White matter hyperintensities evoke cortical atrophy but their influence on cognitive deterioration

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BACKGROUND

- The white matter hyperintensities(WMHs) are high signal lesions seen on T2 or FLAIR MRI images.
- It is known to be a normal aging process but also as a marker of small vascular disease and severe WHMs are thought to cause cerebral cortical and subcortical atrophy.
- But WMHs are also founded in the MRIs of normal aging polulation. So we want to know the effect of WMHs in normal aged subjects as a aging process, especially on the cortical thickness and cognition.

METHODS

Participants

- Total 392 elderly individuals were recruited from the community- based study pool of individuals registered in a National Research Center for Dementia, Gwangju, Korea, from January 2014 to May 2015.
- They have no focal neurological deficits and no history of severe medical illnesses and cerebrovascular accidents and their basic or instrumental daily activities were all normal.

Clinical, Neuropsychological and Radiological assessment

- All participants were assessed 4 times, 1st, a series of questionnaires and mini-mental examination(MMSE), 2nd, Comprehensive neuropsychological (NP) assessment using the Seoul Neuropsychological Screening Battery covering five cognitive domains: attention, memory, language, visuospatial function, and frontal/executive function, 3rd, blood sampling and MRI imaging, and last, interview by well trained doctors(all neuologist or Psychiatrist).
- 223 subjects were cognitively normal (CN) diagnosed by neuropsychological test z score over – 1.5 according to the age-, education-, and gender-specific norms on all cognitive tests.
- 169 subjects were minimally cognitive impairment (MCI) diagnosed by neuropsychological tests z scores were below -1.5 according to the age-, education-, and gender-specific norms on at least one of cognitive tests.
- White matter hyperintensities were assessed by visual scoring by Fazekas et.al into 4 groups(0,1,2,3), by Credos study into 7 groups(0,1,2,3,4,5,6), and multiple scores(total 83) by Scheltens et.al.
- Cortical thickness of various cortical areas and hippocampal and ventricular volumes were measured automatically based on 3D MPRAGE images using Freesurfer software.

Statistical analysis

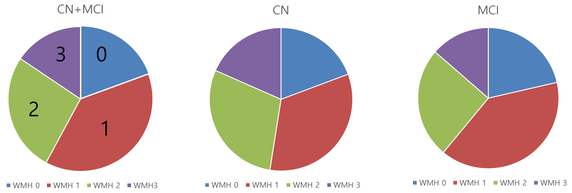
- Demographic, clinical, NP data, cortical thickness and volume data were compared between groups using separate one-way analysis of variance (ANOVA) and χ^2 test for continuous and categorical variables, respectively.
- Analysis of covariance(ANCOVA) was performed to examine the ability of WMH to predict cortical thinning or cognitive change.
- SPSS was utilized with p-values less than 0.05 considering significant.

RESULTS

Table 1. Demographic and Clinical characteristics in 4 WMH subgroups(CN+MCI)

	WMH groups(Fazekas et.al.)				*p*-value
	0	1	2	3	
Numbers(%)	79(20.2)	141(40.0)	108(27.6)	64(16.3)	
CREDOS grade(0-6)	0	1.9±0.8	4.0±0.9	5.8±0.4	
Scheltens score(0-83)	0	6.2±3.0	12.2±3.4	18.1±4.3	
Male(%)	26.6	36.9	42.6	**21.9**	0.017
Age	71.1±4.9	73.0±4.8	**75.0±4.8**	**75.6±4.6**	0.000
Education	11.4±4.6	12.7±4.6	12±4.6	**9.1±4.0**	0.000
Height	157±8.2	157.6±8.0	157.4±8.3	**152.8±7.8**	0.001
Weight	61.3±8.5	62.0±9.2	60.9±8.5	59.5±8.4	0.281
BMI	24.9±2.6	25.0±3.2	24.6±2.8	25.3±2.8	0.342
Dementia family hx	10 (12.7)	21 (14.9)	11 (10.3)	11 (17.5)	0.545
Stroke	8 (10.1)	27 (19.1)	19 (17.6)	4 (6.3)	0.053
Heart disease	8 (10.1)	17 (12.1)	17 (15.7)	8 (12.8)	0.701
Hypertension	36 (45.6)	81 (58.2)	67 (62.0)	**50 (78.1)**	0.001
Diabetes mellitus	14 (17.7)	31 (22.0)	21 (19.4)	17 (26.6)	0.588
Depression	2 (2.5)	2 (1.4)	3 (2.8)	1 (1.6)	0.865
Alcohol	3 (3.8)	9 (6.4)	7 (6.5)	1 (1.6)	0.418
Smoking	4 (5.1)	3 (2.1)	1 (0.9)	2 (3.1)	0.342
ApoE4(%)	13(16.7)	30(22.4)	13(14.0)	4(7.4)	0.073
MMSE	26.8±2.6	26.7±2.5	26.8±2.3	**25.6±3.4**	0.017
SMCQ	3.7±3.0	2.8±2.5	3.5±3.0	3.3±2.6	0.112
KDSQ	4.4±3.2	3.6±2.2	4.0±2.8	3.3±2.0	0.139
GDS	7.8±5.4	7.6±5.5	**9.2±6.2**	**9.6±6.1**	0.044
K-IADL	0.7±1.3	0.6±1.2	0.5±1.2	0.5±0.8	0.651

BMI = body mass index, MMSE = mini-mental examination score, SMCQ = subjective memory complaint questionnaire scores KDSQ = Korean dementia screening qustionnnaire scores, GDS = geriatric depression scores(total 30), K-IADL = Korean version of instrumental activity of daily living , *p* value by ANOVA and χ^2 test



- At cognitively normal group, age, sex, smoking history were statistically significant. At MCI groups, Age, Height, K-MMSE, monthly income, hypertension, ApoE4 were the significant factors.

Table 2. Neuropsychological characteristics in 4 WMH subgroups(CN+MCI)

	WMH groups(Fazekas et.al.)				*p*-value
	0	1	2	3	
DSF	5.57±1.6	5.87±1.6	5.79±1.5	5.42±1.5	0.213
RCFT copy score	31.39±5.2	32.0±5.0	31.6±4.5	**28.95±7.3**	0.002
SVLT imm. recall score	18.78±5.0	18.80±4.4	17.84±4.3	**16.38±4.7**	0.002
SVLT delayed recall score	5.54±2.6	5.45±12.4	4.67±2.3	**4.58±2.5**	0.007
SVLT recognition score	20.23±2.4	20.54±1.9	20.15±2.0	**19.55±2.6**	0.026
RCFT imm. recall score	13.33±6.9	13.28±7.1	11.9±6.2	**9.27±5.7**	0.000
RCFT delayed recall score	1305±6.6	13.23±6.7	12.14±6.0	**9.59±5.6**	0.001
RCFT recognition score	19.63±1.9	19.69±2.0	19.47±1.9	19.05±2.4	0.186
COWAT animal	15.03±4.7	14.35±4.1	13.60±3.9	**13.17±3.7**	0.027
COWAT supermarket	16.78±5.5	15.94±5.1	15.44±5.0	**14.03±4.4**	0.011
Stroop Word Reading	106.7±14.8	109.5±9.0	110.1±5.9	**102.6±19.6**	0.0001
Stroop color reading	81.3±24.1	78.4±23.0	75.1±20.7	**67.7±25.4**	0.003
K-BNT	11.6±2.5	11.6±2.2	11.73±2.3	**10.52±2.9**	0.010
K-Trail A test time	34.9±23.7	32.4±16.3	31.8±15.7	**41.5±20.8**	0.006
K-trail B time	63.1±39.5	66.0±46.7	65.4±35.0	**90.6±52.6**	0.003

DSF = digit span forward; BNT = Boston naming test (15 item); RCFT copy = Rey complex figure test copy score; SVLT_imm = Seoul verbal learning test, immediate recall score;; RCFT imm = RCFT, immediate recall score; COWAT = controlled oral word association test; TMT = trail making test.
*Neuropsychological data presented raw data not adjusted for age, sex, education, p value by ANOVA

- After age, sex, and education period were adjusted by ANCOVA, RCFT copy(p=0.03), RCFT immediate recall score(0.042), stroop word reading(0.003), and trail B time(0.032) were significant factors.
- At cognitive normal group, no significant factor was found.
- At MCI group, RCFT copy, SVLT imm, delayed, recognition score, RCFT imm recall. Delayed recall, Stroop word and color reading were significant factors.

Table 3. Cortical thickness and hippocampus/ventricle volume in 4 WMH groups(CN+MCI)

Brain volume/thickness	WMH groups				*p*-value
	0	1	2	3	
Lt lateral ventricular volume	13549±5735	15537±6733	18070±7975	20271±9340	0.0001
Rt. lateral ventricular volume	11973±5384	14092±6458	16375±7594	18327±9055	0.0001
Lt. Hippocampal volume	3920±431	3831±536	3719±482	3635±468	0.160
Rt. hippocampal volume	4181±413	4035±523	3959±508	3827±449	0.040
Lt. fusiform cortex	2.712±0.13	2.635±0.14	2.611±0.15	2.607±0.15	0.003
Lt cingulate isthmus	2.398±0.20	2.306±0.22	2.305±0.21	2.264±0.16	0.042
Lt lingual cortex	1.921±0.17	1.874±0.11	1.856±0.11	1.840±0.11	0.007
Lt. medial orbitofrontal cortex	2.405±0.13	2.325±0.14	2.328±0.14	2.345±0.14	0.001
Lt. rostral ant cingulate cortex	2.789±0.19	2.705±0.20	2.701±0.22	2.725±0.20	0.043
Lt. transverse temporal cortex	2.292±0.18	2.278±0.18	2.275±0.19	2.206±0.20	0.037
Rt Fusiform cortex	2.721±0.12	2.643±0.15	2.627±0.15	2.602±0.18	0.012
Rt inf. temoral cortex	2.890±0.15	2.831±0.14	2.815±0.14	2.783±0.17	0.046
Rt lingual cortex	1.948±0.11	1.912±0.10	1.901±0.10	1.879±0.10	0.018
Rt pars opercularis	2.549±0.15	2.513±0.15	2.510±0.18	2.472±0.17	0.008
Rt supramarginal cortex	2.444±0.12	2.396±0.12	2.397±0.12	2.371±0.13	0.025
Rt insular cortex	3.004±0.15	2.938±0.14	2.936±0.13	2.861±0.13	0.0001

- After age, sex, education period, ApoE 4 status, hypertension, height, total brain volume, and intracranial volume were adjusted as covariables by ANCOVA, several cortical areas of both hemisphere were found to be related with white matter hyperintensities.

DISCUSSION

- Increased WMHs(more than grade 2) in normal subjects are quite common (38-45%) in our study.
- The older, low-educated, smaller, hypertensive, and depressive females seem to be more susceptible to WMHs.
- When cognitive normal, WMHs did not affected cognitive profiles but as cognition declines WMHs seem to aggravate visuospatial, memory, and frontal cognitive profiles.
- As WMH increases, ventricular volume begins to increase, that means brain atrophy. But does not seem to evoke hippocampal atrophy sufficiently.
- The particular cortical areas vulnerable to increasing WM hyperintensities are fusiform, lingual, insular cortices and some areas of temporal, frontal, and cingulate gyri according to above results.
- We think WMHs is slowly progressing aging phenomenon causing cortical atrophy and cognitive decline but the their effects were not evident until the decompensation developes.