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Quantitative dynamic contrast-enhanced MR imaging shows widespread blood-brain barrier disruption in mild traumatic brain injury patients with post-concussion syndrome

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Abstract

Objectives To explore the utility of dynamic contrast-enhanced (DCE) MR imaging for quantitative analysis of blood-brain barrier disruption in mild traumatic brain injury (mTBI) patients with post-concussion syndrome (PCS).

Methods Forty-four consecutive patients with PCS after mTBI and 32 controls were included in this retrospective study. K^{trans} and v_e from DCE MR imaging were analyzed at contrast-enhancing lesions, T2 hyperintense white matter (WM) lesions, normal-appearing white matter (NAWM), and predilection sites for diffuse axonal injury ($Location_{DAI}$). The Mann-Whitney U-test was performed to compare the parameters between mTBI patients and controls and the parameters were correlated with neuropsychological tests using Mann-Whitney U-test and Spearman rank correlation.

Results The median v_e of the T2 hyperintense WM lesions in mTBI patients (n=21) was higher than that of NAWM in controls (p=.027). Both median K^{trans} and v_e at NAWM were also significantly higher in mTBI patients than in controls (p=.023 and p=.029, respectively). In addition, mTBI patients had higher K^{trans} and v_e at $Location_{DAI}$ than controls (p=.008 and p=.015, respectively). VLT (delayed recall) scores were significantly correlated with v_e values at T2 hyperintense WM lesions (p=−0.767, p=.044). The median v_e at $Location_{DAI}$ was significantly higher in patients with atypical performance in the digit span test (forward) than in those with average or good performance (p=.043).

Conclusions mTBI patients with PCS had higher K^{trans} and v_e values than controls not only at T2 hyperintense WM lesions but also at NAWM and $Location_{DAI}$. BBB disruption may be implicated in development of PCS in mTBI patients.

Key Points

- *mTBI patients with PCS had higher permeability than controls at T2 hyperintense WM lesions on DCE MR imaging.*
- *mTBI patients with PCS had higher permeability than controls also at NAWM and predilection sites for DAI.*
- *BBB disruption may be implicated in the development of PCS in mTBI patients.*

Keywords Blood-brain barrier · Magnetic resonance imaging · Perfusion · Permeability · Post-concussion syndrome (PCS)

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Abbreviations

3D	Three-dimensional
BBB	Blood-brain barrier
CNS	Central nervous system
CNT	Computerized neurocognitive function tests
CPT	Continuous performance test
DAI	Diffuse axonal injury
DCE	Dynamic contrast-enhanced
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted imaging
FLAIR	Fluid-attenuated inversion recovery
FSPGR	Fast spoiled gradient echo
IQR	Interquartile range
mTBI	Mild TBI
NAWM	Normal-appearing white matter
PCS	Post-concussion syndrome
ROC	Receiver operating characteristics
RPQ	Rivermead post-concussion symptoms questionnaire
SWI	Susceptibility-weighted imaging
VLT	Verbal learning test
WM	White matter

Introduction

Mild TBI (mTBI) accounts for the majority of the emergency department visits after head injury in the United States [1]. Although the mortality due to mTBI is extremely low, previous reports have demonstrated that mTBI may be associated with increased morbidity from various conditions, representing a major contributor to the increased socioeconomic burden. In particular, patients may suffer from post-concussion syndrome (PCS), which is defined as a variety of somatic, cognitive, and behavioral deficits such as headaches, dizziness, fatigue, irritability, anxiety, insomnia, loss of consciousness and memory, and noise sensitivity. PCS may last for weeks, months, or a year or more after mTBI [2, 3].

In routine practice, CT and conventional MR imaging often fail to reveal any imaging abnormalities [4]. Several attempts were made to facilitate the identification of subtle imaging findings related to mTBI and outcome prediction by using various advanced MR imaging modalities which reflect different steps of the pathophysiology following TBI [5]. Among them, susceptibility-weighted imaging (SWI) and diffusion tensor imaging (DTI) are widely used to depict intracranial hemorrhage and fibre track injuries. Specifically, some DTI measures have been shown to correlate well with clinical severity and to potentially serve as a predictor of patients' outcome [6, 7]. In addition, a few studies have demonstrated that cerebral blood flow or cerebral blood volume from arterial spin labelling or dynamic susceptibility contrast perfusion-weighted imaging have significant positive correlations with various neuropsychological measures in mTBI patients [8–10].

Over the past few years, blood-brain barrier (BBB) disruption has been increasingly recognized as a crucial secondary injury mechanism following TBI [11]. Dynamic contrast-enhanced (DCE) MR imaging is a noninvasive perfusion MR imaging technique, from which numerous quantitative pharmacokinetic parameters that reflect microcirculatory structure and function can be derived. Of those, K^{trans} (i.e., volume transfer constant between the plasma and extravascular extracellular space) and v_e (i.e., leakage space) are considered imaging biomarkers for permeability or BBB disruption [12–14]. At present, reports on the utility of the DCE MR imaging-based pharmacokinetic parameters as imaging biomarkers of BBB disruption in mTBI are scarce, especially for those with PCS, and available reports are based only on a small number of animals or human subjects [15–17]. Therefore, the purpose of this study was to explore the utility of DCE MR imaging for quantitative analysis of BBB disruption in mTBI patients with PCS.

Materials and methods

This retrospective study was approved by the institutional review board of our hospital, and the requirement for informed consent was waived due to its retrospective nature.

Patient Selection

Sixty-three consecutive patients with PCS after mTBI, who underwent MR imaging at our institution between November 2016 and September 2017 were selected from our radiology report database. The inclusion criteria were as follows: the patient had (a) clinical diagnosis of mTBI as defined by loss of consciousness for 0–30 min, posttraumatic amnesia or alteration of consciousness for less than 24 h [4], (b) constellation of physical, cognitive, and emotional/behavioral symptoms suggestive of PCS [2, 3, 18, 19], and (c) undergone MR imaging including dynamic contrast-enhanced MR imaging. The clinical diagnosis of mTBI and PCS were made at the outpatient concussion clinic by a rehabilitation physician (B.M.O). The exclusion criteria were as follows: the patient had (a) a significant psychiatric or neurological disorder other than TBI, (b) dependence on alcohol or other substances, and (c) trauma-related hemorrhagic lesions on MR imaging.

For the comparison, 33 control patients were selected from our radiology report database. Inclusion criteria were as follows: the patient had (a) visited the outpatient clinic of the neurology department at our institution for various neurologic symptoms, (b) undergone MR imaging including DCE-MR imaging at our institution between October 2016 and June 2017, and (c) normal structural findings on MR with or without

a few T2 hyperintensities not exceeding the age threshold [4]. Exclusion criteria were as follows: the patient had (a) prior trauma history and (b) other serious illness outside the brain that may potentially cause neurologic dysfunction.

As a result, a total of 44 mTBI patients (14 men and 30 women; mean age, 47 years; age range, 23–81 years) and 32 controls (9 men and 23 women; mean age, 59 years; age range, 34–77 years) were included in this study. Electronic medical records of the mTBI patients and controls were reviewed for the presence of comorbidities. Some of the mTBI patients (n = 19) received medications for the symptomatic control of various PCS symptoms prior to MR imaging. The Rivermead post-concussion symptoms questionnaire (RPQ) [18] and computerized neurocognitive function tests (CNTs) were performed at the outpatient concussion clinic of the department of rehabilitation (See Supplementary Materials and Methods for more details on neuropsychological tests).

Image Analysis of DCE MR Imaging

All MR images, including Pre- and postcontrast 3D FSPGR, T2 FLAIR, DWI, SWI, and DCE MR imaging, were acquired at a 3.0T scanner (Discovery 750, GE Healthcare, Milwaukee, Wisconsin) using a 32-channel head coil (see Supplementary Table 1 for specific imaging parameters). For mTBI patients, two reviewers (R.E.Y. and S.H.C. with 7 and 15 years of experience in neuroradiology, respectively), blinded to the results of neuropsychological tests, manually defined regions of interest of approximately 30 mm^2 in size on the transverse T2 FLAIR and postcontrast T1-weighted MR imaging by consensus at the following four locations: (1) contrast-enhancing lesions on postcontrast T1-weighted MR imaging, (2) T2 hyperintense white matter (WM) lesions on T2 FLAIR imaging, (3) bilateral normal-appearing white matter (NAWM) at the centrum semiovale level on T2 FLAIR imaging, and (4) predilection sites for diffuse axonal injury ($Location_{DAI}$) (i.e., bilateral frontal and temporal gray-white matter interfaces, corpus callosum [splenium], and dorsolateral midbrain) on T2 FLAIR imaging. For the controls, the same two reviewers drew region of interests (ROIs) at the following locations: (1) bilateral NAWM at the centrum semiovale level and (2) $Location_{DAI}$ (Fig. 1). More details on post-processing of DCE MR imaging are provided in Supplementary Materials and Methods.

Statistical analysis

All statistical analyses were performed using the statistical software MedCalc, version 11.1.1.0 (MedCalc, Mariakerke, Belgium). The data for each parameter were assessed for

Table 1 Clinical characteristics of mTBI patients and controls

	mTBI (n = 44)	Controls (n = 32)	*p* value
Age (years)*	49.0 (36.5–56.0)	59.5 (51.0–67.0)	< .001
Sex†			
Male	14 (32)	9 (28)	.804
Female	30 (68)	23 (72)	
Time interval between injury and MR imaging (months)*	4 (2–37.5)	NA	NA
Time interval between injury and neuropsychological testing (months)*	3.9 (1.5–44)	NA	NA
Comorbidity†			
SVD findings (other than leukoaraiosis)‡	1 (2)	0 (0)	1.000
Diabetes mellitus	2 (5)	3 (9)	.644
Hypertension	5 (11)	6 (19)	.511
Dyslipidemia	6 (14)	10 (31)	.088
Chronic kidney disease	0 (0)	0 (0)	NA
Cerebral amyloid angiopathy	0 (0)	0 (0)	NA
Smoking	1 (2)	3 (9)	.304
Coronary artery disease	0 (0)	1 (3)	.421
Sleep apnoea	0 (0)	0 (0)	NA

Unless otherwise indicated, data represent the number of patients. NA not available

* Data are reported as medians (interquartile range)

† Data in the parentheses are percentages

‡ Small vessel disease (SVD) findings (other than leukoaraiosis) include lacunae and cerebral microbleeds at typical locations

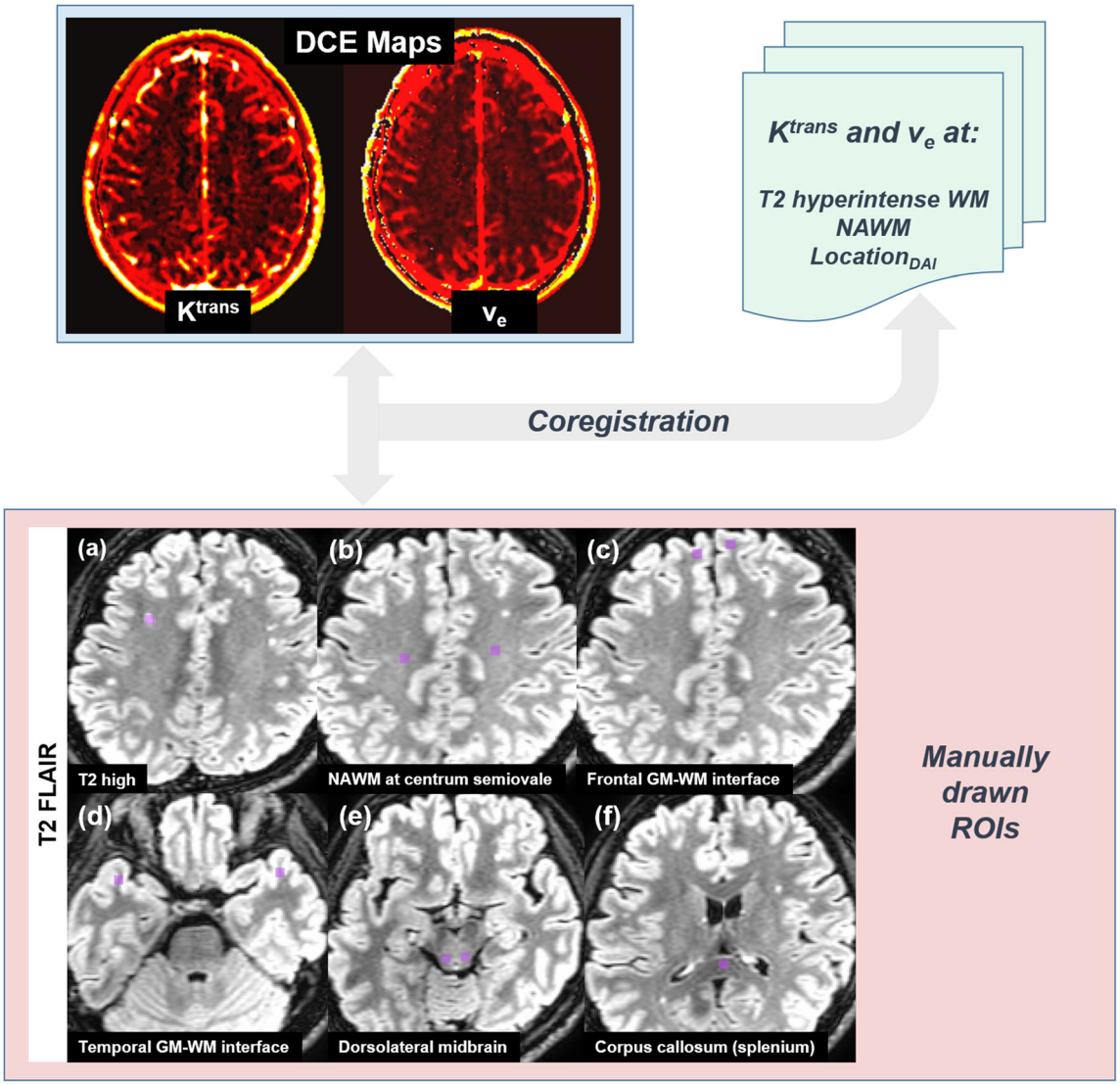

Fig. 1 Image analysis of dynamic contrast-enhanced (DCE) MR Imaging. DCE MR imaging pharmacokinetic parameter maps (K^{trans} and v_e) are coregistered with T2 FLAIR images to obtain K^{trans} and v_e values at three manually drawn regions of interests of approximately 30 mm^2 in size: (1) T2 hyperintense white matter (WM) lesions (**a**), (2) normal-appearing white matters (NAWM) (**b**), and (3) predilection sites for diffuse axonal injury ($Location_{DAI}$) (**c**–**f**). For comparison, ROIs were also drawn at the following two locations for controls, NAWM and $Location_{DAI}$ (not shown on the image)

normality with the Kolmogorov-Smirnov test. In all tests, *p*-values less than .05 were considered statistically significant.

Non-parametric data are presented as the median and interquartile range (IQR, range from the 25th to the 75th percentile), and parametric data are reported as the mean ± standard deviation. Based on the results of Kolmogorov-Smirnov's test, an unpaired Student's t-test or a Mann-Whitney U-test was performed, as appropriate, to compare DCE-MR imaging pharmacokinetic parameters and non-categorical variables among clinical characteristics between mTBI patients and controls. Specifically, we compared pharmacokinetic parameters between the two groups as follows: 1) T2 hyperintense WM lesions in mTBI vs. NAWM in controls, 2) NAWM in mTBI vs. NAWM in controls, and 3) $Location_{DAI}$ in mTBI vs. $Location_{DAI}$ in controls. Categorical variables among clinical characteristics were compared between the two groups using Fisher's exact test. Pearson correlation analysis or Spearman rank correlation test was performed, as appropriate, to evaluate the correlations between pharmacokinetic parameters and various clinical parameters including age, time interval between injury and MR imaging, and neuropsychological test scores. With regard to the neuropsychological tests, the correlation analysis was performed when time intervals between the neuropsychological tests and MR scanning were two weeks or less. For CNTs, Mann-Whitney U-test was performed to compare pharmacokinetic parameters between patients with average or good performance and those with moderately or markedly atypical performance. Receiver operating

characteristics (ROC) curves were constructed to determine the diagnostic performance of the parameters for discrimination of the two groups at its optimum threshold. Intraclass correlation coefficients were calculated to evaluate interobserver agreements for pharmacokinetic parameters.

Results

Clinical characteristics of mTBI patients and controls

mTBI patients (median age, 49.0 years [interquartile range (IQR), 36.5−56.0 years]) were significantly younger than controls (median age, 59.5 years [IQR, 51.0−67.0 years]) ($p < .001$) (Table 1). No statistically significant difference was found with respect to sex ($p = .804$). The incidences of various comorbidities we investigated did not significantly differ between the mTBI patients and controls ($p > .50$). No significant correlation was found between age and DCE MR imaging parameters ($p > .05$).

MR imaging findings of mTBI patients

None of the patients had contrast enhancing lesions. Twenty-one patients showed multifocal T2 hyperintense lesions at either subcortical or deep WM. On conventional MR imaging, no other trauma-related findings were present in any of the patients apart from the T2 hyperintense WM lesions. No discernible abnormality was identified on the visual assessment of pharmacokinetic parameter maps.

DCE-MR Imaging Analysis

Interobserver Agreement for DCE MR Imaging Parameters

The interclass correlation coefficients for mean K^{trans} and v_e were 0.55 (95% CI: 0.40, 0.67) and 0.78 (95% CI: 0.68, 0.85), indicating moderate and substantial agreement, respectively.

Comparison of DCE MR Imaging Parameters of mTBI Patients and Controls

Table 2 provides a summary of K^{trans} and v_e values in the two groups. Median v_e at T2 hyperintense WM lesions in the mTBI patients was higher than that at NAWM in the controls ($p = .027$). Median K^{trans} also tended to be higher at T2 hyperintense WM lesions in the mTBI patients than at NAWM in the controls, although statistical significance was not achieved ($p = .078$). Both median K^{trans} and v_e at NAWM were also significantly higher in mTBI than in controls (for K^{trans}, $p = .023$; for v_e, $p = .029$). In addition, mTBI patients had higher K^{trans} and v_e values at $Location_{DAI}$ than controls (for K^{trans}, $p = .008$; for v_e, $p = .015$). In the subgroup analysis according to specific locations, K^{trans} and v_e at all four locations tended to be higher in mTBI patients than in controls. However, statistical significance was only achieved for K^{trans} at bilateral frontal gray-white matter interfaces ($p = .036$) and K^{trans} and v_e at dorsolateral midbrain (for K^{trans}, $p = .012$; for v_e, $p = .029$) (Table 3).

Results for the correlations between DCE MR imaging and the time interval (between injury and MR imaging) and validation in the independent test set are provided in the Supplementary Results.

Correlations between DCE MR Imaging and Scores of RPQ and CNTs

Medians and interquartile ranges of the RPQ and CNT scores are provided in Table 4 (see Supplementary Table 2 which summarizes specific PCS symptoms of the mTBI patients). For those (n = 25) with the time interval between the neuropsychological tests and MR scanning of 2 weeks or less (median, 4 days [range, 0−14 days]), VLT (delayed recall) scores were significantly correlated with v_e values at T2 hyperintense WM lesions ($\rho = -0.767$, $p = .044$). No statistically significant correlations were noted between other neuropsychological tests and DCE MR imaging parameters ($p > .050$) (Fig. 2). Moreover, the median v_e value at $Location_{DAI}$ was significantly higher in patients with moderately or markedly atypical performance in the digit span test (forward) (n = 8) than in those with average or good performance (n = 17) (median, 0.784 [IQR, 0.677−1.044] vs. median, 0.536 [IQR, 0.433−0.844], respectively; $p = .027$). For other CNTs, no statistically significant differences in DCE MR imaging parameters were noted between the two groups ($p > .05$). In ROC analysis, the median v_e value at $Location_{DAI}$ had a sensitivity of 100% (95% confidence interval [CI]: 63, 100) and specificity of 71% (95% CI: 44, 90) for differentiating the two groups at a cut-off value of 0.647.

Representative images, including T2 FLAIR, K^{trans} and v_e maps, in a mTBI patient with PCS are shown in Fig. 3.

Discussion

Several injury mechanisms have been implicated in the development of brain injury following trauma, including axonal damage, brain oedema, and ischemia [5]. In particular, accumulating evidence suggests that the permeability of the BBB plays a pivotal role in mediating brain damage in TBI, comprising the delayed appearance of neuronal dysfunction and death [20–27]. Many of the previous analyses focused on the CSF protein or plasma protein levels, immunohistochemistry for markers of BBB integrity, or visual assessment of contrast-enhanced MR imaging [22, 28, 29]. More recently, a few animal and human studies have also attempted to

Table 2 Comparison of DCE-MR imaging parameters of TBI patients and controls

	mTBI (n = 44)	Controls (n = 32)	*p* value
T2 Hyperintense WM Lesions			
K^{trans} ($\times 10^{-1}$ min^{-1})	0.015 (0.012–0.029)	NA	NA
v_e	0.454 (0.355–0.617)	NA	NA
NAWM			
K^{trans} ($\times 10^{-1}$ min^{-1})	0.020 (0.011–0.029)	0.011 (0.005–0.022)	.023
v_e	0.431 (0.345–0.556)	0.282 (0.217–0.514)	.029
$Location_{DAI}$			
K^{trans} ($\times 10^{-1}$ min^{-1})	0.031 (0.021–0.039)	0.017 (0.009–0.030)	.008
v_e	0.637 (0.486–0.922)	0.477 (0.266–0.705)	.015

Data represent medians (interquartile range) unless otherwise noted. $Location_{DAI}$ predilection sites for diffuse axonal injury, NAWM normal-appearing white matter, WM white matter

quantitatively demonstrate BBB disruption in TBI using DCE-MRI, given that DCE MR imaging is the most widely used technique for noninvasive in vivo imaging of BBB disruption in various CNS diseases [30–33]. Weissberg et al compared BBB permeability of football players and controls (track and field athletes) and found that the BBB permeability of some football players was higher than that of the controls in both normal-appearing gray and white matter at various locations [16].

In keeping with the results of the previous studies, we also found higher BBB permeability at the WM with or without T2 signal change in mTBI patients with PCS, as compared with controls. Our results are also in line with those of the previous study which reported persistent BBB disruption in mTBI patients even months or years after the injury [24, 34]. In addition, although v_e at T2 hyperintense WM lesions was also influenced by age, the correlation between age and v_e at T2 hyperintense WM lesions was not statistically significant when adjusted for the history of TBI, suggesting a potential influence of TBI on the permeability and T2 signal intensity in mTBI patients.

In addition to the analysis of permeability at WM, we also compared permeability at predilection sites for DAI between mTBI patients with PCS and controls. We hypothesized that the change in BBB permeability at the predilection sites for DAI may serve as a contributing factor to the development of PCS in some mTBI patients, given that DAI is one of the most common causes of unfavorable outcome in TBI patients [35]. Although DAI is known to be typically associated with severe TBI, it has also been reported in a small percentage of patients who were otherwise diagnosed as mild TBI based on their clinical presentation and history [4]. In the study by Riedy et al [4], the diagnosis of DAI was made on the basis of their SWI findings, specifically extensive microhemorrhage affecting multiple brain regions. On the other hand, no demonstrable abnormality was noted on SWI in our patients. However, the permeability parameters at the predilection sites for DAI were shown to be significantly higher in mTBI patients with PCS

Table 3 Comparison of DCE-MR imaging parameters of TBI patients and controls according to specific locations among predilection sites for diffuse axonal injury ($Location_{DAI}$)

	mTBI (n = 44)	Controls (n = 32)	*p* value
Bilateral frontal gray-white matter interfaces			
K^{trans} ($\times 10^{-1}$ min^{-1})	0.033 (0.022–0.049)	0.022 (0.010–0.047)	.036
v_e	0.756 (0.515–1.105)	0.636 (0.392–0.999)	.190
Bilateral temporal gray-white matter interfaces			
K^{trans} ($\times 10^{-1}$ min^{-1})	0.035 (0.020–0.060)	0.022 (0.006–0.047)	.224
v_e	0.839 (0.641–1.211)	0.671 (0.390–1.173)	.230
Corpus callosum [splenium]			
K^{trans} ($\times 10^{-1}$ min^{-1})	0.011 (0.002–0.022)	0.005 (0.001–0.016)	.278
v_e	0.280 (0.088–0.542)	0.204 (0.030–0.408)	.169
Dorsolateral midbrain			
K^{trans} ($\times 10^{-1}$ min^{-1})	0.037 (0.022–0.049)	0.020 (0.011–0.040)	.012
v_e	0.864 (0.655–1.284)	0.684 (0.355–0.948)	.029

Data are reported as medians (interquartile range) unless otherwise noted

Table 4 Scores of post-concussion symptoms questionnaire and neurocognitive function tests

	Scores
Rivermead post-concussion symptoms questionnaire (RPQ)*	41 (31–44)
RPQ-3	7 (5–9)
RPQ-13	35 (22–37)
Auditory CPT (Correct responses)†	44 (29–53)
Auditory CPT (Commission errors)†	55 (31–62)
VLT (Immediate recall)†	50 (45–55)
VLT (Delayed recall)†	50 (38–54)
VLT (Delayed recognition)†	43 (30–55)
Digit span test (Forward)†	42 (35–46)
Digit span test (Backward)†	50 (38–53)
Card sorting test (Perseverative response)†	57 (46–69)

Data are reported as medians (interquartile range). CPT continuous performance test, RPQ Rivermead post-concussion symptoms questionnaire, VLT verbal learning test

* The Rivermead post-concussion symptoms questionnaire (RPQ) is a measure of severity of 16 PCS symptoms, which is reported as a total score within a range of 0 (representing no change in symptoms since the head injury) to 64 (most severe symptoms). The test comprises RPQ-3 (three items assessing headaches, nausea and/or vomiting, and dizziness, which are considered to be early concussion symptoms) and RPQ-13 (13 items assessing cognitive, mood, sleep, and other physical symptoms, which are indicative of later symptoms of PCS) [18]

† T scores

than in controls. Our findings demonstrated that the development of PCS in mTBI patients may be attributed in part to the BBB disruption at predilection sites for DAI. Interestingly, the permeability parameters at $Location_{DAI}$ were found to be significantly higher in the mTBI patients than in the controls when the time interval was 3 months or less, but not when it was longer than 3 months. Based on the result, we speculated that the integrity of BBB might be partly restored at $Location_{DAI}$ beyond 3 months following the TBI.

In terms of the correlations with various neuropsychological tests, we found a statistically significant correlation between VLT (delayed recall) scores and mean v_e values at T2 hyperintense WM lesions, although the sample size was small. Moreover, we also observed a significant difference in the median v_e value at $Location_{DAI}$ between patients with moderately or markedly atypical performance in the digit span test (forward) and those with average or good performance. This finding is in keeping with the previous results, which underscore a close relationship between DAI and the outcome of TBI patients [35].

In routine practice, the clinical significance of the findings is that DCE MR imaging may be incorporated as part of the MR imaging for mTBI with PCS to better depict the abnormal change in the BBB permeability, which plays an important role in the pathophysiology of TBI, in patients with otherwise normal MR findings. Furthermore, the results provide further evidence that the BBB may be an important therapeutic target for the prevention or treatment of PCS in mTBI patients [36].

Apart from the intrinsic limits of any retrospective study, several other limitations of our study should be mentioned. First, the range of the time interval between the injury and MR imaging was wide because we chose to adopt a more generalized definition of PCS rather than to restrict our patient inclusion to those who fulfill the criteria on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-R). Second, not all patients underwent the RPQ survey and CNTs and thus were excluded from the correlation analyses between neuropsychological test scores and pharmacokinetic parameters. Furthermore, there was an inevitable delay in either neuropsychological tests or MR scanning owing to the limited resource availability (especially MR scanners). Although statistical significance was observed for

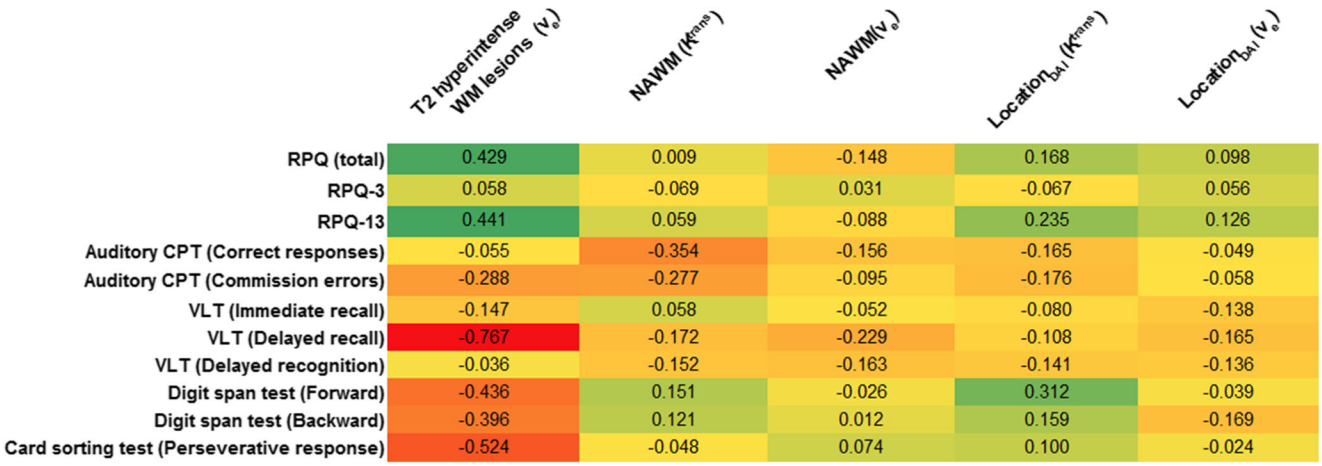

Fig. 2 A heatmap depicting the Spearman correlation coefficients between dynamic contrast-enhanced (DCE) MR imaging parameters and scores of the Rivermead post-concussion symptoms questionnaire (RPQ) (RPQ-3, RPQ-13, and RPQ total scores) and neurocognitive function tests (T-scores). CPT continuous performance test, RPQ Rivermead post-concussion symptoms questionnaire, VLT verbal learning test

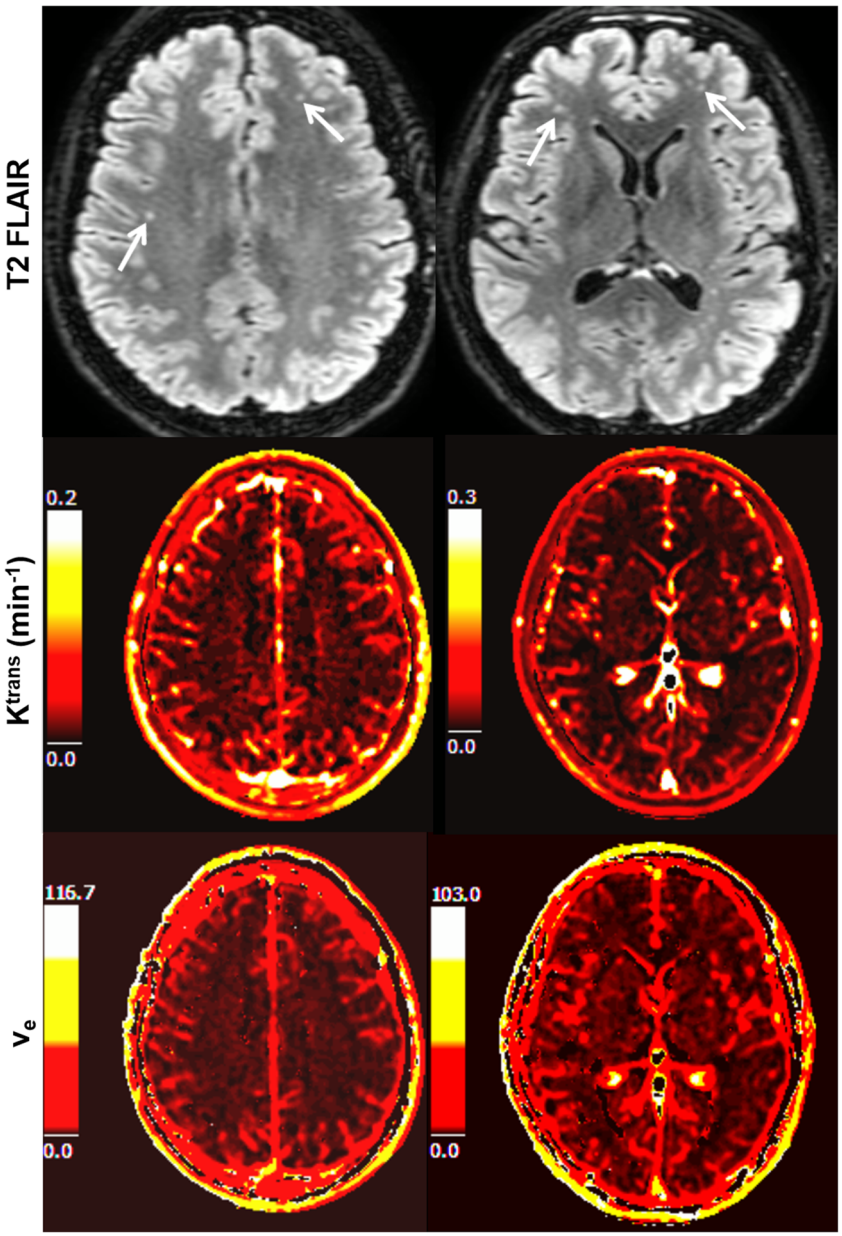

Fig. 3 MR imaging of a 44-year-old man with symptoms suggestive of PCS after mTBI. On the T2 FLAIR image (top row), small subcortical T2 high signal intensities are noted at the bilateral frontal lobes. On DCE MR imaging analysis, the visual assessment of K^{trans} (middle row) and v_e (bottom row) maps did not reveal any discernible gross abnormalities, but the quantitative analysis demonstrated that the median v_e at the T2 hyperintense WM lesions (0.800) was higher than that at NAWM in controls (0.282) (not shown). DCE MR imaging parameters of the patient at NAWM (K^{trans}: 0.020 × 10^{-1} min^{-1}; v_e: 0.433) and $Location_{DAI}$ (K^{trans}: 0.031 × 10^{-1} min^{-1}; v_e: 0.798) were also higher than those of the controls at NAWM (median K^{trans}: 0.011 × 10^{-1} min^{-1}; median v_e: 0.282] and $Location_{DAI}$ (median K^{trans} : 0.017×10^{-1} min^{-1}; median v_e: 0.477]) (not shown)

correlations between permeability parameters and some CNTs within the subgroup with a relatively short time interval (i.e., ≤ 2 weeks), a further study with a larger sample size is warranted to validate the correlation. Third, baseline DCE MR imaging pharmacokinetic parameters at the acute stage after mTBI were not available in the patients, and thus we could not conduct the longitudinal analysis of the permeability parameters. Further research based on serial DCE MR imaging pharmacokinetic parameters is warranted to understand the natural course of BBB disruption in mTBI, to determine the prognostic value of DCE MR imaging pharmacokinetic parameters, and to establish the BBB as a potential treatment target for the prevention of the development of PCS after mTBI. Fourth, the possibility remains that the inclusion of age matched individuals without any comorbidities as controls might have resulted in even lower K^{trans} and v_e for the controls, which could have further amplified the detected differences.

In conclusion, mTBI patients with PCS had higher K^{trans} and v_e values, DCE MR imaging-derived pharmacokinetic parameters reflective of BBB disruption, than controls not only at T2 hyperintense WM lesions, but also at NAWM, and predilection sites for DAI. Furthermore, the median v_e value at $Location_{DAI}$ was higher in patients with atypical performance in the digit span test (forward) than in those with average or good performance. The findings of the present study offer further support that BBB disruption is a crucial secondary injury mechanism following TBI and that BBB disruption may be implicated in the development of PCS in mTBI patients.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Seung Hong Choi.

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
- case-control study / cross sectional study / observational
- performed at one institution

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