を除いては 6.00 点から 8.67 点の範囲であった。MCI では軽度と中等度障害とではプロフィールに差は見られなかった。一方、AD では「数唱」は相対的に高いが、他の下位検査は低くなっており、特に「類似」、「絵画配列」で低下が見られた。また AD は MCI に比べ言語性、動作性の下位検査の評価点が全体的に低い傾向が見られた。

III. 考察と結論

MCI の概念は、Global Deterioration Scale (GDS) で stage 3 であり、正常群に比べ、近時・遠隔記憶、言語機能、概念形成、視空間認知など全般的な認知機能の低下[4]が見られる状態を指すものと、記憶障害の訴えがあり、客観的にも記憶障害が示されているが、全般的な認知機能や日常生活は正常であり、痴呆でない状態[1,5]を指すものがある。後者のように記憶のみの低下が見られる MCI は amnestic MCI とされ、このうち 1 年につき 12% が AD に進行することが示されている[5]。このように MCI の定義は必ずしも一定ではないが、本研究では Petersen の概念を使用し、MCI の操作的定義として使用した。

また Clinical Dementia Rating (CDR) が .5、つまり認知機能の低下が疑われる患者のうち、死亡時には神経病理学的に 84% が AD に進行しており、残り 12% が AD 以外の痴呆性疾患に進行したことが示されている[6]。このように MCI は神経病理学的にも AD の早期段階を示すとされており、AD と連続線上にあると考えられる。このため、本研究では MCI 患者と AD の患者を ADAS の得点を基準にして連続線上に捉え、WAIS-R の得点との相関の検討を行った。先行研究では FSIQ, VIQ, PIQ に加えて一部の下位検査が MCI と対照群、アルツハイマー群との群間の比較に使用されてきた[5-7]。しかしながら、IQ だけではなく様々な下位検査の成績を比較することにより、どのような認知機能が低下しているかについての検討が可能であると考えられる。さらに、群の比較のみならず個人内のプロフィールを検討することにより、各対象者の認知機能の構造の特徴を見ることが可能となると考えられる。

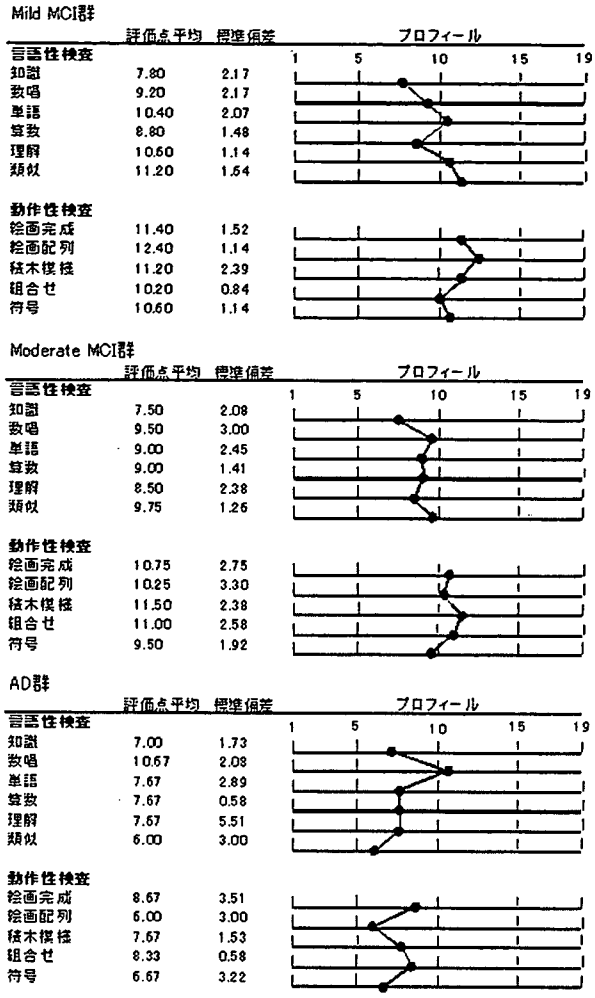

Figure 2. 軽度障害・中等度障害 MCI と AD 患者の WAIS-R のプロフィール
軽度障害・中等度障害 MCI と AD 患者の WAIS-R の下位検査の評価点の各群の平均値と標準偏差を表した．さらに各群ごとに下位検査の平均値をプロットし、プロフィールを図示した．

本研究では、WAIS-R の IQ の検討から認知障害が重くなるほど、PIQ が低くなっていることが示された。また下位検査の項目では認知障害が認められるにつれ、「類似」、「絵画配列」の成績が低下していた。またプロフィール得点を見ると、ADAS と「類似—言語性評価点」・「絵画配列—動作性評価点」との間に負の相関が見られたことから、「類似」、「絵画配列」は障害が進行するにつれ絶対値として低くなっていることに加え、個人内のプロフィールの中で相対的にも他の下位検査に比べ低くなっていた。

先行研究では AD 群は VIQ より PIQ が有意に低いこと[8]や、痴呆の疑いがある群と非痴呆群とでは言語性下位検査よりも動作性下位検査において 2 群間の差が大きいこと[9]、対照群、MCI 群対 AD 群では FSIQ, VIQ, PIQ の全てにおいて有意差が見られたが、対照群対 MCI 群では PIQ でのみ有意な差が見られており[5]、本研究の IQ の検討と一致する結果となった。以上のことから、PIQ で測定される機能は VIQ よりも認知機能障害の進行過程を反映しているといえる。また Petersen らは MCI 群と Mild AD 群との比較で記憶領域では差がないが、他の認知領域においては Mild AD 群が低下していると報告しており[5]、本研究の結果と一致していた。本研究で ADAS と相関の示された「類似」では論理的範疇的思考、「絵画配列」では結果の予測や全体の流れを理解する力、時間的順序の理解および時間概念が測定される能力といわれている[10]。「類似」や「絵画配列」のような下位検査は記憶以外の認知機能を反映するものであり、MCI から AD と重度になるにつれ記憶以外の認知機能において差が生じると考えられる。

一方、「数唱」のプロフィール得点に関しては、障害が重くなるにつれ高くなっていることが示された。しかしながら、ADAS と「数唱」自体との相関は見られなかった。「数唱」についての先行研究を見ると、MCI 群と対照群との比較で有意差は見られなかった[4,7]。一方、AD の患者を対象とした研究では、「数唱」が他の下位検査に比べ有意に高いことが示されている[8]。また「数唱」、「積木模様」は軽度痴呆では比較的維持される傾向が認められている[11]。以上のことから、「数唱」は障害が進行しても維持されるが、障害の進行につれ「数唱」以外の下位検査が低くなる可能性が想定される。

本研究で見られた MCI と AD のプロフィールの違いは、もの忘れを主訴に来院する場合でも認知機能障害の質の違いを示している可能性があると考えられる。「数唱」では暗唱と即時再生が測定される能力といわれるが[10]、その場で集中して記憶し再生する能力は MCI でも AD でも差が認められないといえる。しかしながら、このように WAIS-R で測定される記憶領域では差が認められないが、障害の進行につれ抽象概念や結果の予測、全体の流れを理解する力や時間概念などの認知機能は低下してくると考えられる。AD 患者では、もの忘れの自覚がある群ではもの忘れに対する問題意識のもたれ方が個々の患者によって異なることが報告されてお

り[12]、もの忘れの中でも認知機能の質の違いが存在している可能性が考えられる。このため、今後は物忘れの自覚症状と、もの忘れの質の違いの両方の視点を含めた検討が必要になると思われる。

現段階では、有用なMCIのスクリーニング検査は提唱されておらず、単一の検査だけではなく複数の検査を組み合わせることにより診断的妥当性が上がる可能性が示唆されている[13]。またADへ進行するMCIをスクリーニングできる予測妥当性のある検査が必要であるが、未だ確立されておらず今後の課題といえる。本研究では、障害の進行につれ「数唱」は維持されるが、「類似」や「絵画配列」の下位検査で測定される能力は低下することが示された。つまり、障害の程度によってプロフィールが異なってくるといえる。今回の検討の中でMCIと判定された症例がADに移行していくと仮定すると、障害が進行するにつれプロフィールが変化すると考えられる。以上のことから、プロフィールを利用したスクリーニング検査を考案できる可能性が考えられるが、現段階ではMCI固有の特徴は示されなかった。今後、同一患者で縦断研究を行い、MCIの患者のプロフィールがどのように変化していくかを検討することが必要であると考えられる。また本研究ではMCIとコントロール群との比較ができておらず、今後多数例でのコントロール群を含めた検討を行い、MCIのプロフィールの特徴を明らかにする必要があると考えられる。

要約

本研究ではWAIS-RのIQ、下位検査に加え、プロフィールによりMCIとADの高次脳機能障害の特徴を検討した。Petersen (1995) の基準を満たすMCI患者9名とAD患者3名を対象とし、ADAS, WAIS-Rを実施した。ADASとWAIS-Rの関連を検討した結果、PIQ、「類似」、「絵画配列」で負の相関が、プロフィール得点では「類似－言語性評価点」「絵画配列－動作性評価点」と負の相関が、「数唱－言語性評価点」で正の相関が見られた。認知障害が進行するにつれ「数唱」は維持されるが、PIQ、「類似」、「絵画配列」で測定される他の認知機能は低下することが示された。

謝辞

本研究は、京都府立医科大学附属脳・血管系老化研究センタープロジェクト研究の援助によってなされた。

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Environmental Sciences, 13, 3 (2006) 149–160
MYU Tokyo

ES618

Toenail Arsenic Levels among Residents in Amami-Oshima Island, Japan

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(Received November 14, 2005; accepted March 23, 2006)

Key words: Arsenic, ICPMS, toenail, Amami-Oshima, Japan

In order to evaluate the current arsenic exposure status and its determinants in Japan, we collected toenail samples from 212 subjects residing in a town with a population of 6,900 in Amami-Oshima Island in August 1999. We measured arsenic concentrations of the toenails using inductively coupled plasma mass spectrometry. In addition, we examined the association of arsenic levels with lifestyles and dietary habits, including the consumption of fish, seaweed, and rice. The mean toenail arsenic level was 0.41 ppm (95% confidence interval, 0.36–0.47), which was about 3-fold higher than those observed in other populations of mainland Kagoshima. Arsenic levels were elevated among current smokers (mean = 0.65; 95% confidence interval, 0.32–1.29) when compared with non-smokers (mean = 0.40; 95% confidence interval, 0.34–0.46), and among the residents consuming 4 bowls or more, of rice every day (mean = 1.97; 95% confidence interval, 0.25–15.75) when compared to residents consuming 3 bowls or less (mean = 0.39; 95% confidence interval, 0.34–0.45). Sex, age,

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alcohol intake, fish consumption, or seaweed consumption was not associated with toenail arsenic concentration. Further studies seem warranted to examine the cause of relatively high arsenic levels in our study area.

1. Introduction

Arsenic is a widely present element in the natural environment including the earth's crust, soil, inland water, seawater and biological organisms, although in small quantity. Exposure to arsenic in humans takes place through water, air, food, medicine and so on. Arsenic in drinking water is one of the major threats to health in various Asian countries such as Bangladesh, India, and China.[1]

An international study compared the levels of arsenic and other trace elements in Japan and other countries in the mid-1980s. The Japanese samples showed levels of arsenic in human hair higher than in other countries (Canada, U.S.A. and Poland) except for India.[2] Although arsenic levels are related to dietary habits, it is unknown the extent to which differences in levels can be explained by dietary habits and other lifestyles.

In studies conducted in north America, seafood accounted for almost 90% of the daily arsenic intake in the United States,[3] approximately 70% in Canada,[4] and 60–70% in Japan.[5] In Japan, an additional factor was the consumption of seaweed and rice, which accounted for most of the remaining arsenic intake.[6]

In order to evaluate the current arsenic exposure status and to examine its determinants in Japan, we measured arsenic concentrations in toenail samples collected from residents in the Amami-Oshima Island at the time of a health check-up survey, and determined the association of arsenic levels with lifestyles and dietary habits, including the consumption of fish, seaweed, and rice.

2. Materials and Methods

2.1 *Subjects*

This study was conducted as a part of the health check-up program of elderly people in a town in Amami-Oshima Island, located 380 km southwest from the southern end of mainland Japan. The surveys were conducted by the Third Department of Internal Medicine, Kagoshima University Faculty of Medicine in August 1999. The total number of elderly people who underwent medical check-ups was 759.

We interviewed 212 elderly people using a standardized questionnaire. We did not seek to interview the rest of the participants. At interview, we collected information on name, sex, age, occupation, present address, food consumption (frequency), alcohol drinking, smoking, (or years since a subject quit smoking, the number of cigarettes per day).

We also collected toenail samples from these 212 participants. Each participant was asked to provide toenail clippings from all 10 toes, using a stainless-steel nail-cutter. Collected toenail samples were put into separate plastic envelopes for each participant and the plastic envelop for each subject was tightly sealed and attached to his/her questionnaire.

The aims and objectives of toenail collection were explained to each subject and informed consent was obtained. The Research Ethics Committee of Kagoshima University Faculty of Medicine approved the study.

2.2 *Toe-nail analysis*

Nail samples have been used for arsenic examination in a number of publications [7–10] due to the ease of sample collection, transportation, storage and preparation for analysis. The concentrations of metals in toenails reflect the mean level in the human body during a period of 12–18 months.[11,12] The concentration of arsenic in toenail samples has been found to be higher than in other parts of the human body due to the presence of higher levels of keratins, (up to 22%).[10]

Toenails were cleaned with a neutral detergent and rinsed with plenty of de-ionized water, then dried at room temperature. Wet-digestion to dissolve them into constituent elements was then carried out with 1 ml of pure water and 1 ml of nitric acid using the Microwave-Accelerated Reaction System (MARS) and the MDS-2000, CEM, USA. The digested solution was then used to measure the species of trace elements (arsenic, manganese, lead, selenium, strontium, vanadium, zinc, copper and cobalt) using present on inductively coupled plasma mass spectrometry (ICP-MS) system (Model POEMS 3, Thermo Jarrell-Ash, USA).

For atomic absorption spectroscopy of single element, a multi-element standard solution for calibration was prepared by mixing with 8 species of standard solution. An internal standard solution for a mass weight of each analytical elements was further prepared with 4 species of standard solution of single element for atomic absorption spectroscopy. The two standard solutions were measured after every 5 samples quality control. One sample was measured three times per one sample. When the relative standard deviation of those ICP-MS measurements exceeded 10%, the measured arsenic values were not used for statistical analysis.

2.3 *Statistical analysis*

We calculated geometric means and corresponding 95% confidence intervals for toenail arsenic concentration. Univariate regression analysis was conducted using the log-transformed value of arsenic concentration since the distribution of arsenic concentration was skewed and had a long upper tail.

3. Results

We examined 74 men and 138 women. The characteristics of the study subjects are summarized in Table 1. We could determine toenail arsenic concentrations for 159 subjects (75%). The measurements for 53 subjects were considered invalid because the relative standard deviation of the ICP-MS measurement exceeded 10%.

The geometric mean toenail arsenic level was 0.41 ppm, with minimum and maximum values of 0.147 and 13.75 ppm, respectively. The arsenic level was not related to sex or age (Table 2).

Table 3 shows associations between toenail arsenic levels and smoking status. Toenail arsenic levels were elevated among male smokers but not in females (Table 3). When compared with non-smokers (including ex-smokers), the increase in the arsenic level was statistically significant in male smokers ($p<0.001$). Arsenic levels did not show any evident difference between ex-smokers and never-smokers. Daily cigarette consumption was significantly related to arsenic levels in males ($p<0.001$) as shown in Table 4. Since there were only 4 female smokers, we could not determine such a relationship in women. There

Table 1
Characteristics of the population investigated.

	Male	Female
Total	74 (100%)	138 (100%)
Age(in years)		
60–69	26 (35%)	62 (45%)
70–79	34 (46%)	59 (43%)
80+	14 (19%)	17 (12%)
Smoking		
never smoked	11 (15%)	101 (73%)
ex-smoker	28 (38%)	1 (1%)
current-smoker	14 (19%)	3 (2%)
unknown	21 (28%)	33 (24%)
Fish_fresh		
<1time/month	1 (1%)	4 (3%)
1–2 times/month	0 (0%)	2 (1%)
1–2 times/week	14 (19%)	20 (14%)
3–4 times/week	20 (27%)	42 (30%)
everyday	18 (23%)	37 (27%)
unknown	21 (28%)	33 (24%)
Fish_prosessed		
<1 time/month	12 (16%)	22 (16%)
1–2 times/month	8 (11%)	17 (12%)
1–2 times/week	14 (19%)	33 (24%)
3–4 times/week	6 (8%)	14 (10%)
everyday	13 (18%)	19 (14%)
unknown	21 (28%)	33 (24%)
Seaweed		
<1 time/month	1 (1%)	3 (2%)
1–2 times/month	2 (3%)	3 (2%)
1–2 times/week	12 (16%)	6 (4%)
3–4 times/week	12 (16%)	22 (18%)
everyday	25 (34%)	71 (51%)
unknown	22 (30%)	33 (24%)
Rice		
1–2 bowls**/day	12 (16%)	38 (28%)
3 bowls**/day	37 (50%)	65 (74%)
4–6 bowls**/day	3 (4%)	2 (1%)
unknown	22 (16%)	33 (24%)
Alcohol		
never drank	19 (26%)	97 (68%)
ex-drinker	4 (5%)	1 (1%)
sometimes	14 (19%)	4 (3%)
everyday	16 (22%)	3 (2%)
unknown	21 (28%)	33 (24%)
Type of Work		
company workers	1 (1%)	2 (1%)
self-employed	3 (4%)	2 (1%)
family helpers	1 (1%)	2 (1%)
farmers	25 (34%)	19 (14%)
fishermen	1 (1%)	0 (0%)
house helpers	0 (0%)	50 (36%)
working indside home (Hataori)	0 (0%)	15 (11%)
others	9 (12%)	5 (4%)
unemployed	12 (16%)	10 (7%)
unknown	22 (30%)	33 (24%)

**1bowl is about 150 g.

was no significant relationship between frequency of alcohol drinking and toenail arsenic concentration (Table 5). Arsenic levels did not show any significant differences among occupations either.

We examined the relationship between dietary habits and arsenic concentration (Table 6). Arsenic levels were not significantly associated with fish consumption or seaweed intake. Most of the study subjects consumed seaweed but we could not find any significant relationship between frequency of seaweed consumption and toenail arsenic levels. On the other hand, the mean level of arsenic concentration among residents consuming 4 bowls of