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Myelin loss in white matter hyperintensities and normal-appearing white matter of cognitively impaired patients: a quantitative synthetic magnetic resonance imaging study

Mina Park[1,2] · Yeonsil Moon[3] · Seol-Heui Han[3] · Ho Kyun Kim[4] · Won-Jin Moon[1]

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Abstract

Objectives White matter hyperintensities (WMHs) are implicated in the etiology of dementia. The underlying pathology of WMHs involves myelin and axonal loss due to chronic ischemia. We investigated myelin loss in WMHs and normal-appearing white matter (NAWM) in patients with various degrees of cognitive impairment using quantitative synthetic magnetic resonance imaging (MRI).

Methods We studied 99 consecutive patients with cognitive complaints who underwent 3 T brain MRI between July 2016 and August 2017. Myelin partial volume maps were generated with synthetic MRI. Region-of-interest–based analysis was performed on these maps to compare the myelin partial volumes of NAWM and periventricular and deep WMHs. The effects of myelin partial volume of NAWMs on clinical cognitive function were evaluated using multivariate linear regression analysis.

Results WMHs were present in 30.3% of patients. Myelin partial volume in NAWM was lower in patients with WMHs than in those without (37.5 ± 2.7% vs. 39.9 ± 2.4%, $p < 0.001$). In patients with WMHs, myelin partial volume was highest in NAWMs (median [interquartile range], 37.2% [35.5–39.0%]), followed by deep WMHs (7.2% [3.2–10.5%]) and periventricular WMHs (2.1% [1.1–3.9%], $p < 0.001$). After adjusting for sex and education years, myelin partial volume in NAWMs was associated with the Clinical Dementia Rating Scale Sum of Box ($\beta = -0.189$ [95% CI, -0.380 to -0.012], $p = 0.031$).

Conclusion Myelin loss occurs in both NAWM and WMHs of cognitively impaired patients. Synthetic MRI-based myelin quantification may be a useful imaging marker of cognitive dysfunction in patients with cognitive complaints.

Key Points

- *Quantitative synthetic MRI allows simultaneous acquisition of conventional MRI and myelin quantification without additional scanning time.*
- *Normal-appearing and hyperintense white matter demonstrate myelin loss in cognitively impaired patients.*
- *This myelin loss partially explains cognitive dysfunction in patients with cognitive complaints.*

Keywords Cognitive dysfunction · Dementia · Myelin sheath · Synthetic magnetic resonance imaging · White matter

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✉ Won-Jin Moon
mdmoonwj@kuh.ac.kr

[1] Department of Radiology, Konkuk University Medical Center, Konkuk University School of Medicine, 120-1 Neungdong-ro, Gwangjin-gu, Seoul 05030, Republic of Korea

[2] Department of Radiology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

[3] Department of Neurology, Konkuk University Medical Center, Konkuk University School of Medicine, 120-1 Neungdong-ro, Gwangjin-gu, Seoul 05030, Republic of Korea

[4] Department of Radiology, School of Medicine, Daegu Catholic University, Gyeongsan, Gyeongsangbuk-do, South Korea

Abbreviations

CDR-SB	Clinical Dementia Rating Scale Sum of Boxes
GMF	Gray matter fraction
ICV	Intracranial volume
MMSE	Mini-Mental Status Examination
NAWM	Normal-appearing white matter
WMF	White matter fraction
WMHs	White matter hyperintensities

Introduction

White matter hyperintensities (WMHs), commonly observed in brain magnetic resonance imaging (MRI) of elderly subjects, are associated with cognitive impairment and increased risk of dementia [1, 2]. Myelin and axonal loss due to chronic ischemia induced by cerebral small vessel disease (SVD) is a common pathology underlying WMHs in the healthy elderly and dementia patients [3].

SVD-associated pathological changes in WMHs can also occur outside of WMHs, in normal-appearing white matter (NAWM). SVD constitutes a widespread and continuous spectrum of white matter injury. WMHs may represent extreme injury, while changes in NAWM remain mostly undetected on conventional MRI [4, 5]. Pathologically, SVD-derived changes in NAWM correspond to mild tissue changes with slightly lower myelin density, looser but largely intact axonal networks, and normal glial density [6]. The role of myelin in cognitively impaired patients and elderly individuals is becoming increasingly evident [7, 8]. Advanced techniques may allow assessment of subtle myelin changes in NAWM. Diffusion tensor imaging (DTI) or magnetization transfer imaging can detect subtle changes in NAWM before they are visible on conventional magnetic resonance imaging (MRI) [9, 10], but these techniques do not provide specific information about myelin per se. Rather, they indicate changes in fractional anisotropy, mean diffusivity, or the integrity of lipid macromolecules, which indirectly reflect white matter pathology [11].

Recently, quantitative synthetic MRI has enabled quantification of longitudinal T1 and transverse T2 relaxation times in a single acquisition [12]. It provides conventional T1- and T2-weighted, and FLAIR images, but also myelin partial volume maps, which allow voxel-based myelin quantification in the brain and simultaneous automatic brain segmentation within acceptable scanning times. Synthetic MRI supersedes traditional myelin-mapping methods for assessing myelin content of NAWM in the elderly, as it does not require a long acquisition time or additional acquisition of other contrast images.

We hypothesized that myelin breakdown would occur in NAWM and WMHs in cognitively impaired patients, and that this may be revealed with quantitative synthetic MRI for myelin quantification. Hence, we used quantitative synthetic MRI to investigate the association between myelin partial volume of WMHs and NAWM and the severity of cognitive impairment.

Materials and methods

Study population

The need for written informed consent from patients was waived by the Institutional Review Board of Konkuk University Medical Center, Korea, due to the retrospective nature of the study. Data from 116 consecutive patients with a chief complaint of cognitive impairment who underwent quantitative MRI from July 2016 through August 2017 were reviewed. Of the 116 patients, we excluded six with large territorial infarction, three with unavailable Mini-Mental Status Examination (MMSE) scores, two with metabolic brain disorder, two with major depressive disorder, two with intracranial hemorrhage, one with a giant aneurysm, and one with inadequate image acquisition. Therefore, 99 patients (male:female = 26:73; mean age ± standard deviation, 74.1 ± 10.0 years) were included in the analysis. Of these, 32 patients had Alzheimer's disease, 40 had mild cognitive impairment, three had vascular dementia, 10 had mixed vascular and Alzheimer's dementia, three had other types of dementia, and 11 had subjective cognitive impairment. The median MMSE score was 22 (interquartile range 17–26). The median score of the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) was 2.5 (interquartile range 1–4.8).

Clinical evaluation

We assessed all available patient information, including basic demographic characteristics, other medical conditions (including history of vascular risk factors), laboratory test results (including hemoglobin A1c and serum 25OHD measurements), global cognitive assessment scores (CDR-SB and MMSE scores), apolipoprotein E genotyping, and brain imaging.

MRI acquisition

MRI sequences were performed on a 3 T scanner (Discovery MR750+; GE Healthcare) with a 32-channel head coil. All patients underwent axial quantitative synthetic MRI and sagittal T1-weighted imaging, axial FLAIR, and axial 3D susceptibility-weighted angiography (SWAN).

Quantitative synthetic MRI was performed using the 2D axial quantification of relaxation times and proton density by multiecho acquisition of saturation-recovery using turbo spin-echo readout (QRAPMASTER) pulse sequence [12]. This pulse sequence is a multisection, multiecho, multisaturation delay method of saturation-recovery acquisition by turbo spin-echo readout, with which images are obtained via

different combinations of TE and saturation delay time. Two sets of TE values and four sets of delay time were used to quantify longitudinal T1 and transverse T2 relaxation times, and proton density (PD). The TE values used were 15.1 and 90.3 ms. The delay times were 114.3, 457.1, 1485.7, and 3085.7 ms. The parameters for quantitative MRI were as follows: field of view (FOV), 220 mm; matrix, 320 × 256; echo-train length, 16; band-width, 162.8 kHz; section thickness/gap, 4.0/1.0 mm; and number of sections, 28. The total acquisition time of quantitative synthetic MRI was 4 min, 32 s. Myelin quantification map acquisition and raw data processing were conducted using MAGnetic resonance image Compilation (MAGiC) software on a 64-bit workstation.

Sagittal T1-weighted images were obtained using either a 2D T1-weighted inversion recovery sequence (TR/TE, 2487/24 ms; flip angle, 111°; FOV, 230 mm; matrix, 320 × 226) or a 3D fast spoiled gradient-echo sequence (TR/TE, 8.2/3.2 ms, flip angle, 12°; FOV, 250 mm; matrix, 256 × 256). Standard axial FLAIR images (TR/TE 9000/90 ms; flip angle, 142°; FOV, 220 mm; matrix, 320 × 224) and axial 3D SWAN images (TR/TE 37.3/23.4, 31.2, 39.0, 46.8, and 54.6 ms; flip angle, 15°; FOV, 220 mm, matrix, 512 × 256) were obtained.

Analysis of SVD burden

A neuroradiologist (M.P.) with 4 years of experience assessed the vascular risk factors on MRI. For visual assessment, synthetic T1- and T2-weighted images, synthetic FLAIR, and standard FLAIR images were used. WMHs were defined as hyperintense white matter lesions on FLAIR images as per the Standards for Reporting Vascular Changes in Neuroimaging criteria, and graded in accordance with the Fazekas scale as deep WMHs (0 = absent; 1 = punctate; 2 = early confluent; 3 = confluent) and periventricular WMHs (0 = absent; 1 = caps or pencil-thin lining; 2 = smooth halo; 3 = irregular WMH extending into the deep white matter) [13, 14]. A total Fazekas score was calculated by adding the periventricular and deep WMH scores. A score > 3 was designated as WMH-positive [14]. We then classified patients into the WMHs (-) group ($n = 69$) and WMHs (+) group ($n = 30$). Lacunes were defined as small lesions that were hypointense on T1-weighted images, hyperintense on T2-weighted images, and had perilesional halos on FLAIR images [13]. Microbleeds were defined as small signal voids with associated blooming on T2*-weighted SWAN images. The presence and number of lacunes and microbleeds were recorded as previously described [13].

Quantitative synthetic MRI analysis

The QRAPMASTER pulse sequence allows simultaneous quantification of the relaxation rate of R1 (1/T1), R2 (1/T2), and PD within an acceptable scanning time. Quantifications of R1, R2, and PD can be used to calculate the signal intensity of a pixel by any combination of TR and TE and to create synthetic T1-weighted and T2-weighted images [15].

Myelin quantification can be estimated by synthetic MRI using a model that assumes four compartments in the brain, i.e., the myelin partial volume, excess parenchymal water volume, cellular partial volume, and free water volume. This model postulates that each compartment has its own R1, R2, and PD, and can calculate the myelin partial volume in a voxel, allowing generation of a myelin partial volume map [16]. The myelin partial volume contains myelin water and myelin sheaths, and in the diseased brain, a decreased myelin partial volume indicates decreased myelin [15]. Synthetic T1-weighted images, T2-weighted images, and myelin partial volume maps were created from raw quantification data by MAGiC software. NAWMs were defined as normal-intensity areas on both T1- and T2-weighted images. Referring to T1- and T2-weighted images, a neuroradiologist (M.P.) manually placed six different rectangular ROIs on a myelin partial volume map in the NAWM (81.7 ± 27.4 mm^3); these ROIs were placed in similar locations in each patient. Using the same methods, myelin was quantified in periventricular WMHs (54.3 ± 21.3 mm^3) and deep WMHs (75.4 ± 21.8 mm^3) if patients had WMHs ≥ 2 on the Fazekas scale (Supplemental Fig. 1). Fully automated brain segmentation and volumetric results were obtained from the quantitative values measured with the QRAPMASTER method using MAGiC software. The measured values were coordinated in a 3D feature space and the R1–R2–PD space. Reference values were established from previous studies that included healthy controls and simulations [12, 17]. This method calculates tissue fractions in each voxel and the volume fraction of each tissue multiplied by the volume in each voxel, which are summed to yield the total volumes of white matter (WM), gray matter (GM), cerebrospinal fluid (CSF), and non-WM/GM/CSF. WM volume, GM volume, and intracranial volume (ICV) were calculated and recorded. Brain tissue measurements were normalized to ICV, yielding the WM fraction (WMF = WM volume/ICV) and GM fraction (GMF = gray matter volume/ICV).

Statistical analysis

Assumptions of normal distribution were assessed with the Kolmogorov–Smirnov test. Normally distributed variables are reported as the mean ± SD and non-normally distributed variables as the median and interquartile range. Differences in the means of continuous variables were assessed using the Student's t test or the Kruskal–Wallis test. Differences in proportions were assessed using χ^2 statistics or Fisher's exact test. We determined whether the influence of the myelin partial volume of NAWM on cognition could be explained by age, brain volume, presence of WMHs, lacunar infarcts, or

microbleeds. We performed Pearson's correlation analysis to determine the correlation between the myelin partial volume of NAWM and age, lacunes, microbleeds, ICV, WMF, and GMF. Associations between cognitive scales, CDR-SB, clinical features, and imaging parameters were evaluated using univariate and multivariate linear regression analysis. For multivariate analysis, potential confounding variables were selected based on association ($p < 0.05$) in univariate linear regression analysis and clinical significance (sex and years of education). A variance inflation factor > 10 was considered an indicator of multicollinearity. A p value < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS package (24.0 for Windows).

Results

Demographic characteristics

Among the 99 cognitively impaired patients, 30 (30.3%) patients had WMHs and 69 (69.7%) patients did not. Table 1 compares the baseline demographic characteristics of the WMHs (-) and (+) groups. Patients in the WMHs (+) group were older ($p < 0.001$) and had higher systolic blood pressure ($p = 0.008$), higher frequency of hypertension ($p = 0.021$), and lower frequency of dyslipidemia ($p = 0.02$) than those in the WMHs (-) group. The WMHs (+) group had fewer years of education ($p = 0.024$) and poorer cognitive function (MMSE; $p = 0.001$ and CDR-SB: $p = 0.009$) than those of the WMHs (-) group.

Imaging-derived parameters

SVD disease burden was higher in the WMHs (+) than WMHs (-) group, in terms of the number of lacunes (median [IQR] 1 [0.8–3.3] vs. 0 [0–1], $p < 0.001$) and microbleeds (median [IQR] 2.5 (0.8–16) vs. 0 [0–1], $p < 0.001$). Brain segmentation results showed that WMF was significantly lower in the WMHs (+) group than in the WMHs (-) group (29.0% vs 33.7%, $p < 0.001$). There were no significant differences in ICV and GMF between the WMHs (+) and (-) groups (Table 2).

Myelin partial volume

The myelin partial volume in NAWMs was significantly lower in the WMHs (+) group than in the WMHs (-) group (37.5 ± 2.7% vs. 39.9 ± 2.4%, $p < 0.001$) (Fig. 1). In 40 patients with mild cognitive impairment, a similar trend was observed: the

Table 1 Comparison of demographics, risk factors, and neuropsychological test results of the study population according to presence of WMHs

Characteristic	Total	WMHs (-)	WMHs (+)	p value
No. of participants	99	69	30	
Age, mean (SD), y	74.1 (10.0)	71.7 (10.4)	79.4 (6.5)	< 0.001
Sex				0.851
Male	26 (26.3%)	19 (27.5%)	7 (23.3%)	
Female	73 (73.7%)	50 (72.5%)	23 (76.7%)	
Final diagnosis				< 0.001
Alzheimer's disease	32 (32.3%)	22 (31.9%)	10 (33.3%)	
Mixed dementia	10 (10.1%)	2 (2.9%)	8 (26.7%)	
Mild cognitive impairment	40 (40.4%)	32 (46.4%)	8 (26.7%)	
Vascular dementia	3 (3.0%)	2 (2.9%)	1 (3.3%)	
Subjective cognitive impairment	11 (11.1%)	11 (15.9%)	0 (0%)	
Other	3 (3.0%)	0 (0%)	3 (10.0%)	
ApoE4 carriers/noncarriers	14/24	13/19	1/5	0.383
Hypertension	47 (47.5%)	27 (39.1%)	20 (66.7%)	0.021
Diabetes mellitus	24 (24.2%)	15 (21.7%)	9 (30.0%)	0.531
Dyslipidemia	16 (16.2%)	16 (23.2%)	0 (0%)	0.02
Smoking	2 (2.0%)	2 (2.9%)	0 (0%)	1.000
Cerebrovascular disease	4 (4.0%)	1 (1.4%)	3 (10.0%)	0.082
Depression	7 (7.1%)	6 (8.7%)	1 (3.3%)	0.672
Systolic blood pressure, mmHg ($n = 87$)	128.8 (17.7)	125.0 (14.5)	138.5 (21.6)	0.008
Education, y ($n = 72$), median (IQ)	6 (4.3–12)	8 (6–12)	3.5 (0–11.3)	0.024
MMSE score ($n = 99$), median (IQ)	22 (17–26)	23 (19–27)	19 (13–22.3)	0.001
CDR-SB ($n = 93$), median (IQ)	2.5 (1–4.8)	2 (1–4)	3.3 (2.4–6)	0.009

MMSE Mini-Mental Status Examination, *CDR-SB* Clinical Dementia Rating Scale Sum of Boxes, *WMHs* white matter hyperintensities

Table 2 Comparison of imaging variables from small vessel disease evaluation and brain segmentation in cognitively impaired patients with or without WMHs

	WMHs (-)	WMHs (+)	*p* value
Lacune	0 (0–1)	1 (0.8–3.3)	< 0.001
Microbleed	0 (0–1)	2.5 (0.8–16)	< 0.001
ICV, mean (SD)	1359.1 (130.0)	1315.1 (109.9)	0.109
WMF (%), mean (SD)	33.7 (3.6)	29.0 (2.1)	< 0.001
GMF (%), mean (SD)	36.8 (4.0)	37.4 (2.7)	0.425

ICV intracranial volume, *GMF* gray matter fraction, *WMF* white matter fraction, *WMHs* white matter hyperintensities

WMHs (+) group ($n = 8$) had lower myelin partial volume in the NAWMs than that of the WMHs (-) group ($n = 32$) (38.2 ± 3.2% vs. 40.5 ± 2.1%, $p = 0.017$). Among 32 patients with Alzheimer's disease, the myelin partial volume in the NAWMs was lower in the WMHs (+) group ($n = 10$, 37.6 ± 2.8%) than in the WMHs (-) group ($n = 22$, 39.0 ± 2.9%), although this was not statistically significant ($p = 0.182$).

In 30 patients with WMHs, myelin partial volume was the highest in the NAWMs (median [IQR] 37.2% [35.5–39.0%]), followed by the deep WMHs (median [IQR] 7.2% [3.2–10.5%]) and the periventricular WMHs (median [IQ], 2.1% [1.1–3.9%], $p < 0.001$) (Fig. 2).

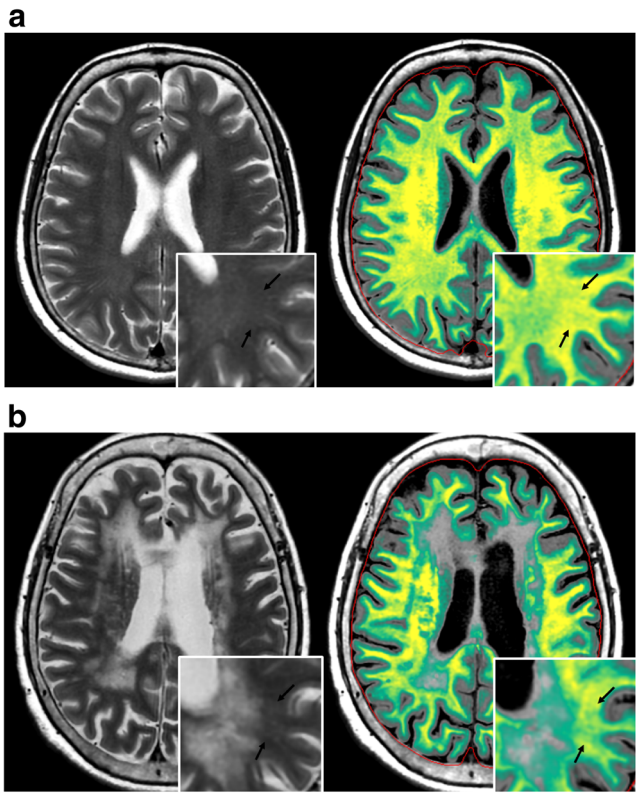

Fig. 1 Synthetic T2-weighted images and myelin partial volume map of a patient without white matter hyperintensities (WMHs) (**a, b**) and with WMHs (**c**, **d**). There is high myelin partial volume in normal-appearing white matter (arrows) of a patient without WMH while decreased myelin partial volume is observed in normal-appearing white matter of a patient with WMH (arrows)

Factors associated with NAWM myelin partial volume

To identify clinical and imaging variables associated with the myelin partial volume of NAWM, partial correlation analysis was performed. Significant correlations were found between myelin partial volume of the NAWM and age (Pearson's $r = -292$, $p = 0.003$), microbleeds (Pearson's $r = -0.237$, $p = 0.018$), and WMF (Pearson's $r = 0.415$, $p < 0.001$) (Supplemental Fig. 2). Conversely, no significant correlations were observed between myelin partial volume of the NAWM and lacunes (Pearson's $r = -0.196$, $p = 0.052$), ICV (Pearson's $r = 0.057$, $p = 0.572$), GMF (Pearson's $r = 0.050$, $p = 0.624$), or systolic blood pressure (Pearson's $r = -0.073$, $p = 0.499$).

Linear regression analysis for cognitive function

Univariable analysis revealed that age ($p = 0.001$), dyslipidemia ($p = 0.037$), WMHs ($p = 0.011$), Alzheimer's disease ($p < 0.001$), ICV ($p = 0.025$), WMF ($p < 0.001$), and myelin partial volume of NAWM ($p < 0.001$) were significantly associated with CDR-SB scores (Table 3). After adjusting for sex and years of education, multivariable analysis revealed that the myelin partial volume of NAWM ($\beta = -0.189$ [95% CI -0.380 to -0.012], $p = 0.037$) was significantly associated with CDR-SB score. The presence of Alzheimer's disease was also associated with the CDR-SB score ($\beta = 0.654$ [95% CI 2.345–5.463], $p < 0.001$).

Discussion

In this study, we observed that the myelin partial volume in NAWM was lower in cognitively impaired patients with WMH than in those without WMH, and was associated with age and microbleeds. Additionally, it was independently associated with global cognitive function after adjusting for sex and education years. The underlying histopathologic changes in WMHs are diverse, encompassing myelin degradation with relative sparing of subcortical U fibers, astrogliosis, spongiosis, axonal loss, and enlarged perivascular spaces [6, 18, 19]. In line with these reports, we observed myelin loss in WMHs, as these regions had significantly smaller myelin partial volume than that of NAWM. Furthermore, we observed a significant difference in myelin quantification of NAWM according to the presence of WMHs. Based on a postmortem study, NAWM on conventional MRI may present with pathological changes corresponding to mild tissue changes, with slight myelin pallor in a fairly intact axonal network and well-preserved glial cell density [6, 20]. Thus, white matter degeneration may be more widespread than expected based on

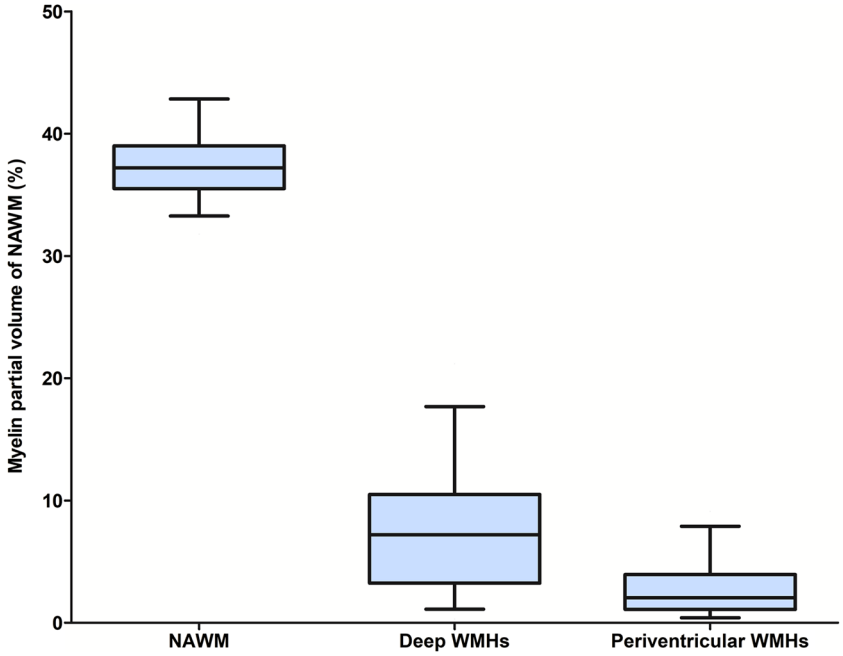

Fig. 2 Myelin partial volume in normal-appearing white matter, and deep and periventricular white matter hyperintensities

conventional imaging [6, 20]. Earlier studies reported structural white matter changes in NAWM using magnetization transfer ratio (MTR) imaging, diffusion-weighted imaging (DWI), and DTI [9, 21]. Fazekas et al reported that MTR changes in the NAWM were associated with clinical disturbances in asymptomatic elderly subjects [9]. However, they did not find any differences in the MTR of NAWM between subjects with and without WMH, unlike our observation. This may be because MTR imaging only aids in visualizing macromolecule-related MTR changes, which are not specific to myelin content change [22]. Our findings, however, are consistent with those of previous studies using DWI and DTI. Thus, myelin loss in NAWM seems to be influenced by the presence of WMH [21, 23].

Table 3 Univariate and multivariate linear regression analysis for predicting cognitive function assessed by CDS-SB

Variable	β CDR-SB ($n = 93$)	95% CI	p value	Adjusted β	95% CI	p value
Age, y	0.097	0.043, 0.151	0.001	0.113	- 0.018, 0.080	0.207
Sex	- 0.175	- 1.513, 1.163	0.796	- 0.051	- 1.405, 0.754	0.55
Diagnosis (vs. SCI)						
Mild cognitive impairment	0.162	- 0.588, 2.453	0.226	0.107	- 0.872, 2.100	0.413
Others*	0.266	0.291, 3.775	0.023	0.036	- 1.629, 2.185	0.772
Alzheimer's disease	0.814	3.303, 6.407	< 0.001	0.654	2.345, 5.463	< 0.001
Hypertension	0.563	- 0.605, 1.730	0.341			
Diabetes mellitus	0.156	- 1.201, 1.513	0.82			
Dyslipidemia	- 1.755	- 3.404, - 0.106	0.037	0.037	- 1.051, 1.649	0.661
Education, y	- 0.106	- 0.220, 0.008	0.068	- 0.029	- 0.115, 0.083	0.744
Presence of WMHs	1.574	0.364, 2.783	0.011	0.127	- 0.368, 1.899	0.183
Lacune	0.074	- 1.150, 0.298	0.513			
Microbleed	0.04	- 0.024, 0.104	0.216			
ICV	- 0.005	- 0.010, - 0.001	0.025	- 0.119	- 0.007, 0.001	0.182
WMF	- 0.288	- 0.424, - 0.153	< 0.001			
GMF	- 0.150	- 0.306, 0.005	0.058			
Myelin partial volume of NAWM	- 0.370	- 0.571, - 0.169	< 0.001	- 0.189	- 0.380, - 0.012	0.037

CDR-SB Clinical Dementia Rating Scale, *GMF* gray matter fraction, *ICV* intracranial volume, *NAWM* normal-appearing white matter, *WMF* white matter fraction, *WMHs* white matter hyperintensities

We observed a significant correlation between age and myelin partial volume in NAWM which is unsurprising given that increased age is a risk factor for WMHs [24, 25]. According to a previous study using DTI and T1 relaxation time, this trend persists even for NAWM [26]. We found that the myelin partial volume in NAWM correlated with the number of microbleeds. The presence of microbleeds is an indication of SVD and cerebral amyloid angiopathy [27]. Collectively, we speculate that myelin loss in NAWM is affected by age-related neurodegenerative changes and disease-related changes, such as those occurring with SVD and/or amyloid pathology. Our observations agree with those of recent studies suggesting that although ischemia is primarily responsible, other factors contribute to the pathogenesis of white matter degeneration, including neuroinflammation, blood–brain barrier alteration, aging, and amyloid pathology [8, 28]. Even after adjusting for age and education effects, myelin quantification of NAWM was an independent predictor of global cognitive function, as reflected in the CDR-SB. This observation supports earlier findings that NAWM can be affected before WMHs appear, and that NAWM changes are associated with cognitive decline [29]. This finding may also explain why many studies have observed only weak association between WMH and cognitive performance, even though WMH substantially affects cognition [27, 28]. The simple dichotomization of heterogeneous white matter as either WMH or NAWM excludes degenerative changes in the NAWM which may be microscopically abnormal, and could have mitigated the effects of WM changes on cognitive performance. The association between myelin loss and cognitive function may be explained by several mechanisms. As myelin increases action potential conduction along axons, myelin loss may lead to neuronal impairment [30]. Myelin contributes to axonal survival, as the myelin sheath reduces the energy consumption of axons [31]. Therefore, myelin loss may lead to neuronal dysfunction and axonal degeneration, which may cause cognitive decline [31]. Cerebral remyelination also improved cognitive function in animal models with cognitive impairments due to causes ranging from irradiation to Alzheimer's disease [32, 33].

Given those findings, to devise potentially novel treatment strategies targeting myelin loss in cognitively impaired patients, tools for monitoring these changes with reasonable scanning times would be required. Myelin partial volume mapping based on quantitative synthetic MRI may thus be beneficial. Although other imaging techniques can measure myelin partial volume or myelin water fraction, they typically require prolonged scan times (8–9 min for whole brain coverage) [8, 34]. Using quantitative synthetic MRI, simultaneous acquisition of T1-, T2-weighted, and FLAIR images and a myelin quantification map was possible within a reasonable scanning time (< 5 min), rendering it advantageous to concurrently evaluate routine clinical images and quantitative myelin information clinically, especially in elderly patients who may not tolerate long scanning times. Fully automated segmentation of brain tissue is another benefit as it is simple and fast, requiring less than 1 min of postprocessing time [15] and can easily be applied in routine clinical practice.

Our study had several limitations. This was a retrospective observational study without follow-up. To explore the true nature of NAWM in vivo, a large-scale longitudinal study that includes younger patients is necessary. Although we observed that age and microbleeds were associated with myelin quantification in NAWM, it is unclear whether myelin loss in NAWM is due to aging-related neurodegeneration and SVD or to direct injury through Alzheimer's disease pathology, such as β-amyloid or neurofibrillary tangles, as recently suggested [8, 25]. Further studies using amyloid and tau as biomarkers could elucidate the main contributor to myelin loss in NAWM in the cognitively impaired population. Additionally, we only assessed global cognitive function. Although MMSE and CDR-SB are widely used for staging dementia severity in clinical and research fields, and are considered quantitative general indexes for global cognitive function [35], the lack of a full cognitive battery limits the assessment of individual cognitive domains. A full cognitive battery may have offered more detailed information on the association between cognitive function and myelin quantification.

In conclusion, we observed myelin loss in the NAWM of cognitively impaired patients with and without WMHs using quantitative synthetic MRI. The myelin content in NAWM was independently associated with clinical cognitive scales. Myelin quantification using quantitative synthetic MRI may be a potential imaging marker of cognitive dysfunction.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Won-Jin Moon.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Retrospective
- Cross-sectional study
- Performed at one institution

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