Table 1 Magnetic resonance imaging detection of cerumen impaction in patients with cognitive disorder

Case no.	Age	Sex	Type of cerumen	MMSE	Side	Cerumen impaction (otoscopic findings)	MRI before or after cerumen removal	Radiologist report of cerumen impaction	Hearing level before/after removal of cerumen impaction
1	86	M	Dry	19	Right	Almost	After	Negative	48/43
					Left	Almost	After	Negative	63/48
2	80	M	Wet	27	Right	Total	Before	Positive	64/37
					Left	Total	Before	Unclear	64/38
3	80	F	Dry	14	Right	Total	After	Negative	35/38
					Left	Total	After	Unclear	56/38
4	85	F	Dry	10	Right	Total	Before	Positive	83/59
					Left	Total	Before	Unclear	53/59
5	74	M	Wet	24	Right	None	Before	Negative	43/34
					Left	Total	Before	Positive	65/40
6	85	F	Wet	16	Right	Total	After	Negative	80/51
					Left	Total	After	Unclear	83/81

Hearing level (dB) was the average of four frequencies of 500 Hz, 1 kHz, 2 kHz and 4 kHz. In the radiologist report of cerumen impaction judged as "unclear," comments of "thin one?" or "small one?" were added. F, female; M, male; MMSE, Mini-Mental State Examination.

Gerontology. Age, sex, results of Mini-Mental State Examination, otoscopic findings, and hearing levels before and after cerumen impaction removal are shown in Table 1. Brain MRI was carried out within 1 month before ($n = 3$) or after ($n = 3$) cerumen impaction removal.

MRI

Images were obtained using a 1.5-T MR scanner (MAGNETOME Avanto; Siemens Medical Solutions, Erlangen, Germany) with a 12-channel head coil. The following sequences were routinely carried out for dementia patients: transverse T1-weighted spin echo (repetition time ms/echo time ms, 485/11; flip angle, 90°; matrix, 194–230 × 256; field of view [FOV], 184–263 mm; slice thickness, 6 mm; gap, 1.5 mm); transverse T2-weighted spin echo (3800/180; flip angle, 180°; matrix, 216–256 × 256; FOV, 184–263 mm; slice thickness, 6 mm; gap, 1.5 mm); transverse fluid attenuated inversion recovery 8000/101; inversion time, 2500 ms; flip angle, 180°; matrix, 184–202 × 256; FOV, 184–263 mm; slice thickness, 6 mm; gap, 1.5 mm); coronal T1-weighted spin echo (485/11; flip angle, 80°; matrix, 194–230 × 256; FOV, 186–263 mm; slice thickness, 6 mm; gap, 1.5 mm); transverse T2*-weighted gradient echo (500/18; flip angle, 20°; matrix, 162–192 × 256; FOV, 186–263 mm; slice thickness, 6 mm; gap, 1.5 mm); sagittal T1-weighted 3-D gradient echo (1700/3.99; inversion time, 800 ms; flip angle, 15°; matrix, 256 × 256; FOV, 230–274 mm; slice thickness, 1.25 mm; gap, 0 mm). Three-dimensional volumetric data were analyzed using an automated voxel-based morphometry method.

A radiologist (SN), blind to the side of cerumen impaction, to whether MRI scans were taken before or after cerumen impaction removal, and to the number of ears with cerumen impaction classified the cerumen impaction in each ear as positive, negative or unclear.

Results

Table 1 shows the six patients from our previous study whose hearing level improved by 15 dB or more unilaterally or bilaterally after the removal of cerumen impaction. In case 2, the hearing level improved by 27 dB on the right side and 26 dB on the left side. In the other five cases, the hearing level improved more than 15 dB unilaterally. Patient ages ranged from 74 to 86 years. The average Mini-Mental State Examination score was 22. Brain MRI was taken before cerumen impaction removal in cases 2, 4 and 5, and after removal of the cerumen impaction in cases 1, 3 and 6. Five ears (both ears of case 2 and Case 4, and left ear of case 5) had cerumen impaction actually at MRI.

The radiologist's report is also shown in Table 1. When the radiologist reported the presence or absence of cerumen impaction, all reports were correct. Three ears classified by the radiologist as impaction positive and five ears classified as impaction negative corresponded accurately to the presence or absence of cerumen impaction. Of the four ears classified as

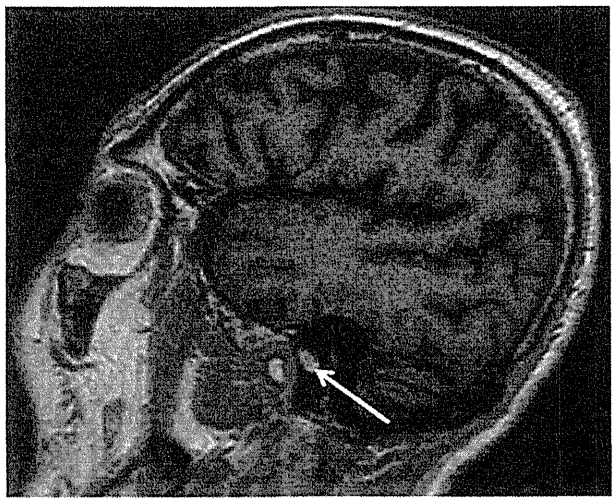

Figure 1 A 3-D T1-weighted image with 1.5 mm thickness. Cerumen impaction is shown on the left external auditory canal (arrow), visualized as a structure with high signal intensity.

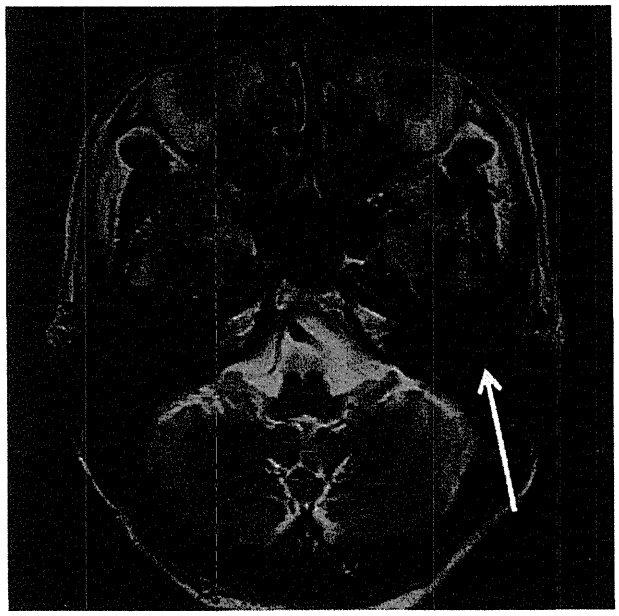

Figure 2 A routine T2-weighted axial image with 5 mm thickness. Cerumen impaction is faintly visualized (arrow).

unclear, two (left ears of case 2 and case 4) had and two (left ears of case 3 and case 6) did not have cerumen impaction.

Representative images showing cerumen impaction are in Figures 1–3 (case 5 in Table 1).

Discussion

Of the eight ears classified by the radiologist as positive or negative, all were accurately classified. If the classifications had been completely at random, the probability would have been $1/2^8 = 0.0039$. It appears that brain MRI was useful for identifying cerumen impaction, especially when the cerumen was large and dense.

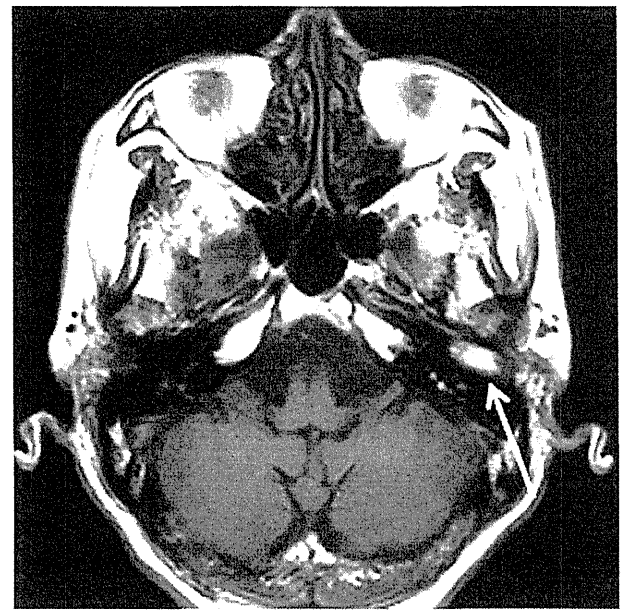

Figure 3 A routine T1-weighted axial image with 5 mm thickness. Cerumen impaction is visualized as a high signal intensity structure similar to fat (arrow).

The incidence of cerumen impaction is generally high in elderly adults.[2–4] Cerumen impaction is more common in patients with dementia or mental disorders who, in many cases, do not complain of hearing loss.[5–7] When MRI is taken for evaluation of brain in these patients, it is usually unclear whether cerumen impaction exists or not. If cerumen impaction can be recognized on brain MRI, we can specify patients with cerumen impaction and remove the cerumen impaction for them. Removal of the cerumen impaction might result in a significant improvement of cognitive function.[1,6] A Web of Science search that included the terms "MRI" and "dementia" revealed more than 5300 papers. There were none for a search with "MRI" and "cerumen." The present study showed for the first time that MRI is useful for finding cerumen impaction, especially when it is large and dense. It is expected that geriatricians and radiologists pay attention to cerumen impaction at the time of MRI evaluation.

Dry and wet cerumen types differ among ethnic groups. The frequency of dry cerumen is high in Mongolian populations and low among Europeans.[8,9] Cerumen impaction is more common in people with wet cerumen. However, the present study showed that dry cerumen impaction could cause significant hearing loss and was visible on brain MRI.

Acoustic noise during MRI is the main source of patient discomfort and leads to verbal communication

problems, especially in children and the elderly. Recently developed silent brain MRI might soon be in wide use for patients with cognitive disorder and dementia. Silent MRI is also expected to provide high-quality images.[10] MRI might provide easy detection of cerumen impaction in the near future.

Acknowledgments

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Disclosure statement

No potential conflicts of interest were disclosed.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Frontal white matter hyperintensity predicts lower urinary tract dysfunction in older adults with amnestic mild cognitive impairment and Alzheimer's disease

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Aim: Lower urinary tract symptoms often limit activities of daily life and impair quality of life in the elderly. The purpose of the present study was to determine whether regional white matter hyperintensity (WMH) can predict lower urinary tract symptoms in elderly with amnestic mild cognitive impairment or Alzheimer's disease.

Methods: The participants were 461 patients aged 65–85 years diagnosed with amnestic mild cognitive impairment or Alzheimer's disease. Patients and their caregivers were asked about symptoms of lower urinary tract symptoms (urinary difficulty, frequency and incontinence). Cognition, behavior and psychological symptoms of dementia and medication were evaluated. WMH and brain atrophy were analyzed using an automatic segmentation program. Regional WMH was evaluated in the frontal, parietal, temporal and occipital lobes.

Results: Patients with urinary incontinence showed significantly greater volume of WMH. WMH increased with age, especially in the frontal lobe. WMH in the frontal lobe was closely associated with urinary incontinence after adjustment for brain atrophy and classical confounding factors.

Conclusions: Frontal WMH was a predictive factor for urinary incontinence in older adults with amnestic mild cognitive impairment or Alzheimer's disease. Urinary incontinence in demented older adults is not an incidental event, and careful insight into regional WMH on brain magnetic resonance imaging might greatly help in diagnosing individuals with a higher risk of urinary incontinence. **Geriatr Gerontol Int 2016; 16: 167–174.**

Keywords: Alzheimer's disease, lower urinary tract symptoms, mild cognitive impairment, urinary incontinence, white matter hyperintensity.

Introduction

White matter hyperintensity (WMH) is detected as hyperintense signals located in periventricular and deep subcortical areas on T2-weighted images of brain magnetic resonance imaging (MRI). WMH are composed of heterogeneous pathological changes, and are mostly related to cerebral small vessel disease.[1] It has been postulated that WMH are associated with cognitive dysfunction[2–4] and several geriatric conditions, such as lower urinary tract dysfunction,[4–6] gait disturbance[4,7,8] and depressive symptoms.[9,10] Damage of nerve fibers connecting the cerebral cortex and subcortical regions or between cortical areas could cause various geriatric symptoms.

Lower urinary tract dysfunction causes lower urinary tract symptoms (LUTS), which often limit activities of daily life and impair quality of life in older adults. In addition, urinary incontinence, which is the most troublesome symptom, is one of the major reasons for increased caregivers' burden in demented older adults.[11] Primary lower urinary tract dysfunction including that due to prostatic hyperplasia and urinary tract infection is important in LUTS, but impaired regulation in the brain could be a potential reason in patients with dementia. Several studies have reported a correlation of WMH with LUTS in older adults.[4–6] However, the role of regional WMH after adjustment for brain atrophy

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and confounding factors in relation to LUTS remains uncertain. The purpose of the present study was to identify the effects of regional WMH on LUTS in older adults diagnosed with amnestic mild cognitive impairment (aMCI) or Alzheimer's disease (AD). The goals of this study were: (i) to clarify the regional progression of WMH with aging; and (ii) to determine the impact of regional WMH on LUTS after adjustment for brain atrophy and other confounding factors. The results of the present study, reported here, were that WMH increased particularly in the frontal lobe with aging, and that WMH in the frontal lobe was critical in urinary incontinence in aMCI and AD patients.

Methods

Participants

The study protocol was approved by the ethical review board of Japan's National Center for Geriatrics and Gerontology (NCGG). Candidate patients and their caregivers provided informed consent before participation in the study. We enrolled 461 outpatients (318 female) consecutively at their initial visit. Patients were aged 65–85 years, attended the NCGG hospital in 2010–2013 and were diagnosed with aMCI (n = 69) or AD (n = 392). AD was diagnosed as probable AD or possible AD based on the criteria published by the US National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association.[12] aMCI was diagnosed based on the criteria defined by Petersen *et al.*[13] Patients with a history of stroke or cortical lesions on MRI, severe conditions such as cardiac failure, renal disorder and liver dysfunction, or neurological disorders other than AD were excluded from the present study.

Medical history and medication

Clinical data were obtained from NCGG Biobank, which collects biological materials of patients with clinical data for biomedical research. Information on history of hypertension, diabetes mellitus and medication were obtained from clinical charts. Participants were asked about use of medication to treat overactive bladder, benign prostatic hyperplasia, hypertension, AD, anxiety/sleeping disorders and psychological problems/depression. Hypertension and diabetes mellitus were defined as a history of disease and/or presently receiving medication.

Evaluation of LUTS and clinical assessment

All participants underwent assessment with Comprehensive Geriatric Assessment batteries (CGA). Cognitive function was evaluated by the Mini-Mental State Examination (MMSE). Behavior and psychological symptoms were evaluated by the Dementia Behavior Disturbance Scale (DBD). To measure obesity, body mass index (BMI) was calculated.

We examined the following LUTS: urinary difficulty, urinary frequency and urinary incontinence. Regarding LUTS, patients and their caregivers were asked the following questions: Have you experienced difficulty with urination? Have you experienced urinary frequency? Have you had urinary incontinence? Urinary difficulty and urinary frequency were assessed by CGA subitems of geriatric syndrome, and the presence and absence of urinary difficulty and urinary frequency were expressed as 0 (absence) and 1 (presence). Assessment of urinary incontinence included the DBD subitems, scored as 0–4 points (0 never, 1 infrequent, 2 sometimes, 3 frequent, 4 always). Absence of urinary incontinence was assigned 0 or 1 points, and presence was assigned 2–4 points.

Brain MRI

MRI were obtained using 1.5T MR scanners. The images obtained during the period between 1 July 2010 and 31 December 2012 were obtained with a Siemens Avanto (Munich, Germany), and those after 1 January 2013 with a Philips Ingenia (Eindhoven, the Netherlands). The slice setting was exactly the same in the two periods; 19 slices with 6-mm thick slices and an interslice gap of 1.2 mm were obtained in parallel with the anterior commissure-posterior commissure line, covering a 135.6-mm range from the vertex down to the lower end of the pons in each session. Standard head coils (12 elements for Siemens Avanto and 16 elements for Philips Ingenia) were used for MR signal acquisition, and standard body coils were used for transmission. T2-weighted (fast spin echo sequence; repetition time [TR], 3800 ms; echo time [TE], 98 ms; echo train length [ETL], 11; field of view [FOV], 220 × 220 mm; acquisition matrix, 512 × 256; number of acquisition [NA], 1) and fluid-attenuated inversion recovery (FLAIR; FLAIR sequence, TR, 8000 ms; TE 101 ms; inversion time [TI], 2500 ms; ETL, 21; FOV, 192 × 220 mm; acquisition matrix, 256 × 202; NA, 1) images were obtained with a Siemens Avanto 1.5T MR scanner. The imaging parameters for Philips Ingenia were as follows: T2-weighted (fast spin echo sequence; TR, 3900 ms; TE, 100 ms; ETL, 13; FOV, 230 × 230 mm; acquisition matrix, 352 × 262; NA, 2) and FLAIR (FLAIR sequence; TR, 10000 ms; TE 110 ms; TI, 2600 ms; ETL, 32; FOV, 230 × 230; acquisition matrix, 224 × 164, NA, 2).

Evaluation of WMH and brain atrophy

WMH and brain atrophy were evaluated using an automatic segmentation application (Software for NeuroImage Processing in Experimental Research: SNIPER,

Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands).[14] The obtained T2-weighted and FLAIR images were imported from DICOM format files and processed as follows:

1 Adaptive level processing. FLAIR images were coregistered to T2-weighted images by six-parameter rigid body transformation. Next, intracranial (IC) segmentation to extract brain tissue was applied to T2-weighted and FLAIR images using a fuzzy C-mean (FCM) clustering algorithm. To estimate gray matter, white matter (WM) and cerebrospinal fluid (CSF) components, the Montreal Neurological Institute template was used as the reference probability map.
2 Reasoning level processing. After brain stripping using a binary mask image to improve removal of the signals from subcutaneous and bone marrow tissue of the head, second level tissue segmentation to separate WMH from WM and CSF was carried out using FCM clustering. It is known that this two-level segmentation procedure is robust against the variability of MRI conditions across different MR scanners, such as image intensity range or image contrast.[14]

In order to improve the accuracy of WMH volumetry, manual optimization of segmentation parameters was applied using the following procedure. The five intensity parameters of the FCM algorithm to discriminate WMH and CSF were optimized to better match the anatomical brain structure by visual inspection. After manual operations to add or remove WMH were carried out, the volume of WMH, which appeared as hyperintense areas on T2-weighted and FLAIR images, was quantified for each cluster. In order to fully include small ischemic lesions, such as lacunar infarcts, as WMH, centric low intensity areas surrounded by hyperintensity on FLAIR were appended to the area of WMH. Finally, the class of the determined WM was assigned according to a built-in atlas.[15] To avoid misclassification of WMH, we repeated analysis in 23 out of 461 participants (5%) to evaluate intrarater reliability (intraclass correlation coefficient was 0.96), suggesting that the method of measurement used for the present study was reliable. The brain tissue was classified into frontal, parietal, temporal and occipital lobes. WMH were automatically classified as periventricular hyperintensity (PVH) or deep white matter hyperintensity (DWMH), and their corrected volumes were calculated. To minimize the bias of brain atrophy, individual WMH, parenchyma (PAR), CSF and ventricular (VCL) were divided by IC, and the brain volume was adjusted. These indices were used to evaluate whether: (i) brain atrophy can predict the risk of LUTS; and (ii) adjustment of WMH volume by brain atrophy significantly improves evaluation of LUTS risk. The results of all this processing, the WMH volume of each cluster and the index of brain atrophy are presented in Table 1.

Table 1 Clinical characteristics

	Mean (SD)	%
Age (years)	77.2 (5.1)	
Female		69.0
Education (years)	10.2 (2.5)	
Body mass index (kg/m^2)	22.0 (3.4)	
Mini-Mental State Examination	19.9 (5.0)	
Dementia Behavior Disturbance Scale	16.3 (11.3)	
Barthel index	96.5 (8.9)	
Bladder control	9.1 (2.2)	
History of		
Hypertension		55.6
Diabetes		28.3
Medication for		
Overactive bladder		8.9
Benign prostatic hyperplasia		3.6
Hypertension		39.6
Calcium channel blocker		36.2
Diuretics		8.3
Alpha blocker		1.6
Alzheimer's disease		26.9
Anxiety/sleeping disorder		21.4
Psychological problem/depression		10.5
MRI analysis		
IC (mL)	1373.9 (128.1)	
PAR, mL (% of IC)	1022.5 (101.4)	74.5
CSF, mL (% of IC)	351.9 (60.4)	25.6
VCL, mL (% of IC)	62.2 (22.4)	4.5
WMH total, mL (% of IC)	19.2 (20.1)	1.39
Frontal lobe, mL (% of IC)	10.7 (10.9)	0.78
Parietal lobe, mL (% of IC)	6.5 (7.9)	0.47
Temporal lobe, mL (% of IC)	1.3 (1.7)	0.09
Occipital lobe, mL (% of IC)	0.6 (0.8)	0.05
Periventricular area, mL (% of IC)	18.1 (19.7)	1.31
Deep subcortical areas, mL (% of IC)	1.1 (1.3)	0.08

Data are presented as mean (SD), n = 461. CSF, cerebrospinal fluid; IC, intracranial; PAR, parenchyma; VCL, ventricular; WMH, white matter hyperintensity.

Statistical analysis

All analyses were carried out using the Japanese version of SPSS for Windows version 19.0 (IBM Corporation, Armonk, NY, USA). WMH and brain atrophy volumes were analyzed by non-parametric tests, because these variables did not show a normal distribution.

When analyzing the significance of differences between patients with and without LUTS, Mann–Whitney U-test and χ^2-tests were used. Progression of regional WMH with aging was analyzed by Kruskal–Wallis test. To explore independent risk factors for LUTS, total and regional WMH were entered into a logistic regression model with the following variables selected as possible confounders: age, sex, MMSE, BMI, diabetes, brain atrophy and medication (for overactive bladder, benign prostatic hyperplasia, hypertension, AD, anxiety/sleeping disorder and psychological

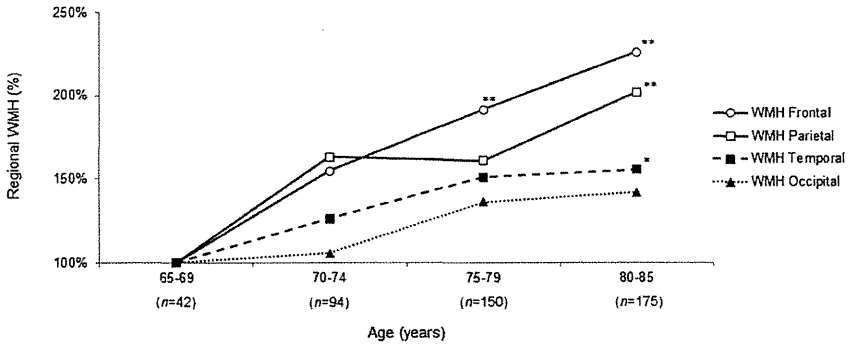

Figure 1 The transition of regional white matter hyperintensity volumes (WMH) in each age group is shown. The *y*-axis shows regional WMH after adjustment for intracranial volumes. $^{**}P < 0.01$, $^{*}P < 0.05$ compared with 65–69 years.

problems/depression). Predictors of LUTS were tested by receiver operating characteristic analysis. Results were considered significant at $P < 0.05$.

Results

Clinical data

The clinical characteristics of the study participants are shown in Table 1. Mean (±SD) age was 77.2 ± 5.1 years, and 69% were female. The mean score of WMH was 19.2 ± 20.1 mL, IC 1373.9 ± 128.1 mL, PAR 1022.5 ± 101.4 mL, CSF 351.9 ± 60.4 mL and VCL 62.2 ± 22.4 mL.

Progression of regional WMH and LUTS with aging

Age-related changes in regional WMH are shown in Figure 1. At 65–69 years, the frontal and parietal lobes had greater WMH than did the temporal and occipital lobes (5.77, 3.86, 0.91 and 0.51 mL, respectively). Frontal and parietal WMH markedly increased in size with aging, being approximately twice the volumes in participants aged over 80 years compared with those in participants aged 65–69 years ($P < 0.001$). WMH in the temporal lobe slowly increased in participants aged over 80 years ($P = 0.03$), whereas WMH in the occipital lobe did not significantly increase with aging.

The frequency of urinary incontinence significantly increased with age; 4.8% of participants had urinary incontinence at 65–69 years, 8.7% at 70–74 years ($P = 0.813$, compared with 65–69 years), 15.4% at 75–79 years ($P = 0.084$) and 17.9% at over 80 years ($P = 0.019$). However, urinary difficulty and urinary frequency were not statistically different between each age group.

Clinical characteristics and MRI analysis in participants with and without LUTS

The frequency of LUTS and clinical characteristics and MRI analysis in participants with and without LUTS are shown in Table 2. Older age was associated with high frequency of urinary incontinence ($P = 0.033$), and patients with urinary difficulty and urinary frequency ($P < 0.001$ and $P = 0.007$) were predominantly male. Participants with urinary incontinence showed a decline of cognitive function ($P < 0.001$).

Medication for overactive bladder was frequently used for all LUTS ($P = 0.003$, $P < 0.001$ and $P = 0.001$). Participants with urinary difficulty were more frequently prescribed drugs for benign prostatic hyperplasia and anxiety/sleeping disorder ($P = 0.016$ and $P = 0.006$, respectively). Participants with urinary frequency were more frequently prescribed drugs for hypertension ($P = 0.021$).

Significantly greater volumes of WMH in all brain regions were observed in participants with urinary incontinence. Participants with urinary difficulty had decreased PAR ($P = 0.002$), and increased CSF and VCL volumes ($P = 0.002$ and $P = 0.045$). Enlargement of VCL was also observed in participants with urinary frequency ($P = 0.002$) and urinary incontinence ($P < 0.001$).

Association of WMH and brain atrophy with LUTS

The effect of regional WMH on LUTS was tested by multivariate logistic regression (Table 3). Adjusting for confounding factors, the analysis showed that male sex and use of medication for anxiety/sleeping disorder or benign prostatic hyperplasia were independently associated with urinary difficulty, whereas enlarged VCL and use of medication for hypertension or overactive bladder predicted urinary frequency. Regional WMH in the frontal lobe was a specific risk factor for urinary incontinence, as well as VCL, performance of MMSE and use of medication for overactive bladder. The area under the curve of urinary difficulty, urinary frequency and urinary incontinence was 0.78, 0.65 and 0.77, respectively.

Discussion

In the present study, we reported two main findings. First, WMH progressed with aging, especially in the

Table 2 Clinical characteristics and magnetic resonance imaging analysis in study participants with and without lower urinary tract symptoms

		Urinary difficulty			Urinary frequency			Urinary incontinence		
		Absence (n = 416)	Presence (n = 45)	P-value	Absence (n = 305)	Presence (n = 156)	P-value	Absence (n = 392)	Presence (n = 64)	P-value
Clinical profile										
	Age (years)	77.1 (5.1)	78.1 (5.3)	0.190	76.9 (5.3)	77.7 (4.7)	0.131	77.0 (5.2)	78.5 (4.2)	0.033
	Male (%)	27.2	66.7	<0.001	26.9	39.1	0.007	29.6	39.1	0.129
	Mini-Mental State Examination	20.0 (4.9)	19.1 (5.3)	0.298	19.8 (4.8)	20.2 (5.2)	0.255	20.4 (4.7)	17.1 (5.5)	<0.001
	Body mass index (kg/m^2)	21.9 (3.4)	22.9 (3.1)	0.037	21.9 (3.4)	22.1 (3.3)	0.470	21.8 (3.4)	22.7 (3.4)	0.100
	Hypertension (%)	55.2	59.1	0.620	52	62.6	0.031	54.7	60.3	0.408
	Diabetes (%)	26.8	42.9	0.028	25.2	34.5	0.042	28.1	28.8	0.904
Medication (%)										
	Overactive bladder	7.6	21.4	0.003	5.3	16.2	<0.001	7.3	20.3	0.001
	Benign prostatic hyperplasia	8.1	24.1	0.016	9.8	13.8	0.460	11.4	12.5	0.879
	Hypertension	39.5	40.5	0.902	35.8	47.3	0.021	38.9	44.1	0.454
	Alzheimer's disease	27.2	23.8	0.636	27.5	25.7	0.684	26.9	25.4	0.806
	Anxiety/sleeping disorder	19.7	38.1	0.006	20.3	23.6	0.411	21.8	20.3	0.797
	Psychological problem/ depression	9.8	16.7	0.168	10.3	10.8	0.868	10.4	11.9	0.732
MRI analysis (% of IC)										
	WMH total	1.37 (1.43)	1.55 (1.36)	0.217	1.38 (1.50)	1.40 (1.26)	0.198	1.27 (1.33)	2.05 (1.78)	<0.001
	Frontal lobe	0.77 (0.79)	0.84 (0.68)	0.289	0.77 (0.80)	0.79 (0.73)	0.377	0.71 (0.72)	1.17 (1.00)	<0.001
	Parietal lobe	0.46 (0.55)	0.55 (0.61)	0.271	0.47 (0.59)	0.48 (0.49)	0.079	0.43 (0.52)	0.69 (0.69)	<0.001
	Temporal lobe	0.09 (0.12)	0.11 (0.13)	0.411	0.09 (0.13)	0.09 (0.10)	0.186	0.09 (0.12)	0.13 (0.13)	0.008
	Occipital lobe	0.05 (0.06)	0.06 (0.06)	0.168	0.05 (0.06)	0.05 (0.06)	0.370	0.04 (0.06)	0.06 (0.07)	0.018
	PAR	74.62 (3.35)	72.95 (3.12)	0.002	74.67 (3.33)	74.03 (3.39)	0.112	74.54 (3.28)	73.88 (3.85)	0.063
	CSF	25.42 (3.35)	27.08 (3.12)	0.002	25.36 (3.33)	26.00 (3.40)	0.109	25.49 (3.29)	26.15 (3.84)	0.062
	VCL	4.46 (1.46)	4.93 (1.58)	0.045	4.39 (1.51)	4.74 (1.38)	0.002	4.36 (1.43)	5.37 (1.50)	<0.001

Data are presented as mean (SD). Differences between patients with and without lower urinary tract symptoms were determined using the Mann–Whitney U-test and χ^2-test. CSF, cerebrospinal fluid, IC, intracranial; PAR, parenchyma; VCL, ventricular; WMH, white matter hyperintensity.

Table 3 Prediction of risk factors for lower urinary tract symptoms

	Risk factor	Odds ratio	95% CI	*P*-value	AUC
Urinary difficulty	Male	6.80	3.10–14.88	<0.001	0.78
	Medication for anxiety/sleeping disorder	4.28	1.97–9.30	<0.001	
	Medication for benign prostatic hyperplasia	3.50	1.13–10.84	0.03	
Urinary frequency	VCL	1.15	1.01–1.32	0.042	0.65
	Medication for hypertension	1.64	1.09–2.47	0.019	
	Medication for overactive bladder	3.35	1.71–6.57	<0.001	
Urinary incontinence	WMH frontal lobe	1.47	1.06–2.06	0.023	0.77
	VCL	1.39	1.14–1.68	0.001	
	MMSE	0.90	0.85–0.95	<0.001	
	Medication for overactive bladder	3.02	1.36–6.70	0.006	

Total and regional white matter hyperintensity (WMH) were entered into a logistic regression model with the following confounders: age, sex, Mini-Mental State Examination (MMSE), body mass index, diabetes, brain atrophy and medication (for overactive bladder, benign prostatic hyperplasia, hypertension, Alzheimer's disease, anxiety/sleeping disorder and psychological problems/depression). AUC, area under the curve; CI, confidence interval; LUTS, lower urinary tract symptoms; VCL, ventricular.

frontal lobe. Second, urinary incontinence was associated with WMH in the frontal lobe even after adjustment for brain atrophy and classical confounding factors. Our observation strongly suggests that urinary incontinence might be preventable by efficient treatment of WMH in older adults.

Previous studies have reported that larger WMH volume was associated with urinary incontinence in AD patients, and severe WMH was associated with urinary urgency, independent of other potential confounders.[5,6] In another study, Takahashi suggested that WMH is a more significant contributor to overactive bladder and incontinence than is neurodegeneration of AD.[16] Regional analyses suggested that the frontal lobe seems to be an important area for urinary function. A recent study using single photon emission computed tomography imaging showed that urinary dysfunction was closely related to right frontal hypoperfusion in patients with idiopathic normal pressure hydrocephalus.[17] Furthermore, subjects with detrusor overactivity showed decreased activation of the prefrontal cortex.[18] Normal micturition is dependent on the central and peripheral nervous systems. The frontal cortex is thought to have an inhibitory action on micturition, because lesions in the frontal cortex led to exaggerated micturition reflexes in experimental animals and micturition disturbance in patients.[19,20] It was previously considered that dilated cerebral ventricles leads to urinary urgency and incontinence in normal-pressure hydrocephalus; however, it has become evident in the present study that urinary incontinence has a significant relationship with WMH in the frontal lobe as well as enlargement of VCL in patients with aMCI or AD.[21,22] Furthermore, in analysis of the sexes separately, a similar result that WMH in the frontal lobe was associated with urinary incontinence was observed (data not shown). These results suggest that WMH in the frontal lobe is a risk factor for urinary incontinence irrespective of sex.

Multivariate logistic regression showed that the use of medication for overactive bladder or benign prostatic hyperplasia was independently associated with LUTS. This suggests that medication for overactive bladder is frequently used in patients with urinary frequency or urinary incontinence. Also, medication for benign prostatic hyperplasia is frequently used in patients with urinary difficulty, and these medications are only used in men. Therefore, it seems likely that these medications are associated factors, but not risk factors for LUTS.

WMH in the frontal lobe was markedly increased at 75–79 years, and frontal WMH was associated with urinary incontinence. Also, urinary incontinence was significantly increased at over 80 years, although urinary difficulty and urinary frequency were not different in each age group. Gouw *et al.* reported that WMH progressed with age, mainly in the frontal lobe.[23] Also, lifestyle-related diseases, such as hypertension, diabetes, high blood glucose level and high BMI, were risk factors for WMH progression and new lacunae. In the present study, WMH in the parietal lobe showed slow progression in patients aged 75–79 years compared with those aged 70–74 years. We analyzed each age group separately; however, we did not find any difference in background information of patients. The present study had a cross-sectional design, so we could not confirm a time change in the same subjects. It is considered that a longitudinal study is necessary to clarify which factors influence the progression of WMH. To maintain healthy urinary function of the elderly, preventive intervention for WMH should be carried out in middle age. Correction of lifestyle could delay the onset or progression of LUTS by controlling WMH. Detailed studies are

required to clarify the relevant risks, natural history and efficient treatment for WMH.

The present study had inherent limitations. First, this was a cross-sectional study. Therefore, no causality can be inferred between WMH and LUTS. Second, all MR images were analyzed using a fully automatic segmentation program for WMH. However, it was sometimes difficult to completely distinguish PVH from DWMH. A previous article reported that categorical distinctions between PVH and DWMH are arbitrary, because PVH and DWMH are highly correlated, and that the relationship between causal factors for PVH and DWMH was merely a reflection of total WMH volume.[24] Because the volume of DWMH was markedly less than that of PVH, we analyzed PVH and DWMH as a whole in all brain regions. Third, the assessment of LUTS, which was carried out only through clinical interview, was limited, and more detailed diagnosis by urologists and the use of established questionnaires is required.

Several strengths should be emphasized. First, the present study showed the clinical relevance of regional WMH in LUTS. Second, we evaluated a wide range of risk factors, including age, sex, clinical history, cognitive function, medication and brain atrophy, which suggested the specific contribution of WMH.

In conclusion, the present study provides evidence of an interaction between frontal WMH and urinary incontinence in patients with AD or aMCI. WMH increased with age, especially in the frontal lobe. Urinary incontinence in demented older adults is not an incidental event, but rather an important clinical manifestation of WMH.

Acknowledgments

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Disclosure statement

No potential conflicts of interest were disclosed.

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V. 特　　論

フレイルとサルコペニア
—認知症との新たな接点—

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Frailty and sarcopenia: a new bridge to dementia

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Abstract

Frailty is a predictor of functional decline, falls, hospitalization, and mortality. Fried et al. developed the frailty index, which include 5 simple items: weight loss, weakness, exhaustion, slowness, and low activity. Likewise, sarcopenia indicates an age-related decline in skeletal muscle mass as well as muscle function, which may result in reduced physical capability, poorer quality of life, impaired cardiopulmonary performance, unfavorable metabolic effects, falls, disability, and mortality. Both frailty and sarcopenia could be associated with mild cognitive impairment which leads to dementia. Thus, early initiation of a comprehensive geriatric health examination and a multidomain intervention such as diet, exercise, cognitive training, and vascular risk monitoring may be useful to prevent frailty and sarcopenia in community-dwelling older adults.

Key words: dementia, frailty, mild cognitive impairment, sarcopenia

1. 概　　念

フレイル(frailty)[1]とは，高齢期における生理的予備能の低下，ストレスに対する脆弱性の亢進を背景にした，①筋力低下による動作能力の低下，易転倒性の亢進や，生活機能障害や要介護状態，死亡のリスク増加，などの身体的問題，②認知機能障害やうつなどの精神・心理的問題，③独居や経済的困窮などの社会的問題，を含めた概念である．また，サルコペニア(sarcopenia)[2]は，加齢に伴う筋肉減少や，握力や歩行速度の低下など，機能面を含めた概念である．サルコペニアが進行すると転倒や活動度の低下が生じやすく，フレイルが進行して要介護状態につながる可能性が高くなる．海外では，フレイルとサルコペニアについて比較的早期から着目されてきたが，本邦では，それらの概念が医療・介護専門職に認識されておらず，介護予防の大きな障壁であった．また，フレイルと軽度認知障害(mild cognitive impairment: MCI)との関連も判明し[3]，フレイルの早期診断と介護予防，認知症対策の観点から，その重要性が最近注目されている．

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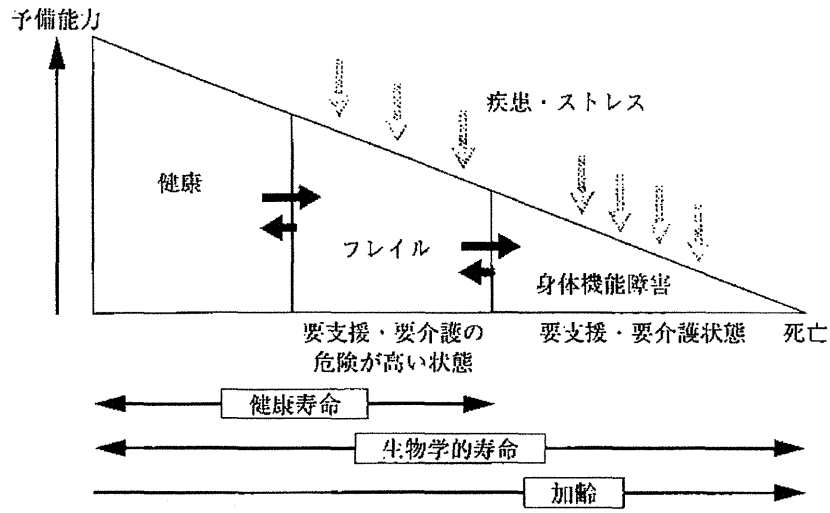

図1　フレイルの位置づけ

2. 疫　　学

おおよそ7-12％の地域在住高齢者が身体的フレイルを有しており，加齢に伴って有病率は上昇する[1]．17カ国を対象にした地域在住高齢者のコホート研究[3]では，歩行速度の低下したMCI高齢者(運動認知リスク症候群)の有病率は9.7％であり，運動認知リスク症候群は認知症発症の予測因子であった(補正後ハザード比1.9倍)．当センターで実施した愛知県大府市の地域コホート研究[4]では，身体的フレイルの有病率は11.3％，MCIは18.8％であり，2.7％がMCIを伴う身体的フレイルの高齢者であった．

3. 病　　態

健康状態からフレイル，身体機能障害に至る概念の模式図[5]を示す(図1)．加齢や疾患の発症によるストレスによって個体の予備能力が徐々に低下し，フレイルに至る．この概念は，以前は不可逆的な意味をもつ「虚弱」としてとらえられていたが，最近では，可逆的な意味をもつ「フレイル」に置き換えられた．医療政策の目標に国民の健康寿命延伸が挙げられているが，早期からのフレイル予防や適切な対策が重要であることが模式図から読み取れる．

フレイルとサルコペニアは密接な関係がある(図2)[5,6]．サルコペニアの発症機序には，①タンパク質の合成と分解，②神経と筋の統合性，③筋肉内の脂肪含有量，などがある．サルコペニアの要因は多岐にわたり，一次性(加齢性)と二次性(①活動関連：寝たきりや無重力状態，②疾患関連：重症臓器不全や悪性腫瘍，神経変性疾患など，③栄養関連：吸収不良や消化管疾患，タンパク質の摂取量不足)に大きく分類される．

4. 診　　断

1) 診断基準

フレイルの診断には，Friedの基準[1]を用いる(表1)．5項目のうち3項目が該当するとフレイルと診断され，2項目以下の場合はプレフレイルと評価される．この基準には，記憶力などの脳機能に関する評価項目が内包されておらず，新しい基準が今後発表される可能性もある．サルコペニアの診断基準としては，欧州発の統一基準(表2)[2]や，アジア人を対象にした診断アルゴリズム[7]が発表されている(図3)．

2) 臨床症候

身体的フレイルやサルコペニアについては，体重減少や筋力低下，歩行速度の低下が主な臨床症候となる．また，バランス保持能の低下，易転倒性もフレイルやサルコペニアを疑う症候である．

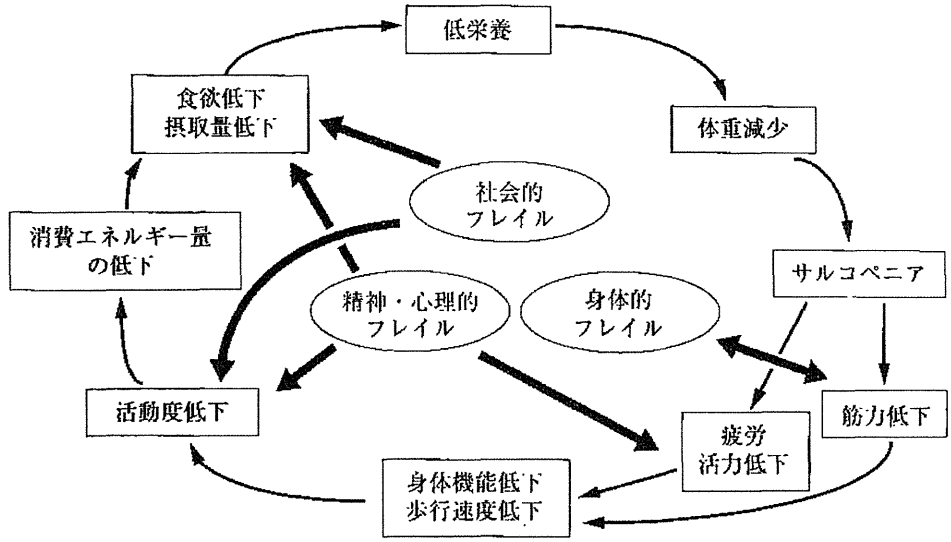

図2 フレイルとサルコペニアの相関図

表1 フレイルの診断基準

体重減少	年間4.5kgまたは5％以上の意図しない体重減少
疲れやすさの自覚	何をするのも面倒，何かを始めることができない，と週に3-4日以上感じる
活動量低下	1週間の活動量が低下 男性：383kcal未満，女性：270kcal未満
歩行速度低下	標準より20％以上の低下
筋力低下	標準より20％以上の低下

3つ以上該当でフレイル，2つ以下でプレフレイル．

表2 サルコペニアの診断基準

1. 筋肉量の減少
2. 筋力の低下
3. 身体能力の低下

基準1+基準2もしくは基準3．

3）検査所見

サルコペニアに関連する筋肉量は，CTやMRI画像で評価できるが，保険適用やコストの問題もある．そのため，バイオインピーダンス法を用いた体組成計で体脂肪や筋肉量を間接的に測定することもできる．筋力は，握力や膝の屈伸筋力測定で評価する．身体能力は，通常歩行速度で評価する．椅子から立ち上がり，短距離歩行後に方向転換し，戻ってきてまた椅子に座る，この動作に要する時間を計測するTimed get-up-and-goテストも有用である．握力や歩行速度などは，簡便に測定でき，数値として検出できて，客観性も担保されるため有用である．

社会的フレイルの評価としては，高齢者の社会的孤立をスクリーニングする尺度として国際的に広く使用されているLubben Social Network Scaleの短縮版がある．精神・心理的フレイルの評価には，Geriatric Depression Scaleなどのうつ評価が有用である．

5. 治　　療

身体的フレイルの介入には，運動や栄養が挙げられる．1回60分程度の筋力トレーニングを週2-3回実施して3カ月後に効果判定する[8]．高強度のレジスタンストレーニングは有用であるが[9]，フレイルを伴う高齢者の基礎体力を勘案すると，トレーニングは必ずしも高強度では

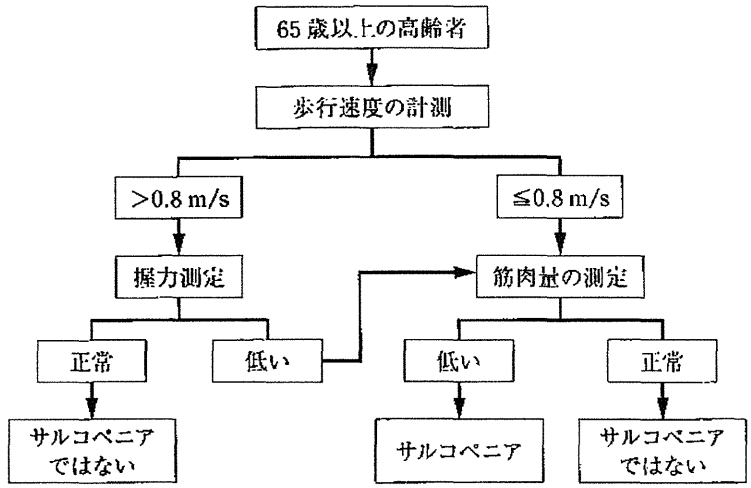

図3　アジア人におけるサルコペニア診断アルゴリズム
個々の調査結果を説明する併存疾患や状況などが考慮されるものとする.
このアルゴリズムはサルコペニアのリスクを有する若年対象者にも適応できる.

なく，ウォーキングのような軽負荷の強度でもよい[10]．本邦における地域在住高齢者の検討[11]では，運動プログラム提供群の8.1％，提供しない群の18％が新規要介護認定を受け，フレイルに対する運動介入の有用性が示唆された．認知機能リハビリテーションのエビデンスはまだ十分ではないが，運動・栄養・認知トレーニング・血管リスク評価による多因子介入が認知機能の維持に寄与するかもしれない[12]．

栄養介入については，ビタミンDの補充と高タンパク食が推奨されている．栄養の単独介入による筋肉増強効果は乏しいが[13]，レジスタンストレーニングとタンパク質の追加摂取によって高齢者の筋力と筋肉量が改善する[14]．

精神・心理的フレイルの介入には，認知症による周辺症状や心理症状の有無をまず評価する．この場合，回想法や音楽療法，または家族への介入が，患者の精神・心理的フレイルを軽減することもある．社会的フレイルの介入には，ガーデニングによる心理社会的効果の報告などがあり[15]，何らかのソーシャルサポート，社会とのつながりや社会的役割が，高齢者の要介護発生や死亡のリスクを軽減する可能性がある．

6. 今後の展望—認知症との接点

フレイルとサルコペニア，MCIは相関関係にある．MCIから認知症への移行はよく知られているが，MCIには可逆的な要素もあると考えると，MCIは「認知フレイル」と位置づけることも可能であろう．フレイルやサルコペニアに伴うMCIは，運動認知リスク症候群として認知症の発症リスクが高くなる．これらの疾患に対する早期からの介入が認知症の発症予防につながり，介護予防や健康寿命の延長に寄与しうる．今後，MCIやフレイルなど運動認知リスク症候群のさらなる病態解明やよりよい治療法の開発が期待される．

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第１章　認知症ケア・認知症グループホーム

Ⅰ　認知症ケア総論

はじめに

認知症の診断基準は、アルツハイマー病も脳血管性認知症も、「社会的活動に支障がある」ことが診断要件に盛り込まれており、社会的活動を測定する身近なツールとして生活機能評価がある。認知症の日常生活活動度低下は疾患の重症度、病型に影響され、ケアを行ううえで、認知症の診断と機能評価の双方が重要である。多くの非薬物療法の成績が蓄積され、これを踏まえた認知症短期集中リハビリテーションが行われており、実施施設の普及、効果の長期的検証が求められている。

〔ケア事例七九〕

１　認知症ケアが必要となる認知症の生活機能低下項目

（１）　認知症の診断基準に含まれる日常生活活動度

アルツハイマー型認知症の診断基準（ＤＳＭ―Ⅳ）では、中核症状である短期記憶、長期記憶の障害があること。抽象思考、判断の障害、構成力の障害、失語／失認／失行、性格変化のうち少なくとも１つが存在することとともに、社会生活、職業、対人関係の障害が存在することが診断の要件として定められているが、抽象的な表現のため分かりにくい。日常生活活動度と認知症の重症度に関する記述は、ＦＡＳＴ（Functional Assessment of Staging in Alzheimer's Disease）（表１）が、アルツハイマー病に限定された重症度記述であるが、分かりやすい（表１）。

表１　ＦＡＳＴ（Functional Assessment of Staging in Alzheimer's Disease）によるアルツハイマー型認知症の日常生活活動度と重症度

１．正常	
２．年齢相応	物の置き忘れなど
３．境界	新しい場所への旅行困難

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4．軽度	過不足ない買い物、家計、行事の段取り障害
5．中等度	***買い物*** 不能、自動車運転危険、***入浴*** 促し要 適切な***洋服選択*** 介助
6．やや高度	a）***着衣*** 失行、b）***入浴*** 介助、 c）***トイレ*** の水を流さない、d）***尿失禁***、 e）***便失禁***
7．最高度	a）最大6語の言語、b）一つの単語のみ理解、 c）***歩行障害***、d）***着座障害***、e）表情喪失、 f）混迷

＿＿：手段的ＡＤＬ、太字斜体：基本的ＡＤＬ

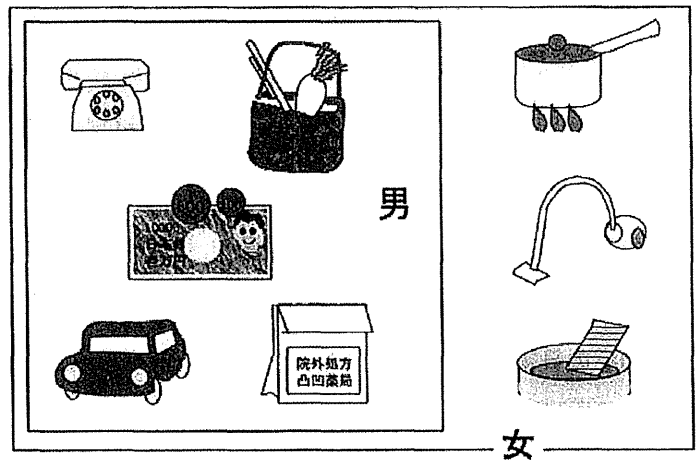
出典：Sclan SG, Reisberg B:Functional assessment staging(FAST)in Alzheimer's disease: reliability, validity, and ordinality. Int Psychogeriatr 4 (Suppl 1):55-69, 1992.

買い物などが早期に阻害され、その後、中等度になると基本的ＡＤＬの項目で複雑な行動である入浴や着衣などに軽度の自立低下がみられるようになり、やや高度になると、入浴や着衣の介助に加え、尿失禁が出現し、最高度になって初めて、移動障害である歩行や姿勢の維持の障害が観察される。この表はアルツハイマーの進行を表しているため、認知機能と生活活動の乖離があった場合に、アルツハイマー以外の病態を示唆することもあり、有用な表であるといえる。

（2） 軽度認知障害（ＭＣＩ）の生活機能低下項目

ＦＡＳＴに記載されていない生活項目でも、早期に異常が指摘されることが少なくない。手段的 ADL; Lawton&Brody[2] は、独居機能に関連する買い物、金銭管理、交通機関の利用、服薬管理、電話の利用、料理、家事、洗濯の８項目である（図１）。

図１　手段的ＡＤＬ（Lawton）＝独居機能の評価



筆者作成

図１の手段的ＡＤＬは、男女共通のものとして、左上から電話、買い物、金銭管理、

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交通機関の利用、服薬管理。独居機能としては男女とも重要であるが、個体間で比較しうる場合、性差を考慮する必要がある、炊事、家事、洗濯の合計８項目に分類される。

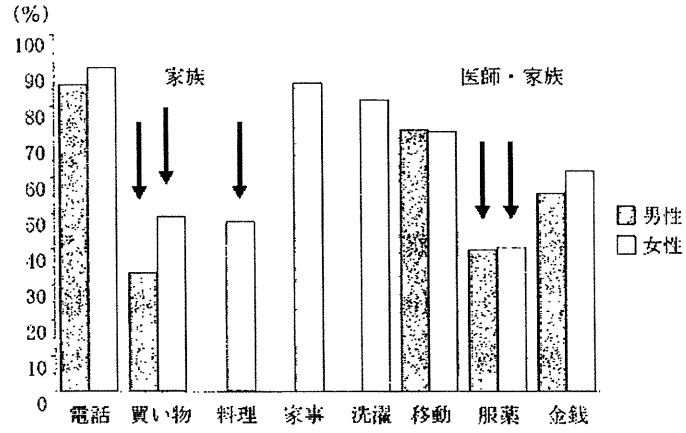
集団で比較する場合には、男性では料理、家事、洗濯をもともとしない（できない）場合があり注意する。

杏林大学もの忘れセンターの受診者697人で手段的ＡＤＬを測定し、早期に低下する項目を抽出した。さらにＣＤＲ（Clinical Dementia Rating：臨床認知症評価法）0.5を満たし、ＭＣＩと診断された113人と、ＭＭＳＥ（Mini-Mental State Examination：ミニメンタルステート検査）が20点以上の軽度認知障害を対象に、ＭＣＩであることを従属変数として、総合的機能評価各項目（ADL; Barthel Index, I-ADL)、抑鬱（Geriatric Depression Scale)、意欲（Vitality Index)、認知機能（ＭＭＳＥ）をＭＣＩと認知症で評価し、各スケールが２群間で有意に異なるかを対応のないＴ検定を行うとともに、有意な項目については、年齢、性を強制注入したモデルにおいて多変量解析を行い、独立した危険因子を決定した。

外来で認知症またはＭＣＩ患者に行った手段的ＡＤＬ検査では、買い物、料理、服薬管理が早期に低下しており、認知症の早期発見に役立つことを報告した[3]（図２）。

〔ケア事例七九〕

図２　どの生活手段が失われやすいか（Ｉ－ＡＤＬ　項目別得点率）



出典：鳥羽研二：認知症高齢者の早期発見　臨床的観点から．日老医誌　44：305-307，2007.

さらにＭＣＩの113人との対比の検討から、男性では買い物、女性では料理ができないことが、初期認知症とＭＣＩとの鑑別に役立つことが判明した[4]。これらのオッズ比は５倍を超えており、80%以上の確率で、認知症をＭＣＩと区別できることを意味する。

しかしながら、正常とＭＣＩを手段的ＡＤＬのLawton & Brodyの配点で区別する

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ことは不可能で、各下位項目の配点を重み付けし再検討する必要がある。さらに、料理にしても、作れる・作れないといった二者択一ではなく、レパートリーや味付けの変化など、微細な変化が記述された事例の集積による研究（Narrative Based Medicine）が求められている。

（3） 中等度認知症に認められる生活機能障害

認知症が進行すると、ある日突然、尿失禁が出現し、家族は狼狽（ろうばい）することが少なくない。もしかすると泌尿器科の病気なのかもしれないと考え、不安の種にもなる。そこで、泌尿器科受診をして、切迫性尿失禁との診断で抗コリン剤が処方されることも少なくないが、アルツハイマーには不適切な薬剤も含まれていることに注意すべきであろう。認知症の自然経過かどうかは、ＦＡＳＴ分類ではやや精密度に欠ける。筆者らは、改訂長谷川式簡易知能評価スケール（ＨＤＳ-Ｒ）と尿失禁の出現頻度を検討し、ＨＤＳ-Ｒ10点で約半数が尿失禁となることを報告している[3]。

（4） 認知症の治療過程における生活機能の変化

認知症の長期予後を生活機能を含めて調査した研究はわが国では見当たらない。

筆者らは、認知症の経過を介護状況を含む総合的機能評価（ＣＧＡ）を用いて解析した[5]。対象は杏林大学もの忘れセンターの通院症例171人（78.0±6.1歳）で、男性57人：77.54±6.06歳、女性114人：78.40±6.12歳であった。測定項目は、日常生活機能：基本的ＡＤＬ（Barthel Index）、手段的ＡＤＬ（Lawton&Brody）を記録しほかに、ＭＭＳＥやＡＤＬに対する意欲（Vitality Index）で測定し、周辺症状は認知症行動障害尺度（ＤＢＤ）を用いて縦断的に記録し、解析した。平均観察期間：平均16カ月である。

１年未満の群64例の解析（平均観察期間８カ月）では、ＭＭＳＥ（20.16→20.23）、Ｉ-ＡＤＬ（%）（62→57）、ＡＤＬ（91→89）ともに有意な変化は認められなかった。

一方、１年以上の群107例の解析（平均観察期間21カ月）では、ＭＭＳＥは20.2から19.6と有意な低下ではない状態で、ＡＤＬの軽度ではあるが有意な低下（96→89）と、Ｉ-ＡＤＬ（%）の著明な低下（70→53）を認めた（表２）。

表２　生活機能各項目の変化量（１年以上の観察群）

n＝107、平均期間（カ月）＝21.0±8.0

	初診時	最終	p値
ＢＲＴＬ*1（100）	96.21±0.75	88.56±1.84	0.0001
Ｉ-ＡＤＬ*2（100%）	70.29±2.37	52.60±2.98	＜0.0001
ＭＭＳＥ*3（30）	20.19±0.45	19.56±0.56	0.3796

〔ケア事例七九〕

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