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ORIGINAL ARTICLE

Correlation between instrumental activities of daily living and white matter hyperintensities in amnestic mild cognitive impairment: results of a cross-sectional study

Bora Yoon · Yong S. Shim · Yong-Duk Kim · Kee Ook Lee · Sang-Jun Na · Yun-Jeong Hong · Yoon-Sang Oh · Duk L. Na · Sang Won Seo · Kyung Won Park · So Young Moon · Sang Yun Kim · Jae-Hong Lee · Seong Hye Choi · Dong-Won Yang

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Abstract Although some studies have supported the association between white matter hyperintensities (WMH) and cognitive impairment, whether WMH are associated with the impairments in instrumental activities of daily living (IADLs) remains unknown. This cross-sectional study investigated differences in basic ADLs and IADLs among different severity of WMH in a large, well-defined registry of patients with amnestic mild cognitive impairment (aMCI). 1,514 patients with aMCI were divided into three groups according to the degree of WMH (1,026 mild, 393 moderate, and 95 severe). We compared the total IADL scores and analyzed the prevalence of the impairment for each IADL item for each group. The severity of WMH was associated with the impairments in IADLs. Among 15 Seoul IADL items, "using public transportation", "going out (short distance)", "grooming" and "participating in leisure activities/hobbies" showed greater positive association with the severity of WMH. WMH in patients with aMCI were associated with the impairments in IADLs but not in basic ADLs. These findings are likely to be more obvious with respect to using public transportation, going out (short distances), shopping, grooming and participating in leisure activities/hobbies.

Keywords Mild cognitive impairment · Instrumental activities of daily living · White matter · Small vessel disease · Activities of daily living

B. Yoon · Y.-D. Kim · K. O. Lee · S.-J. Na
Department of Neurology, Konyang University Hospital, Konyang University College of Medicine, Daejeon, Republic of Korea

Y. S. Shim
Department of Neurology, Bucheon St Mary's Hospital, College of Medicine, The Catholic University of Korea, Bucheon, Republic of Korea

Y.-J. Hong · Y.-S. Oh · D.-W. Yang (✉)
Department of Neurology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 505 Banpo-dong, Seocho-gu, Seoul 137-040, Republic of Korea
e-mail: neuroman@catholic.ac.kr

D. L. Na · S. W. Seo
Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

K. W. Park
Department of Neurology, Dong-A Medical Center, Dong-A University College of Medicine, Busan, Republic of Korea

S. Y. Moon
Department of Neurology, Ajou University School of Medicine, Suwon, Republic of Korea

S. Y. Kim
Department of Neurology, Seoul National University College of Medicine, Clinical Neuroscience Center, Seoul National University Bundang Hospital, Sungnam, Republic of Korea

J.-H. Lee
Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

S. H. Choi
Department of Neurology, Inha University College of Medicine, Incheon, Republic of Korea

Introduction

Cerebral white matter hyperintensities (WMH) are relatively common in elderly individuals. Several studies, including the Leukoaraiosis and Disability (LADIS) study, found the association of WMH not only with cognitive dysfunctions [1–6] but also with problems with mobility, motor performance [7, 8], and urination [9, 10] in normal elderly people and Alzheimer's disease (AD) with WMH. Moreover, The LADIS study demonstrated that the severity of WMH affected functional abilities, that is, baseline severe WMH had independent predictor of disability as well as association with worse functional status [11–13]. In addition, recent study has shown that WMH are negatively associated with instrumental ADL (IADL) and physical ADL in dementia [5, 14]. Although previous studies have demonstrated that WMH were related to cognitive decline among those with mild cognitive impairment (MCI), known prodromal AD dementia [15–17], the association between WMH and IADL in MCI remains unknown. Since IADL needs higher complex cognitive demand than basic ADL, it could be more sensitive and useful marker for detecting very subtle changes in functional abilities. In 2004, the International Working Group on MCI proposed the inclusion of "preserved basic ADL with some minimal impairment in complex instrumental functions" in the diagnostic criteria of MCI [18]. However, there is currently no consensus regarding not only which IADLs are affected in MCI but also which IADLs are related to WMH in MCI. Luck et al. [19] have found that when IADL was considered as part of the criteria for diagnosing MCI, reversion rates from MCI to normal decreased from 35 to 11 %. We hypothesized that WMH would have more influence on IADLs. The purpose of the present study was to determine the relationship between WMH and IADLs and to identify which functional abilities of IADLs are influenced by WMH in a large, well-defined registry of patients with amnestic MCI (aMCI).

Methods

Subjects

A total of 1,514 patients with aMCI were consecutively recruited from 43 dementia clinics in university-affiliated hospitals in South Korea from November 2005 to March 2009. This study was performed as part of the national multicenter study on dementia: the Clinical Research Center for Dementia of South Korea (CREDOS) study. It was a large, well-defined, hospital-based registry. The CREDOS study had aimed to understand the characteristics of Korean patients with dementia. It had developed common protocols, including its own ischemic scale, and recruited patients with subjective memory impairment, MCI, AD, and vascular dementia. This study was approved by the Institutional Review Boards of all participating hospitals, and written informed consents were obtained from the patients and their caregivers after they received a complete description of the study.

We generally adhered to the diagnostic criteria for aMCI defined by Petersen et al. [20] and Winblad et al. [18]. The inclusion criteria for aMCI were as follows: (1) memory complaints by patients and caregivers; (2) objective cognitive impairment (at least 1.0 SD below age- and education-adjusted norms) in memory only or memory and $\geq$1 other cognitive domain (executive functioning, language or visuospatial abilities) in standard neuropsychological tests; (3) normal functional activities; (4) Clinical Dementia Rating (CDR) [21] scores of 0.5; and (5) 'not demented' according to the DSM-IV criteria. We excluded the patients with hemiparesis or a history of clinical stroke because these events could affect their physical activity. Additionally, we excluded the patients with histories of neurological disorders (e.g., active epilepsy) or psychiatric illnesses (e.g., schizophrenia, cognitive developmental delay, major depression, and mania), those taking psychotropic medications, and those in significant alcohol and/or other substance abuse. Patients were also excluded if the presence of the secondary causes of cognitive deficits had been suggested by abnormal laboratory findings including complete blood counts, blood chemistry, vitamin B12/folate levels, syphilis serology and thyroid function tests. We also excluded those with large-territory infarctions and those exhibiting high MRI signal abnormalities that were related to brain tumors, radiation injury, hippocampal sclerosis, and multiple sclerosis according to brain MRIs conducted to detect organic brain lesions that were related to cognitive impairment.

Cognitive and functional assessments

We used the Barthel Index of ADL (B-ADL) (ratings between 0 and 20, with higher scores reflecting lower levels of dependence) [22] to evaluate basic ADLs and the Seoul-Instrumental Activities of Daily Living (S-IADL) (Table 3) [23] to evaluate IADLs.

S-IADL is a caregiver-administered instrument designed to measure IADLs. This questionnaire was completed by the informants after they have received appropriate instructions and while the patients were undergoing neuropsychological assessment. The S-IADL consisted of 15 items: using the telephone, shopping, preparing food/cooking, household chores, using public transportation, going out (short distances), taking medication, managing finances, grooming, using household appliances, managing belongings, locking a door, keeping appointments, talking about recent events and participating in leisure activities/hobbies. All items in the S-IADL were scored on a 4-point scale ranging from 0 to 3; 0 indicates normal performance, and higher scores indicate poorer performance on IADLs. All S-IADL items had been carefully reviewed by experts at the meetings in which they were adopted with consensus and, in addition, had been validated to be the items widely practiced in the Republic of Korea [5, 14].

Cognitive functions were assessed by neuropsychologists with a standard comprehensive neuropsychological battery, which was composed of cognitive subsets for attention and working memory (digit span-forward/backward), visuospatial function (Rey–Osterrieth Complex Figure test [RCFT]), language (Korean version of Boston Naming Test), verbal memory (Seoul Verbal Learning Test, which is the modified Korean version of the Hopkins Verbal Learning Test-immediate/delayed recall), visual memory (RCFT-immediate/delayed recall) and frontal lobe function (Word fluency test-semantic/phonemic, Stroop-word/color reading test).

Assessment of WMH

All subjects received an MRI scan using a standard protocol. MRI scans performed at each center using 1.5 or 3.0 T MRI with anterior commissure–posterior commissure line as a reference. MRIs were set as ideal parameters on their own. Axial T2, T1 and fluid attenuated inversion recovery (FLAIR) images were cut in 5 mm thickness without gap. The severity of WMH was rated based on the FLAIR sequences. The neurologist and radiologist who worked at the attended centers performed rating and, if there is a case with debatable rating at each center, the central committee members decided the rating again after discussion. The CREDOS white matter (WM) rating scales were developed by the central committee of the CREDOS study and modified using the scales developed by Fazekas [24] and Scheltens [25]. The longest diameter WMH around the lateral ventricles (capping or banding on the periventricular areas) or deepest WMH (especially in the centrum semiovale) was evaluated separately. Periventricular WMH were rated as P1 (<5 mm), P2 (≥5 mm, <10 mm) or P3 (≥10 mm), and deep WMH were rated as D1 (<10 mm), D2 (≥10 mm, < 25 mm) or D3 (≥25 mm). Periventricular and deep WMH were combined to produce the final scores for mild, moderate or severe degree. The combinations of D1 with P1 (D1P1) and of D1 with P2 (D1P2) were classified as "mild". Combinations of D2P1, D3P1, D2P2, D3P2, D1P3 and D2P3 were classified as "moderate", whereas D3P3 was classified as "severe". Table 1 summarized the information given above. For assessing the reliability, 138 MRI scans were randomly selected and rated by two neurologists. The inter-rater reliabilities for the periventricular WMH ($\kappa = 0.595$), deep WMH ($\kappa = 0.787$), and WMH ($\kappa = 0.785$) were good as well as intra-rater reliabilities of the WMH including periventricular and deep WMH ($\kappa = 0.694$–0.979) were also satisfactory [5, 6, 14, 26]. We divided participants into three groups according to the severity of their WMH.

Table 1 The matrix for staging of white matter changes

	D1 (<10 mm)[a]	D2 (10< and <25 mm)[a]	D3 (≥25 mm)[a]
P1 (<5 mm)[b]	Mild	Moderate	Moderate
P2 (<5 and <10 mm)[b]	Mild	Moderate	Moderate
P3 (≥10 mm)[b]	Moderate	Moderate	Severe

[a] D1, D2, and D3 represent the three stages of deep white matter changes by the longest length of the deep white matter change in axial and coronal views

[b] P1, P2, and P3 represent the three stages of periventricular white matter changes by capping and banding length vertical to the lateral ventricle, in axial view

Statistical Analysis

We used the Chi-square test for categorical variables and Analysis of Variance (ANOVA) and Tukey's post hoc analysis for continuous variables. We compared the proportion of patients in each group who showed abnormal performance in each S-IADL item using Analysis of Covariance (ANCOVA) adjusted for age and hypertension. We estimated the adjusted odds ratios (OR) and corresponding 95 % confidence intervals (CI) for each 1-point increase in the scores (from the absence to the presence of each dysfunction) for each item of the S-IADL for different the severity of WMH in patients with aMCI (mild vs. moderate group, mild vs. severe group, moderate vs. severe group) using a logistic regression analysis after controlling for age and hypertension. Statistical analyses of groups were performed using SPSS for Windows ver. 12.0 (SPSS, Chicago, IL, USA). The significance level was set to $P < 0.05$.

Results

Demographics and clinical characteristics of the groups

Of a total of 1,514 patients, 1,026 (67.7 %) had mild, 393 (26.0 %) had moderate and 95 (6.3 %) had severe WMH. Patients with severe WMH had the oldest mean age and highest percentage of hypertension, followed by, in order of, those with moderate WMH and those with mild WMH ($P < 0.0001$). The groups differed significantly with respect to the HIS ($P < 0.0001$). No significant differences among the groups were observed in terms of educational

Table 2 Demographic characteristics of study patients ($n = 1{,}514$) according to degree of white matter changes

Characteristic	Mild ($n = 1{,}026$)	Moderate ($n = 393$)	Severe ($n = 95$)	*P* value
Female, *n* (%)	706 (68.8)	246 (62.6)	64 (67.4)	0.083
Age (years)	70.38 ± 8.18	72.93 ± 6.66	73.12 ± 5.96	*0.005**,†
Education (years)	7.74 ± 5.15	7.46 ± 5.03	7.16 ± 5.11	0.405
Diabetes, *n* (%)	196 (19.1)	97 (24.7)	19 (20.0)	0.102
Hypertension, *n* (%)	438 (42.7)	243 (61.8)	51 (62.1)	*<0.001**,†
Heart disease, *n* (%)	157 (15.3)	70 (17.8)	18 (18.9)	0.414
Hyperlipidemia, *n* (%)	155 (15.1)	58 (14.7)	13 (13.7)	0.890
B-ADL	19.80 ± 1.38	19.80 ± 0.79	19.64 ± 1.27	0.498
S-IADL	5.47 ± 4.63	6.44 ± 5.44	6.84 ± 5.01	*<0.001**,†
K-MMSE	24.67 ± 3.62	24.27 ± 4.03	23.84 ± 4.33	0.058
CDR-SB	1.61 ± 0.90	1.67 ± 0.91	1.78 ± 0.94	0.132
HIS	1.67 ± 1.57	2.35 ± 1.97	3.12 ± 2.47	*<0.001**,†,‡
GDS	6.36 ± 4.23	6.19 ± 4.20	6.43 ± 4.26	0.764

B-ADL Barthel Activities of Daily Living, *S-IADL* Seoul-Instrumental Activities of Daily Living, *K-MMSE*, Korean version of the Mini-Mental Status Examination, *CDR-SB* Clinical Dementia Rating-Sum of Boxes, *HIS* Hachinski Ischemic Score, *GDS* Geriatric Depression Scale Data for age, years of education, B-ADL, S-IADL, K-MMSE, CDR-SB, HIS, GDS, and NPI: mean ± SD

P values <0.05 have been italicized; *P* values <0.05 resulting from post hoc analyses were categorized into the following groups in terms of WMCs: * between mild and moderate, † between mild and severe, ‡ between moderate and severe

level, diabetes mellitus, heart disease, hyperlipidemia or scores on the Korean version Mini-mental state examination, CDR-SB, GDS and B-ADL (Table 2).

IADLs

The total S-IADL score was highest in patients with severe WMH, followed by, in order of, those with moderate WMH and those with mild WMH ($P < 0.0001$). The three groups showed different results in public transportation, grooming and participating in leisure activities/hobbies after the adjustment for both age and hypertension (Table 2). Of the 15 S-IADL items, the moderate-WMH group showed higher ORs than the mild-WMH group in: (1) shopping (OR = 1.85, 95 % CI = 1.26–2.72, $P = 0.002$); (2) grooming (OR = 2.43, 95 % CI = 1.12–5.24, $P = 0.024$); and (3) participating in leisure activities/hobbies (OR = 1.82, 95 % CI = 0.97–3.10, $P = 0.027$). The severe-WMH group demonstrated higher ORs than the mild-WMH group in: (1) using public transportation (OR = 1.81, 95 % CI = 1.08–3.02, $P = 0.024$); (2) going out (short distances) (OR = 2.29, 95 % CI = 1.06–4.94, $P = 0.035$); (3) taking medication (OR = 2.15, 95 % CI = 1.26–3.67, $P = 0.005$); (4) grooming (OR = 4.09, 95 % CI = 1.42–11.76, $P = 0.009$); and (5) participating in leisure activities/hobbies (OR = 2.11 95 % CI = 1.27–3.51, $P = 0.004$) after the adjustment for age and hypertension (Table 3). No variables except grooming had statistically significant higher ORs (OR = 1.92, 95 % CI = 1.13–3.36, $P = 0.041$) in the severe-WMH group than in the moderate-WMH group (Table 4).

Discussion

The aim of this study was to compare the IADLs among three groups of aMCI patients with different severity of WMH. In this large, well-defined aMCI registry, we found that the degree of WMH was associated with the impairments in IADLs.

This study showed that patients with aMCI with severe WMH were more likely to have more frequent and more severe impairments in IADLs, which corresponds well with the findings of previous studies on dementia which reported that IADL functions were related to WMH severity [5, 14] as well as a study on a cohort of stroke patients which reported that IADL functions were independent correlates of severe WMH [27]. Impairments in cognitive functions such as execution, planning and mental processing that are connected to the severity of WMH may affect the individual and social performances of complex activities, which can contribute to the impaired IADLs.

Among S-IADL items, poorer performances in using public transportation, going out (short distance) and participating in leisure activities/hobbies according to the severity of WMH coincide well with the results of Moon et al. [14]. This could imply that WMH in aMCI and dementia commonly influence poorer performances of these activities. Especially, using public transportation and

Table 3 Comparison of performances among groups with different degrees of white matter changes in the Seoul-Instrumental Activities of Daily Living (S-IADL) Scale

Variable	Mild ($n = 1{,}026$)	Moderate ($n = 393$)	Severe ($n = 95$)	*P* value[1]	*P* value[2]
Using the telephone	361 (35.2)	167 (42.5)	49 (51.6)	*<0.001*	0.107
Shopping	89 (8.7)	69 (17.6)	10 (10.5)	*<0.001*	0.884
Preparing food/cooking	370 (36.1)	176 (44.8)	41 (43.2)	*0.043*	0.303
Performing household chores	254 (24.8)	144 (36.6)	34 (35.8)	*<0.001*	0.254
Using public transportation	190 (18.5)	95 (24.2)	34 (34.7)	*0.001*	*0.012*
Going out (short distances)	57 (5.6)	37 (9.4)	11 (11.6)	*0.033*	0.783
Taking medication	192 (18.7)	79 (20.1)	28 (29.5)	0.336	0.412
Managing finances	275 (26.8)	121 (30.8)	31 (32.6)	0.234	0.867
Grooming	21 (1.8)	16 (4.1)	7 (7.4)	*0.002*	*0.001*
Using household appliances	124 (12.1)	59 (14.0)	14 (14.7)	0.197	0.768
Managing belongings	540 (52.6)	188 (47.8)	53 (55.8)	0.629	0.180
Locking a door	78 (7.6)	39 (9.9)	12 (12.6)	0.063	0.534
Keeping appointments	412 (40.2)	159 (40.5)	41 (43.2)	0.791	0.883
Talking about recent events	473 (46.1)	184 (46.8)	39 (41.1)	0.515	0.112
Participating in leisure activities/hobbies	463 (45.1)	190 (48.3)	57 (60.0)	*0.039*	*0.028*

The numbers in the table reveal the number of patients obtaining scores indicative of decreased (not normal) performance for each item; the respective percentages of each group appear in parentheses

P values <0.05 are italicized; [1] *P* values resulted from comparison among three groups without adjustment of any variables; [2] *P* values resulted from comparison among three groups after the adjustment for both age and hypertension

Table 4 Odds Ratios of Items of in the Instrumental Activities of Daily Living (S-IADL) Scale

Variable	OR[1]	95 % CI[1]	*P* value[1]	OR[2]	95 % CI[2]	*P* value[2]
Using the telephone	1.05	0.81–1.35	0.721	1.52	0.98–2.35	0.061
Shopping	1.85	1.26–2.72	*0.002*	1.28	0.63–2.59	0.492
Preparing food/cooking	1.41	0.99–1.99	0.057	1.51	0.84–2.71	0.169
Performing household chores	1.26	0.92–1.74	0.152	1.06	0.59–1.90	0.849
Using public transportation	1.06	0.76–1.47	0.740	1.81	1.08–3.02	*0.024*
Going out (short distances)	1.40	0.81–2.40	0.230	2.29	1.06–4.94	*0.035*
Taking medication	1.00	0.68–1.45	0.957	2.15	1.26–3.67	*0.005*
Managing finances	1.07	0.78–1.46	0.691	1.12	0.65–1.93	0.687
Grooming	2.43	1.12–5.24	*0.024*	4.09	1.42–11.76	*0.009*
Using household appliances	1.03	0.71–1.49	0.871	0.92	0.47–1.79	0.801
Managing belongings	0.94	0.67–1.07	0.084	1.21	0.77–1.89	0.407
Locking a door	1.03	0.63–1.69	0.914	1.56	0.74–3.30	0.241
Keeping appointments	0.97	0.74–1.26	0.790	1.12	0.71–1.78	0.622
Talking about recent events	0.89	0.68–1.17	0.411	0.75	0.46–1.20	0.230
Participating in leisure activities/hobbies	1.82	0.97–3.10	*0.027*	2.11	1.27–3.51	*0.004*

OR odds ratio, *CI* confidence intervals

P values <0.05 are italicized

[1] Logistic regression between mild and moderate WMC groups

[2] logistic regression between mild and severe WMC groups

going out (short distance) in the absence of definitive impairment in basic ADLs may represent the compensatory changes that are related to WMH, which is consistent with the results showing that WMH were related to functional changes in the organization of the motor network for lower-limb movements [28]. In other words, WMH may lead to disturbed movement preparation and motor execution by disrupting the frontosubcortical loops, which may then lead to poorer performance in these two areas. In addition, we found that shopping, grooming and participating in leisure activities/hobbies were closely correlated with the severity of WMH. The significant differences in these items among three groups may be explained by decreased interest, worrisomeness or apathy which was associated with WMH [29]. This were also supported by our sub-analysis results that the frequency score of apathy in NPI was shown statistical significance ($P = 0.032$), that is, the frequency of apathy have increased as WMH severity have worsened, although there were no statistical significance in the composite score (frequency x severity) of apathy in NPI (Data was not presented).

The present study has several limitations. First, the incidences of WMH increase with age. Thus, the sample used was unbalanced with regard to the age. We therefore corrected all analyses by including age as a covariate. Nevertheless, it is likely that the differences observed resulted from the interactions between the effects of aging on IADLs and WMH rather than from the effects of WMH alone. Second, this study focused on WMH rather than on other differences (e.g., lacunar infarcts and hippocampal atrophy), which may also has affected the functional performances of the groups. Third, this study used a cross-sectional design. Nevertheless, the strengths of the study include its large sample size, the standardized assessment of WMH and the detailed clinical evaluation. Moreover, to our knowledge, this study was the first to have conducted a detailed analysis of the impact of WMH on IADLs in patients with aMCI. The longitudinal observation of these patients will clarify whether WMH independently predict overt functional impairment in IADLs in patients with aMCI.

Taken together, our findings suggest that WMH are associated with impaired IADLs in patients with aMCI. Furthermore, severe WMH may be associated with greater impairments in 'using public transportation' and 'going out (short distance)', which may be related to functional decline in mobility, 'shopping', 'grooming' and 'participation in leisure activities/hobbies', which may, in turn, be related to the loss of interest/worrisomeness or apathy.

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