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Myelin Content in Mild Traumatic Brain Injury Patients with Post-Concussion Syndrome: Quantitative Assessment with a Multidynamic Multiecho Sequence

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Objective: This study aimed to explore the myelin volume change in patients with mild traumatic brain injury (mTBI) with post-concussion syndrome (PCS) using a multidynamic multiecho (MDME) sequence and automatic whole-brain segmentation.
Materials and Methods: Forty-one consecutive mTBI patients with PCS and 29 controls, who had undergone MRI including the MDME sequence between October 2016 and April 2018, were included. Myelin volume fraction (MVF) maps were derived from the MDME sequence. After three dimensional T1-based brain segmentation, the average MVF was analyzed at the bilateral cerebral white matter (WM), bilateral cerebral gray matter (GM), corpus callosum, and brainstem. The Mann–Whitney U-test was performed to compare MVF and myelin volume between patients with mTBI and controls. Myelin volume was correlated with neuropsychological test scores using the Spearman rank correlation test.
Results: The average MVF at the bilateral cerebral WM was lower in mTBI patients with PCS (median [interquartile range], 25.2% [22.6%–26.4%]) than that in controls (26.8% [25.6%–27.8%]) (p = 0.004). The region-of-interest myelin volume was lower in mTBI patients with PCS than that in controls at the corpus callosum (1.87 cm^3 [1.70–2.05 cm^3] vs. 2.21 cm^3 [1.86–3.46 cm^3]; p = 0.003) and brainstem (9.98 cm^3 [9.45–11.00 cm^3] vs. 11.05 cm^3 [10.10–11.53 cm^3]; p = 0.015). The total myelin volume was lower in mTBI patients with PCS than that in controls at the corpus callosum (0.45 cm^3 [0.39–0.48 cm^3] vs. 0.48 cm^3 [0.45–0.54 cm^3]; p = 0.004) and brainstem (1.45 cm^3 [1.28–1.59 cm^3] vs. 1.54 cm^3 [1.42–1.67 cm^3]; p = 0.042). No significant correlation was observed between myelin volume parameters and neuropsychological test scores, except for the total myelin volume at the bilateral cerebral WM and verbal learning test (delayed recall) (r = 0.425; p = 0.048).
Conclusion: MVF quantified from the MDME sequence was decreased at the bilateral cerebral WM in mTBI patients with PCS. The total myelin volumes at the corpus callosum and brainstem were decreased in mTBI patients with PCS due to atrophic changes.
Keywords: *Mild traumatic brain injury; Multidynamic multiecho; Myelin volume; Post-concussion syndrome*

INTRODUCTION

Post-concussion syndrome (PCS), characterized by a variety of somatic, cognitive, and behavioral deficits, may occur following mild traumatic brain injury (mTBI), which constitutes the majority of TBIs [1-3]. Although the reported incidence of PCS after mTBI varies from 40% to 80% during the first several weeks, symptoms have been

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reported to persist up to 3 months after injury in as many as 50% of patients and for more than a year in 10% to 15% of patients, imposing a considerable socioeconomic burden worldwide [4-6].

In the clinical setting, MR imaging performed to exclude any structural abnormality in PCS patients often causes patient frustration because conventional MR imaging does not reveal any abnormalities that can explain the obvious somatic, cognitive, or behavioral deficits experienced by patients. The limited role of conventional MR imaging in revealing microstructural changes in the brain of mTBI patients with PCS has led to increased efforts to detect these changes using advanced neuroimaging techniques. Over the past several decades, diffusion tensor imaging (DTI) has been used as the key imaging modality to assess axonal and myelin integrity in mTBI patients with PCS; however, studies have yielded mixed results [7-10].

More recently, several studies have demonstrated that myelin volume can be estimated in terms of the myelin volume fraction (MVF) using a multidynamic multiecho (MDME) sequence [11-15]. In a study comparing various quantitative MR parameters in patients with multiple sclerosis, myelin partial volume and excess parenchymal water partial volume were demonstrated to be more sensitive to the disease process than R1, R2, and proton density [14,16]. A recent study that evaluated the performance of quantitative values of various MDME sequences from different vendors reported that intrascanner repeatability and interscanner reproducibility of MVF are high across different scanners [12]. Moreover, MVF based on an MDME sequence has been shown to correlate well not only with other myelin estimation methods [13] but also with histological measures in postmortem human brain [15]. However, to the best of our knowledge, no previous studies have used MVF from an MDME sequence to quantify potential myelin loss in patients with mTBI. This study aimed to explore the myelin volume change in mTBI patients with PCS using an MDME sequence and automatic whole-brain segmentation.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of Seoul National University Hospital, and the requirement for informed consent was waived due to the retrospective nature of the study (IRB No. 1905-167-1035).

Patient Selection

Our radiology report database was searched for 45 consecutive mTBI patients with PCS who underwent MR imaging at our institution between October 2016 and April 2018. The specific inclusion criteria were as follows: 1) clinical diagnosis of mTBI according to the American Congress of Rehabilitation Medicine [17], 2) clinical diagnosis of PCS based on the International Classification of Diseases, 10th Revision [18], 3) presence of MR imaging including an MDME sequence, 4) no other clinically significant neurological or psychiatric disorders, and 5) no alcohol or other substance dependence. Four patients were excluded for the following reasons: 1) overt traumatic hemorrhage (n = 2), 2) failure of automatic brain segmentation (n = 1), or 3) poor image quality of the MDME sequence (n = 1).

For comparison, 35 control subjects were selected from our radiology report database between November 2016 and March 2018. The inclusion criteria were 1) presence of MR images including MDME sequence for various neurologic symptoms (headache [n = 25], mild memory impairment [n = 2], visual disturbance [n = 1], and dizziness [n = 1]), 2) normal findings on structural MRI other than nonspecific T2 hyperintensities not exceeding the age threshold [19], and 3) no previous trauma history. Six subjects were excluded because of failure of automatic brain segmentation.
The MDME sequence was included as part of our routine protocols for mild TBI patients and other patients with suspected subtle blood-brain barrier (BBB) disruption to detect subtle gadolinium contrast leakage due to mildly elevated BBB permeability.

Finally, 41 consecutive patients with mTBI (13 male and 28 female; mean age, 45 years; age range, 19–60 years) and 29 controls (7 male and 22 female; mean age, 49 years; age range, 24–60 years) were included (Fig. 1). For the mTBI patients, results of neuropsychological tests (Rivermead post-concussion symptoms questionnaire [RPQ] [20] and computerized neurocognitive function tests [CNTs] [21]) performed at the concussion clinic of the Department of Rehabilitation were recorded (details on the neuropsychological tests are shown in Supplementary Methods).

MR Image Acquisition and Postprocessing of the MDME Sequence

All MR images were obtained using a 3T scanner (Discovery 750, GE Healthcare) using a 32-channel head coil. MR

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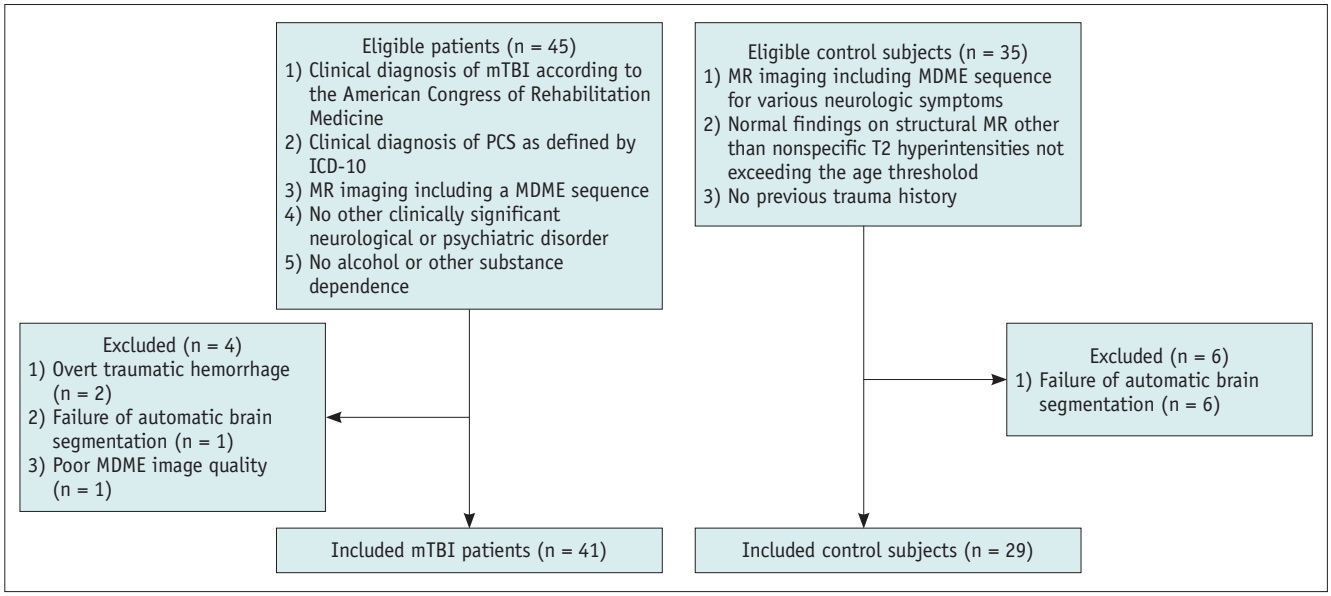

Fig. 1. Flowchart for the study patient selection. ICD-10 = International Classification of Diseases, 10th Revision, MDME = multidynamic multiecho, mTBI = mild traumatic brain injury, PCS = post-concussion syndrome

sequences included the two-dimensional (2D) fast spin-echo (FSE) MDME sequence as well as the 3D fast spoiled gradient-echo T1-weighted, T2 fluid-attenuated inversion recovery and susceptibility-weighted imaging sequences. The MDME is a multislice, multisaturation delay, multiecho, FSE sequence acquired using four automatically calculated saturation delays (inversion times) and two echo times of 10.7–75.3 ms and 64.5–129 ms (imaging parameters for all sequences are provided in Supplementary Table 1). After MR image acquisition, postprocessing of the MDME sequence was performed to obtain MVF maps using the SyMRI software (version 8.0.4; SyntheticMRAB) (details on the postprocessing of the MDME sequence are provided in Supplementary Methods).

Regional Myelin Content Quantification Using Automated Segmentation

Automated segmentation of the whole brain based on 3D T1-weighted images was performed using FreeSurfer software (version 6.0; Laboratory for Computational Neuroimaging). Subsequently, Nordic ICE (version 4.1.2; NordicNeuroLab) was used to extract masks at four different regions of interest (ROIs) (i.e., bilateral cerebral white matter [WM], bilateral cerebral gray matter [GM], corpus callosum, and brainstem) and coregister the masks with MVF maps to obtain the average MVFs in the brain regions. Prior to the coregistration, the masks were first resampled based on myelin maps to minimize potential errors attributable to the differences in slice thickness, matrix size, and slice gap. Coregistration was automatically performed afterward by means of rigid body registration with the optimization of a mutual information metric to obtain the average MVFs at the ROIs. The total myelin volume was approximated by multiplying the average MVF by the ROI volume (Fig. 2).

Statistical Analysis

The statistical software MedCalc, version 11.1.1.0, was used for all statistical analyses. The normality of the data for each continuous parameter was assessed using the Kolmogorov–Smirnov test. Categorical and noncategorical clinical variables were compared between the two groups using Fisher's exact test and the Mann–Whitney U-test, respectively. For the myelin content, the Mann–Whitney U-test was used to compare the average MVFs and total myelin volume at various locations between mTBI patients and controls. The Spearman rank correlation test was used to correlate the myelin volume parameters with the time interval between injury and MR imaging. For patients with an interval of 2 weeks or less between neuropsychological tests and MR images, the Spearman rank correlation test was also used to obtain correlations between myelin volume parameters and neuropsychological test scores. p values < 0.05 were considered statistically significant.

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RESULTS

The normality test showed that continuous clinical and imaging variables, including age and myelin volume parameters, did not follow a normal distribution ($p < 0.05$).

Clinical Characteristics of mTBI Patients and Controls

The age of mTBI patients (median age, 47.0 years; range, 19–60 years [interquartile range, 36.0–53.0 years]) did not significantly differ from that of the control group (52.0 years; 24–60 years [42.8–57.0 years]) ($p = 0.075$). No statistically significant difference in sex was observed between the two groups ($p = 0.595$) (Table 1).

Conventional MR Imaging Findings

A few scattered T2 high signal intensity foci not

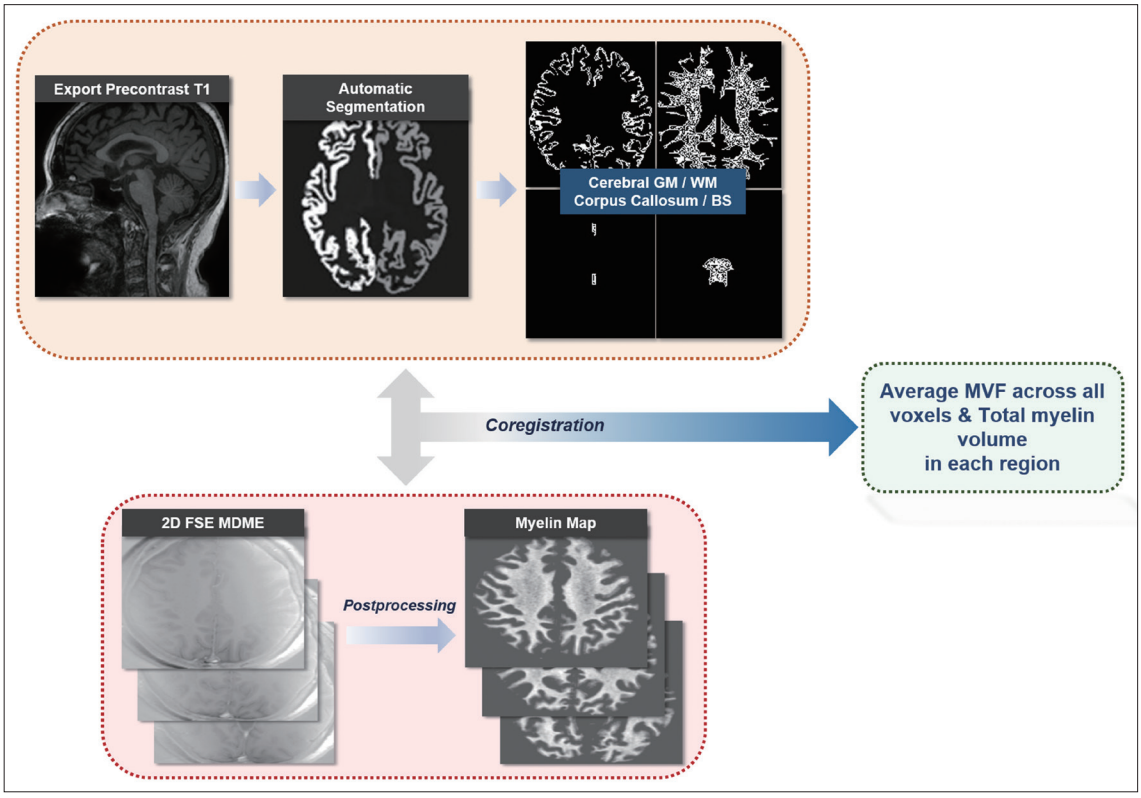

Fig. 2. A schematic diagram for the regional myelin content quantification using automated segmentation. Automated segmentation of the whole brain was performed based on precontrast 3D T1-weighted images. Masks at four different ROIs (bilateral cerebral WM, bilateral cerebral GM, corpus callosum, and BS) were extracted and coregistered with MVF maps to obtain the average MVFs at the brain regions. Total myelin volume was approximated by multiplying the average MVF by the ROI volume. BS = brainstem, D = dimensional, FSE = fast spin echo, GM = gray matter, MDME = multidynamic multiecho, MVF = myelin volume fraction, ROI = region of interest, WM = white matter

Table 1. Clinical Characteristics of mTBI Patients with PCS and Controls

	mTBI Patients with PCS (n = 41)	Controls (n = 29)	*P*
Age, years*	47.0 (19.0–60.0) [36.0–53.0]	52.0 (24.0–60.0) [42.8–57.0]	0.075
Sex			0.804
Male	13 (32)	7 (24)	
Female	28 (68)	22 (76)	
Time interval between injury and MR imaging, month*	2 (1–5)	NA	NA
Time interval between injury and neuropsychological test, days*			
RPQ (n = 29)	12.0 (1.0–160.0) [5.0–23.0]	NA	NA
CNT (n = 26)	5.0 (0.0–110.0) [0.3–12.0]	NA	NA

*Data are reported as median (range) [interquartile range] or median (range). Otherwise, data represent the number of patients with % in parentheses. CNT = computerized neurocognitive function test, mTBI = mild traumatic brain injury, NA = not available, PCS = post-concussion syndrome, RPQ = Rivermead post-concussion symptoms questionnaire

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exceeding the age threshold were found in the cerebral WM in 70.7% (29 of 41) of the mTBI group and 58.6% (17 of 29) of the control group (p = 0.318). No other discernible structural abnormalities were noted on the conventional MR imaging.

Myelin Content Quantification

Comparison of MVF between mTBI Patients and Controls

The average MVF at the bilateral cerebral WM was significantly lower in mTBI patients with PCS (25.2%; 18.2%–29.2% [22.6%–26.4%]) than that in controls (26.8%; range, 21.7%–29.4% [25.6%–27.8%]) (p = 0.004) (Figs. 3, 4, Table 2). The average MVF at the bilateral cerebral WM was not significantly correlated with the time interval between injury and MR imaging (r = -0.062, p = 0.699). In the subgroup analysis (time interval between injury and MR imaging < 3 months vs. ≥ 3 months), the average MVF at the bilateral cerebral WM was significantly lower in mTBI patients with PCS than that in controls in both subgroups (for < 3 months, 25.4%; 18.2%–29.2% [22.6%–26.4%] vs. 26.8%; 21.7%–29.4% [25.6%–27.8%], respectively; p = 0.011; for ≥ 3 months, 24.4%; 18.3%–28.5% [22.8%–26.7%] vs. 26.8%; 21.7%–29.4% [25.6%–27.8%], respectively; p = 0.024). Meanwhile, the average MVF at the bilateral cerebral GM (p = 0.524), corpus callosum (p = 0.151), and brainstem (p = 0.789) did not significantly differ between the two groups.

Comparison of ROI Volume and Total Myelin Volume between mTBI Patients and Controls

The ROI volume was significantly lower in mTBI patients with PCS than that in controls at the corpus callosum (1.87 cm^3; 1.28–2.72 cm^3 [1.70–2.05 cm^3] vs. 2.21 cm^3; 1.52–5.06 cm^3 [1.86–3.46 cm^3], respectively; p = 0.003) and brainstem (9.98 cm^3; 7.80–13.36 cm^3 [9.45–11.00 cm^3] vs. 11.05 cm^3; 8.96–13.43 cm^3 [10.10–11.53 cm^3], respectively; p = 0.015), but not at the bilateral cerebral WM (225.15 cm^3; 182.32–278.49 cm^3 [208.67–249.85 cm^3] vs. 220.44 cm^3; 169.43–292.29 cm^3 [211.38–235.82 cm^3], respectively; p = 0.302) and GM (223.33 cm^3; 188.81–266.17 cm^3 [212.74–230.96 cm^3] vs. 224.05 cm^3; 172.72–268.37 cm^3 [207.16–234.02 cm^3], respectively; p = 0.938).

The total myelin volume was significantly lower in mTBI patients with PCS than that in controls at the corpus callosum (p = 0.004) and brainstem (p = 0.042), but not at the bilateral cerebral WM (p = 0.165) and GM (p = 0.508) (Table 2). The total myelin volumes at the corpus callosum and brainstem were not significantly correlated with the time interval between injury and MR imaging (r = -0.004, p = 0.979; r = -0.267, p = 0.091, respectively). In the subgroup analysis, the total myelin volume at the corpus callosum was significantly lower in mTBI patients with PCS than that in controls in both subgroups (for < 3 months,

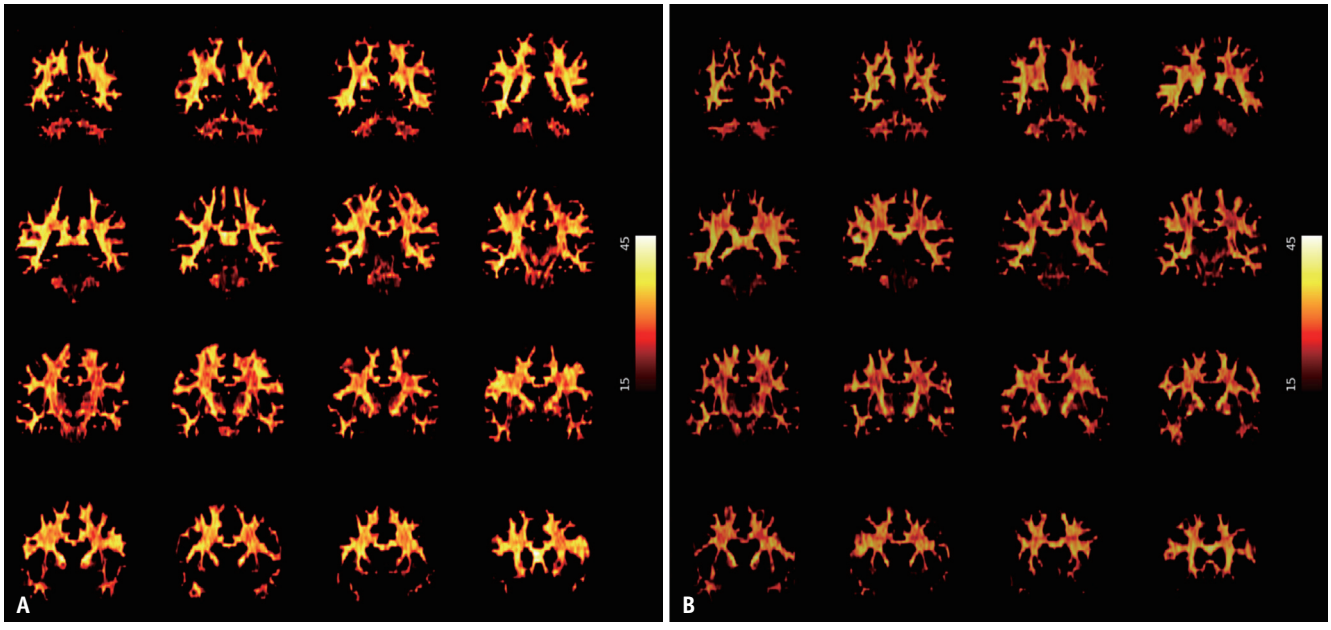

Fig. 3. Representative myelin maps in a 43-year-old female control (A) and a 43-year-old female mTBI patient with PCS (B).
A, B. Myelin maps displaying the MVF for each voxel demonstrate that MVF at bilateral cerebral white matter is lower in the mTBI patient with PCS **(B)** than that in the control **(A)**. mTBI = mild traumatic brain injury, MVF = myelin volume fraction, PCS = post-concussion syndrome

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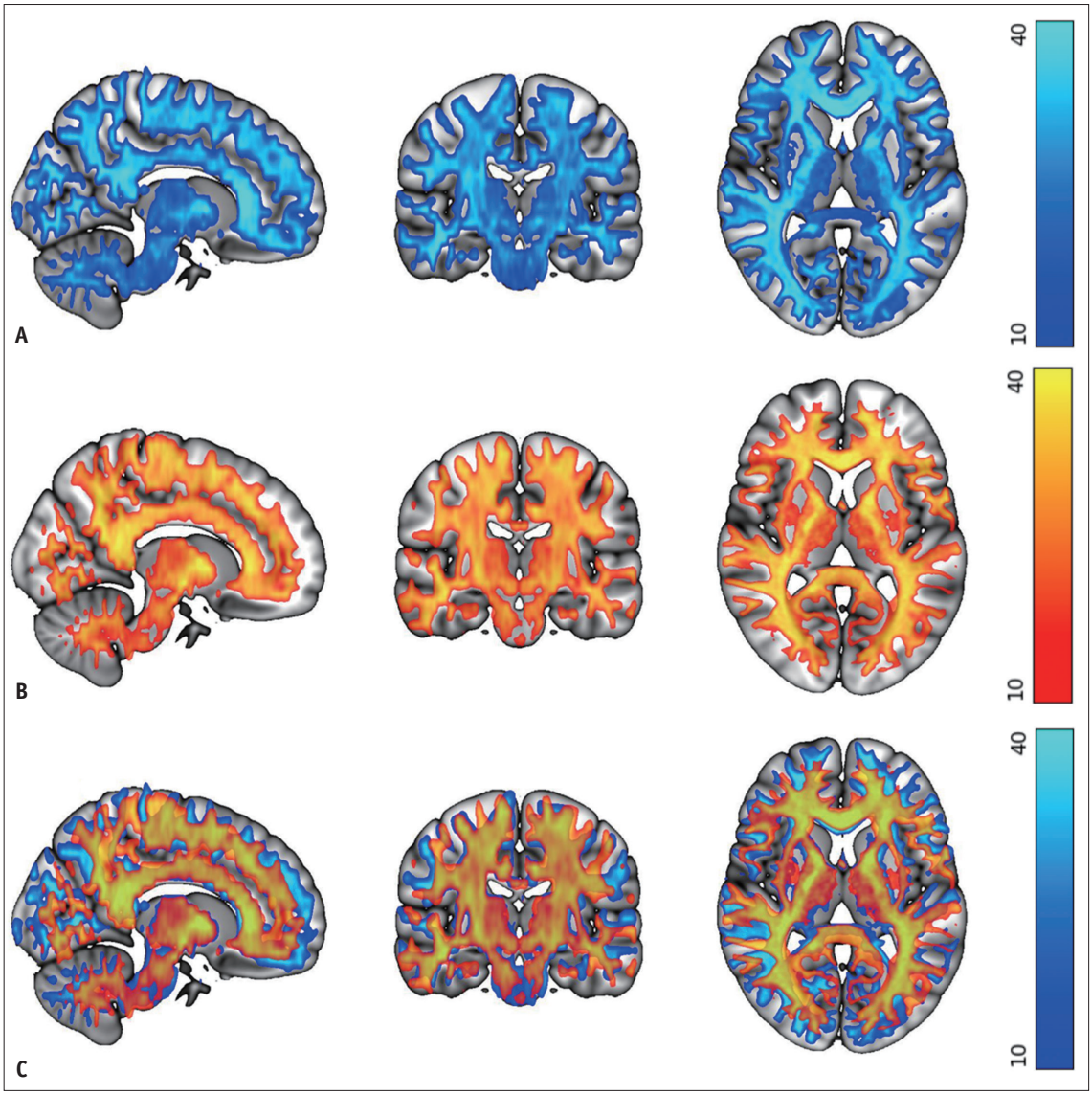

Fig. 4. Postprocessed myelin maps in a 43-year-old female control (A) and a 43-year-old female mTBI patient with PCS (B) (same patients as above).
A-C. Myelin maps were postprocessed to display only the voxels with the MVF of 10% or higher on a normative atlas of the brain. When the two maps were overlaid **(C)**, it became apparent that there were fewer voxels with MVFs of 10% or higher in the mTBI patient **(B)** than that in the control **(A)**. mTBI = mild traumatic brain injury, MVF = myelin volume fraction, PCS = post-concussion syndrome

0.45 cm^3; 0.27–0.66 cm^3 [0.37–0.49 cm^3] vs. 0.48 cm^3; 0.33–0.79 cm^3 [0.45–0.54 cm^3], respectively; p = 0.015; for ≥ 3 months, 0.44 cm^3; 0.26–0.56 cm^3 [0.39–0.47 cm^3] vs. 0.48 cm^3; 0.33–0.79 cm^3 [0.45–0.54 cm^3], respectively; p = 0.018). The total myelin volume at the brainstem was significantly lower in mTBI patients with PCS than that in controls in the subgroup with the interval ≥ 3 months (1.37 cm^3; 1.17–1.69 cm^3 [1.22–1.46 cm^3] vs. 1.54 cm^3; 1.17–1.87 cm^3 [1.42–1.67 cm^3], respectively; p = 0.005), but not in the subgroup with the interval < 3 months (1.48 cm^3; 0.88–1.93 cm^3 [1.35–1.61 cm^3] vs. 1.54 cm^3; 1.17–1.87 cm^3 [1.42–1.67 cm^3], respectively; p = 0.328). Meanwhile, the total myelin volume at the bilateral cerebral WM tended to be lower in patients (56.56 cm^3; 36.93–76.15 cm^3 [49.85–60.55 cm^3]) than that in controls (60.34 cm^3; 44.03–75.03 cm^3 [53.73–62.67 cm^3]) (p = 0.165) (Table 2).

Correlations between Myelin Volume Parameters and Neuropsychological Tests

The scores of neuropsychological tests and specific PCS symptoms of mTBI patients are summarized in Supplementary Tables 2 and 3. Of the 41 mTBI patients,

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Table 2. Comparison of Average MVF and Total Myelin Volume between mTBI Patients with PCS and Controls

Location	Average MVF (%)		*P*	Total Myelin Volume (cm^3)		*P*
	mTBI Patients with PCS (n = 41)	Controls (n = 29)		mTBI Patients with PCS (n = 41)	Controls (n = 29)	
Bilateral cerebral WM	25.2 (18.2–29.2) [22.6–26.4]	26.8 (21.7–29.4) [25.6–27.8]	0.004	56.56 (36.93–76.15) [49.85–60.55]	60.34 (44.03–75.03) [53.73–62.67]	0.165
Bilateral cerebral GM	4.0 (1.7–7.4) [3.0–4.7]	3.6 (2.4–5.8) [2.9–4.3]	0.524	8.49 (3.80–17.90) [6.31–10.88]	8.32 (5.54–13.23) [6.23–9.94]	0.508
Corpus callosum	23.8 (13.2–29.3) [20.1–25.8]	23.0 (10.5–27.5) [15.0–25.7]	0.151	0.45 (0.26–0.66) [0.39–0.48]	0.48 (0.33–0.79) [0.45–0.54]	0.004
Brainstem	14.3 (11.2–17.0) [13.0–14.9]	14.1 (12.2–17.2) [13.1–15.2]	0.789	1.45 (0.88–1.93) [1.28–1.59]	1.54 (1.17–1.87) [1.42–1.67]	0.042

Data represent median (range) [interquartile range]. GM = gray matter, mTBI = mild traumatic brain injury, MVF = myelin volume fraction, PCS = post-concussion syndrome, WM = white matter

Table 3. Correlations between Myelin Volume Parameters at Bilateral Cerebral WM and Neuropsychological Tests

	Average MVF		Total Myelin Volume	
	Correlation Coefficient	*P*	Correlation Coefficient	*P*
RPQ*	-0.003	0.990	0.020	0.938
RPQ-3	0.150	0.553	0.311	0.209
RPQ-13	-0.034	0.893	-0.022	0.932
Auditory CPT (correct responses)†	0.002	0.992	-0.010	0.965
Auditory CPT (commission errors)†	0.050	0.824	0.021	0.926
VLT (immediate recall)†	-0.063	0.782	0.096	0.671
VLT (delayed recall)†	0.252	0.258	0.425	0.048
VLT (delayed recognition)†	0.223	0.318	0.391	0.072
Digit span test (forward)†	0.107	0.637	0.225	0.314
Digit span test (backward)†	0.089	0.694	0.270	0.223
Card sorting test (perseverative response)†	0.322	0.144	0.356	0.104

*The RPQ measures the severity of 16 PCS symptoms [21]. The total score ranges from 0 (no change in symptoms since head injury) to 64 (most severe symptoms). The test consists of the RPQ-3 (three items to assess early concussion symptoms, including headaches, nausea and/or vomiting, and dizziness) and RPQ-13 (13 items to assess later symptoms of PCS, including cognitive, mood, sleep, and other physical symptoms) [18], †T scores. CPT = continuous performance test, MVF = myelin volume fraction, RPQ = Rivermead post-concussion symptoms questionnaire, VLT = verbal learning test, WM = white matter

22 patients had an interval of 2 weeks or less between the CNTs and MR scanning, whereas 18 had an interval of 2 weeks or less between the RPQs and MR scanning. In the subgroup analysis, the average MVF at the bilateral cerebral WM did not have significant correlations with any neuropsychological tests (all $p > 0.05$). However, the total myelin volume in the bilateral cerebral WM had a significant positive correlation with VLT (delayed recall) ($r = 0.425$; $p = 0.048$) and a borderline positive correlation with VLT (delayed recognition) ($r = 0.391$; $p = 0.072$) (Table 3). No significant correlations were noted between the total myelin volume at the bilateral cerebral WM and other neuropsychological tests ($p > 0.05$). The total myelin volumes at the corpus callosum and brainstem did not show significant correlations with any neuropsychological tests (all $p > 0.05$) (Supplementary Table 4).

DISCUSSION

In this study, the utility of the 2D FSE MDME sequence was investigated to quantify the myelin volume change in mTBI patients with PCS. The key findings of this study were as follows: 1) the average MVF at the bilateral cerebral WM was lower in mTBI patients with PCS than that in controls, 2) the total myelin volumes at the corpus callosum and brainstem were lower in mTBI patients with PCS than that in controls, and 3) no significant correlation was observed between myelin volume parameters and neuropsychological test scores, except that between the total myelin volume at the bilateral cerebral WM and verbal learning test (delayed

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recall).

Traditionally, considerable attention has been devoted to the pathological alterations in neuronal cells within the GM in prior studies on brain injury [22]. However, recent studies have underscored that the loss of WM integrity is also implicated in the long-term prognosis of TBI patients [23,24]. In the analysis of WM integrity in mTBI, myelin is an attractive target because it mainly consists of bundles of myelin-ensheathed axons [22]. Several preclinical studies have reported that myelin loss can occur even after mTBI and that it can persist chronically, particularly after repeated injury [25,26]. Moreover, it has been shown that myelin loss can subsequently lead to reciprocal damage of the underlying axon in WM injury because demyelination in WM injury accompanies the death of myelin-producing oligodendrocytes, which actively sense the axonal energy needs and thus play an important role in maintaining axonal integrity [27,28].

Over the past several years, DTI has been shown to have an advantage over conventional structural MR imaging in detecting subtle changes in WM integrity [29]. In DTI, the direction and magnitude of diffusion in a given voxel are represented by various anisotropy indices, including fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity [30]. Fractional anisotropy, the most widely used DTI measure, has been reported to be decreased in several WM tracts (e.g., anterior corona radiata, cingulum bundle, uncinate fasciculus, and superior longitudinal fasciculus), representing less restricted (more isotropic) diffusion in the injured WM [7-9]. However, the decrease in fractional anisotropy value is not specific to myelin loss and may be attributable to several other causes, including disturbances in axonal membranes, neurofilaments, or microtubules [31]. In comparison, radial diffusivity is known to be more specific to myelin injury because it measures the diffusion perpendicular to the predominant orientation of axonal fibers [32,33]. However, previous studies have shown mixed results with reports on both increased and decreased radial diffusivity values in mTBI as compared with controls [9,34,35]. Moreover, factors such as inflammation, axonal properties, and the presence of crossing fibers have been shown to have a significant influence on radial diffusivity [36-38].

More recently, multicomponent relaxometry, a quantitative MR technique that provides a more specific measure of the myelin–myelin water fraction (MWF) (i.e., a surrogate marker of myelin volume)–as compared with DTI, has been developed. Using a 32 echo T2 scan sequence to quantify MWF, Wright et al. [39] demonstrated decreased MWF in several regions of concussed athletes (hockey players), including the corpus callosum, corona radiata, internal capsule, posterior thalamic radiation, and superior longitudinal fasciculus at 2 weeks post-injury as compared to the baseline. In addition, a previous study on veterans with mTBI used multicomponent-driven equilibrium single-pulse observation of T1 and T2 to derive MWF and revealed that MWF was significantly lower in a small number of veterans with a history of mTBI than in those without a history [40]. In this study, we used an MDME sequence to quantify MVF and showed that the average MVF at the bilateral cerebral WM was lower in mTBI patients with PCS than that in controls, in keeping with those of previous studies [39,40]. However, Wright et al. [39] found that MWF values recovered at 2 months post-injury. Moreover, in a prospective study of MWF changes after mTBI in football and rugby players [41], increased myelination was observed in contact sports players at the time of injury than that in noncontact sports players, and even larger increases were found at 3 months afterward. In contrast, decreased MVF even in the mTBI subgroup with the time interval between injury and imaging longer than 3 months in our study may suggest that myelin loss following mTBI may persist chronically. The possibility remains that our mTBI patients may have had partial remyelination, but a future study with longitudinally collected data is warranted to elucidate the exact natural course of myelin loss in mTBI.

Despite the lack of significant difference in MVF, we found that the total myelin volumes at the corpus callosum and brainstem were lower in mTBI patients with PCS than that in controls, which was attributed to the decrease in ROI volume in mTBI patients with PCS. This finding is in line with a previous study that reported that the corpus callosum and brainstem are sites commonly involved in focal atrophy following TBI, along with the thalamus, hippocampus, cerebellar GM, and corona radiata [42].

In this study, clinical correlations between the myelin volume parameters and various neuropsychological tests were also performed. Unlike the previous study, which reported the association between lower MWF across several ROIs and worse performance on a speeded attention task [40], we did not find significant correlations between MVF and any of the neuropsychological tests. Furthermore, no correlation was noted between the total myelin volume and neuropsychological test scores, except for the total myelin

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volume at the bilateral cerebral WM and verbal learning test (delayed recall). Although the preliminary result may imply that the total myelin volume at the bilateral cerebral WM was more important than the average MVF in terms of verbal learning, the possibility remains that the finding is opportunistic. Therefore, a future study including a larger number of patients is warranted to explore the relationship between myelin volume and clinical parameters.

The clinical implications of the findings of this study are as follows. At present, the diagnoses of mTBI and PCS are made clinically based on subjective questionnaires and neuropsychological tests. Nonetheless, there is considerable overlap in the symptoms and cognitive test performance between PCS and psychiatric disorders such as depression or posttraumatic stress disorder [29], hindering the clinical diagnosis. In this regard, MVF from the 2D FSE MDME sequence may provide more objective and quantitative data for the microstructural changes in myelin, thereby helping differentiate PCS from psychiatric disorders.

Our study has several limitations. First, owing to the retrospective nature of the study, a correlational analysis between myelin volume parameters and neuropsychological tests was performed in a subgroup of patients who had a relatively short time interval between the two tests. A future prospective study with a larger sample size is needed to validate the correlation. Second, the comparison was made with the controls without TBI who were not explicitly matched for age and sex. Although there was no significant difference in age and sex between the two groups, the group difference could have been higher if the age and sex were matched between mTBI patients and controls for comparison. Third, the study lacked longitudinal data; thus, the natural course of myelin loss or the prognostic value of MVF could not be elucidated from the present study. Fourth, although the MR imaging of the controls included in this study revealed no structural abnormalities except nonspecific T2 hyperintensities that did not exceed the age threshold, they presented with various neurologic symptoms prior to MRI. The possibility remains that the detected difference in myelin volume could have been higher if we included individuals without any neurologic symptoms as controls.

In conclusion, the MDME sequence can readily depict myelin loss in patients with mTBI with PCS. In particular, MVF quantified from the MDME sequence was decreased in the bilateral cerebral WM in mTBI patients with PCS. Moreover, the total myelin volumes at the corpus callosum and brainstem were decreased in mTBI patients with PCS due to atrophic changes.

Supplement

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Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Seung Hong Choi and Ji-hoon Kim who is on the editorial board of the *Korean Journal of Radiology* was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

Conceptualization: Roh-Eul Yoo, Seung Hong Choi. Data curation: Roh-Eul Yoo, Seung Hong Choi, Eunkyung Kim, Byung-Mo Oh. Formal analysis: Roh-Eul Yoo, Seung Hong Choi, Eunkyung Kim, Byung-Mo Oh. Funding acquisition: Roh-Eul Yoo, Seung Hong Choi. Investigation: Roh-Eul Yoo, Seung Hong Choi. Methodology: Roh-Eul Yoo, Seung Hong Choi. Resources: Sung-Won Youn, Moonjung Hwang. Software: Sung-Won Youn, Moonjung Hwang. Supervision: Seung Hong Choi. Validation: Roh-Eul Yoo, Seung Hong Choi. Writing—original draft: Roh-Eul Yoo, Seung Hong Choi. Writing—review & editing: all authors.

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