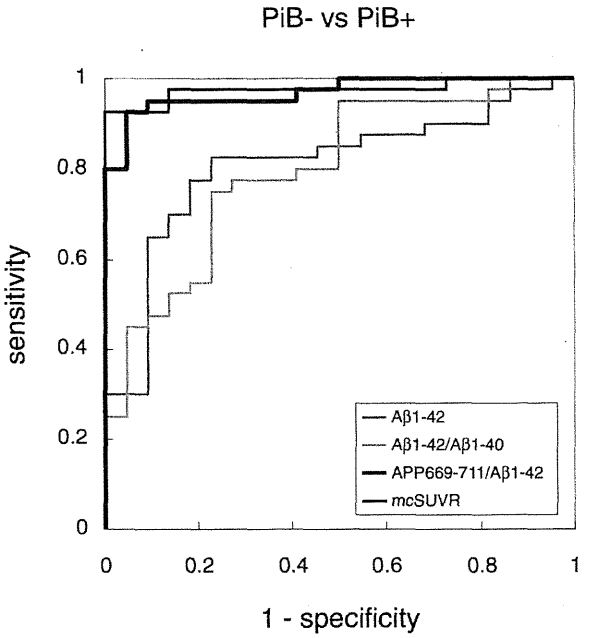

Fig. 3. ROC analysis of the biomarkers as discriminators of PiB+ and PiB− individuals. ROC curves of plasma biomarkers and PiB-mcSUVR are shown in discriminating PiB+ individuals from PiB− individuals. The associated statistical values are displayed in the middle part of Table 2.

showed statistically significant correlation with PiB-mcSUVR. In particular, APP669-711/Aβ1-42 demonstrated high correlation coefficients both in the simple correlation (single $r = 0.687$, $P < 0.001$) and the correlation adjusted for age (partial $r = 0.668$, $P < 0.001$) (Fig. 4A). Multiple regression analysis showed there were no significant ageing effects. Moreover, the regression analysis of PiB-SUVR images using biomarker levels as covariate vectors demonstrated that plasma APP669-711/Aβ1-42 significantly correlated with regional PiB retention (FWE corrected $P < 0.05$, $T = 5.18$, extent threshold $k = 200$ voxels). The visualized areas, robustly involving the frontal, precuneus, and posterior cingulate, and the parietotemporal cortices, appeared to correspond to the typical pattern of Aβ accumulation in AD (Fig. 4B, right).[29),30)] Although no significant clusters were found with the same threshold as the APP669-711/Aβ1-42 threshold, the results with a lowered threshold (uncorrected $P < 0.0001$, $T = 3.97$) suggest that the plasma Aβ1-42 level and Aβ1-42/Aβ1-40 also reflect the cortical Aβ accumulation (Fig. 4B, left and middle).

Performances across clinical categories. Additionally, the performances of the biomarkers were tested across the clinical categories. The results of ANCOVA (adjusted for age) demonstrate that APP669-711/Aβ1-42 showed highly significant group differences with a large effect size (Table 3, upper part), which were almost comparable to those of PiB-mcSUVR. The post-hoc group comparisons demonstrated that APP669-711/Aβ1-42 is sensitive in distinguishing between HC− and any other PiB+ groups (HC+, MCI and AD) (Fig. 5). On the other hand, APP669-711/Aβ1-42 appeared not so sensitive in distinguishing groups classified according to the clinical severity of AD. Within the PiB+ group, only a comparison between HC+ and AD showed a significant difference. We also conducted ROC analysis to evaluate the discriminative capability of the plasma biomarkers across the clinical categories (Table 3, lower part, and Fig. 6). APP669-711/Aβ1-42 showed very high sensitivity and specificity in discriminating HC-individuals from AD and MCI individuals. Importantly, the results demonstrated that APP669-711/Aβ1-42 could identify PiB+ individuals within a cognitively healthy group (HC− vs HC+) with 90.9% sensitivity and 90.9% specificity with a cut off value of 0.863.

Discussion

This study shows that APP669-711/Aβ1-42 in plasma has a big potential as a biomarker precisely surrogating cerebral amyloid deposition. Our biomarker clearly discriminated between PiB− and PiB+ groups with a large effect size ($\eta^2 = 0.56$), and the sensitivity and specificity in discriminating PiB+ individuals from PiB− individuals were very high (0.925 and 0.955, respectively). Furthermore, APP669-711/Aβ1-42 significantly correlated with cortical PiB retention with a high correlation coefficient (age-adjusted partial $r = 0.668$). As a surrogate marker for cerebral amyloid deposition, the performances of APP669-711/Aβ1-42 were far beyond those of reported plasma biomarkers[13),31),32)] and were comparable to those of CSF biomarkers.[27),28),33)] Considering invasiveness and cost, the clinical, as well as social, impact of our novel plasma biomarker would be very significant.

A great deal of effort has been made to determine whether plasma Aβs can be diagnostic and/or predictive biomarkers for AD; however, so far the results were contradictory and, in most studies, there was a broad overlap in the levels of plasma Aβs between controls and patients. This may be due to the difficulties in Aβ measurement in plasma, which are likely caused by various factors,[14)] including low

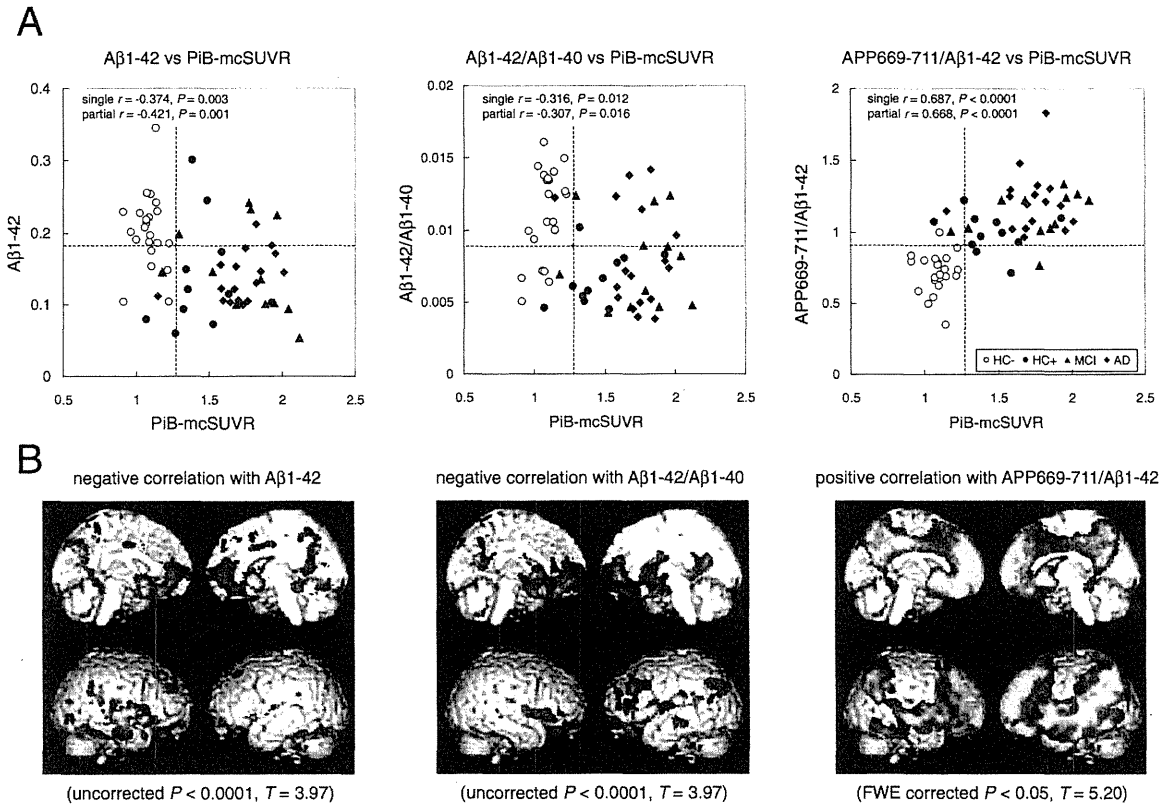

Fig. 4. Correlations between plasma biomarkers and PiB-mcSUVR. A) Scatter plots for biomarkers and PiB-mcSUVR. The open and closed symbols in the scatter plots indicate PiB− and PiB+ groups, respectively. The dashed lines represent cut-off values estimated by the ROC analyses as shown in Fig. 3 and Table 2. B) Regression analysis of PiB-SUVR images for each biomarker adjusted for age. Brain areas that showed statistically significant correlation between regional PiB retention and each biomarker are visualized. Please note that the height threshold of APP669-711/Aβ1-42 is different from the others. The extent thresholds of all are the same ($k = 200$ voxels).

Aβ concentrations and unavoidable Aβ binding to other proteins, which may mask the antibody epitope of Aβ.[34] The utility of the plasma Aβs as AD biomarkers may also be complicated by the fact that plasma Aβs can originate from peripheral organs.[2),35] In addition to these technical and biological aspects of plasma Aβs, the development of biomarkers for AD is generally hampered by a difficulty in correctly recruiting "control subjects" because a large proportion of cognitively normal aged individuals exhibit AD pathologic features, including cerebral amyloid deposition,[19)–21] which has recently been corroborated by amyloid PET studies.[36),37]

To overcome these obstacles, we designed this study as follows. First, to increase detection sensitivity and specificity, we employed our novel IP-MS system.[16] In this system, we used hetero-F(ab′) fragments of two monoclonal antibodies (6E10 and 4G8), which are specific to different Aβ epitopes, that were coupled to PEG on magnetic beads [hetero-F(ab′)-$(PEG)_{24}$ beads],[16] and then, the molecular species of the captured Aβs and AβAPs were precisely and simultaneously determined by MALDI-TOF MS. Compared with the performance of conventional sandwich ELISA measurements, the efficiency and accuracy of Aβ detection in our IP-MS system were markedly high.[17] Indeed, the performances of Aβ1-42 in the present study (Table 2, Figs. 3 and 4) were much higher than those in previous studies.[13),31),32] Second, to decipher the pathological significance of unpredictable changes of Aβ1-42 in plasma, we used APP669-711 as a reference against Aβ1-42. Using the APP669-711 to Aβ1-42 ratio, the performances were extremely high compared with those obtained from Aβ1-42 and Aβ1-40 (Table 2, Figs. 3 and 4). Third, to correctly classify participants in terms of cerebral amyloid deposition, we carried out PiB amyloid imaging by PET of all the subjects. By objective

Table 3. Summary of statistical results for biomarkers for discriminating across clinical categories

	Aβ1-42	Aβ1-42/Aβ1-40	APP669-711/Aβ1-42	PiB-mcSUVR
ANCOVA group comparisons				
HC− (n = 22) mean (95% CI)	0.21 (0.18–0.24)	0.011 (0.009–0.012)	0.72 (0.64–0.81)	1.10 (0.99–1.20)
HC+ (n = 11) mean (95% CI)	0.14 (0.11–0.17)	0.007 (0.005–0.009)	0.99 (0.88–1.09)	1.45 (1.33–1.57)
MCI (n = 12) mean (95% CI)	0.14 (0.10–0.17)	0.008 (0.006–0.010)	1.11 (1.01–1.21)	1.74 (1.61–1.86)
AD (n = 17) mean (95% CI)	0.14 (0.11–0.17)	0.008 (0.006–0.009)	1.24 (1.15–1.33)	1.74 (1.63–1.84)
F-value	5.21	3.52	15.22	19.23
P-value	<0.001	0.003	<0.001	<0.001
coefficient of determination (η^2)	0.403	0.313	0.664	0.714
ROC analysis				
HC− vs HC+ (AUC/sensitivity/specificity)	0.789/0.818/0.818	0.876/0.909/0.773	0.930/0.909/0.909	0.934/0.909/1.000
HC− vs MCI	0.746/0.667/0.909	0.803/0.750/0.773	0.966/0.917/1.000	0.989/0.917/1.000
HC− vs AD	0.864/0.941/0.773	0.743/0.706/0.727	0.997/1.000/0.955	0.992/0.941/1.000

Upper part: Results of the ANCOVA for comparisons among classified groups for biomarkers and PiB-mcSUVR. Values in the parentheses represent 95% confidence interval (CI). All results are adjusted for age. The post-hoc results are displayed in Fig. 5.
Lower part: Results of the receiver operating characteristics (ROC) analyses for each biomarker and PiB-mcSUVR to discriminate across the clinical categories; HC− vs. HC+, MCI, and AD. The cutoff value for each analysis was determined by the nearest point in the curve from the left upper corner. ROC curves are shown in Fig. 6.

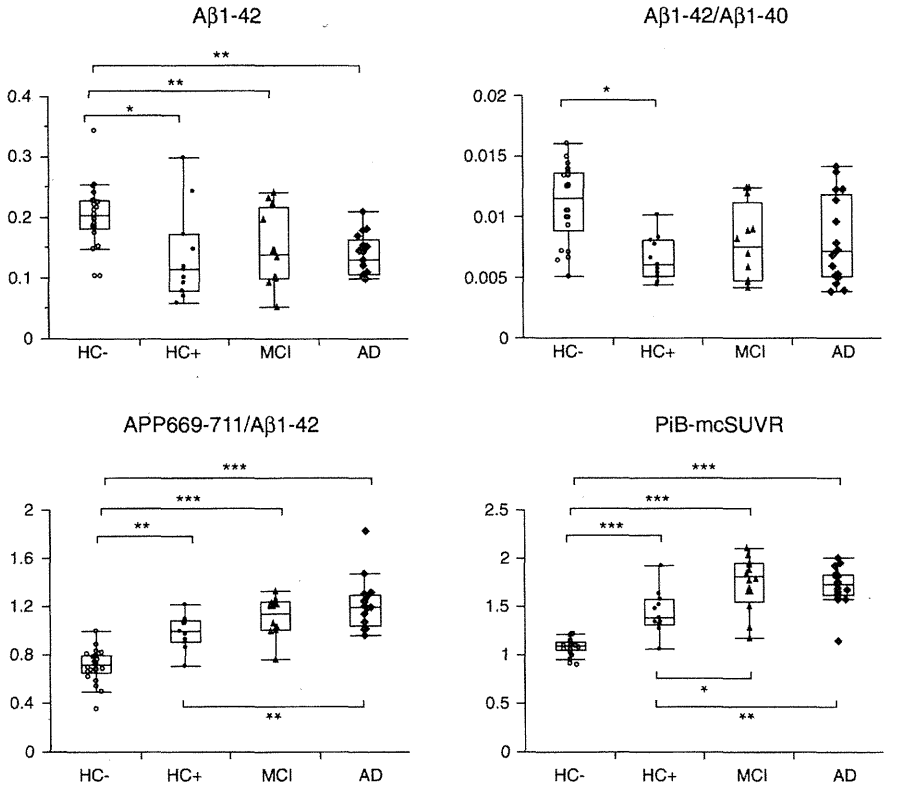

Fig. 5. Group comparisons of the plasma biomarkers and PiB-mcSUVR across clinical categories. Distribution of each value is shown by a box-whisker plot. The boxes represent the 25th, 50th (median) and 75th percentiles of the data. The ends of whiskers represent the lowest (or highest) datum within 1.5-times interquartile range from the 25th (or 75th) percentile. The plotted values were original, but the results of the multiple comparisons were adjusted for age. All p-values were Bonferroni corrected, and the significance levels are represented by the number of asterisks: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

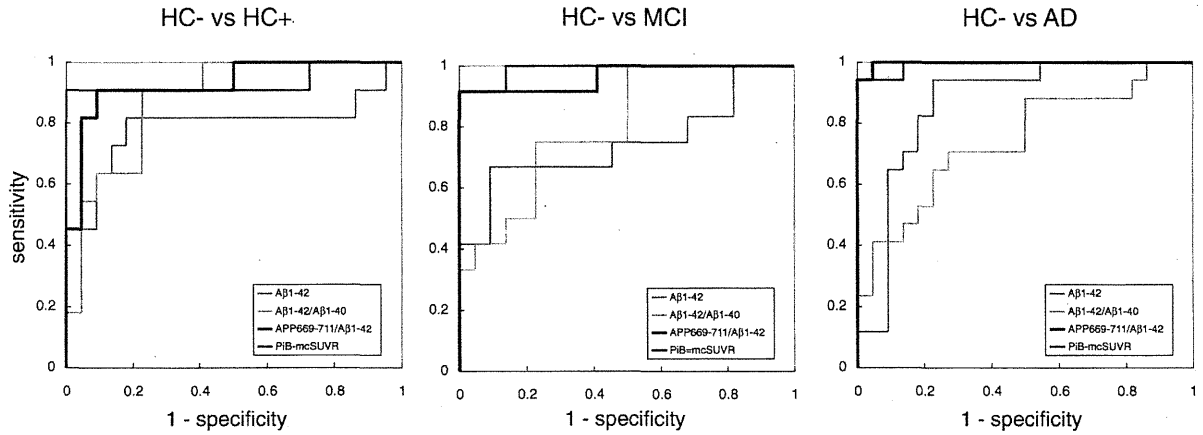

Fig. 6. ROC curves to discriminate across the clinical categories. ROC curves of the plasma biomarkers and PiB-mcSUVR to discriminate between HC− vs. HC+ (left), HC− vs. MCI (middle), and HC− vs. AD (right). The associated statistical values are displayed in the lower part of Table 3.

determination of the state of cerebral amyloid deposition in each participant, we were able to confirm the usefulness of our biomarkers.

It remains to be elucidated why the APP669-711/Aβ1-42 ratio in the plasma showed the highest significance in correlation with the presence of cerebral amyloid deposition. One possible explanation is as follows. APP669-711 has almost the same size and amino acid sequence as Aβ1-42; thus, these two peptides may show the same metabolism rate, binding tendency to other molecules in the brain and plasma, and also penetration capability through the blood-brain barrier. In contrast, the aggregation tendency of APP669-711 may be extremely lower than that of Aβ1-42 because of the difference in both amino- and carboxyl-termini. Collectively, the coexistence of similar and dissimilar characteristics of Aβ1-42 likely allows APP699-711 in plasma to function as a good reference against Aβ1-42.

In conclusion, we found that APP669-711/Aβ1-42 is a highly sensitive plasma biomarker that precisely surrogates cerebral amyloid deposition. This simple and minimally invasive biomarker should be beneficial in the clinical diagnoses of AD, possibly substituting the CSF examination. In addition, our biomarker can be a very powerful screening tool to identify people at risk of AD development from a community, and thereby likely facilitates development of disease-modifying clinical trials for AD.

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Original Article

Clinical examination of reliability/validity of scoring methods for Cube-Copying Test (CCT)

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ABSTRACT

Mori S, Osawa A, Maeshima S, Ozaki K, Sakurai T, Kondo I, Saito E. Clinical examination of reliability/validity of scoring methods for Cube-Copying Test (CCT). Jpn J Compr Rehabil Sci 2014; 5: 102–108.

Objective: Various scoring methods for the Cube-Copying Test (CCT) have been assessed for their validity, but few have been examined for reliability. Additionally, a comparison of multiple scoring methods applied to an identical group of patients has not been reported to date. The present study examined both the reliability and validity of multiple scoring methods and their role in the evaluation of spatial cognitive function.

Method: Thirty-three patients who visited the Medical Center for Dementia at our hospital were included in the study. The Cube-Copying Test was independently scored by two raters using two different scoring methods.

Results: Both scoring methods showed significant inter- and intra-rater reliability. The assessment of criterion-related validity showed a significant correlation with Raven's Colored Progressive Matrices and Frontal Assessment Battery, demonstrating that the CCT reflects visual cognitive functioning and executive functioning. The CCT also showed a significant correlation with education years, suggesting that the CCT scores are more affected by years of education than by age or duration of illness.

Key words: Cube-Copying Test, dementia, reliability, validity

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Introduction

The number of dementia patients is steadily increasing along with the growing population of older adults, which makes it particularly important to take measures to address the disease. It has been found that patients in the early stages of dementia are likely to develop not only memory impairment but also impaired spatial cognitive function – particularly visuo-spatial function – and constructional inability, as well as abnormal motor programming; therefore, evaluation of these functions is imperative in making a diagnosis of dementia [1–3]. Particularly in Alzheimer's Disease (AD), which in the early stages is characterized by decreased blood flow in the parietal lobe region and the medial temporal lobe, impaired visuo-spatial cognitive function and constructional inability are often manifested in the early phase of the illness [3–7].

In the Cube-Copying Test (CCT), the examinee is asked to copy a perspective drawing of a cube, which is then evaluated. The test allows nonverbal assessment of visuo-spatial function and constructional ability and is widely used in ordinary clinical settings. Other methods for evaluating visuo-spatial function include the Wechsler Adult Intelligence Scale (WAIS) performance IQ test [8], Raven's Colored Progressive Matrices (RCPM) [9], and Kohs Block Design Test [10]. However, these tests are difficult to conduct during an outpatient visit due to their relatively long administration time. In this respect, the CCT offers high clinical utility due to its advantage of fast application time. Nevertheless, a definitive method for evaluation or interpretation has not yet been established for the CCT; currently, scoring systems that can quantify the accuracy of figure reproduction and the

presence of a trend in reproduction error types by disease remain under examination and debate [11–13]. To date, a number of scoring systems have been reported including those developed by Kato et al. [12], Maeshima et al. [3, 13, 14], Shimada et al. [6], Takeda et al. [15], Otomo [16], and Yorimitsu et al. [17]. Although the validity of the CCT using each of these scoring methods has been examined and reported [14, 17], few studies have been conducted to assess both reliability and validity, and there have been no studies that assessed the reliability and validity of multiple scoring methods at the same time. In the present study, we examined the reliability of the CCT using two different methods of scoring by two raters multiple times. Additionally, the validity of the CCT was examined through a comparison with patient background and results of other neuropsychological tests.

Subjects and Methods

1. Subjects

The study included 33 patients (11 male and 22 female) who visited the Medical Center for Dementia at our hospital. Mean age was 76.5±8.3 (50–89 years), mean years of education was 10.2±2.5 (6–18 years), and mean duration since forgetfulness was first noted (duration of illness) was 27.8±23.0 months (5–84 months). Clinical diagnosis was as follows: 26 AD patients, 2 Vascular Dementia (VaD) patients, 3 combination of AD and VaD (AD+VaD) patients, and 2 normal patients. AD and VaD were diagnosed in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [18] (American Psychiatric Association 1994).

2. Methods

The results of the CCTs and the following neuropsychological tests administered at the memory clinic at our hospital for diagnosis of dementia were retrospectively collected from electronic medical records and the data were analyzed.

2.1. CCT

A perspective drawing of a cube printed on a sheet of paper was visually presented to the examinee, who was verbally asked to reproduce the figure on a sheet of blank A4 paper. No time limit was set for the task. The various scoring systems developed for the CCT include a qualitative method that measures the examinee's ability to provide an accurate reproduction; a method that grades the examinee's way of joining vertices and constructing lines; and a method that evaluates the resultant figure by pattern classification. The present study used the method by Maeshima et al. (hereinafter the M method) [3, 13, 14], in which assessment is made by scoring both the vertices and lines, and the method by Shimada et al. (hereinafter the S method) [6], in which the assessment is based on pattern classification. The scoring system of each evaluation method is described separately. Scoring was independently performed by two specialists who are members of the Japan Society for Dementia Research and who were blinded to the patients' profiles (including diagnosis, symptoms, and severity), using both CCT scoring methods. Additionally, each scoring method was administered twice at an interval of one week to examine intra-rater reliability.

2.2. Neuropsychological Tests

The results of Mini-Mental State Examination (MMSE) [19], Frontal Assessment Battery (FAB) [20], and Raven's Colored Progressive Matrices (RCPM) [9] were collected from medical records as the data for neuropsychological tests. The reason for adopting these tests was to examine the relationship between the CCT and tests that are considered to reflect constructional and visuospatial abilities, language comprehension and intellectual functioning, frontal lobe functioning, and memory – namely, to examine criterion-related validity of the CCT. MMSE is a screening test that measures cognitive function by assessing orientation, naming, attention and calculation, recall, and language, and the maximum score for assessment is 30 points. FAB consists of six items that are indicators of frontal lobe functioning, i.e., similarities, literal fluency, motor series, conflicting instructions, go/no-go task, and prehension behavior. Three points are allocated to each item, resulting in a maximum score of 18 points. In RCPM for assessing visual cognition, the examinee is asked to determine the element that fits the missing section of a large pattern from among six alternative patterns. No time limit is set and the number of correctly chosen patterns in 36 items is counted as the total points.

2.3. Statistical Analysis

All analyses were performed using SPSS Ver. 21.0.0.0 for Windows. Reliability of the CCT scoring methods was examined using Cronbach's reliability coefficient (α) and Intraclass Correlation Coefficient (ICC). Models ICC (2,1) and (2,k) were used for inter-rater reliability and ICC (1,1) and (1,k) were used for intra-rater reliability [21]. Additionally, to examine criterion-related validity, the correlation between each CCT scoring method and the neuropsychological tests (MMSE, FAB, and RCPM), age, education yaers, and duration of illness was examined using Spearman's rank correlation coefficient.

Results

Patient background and results of neuropsychological tests by clinical diagnosis are presented in Table 1.

Table 1. Patient background and neuropsychological tests by clinical diagnosis.

		Clinical Diagnosis			
	Total Cases (n=33)	AD (n=26)	AD+VaD (n=3)	VaD (n=2)	Others (n=2)
Number of patients (male/female)	33 (11/22)	26 (9/17)	3 (1/2)	2 (0/2)	2 (1/1)
Age (years)	76.5±8.3	77.0±7.4	81.0±5.6	76.5±3.5	63.0±18.4
Educational level (years)	10.2±2.5	10.0±2.2	10.0±2.0	11.0±2.8	13.5±6.4
Duration of illness (months)	27.8±23.0	30.9±23.9	14.0±9.2	8.5±3.5	27.0±29.7
MMSE (/30)	18.5±4.4	18.7±4.1	14.0±6.0	18.5±2.1	23.0±2.8
FAB (/18)	8.5±3.0	8.3±2.8	10.0±2.7	5.5±0.7	12.0±5.7
RCPM (/36)	21.9±6.4	21.6±6.4	26.5±3.5	16.0±2.8	27.0±8.5

The values are mean±standard deviation.

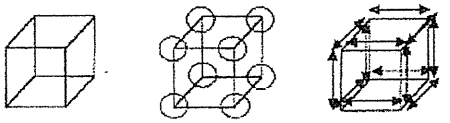
AD, Alzheimer's Disease.
VaD, Vascular Dementia.
MMSE, Mini-Mental State Examination.
FAB, Frontal Assessment Battery.
RCPM, Raven's Colored Progressive Matrices.

Notes

Maeshima,et al. (1997)

Number of Vertices: (Score 0–8) Number of joining points of 3 sides (vertical, horizontal, and diagonal). One point is awarded for every vertex where 3 sides are joined; since a correct cube has 8 vertices, it scores 8 points.

Number of Axial Errors: (Score 0–6) In each quartet of (vertical, horizontal, and diagonal) parallel lines, the presence of any side that is not parallel with the axis of each group of lines, omission of sides, inclusion of extra sides, and so forth are defined as axial errors. If there is an error or omission of an item, it scores 1 point. A correct cube scores 0 point.



Shimada,et al. (2006)

* The items described in ( ) are optional.

Pattern 0: Lines only. Absence of rectangle.

Pattern 1: One quadrilateral (plus).

Pattern 2: Two or more quadrilaterals (plus lines) However, the drawing couldn't be judged to be a three-dimensional (3D) figure.

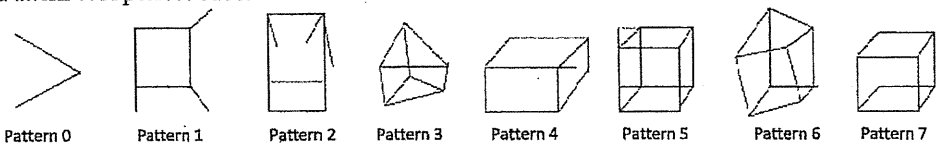
Pattern 3: 3D but not a cube: Participants succeeded in constructing a 3D figure, but failed to make it a cube.

Pattern 4: Cube (plus lines): Participants succeeded in drawing a cube, but fell short of the Necker cube.

Pattern 5: Distorted model: Although the figure consisted of 12 or more lines and could be judged to be the Necker cube, the relationship between these line segments was different from that of the model, based on at least one of the following criteria: (i) each side of the figure could not be judged to be a quadrilateral, or the figure had more than six sides; and (ii) the two overlapping squares of the Necker cube were transposed from the left-lower-right upper pattern to the left-upper–right-lower pattern, or the two squares did not overlap each other.

Pattern 6: Almost the same as the model: Participants were able to copy a figure almost correctly, only some angles were incorrect.

Pattern 7: A perfect cube.



1. Reliability of the CCT

Table 2 shows the mean values and standard deviations of the scoring results and the ranges of scores given by rater (i) and rater (ii) in the first and second testing sessions. Regarding inter-rater reliability, as demonstrated in Table 3, Cronbach's reliability coefficient (α) was higher than 0.9 for the number of vertices and axial errors in the M method and the S method (Number of vertices, 1st session α = 0.997 / 2nd session α = 0.934; Number of axial errors, 1st session α = 0.973 / 2nd session α = 0.936; and S method, 1st session α = 0.958 / 2nd session α = 0.902). In all cases, the ICC was higher than 0.81, thereby demonstrating extremely high (almost perfect) reliability. Also regarding intra-rater reliability, every Cronbach's reliability coefficient (α) was over 0.9 for the number of vertices and axial errors and the S method (Number of vertices, rater (i) α = 0.993 / rater (ii) α = 0.942; Number of axial errors, rater (i) α = 0.990 / rater (ii) α = 0.956; and S method, rater (i) α = 0.977 / rater (ii) α = 0.925) and every ICC was also higher than 0.81.

2. Validity of the CCT

Since the reliability of the CCT was demonstrated by result 1, we then examined its validity using the resultant scores given by the rater (i) in the first testing sessions as representative values. The analysis results of the correlation between representative values and basic patient information (Table 4) showed a significant correlation with education years in all scoring methods for the number of vertices and axial errors of the M method and the S method (M method, $\rho = 0.4521$ for number of vertices and $\rho = -0.4408$ for number of axial errors; and S method, $\rho = 0.4589$), whereas no significant difference was exhibited for age or duration of illness. Additionally, the analysis results of the correlation between representative values and neuropsychological tests (Table 5) demonstrated a significant correlation with RCPM in both scoring methods, i.e., the number of vertices and axial errors of the M method and the S method (M method,

Table 2. Mean values, standard deviations, and ranges of scores in each evaluation method by raters/testing sessions.

	Rater (i)		Rater (ii)	
	1st Session	2nd Session	1st Session	2nd Session
Maeshima Method (Number of Vertices)	3.6±2.5 (0-8)	3.6±2.5 (0-8)	3.5±2.3 (0-8)	3.0±2.6 (0-8)
Maeshima Method (Number of Axial Errors)	3.6±2.6 (0-9)	3.7±2.6 (0-9)	3.3±2.6 (0-9)	3.4±2.6 (0-9)
Shimada Method	4.2±1.9 (1-7)	4.5±2.0 (1-7)	4.1±1.9 (0-7)	4.4±1.9 (1-7)

Mean±Standard Deviation (SD) (Ranges of Scores)

Table 3. Inter-rater reliability and intra-rater reliability of each evaluation method.

	Maeshima Method (Number of Vertices)		Maeshima Method (Number of Axial Errors)		Shimada Method	
Inter-rater Reliability (Rater (i) vs. Rater (ii))	1st Session	2nd Session	1st Session	2nd Session	1st Session	2nd Session
Cronbach's Reliability Coefficient (α)	0.997*	0.934*	0.973*	0.936*	0.958*	0.902*
ICC (2,1) (ρ)	0.993*	0.957*	0.943*	0.877*	0.921*	0.824*
ICC (2,k) (ρ)	0.996*	0.923*	0.971*	0.935*	0.959*	0.903*
Intra-rater Reliability (1st session vs. 2nd session)	Rater (i)	Rater (ii)	Rater (i)	Rater (ii)	Rater (i)	Rater (ii)
Cronbach's Reliability Coefficient (α)	0.993*	0.942*	0.990*	0.956*	0.977*	0.925*
ICC (1,1) (ρ)	0.985*	0.873*	0.980*	0.918*	0.942*	0.856*
ICC (1,k) (ρ)	0.993*	0.932*	0.990*	0.957*	0.970*	0.922*

ICC, Intraclass Correlation Coefficient. *p (two-sided) <0.001

Table 4. Relationship between each evaluation method and patient background.

	Age	Education in Years	Duration of Illness
Maeshima Method (Number of Vertices) (ρ)	−0.2043	0.4521**	−0.2342
Maeshima Method (Number of Axial Errors) (ρ)	0.1668	−0.4408*	0.2993
Shimada Method (ρ)	−0.1629	0.4589**	−0.2468

Spearman's rank correlation coefficients.
Compared with the scores given by Rater (i) in the 1st testing session.
*p<0.05, **p<0.01.

Table 5. Relationship between each evaluation method and results of the neuropsychological tests.

	MMSE	FAB	RCPM
Maeshima Method (Number of Vertices) (ρ)	0.2366	0.4467*	0.7018**
Maeshima Method (Number of Axial Errors) (ρ)	−0.1727	−0.4300*	−0.6594**
Shimada Method (ρ)	−0.1767	0.2715	0.5248**

MMSE, Mini-Mental State Examination.
FAB, Frontal Assessment Battery.
RCPM, Raven's Colored Progressive Matrices.
Spearman's rank correlation coefficients.
Compared with the scores given by Rater (i) in the 1st testing session.
*p<0.05, **p<0.01.

ρ=0.7018 for number of vertices and ρ=−0.6594 for number of axial errors; and S method, ρ=0.5248). Furthermore, a significant correlation was also found with FAB in the number of vertices and axial errors of the M method (ρ=0.4467 for number of vertices and ρ=−0.4300 for number of axial errors). Conversely, there was no significant correlation with total MMSE score in either the scoring methods or outcome measures (M method, ρ=0.2366 for number of vertices and ρ=−0.1727 for number of axial errors; and S method, ρ=−0.1767). Additionally, the S method showed no significant difference for FAB as well (ρ=0.2715) and thus the only neuropsychological test that showed a significant correlation with the S method was RCPM.

Discussion

1. Reliability and Validity of the CCT

Both the M method and the S method with the two raters showed extremely high intra-rater reliability as well as very high inter-rater reliability, thereby demonstrating the reliability of these two scoring methods.

Additionally, both scoring methods showed a significant correlation with RCPM. As mentioned earlier, previous studies have reported that the CCT reflects visual cognitive functioning at a high rate and the present study has also shown a significant correlation between the CCT and RCPM. Thus, it was demonstrated that both the M method and the S method are likely to be valid scoring methods when the basic scale for assessment is visual cognitive functioning.

On the other hand, in the present study, the M method exhibited no significant correlation with MMSE although it showed a significant correlation with RCPM and FAB. This is likely related to the fact that MMSE includes less visual cognitive tasks in the test items. Additionally, the FAB results suggested a relationship between executive functions proposed by Lezak et al. [22] and constructional ability. That is, copying of a cube requires strategic procedures, which may make the task difficult for an examinee suffering from executive dysfunction. It has also been reported that accurate reproduction of a perspective drawing of a cube is affected by verbal IQ in addition to executive functions [23], and an association with language functioning and visual information processing ability

has also been reported [24]. In the present study, MMSE and FAB include verbal tasks in the test items. However, they are extremely easy screening tasks as measures of assessing verbal functioning, and thus further examination is necessary to discuss the relationship between the perspective drawing of a cube and language dysfunction in dementia patients. Additionally, with respect to the relationship with visual information processing, both the M method and the S method showed a significant correlation with RCPM, thereby suggesting a correlation between the perspective drawing of a cube and not only visual cognitive functioning but also performance IQ.

In addition, both scoring systems of the M method and the S method presented a significant correlation with education years, which is in agreement with previous reports on the relationship between constructional inability and years of education [6, 25]. Furthermore, it has also been reported that accurate reproduction of a perspective drawing of a cube requires six or more years of education [6]. The distribution of education level in the present study was 6–18 years, indicating that all patients had six or more years of education. This would suggest that in the present study, the short period of education was unlikely to be a confounding factor making the cube-copying task difficult for the examinee. Additionally, no significant correlation was found between the M and S scoring methods and age or duration of illness. This result suggests that age and duration of illness have less effect on cube reproduction compared with years of education. On the other hand, however, since AD is a progressive disease, it can clearly be predicted that constructional inability will be aggravated as the duration of illness becomes longer. When considering the factors behind the absence of significant correlation between both scoring methods and duration of illness, it is possible that the length of illness used in the present study is inaccurate. Determination was based on subjective observation by the examinee's family that was written on the inquiry sheet at the time of the first consultation, or based on the information collected retrospectively from the medical records produced by the physician in charge. The effects of these information biases need to be examined in future studies.

2. Role of the CCT in Evaluation of Spatial Cognition and Constructional Inability

Constructional inability was first reported by Kleist in 1914 as a local cerebral symptom for which the responsible lesion is the parietal lobe of the dominant hemisphere. Since then, its pathogenic mechanism has been a constant topic of discussion. It is now considered that constructional inability develops as a result of an injury to either the right or left hemisphere, occurring mostly in the posterior foci while there has also been a report of the disorder caused by an injury to the frontal lobe [22]. Furthermore, it has been reported that constructional inability occurs at a high rate due not only to disorder of lesions in the parietal-occipital lobes of the right and left cerebral hemispheres but also to diffuse lesions including cerebral atrophy and cerebral ventriculomegaly [12], and that constructional inability is observed in approximately half the patients with Parkinson's disease [13], while some researchers have reported that constructional inability can occur at a high rate with autoimmune diseases including Systemic Lupus Erythematosus (SLE) as part of the neurologic symptoms [26]; thus, constructional inability may be caused by a diverse range of pathologies.

As suggested by many previous studies and the present study, the CCT can measure visual cognitive functioning and constructional ability with validity, with the added advantage of being fast and easy to administer. In addition, the CCT can assess both aspects of cognition and behavior and may also reflect abnormalities in motor programming, thus making it a highly useful test. In the future, to optimize the utility of the CCT, effective combinations with other neuropsychological tests need to be explored and the pathological diagnostic significance should be examined.

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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 2015; ••: ••–••.**

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

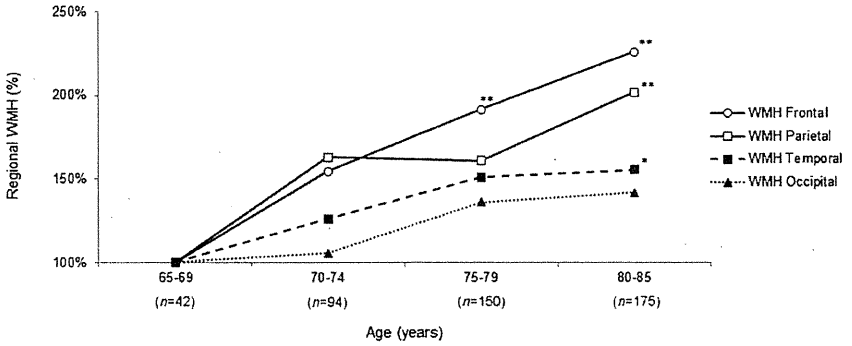

Figure 1 The transition of regional white matter hyperintensity volumes (WMH) in each age group is shown. The *y*-axis shows regional WMH after adjustment for intracranial volumes. $^{**}P < 0.01$, $^{*}P < 0.05$ compared with 65–69 years.

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.

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Disclosure statement

No potential conflicts of interest were disclosed.

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