

*TMR Integrative Medicine***Application of diffusion kurtosis imaging technology in evaluating early mild traumatic brain injury**

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Highlights

The study explored the value of MR diffusion kurtosis imaging in diagnosing early tiny changes of brain tissue after mild traumatic brain injury and found that diffusion kurtosis imaging techniques can sensitively detect the early tiny pathologic changes of cerebral tissue in mild traumatic brain injury patients, providing more imaging evidence for the clinical early diagnosis treatment and prognosis.



Abstract

Objective To explore the value of magnetic resonance diffusion kurtosis imaging in diagnosing early tiny changes of brain tissue after mild traumatic brain injury. **Methods** A total of 22 patients with mild traumatic brain injury (study group) and 20 healthy subjects (control group) were enrolled in this study, and diffusion kurtosis imaging magnetic resonance scanning was employed in all subjects. fractional anisotropy, fractional anisotropy of kurtosis, mean kurtosis, axial kurtosis and radial kurtosis of diffusion kurtosis imaging parameters in the genu of corpus callosum, splenium corporis callosi, internal capsule, thalamus, putamen, cortex of frontal lobe, temporal lobe and parietal lobe at control group, the injured side and the mirror regions were measured, and the results were compared between the two groups. The receiver operating characteristic curve was used to evaluate the ability of different parameters in diagnosing mild traumatic brain injury. **Results** Compared with the control group, in the study group fractional anisotropy values of bilateral genu of corpus callosum, splenium corporis callosi, internal capsule and thalamus were significantly reduced, and fractional anisotropy of kurtosis values of bilateral thalamus and putamen were significantly reduced, and the differences were statistically significant ($P < 0.05$). Compared with the control group, in the study group mean kurtosis and axial kurtosis values of bilateral genu of corpus callosum, posterior limb of Internal capsule, thalamus, putamen and cortex of temporal lobe were significantly reduced, while radial kurtosis values in the genu of corpus callosum, thalamus, cortex of frontal lobe, temporal lobe at the injured side were increased, and the differences were statistically significant ($P < 0.05$). **Conclusion** DKI techniques can sensitively detect the early tiny pathologic changes of cerebral tissue in mild traumatic brain injury patients, which provide more imaging evidence for the clinical early diagnosis treatment and prognosis.

Keywords: Mild traumatic brain injury, Magnetic resonance imaging, Diffusion kurtosis imaging

Abbreviations:

mTBI, mild traumatic brain injury; DAI, diffuse axonal injury; CT, computed tomography; MRI, magnetic resonance imaging; DKI, diffusion kurtosis imaging; GCS, Glasgow Coma Scale; T1WI, T1-weighted images; T2WI, T2-weighted images; FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted images; TR, repeat time; TE, echo time; FOV, field of view; ROI, region of interest; FA, fractional anisotropy; FAK, fractional anisotropy of kurtosis; MK, mean diffusion kurtosis; AK, axial kurtosis; RK, radial kurtosis; ANOVA, analysis of variance; ROC, receiver operating characteristic; DTI, diffusion tensor imaging; DTT, diffusion tensor tractography.

Competing interests:

The authors declare that there is no conflict of interest.

Acknowledgments:

This work was supported by the Zhangjiakou Key Research and Development Program (1921136H).

Citation:

Zhi-jie Zhang, Wei Liu, Guo-shi LV, et al. Application of diffusion kurtosis imaging technology in evaluating Early Mild Traumatic Brain Injury. TMR Integrative Medicine 2020, 4: e20011..

Executive Editor: Shan-Shan Lin.

Submitted: 20 April 2020, **Accepted:** 26 May 2020.

Background

Patients with mild traumatic brain injury (mTBI) exhibit transient sensory and cognitive dysfunction following a head injury, with diffuse axonal injury (DAI) representing the primary manifestation. Approximately 6.8 million TBI cases occur each year globally, approximately 75%–85% of which are mTBI cases. Between 15%–30% of mTBI patients experience cognitive and sensory symptoms, even 3 months after the trauma occurred, such as dizziness, headache, irritability, poor concentration, memory impairments, and depression [1–3]. However, conventional computed tomography (CT) and magnetic resonance imaging (MRI) are unable to reflect the diffusiveness and running direction of nerve fibers, and generally display as “normal” in mTBI patients. The objective and accurate diagnosis of mTBI in the early stages remains a focus of clinical research. Diffusion kurtosis imaging (DKI) is an emerging diffusion MRI technology that can sensitively reflect the complexities of gray and white matter microstructures in the brain. DKI has primarily been used to study the nervous system for the early detection of demyelinating neuropathy and axonal injuries and the prediction of nerve recovery and is not impacted by peripheral edema. Few studies have examined the use of DKI in mTBI patients and those that have were limited to white matter nerve fibers and the thalamus. Studies examining early gray matter lesions remain relatively few [4].

This study aimed to obtain a more comprehensive understanding of early changes in gray matter that occur in the brains of mTBI patients. We used 1.5 Tesla DKI technology to explore early changes in the brain tissue microstructure of 22 mTBI patients who were treated in our hospital, to provide additional evidence for the early clinical diagnosis and treatment of mTBI.

Materials and methods

Demographic data

A total of 22 patients with mTBI, who were admitted to our hospital from June 2018 to October 2019, were included in this study, including 16 males and 6 females, aged 8–60 years, with an average age of 36 years. All patients received routine CT, MRI, and DKI examinations, within 1 week after injury, and they all met the diagnostic criteria for mTBI established by the American Congress of Rehabilitation Medicine, the World Federation of Neurosurgical Societies, and the Brain Injury Foundation [5]: (1) a clear history of trauma, with clinical manifestations including subjective symptoms of dizziness, headache, attention deficit disorder, irritability and anxiety, nervousness, and insomnia; (2) a transient loss or change of

consciousness (< 30 min), within 24 h after the injury; (3) a Glasgow Coma Scale (GCS) score of ≥ 13 points 24 h after the injury; (4) no signs of parenchymal brain abnormalities or damage during routine cranial CT and MRI examinations; and either (5) with or without skull fracture. Exclusion criteria included patients with indications for immediate surgery, those with any history of craniocerebral trauma or of intracranial space-occupying lesions or tumors, and those who could not cooperate with the doctor for any reason. The 22 cases included 11 car accident injuries, 3 fall injuries, 5 injuries by blow, 2 tumble injuries, and 1 explosion injury.

The normal control group included 20 subjects who received routine MRI and DKI examinations. Their genders and ages matched those of the mTBI patients, including 16 males and 4 females, aged between 9–59 years, with an average age of 40 years. The control group participants had no history of mental or neurological disease, brain trauma, surgery, or family history (epilepsy, psychosis, migraine). MRI revealed no clear positive findings in these subjects.

Method of examination

The conventional head CT scan was performed, using a 64-row spiral CT scanner (GE LightSpeed VCT), with the lower edge of the axis as the reference, and a slice thickness of 5 mm. MRI scanning was conducted, using a GE SignaHDxt1.5T superconducting MR scanner, with 8-channel standard head coils. Routine MRI examination of the head included T1-weighted images (T1WI), T2-weighted images (T2WI), fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted images (DWI). The DKI scan was performed using a double-spin echo sequence, with diffusion coefficients of sensitivity (b-values) of 0, 1,000, and 2,000 s/mm². The diffusion gradient field of sensitivity used 30 directions, with a repeat time (TR) of 8,000 ms, an echo time (TE) of 112 ms, a field of view (FOV) of 24 cm × 24 cm, a matrix of 128 × 128, a slice thickness of 5 mm with slice spacing set to 0, and an acquisition time of approximately 10 minutes.

Image processing

The DKI data were analyzed on the GEAW4.5 workstation, and regions of interest (ROIs) were placed at the genu and splenium of the corpus callosum, the internal and posterior limbs of the internal capsule, thalamus, putamen, and the frontal, temporal and parietal cortices. Each ROI was approximately 24 mm² and was measured 3 times, to obtain an average value. The following parameters were measured: partial anisotropy score [fractional anisotropy (FA)], dispersion anisotropy [fractional anisotropy of kurtosis (FAK)], mean diffusion kurtosis (MK), axial kurtosis (AK), and radial kurtosis (RK).

Statistical analysis

SPSS20.0 software was used for statistical analysis. The measurement data were expressed as the mean standard deviation. The bilateral values of the normal group were averaged and compared with the values for both the injured side and the mirror side of the mTBI group, using a one-way analysis of variance (ANOVA). $P < 0.05$ indicated a significant difference. The receiver operating characteristic (ROC) curve was used to evaluate the efficacy of the DKI parameter values for the diagnosis of mTBI.

Results

DKE post-processing software was used to analyze the DKI data and obtain FA, FAK, MK, AK, and RK pseudo-color images (Figure 1a – e). DKI is an emerging MRI diffusion imaging technology, extended from the basis of diffusion tensor imaging (DTI) technology. Diffusion tensor tractography (DTT) technology may also be used to display the movement, signals, and lesions associated with cerebral corticospinal tracts. Figure 1f shows a pseudo-colored image of DTT based, on FA values. The color scale

display range is 0–0.60.

The parameter values and statistical results for different areas of the mTBI group and the control group were as follows (Table 1).

FA is a scalar value, with a measurement range from 0 to 1. A value of 0 indicates that the water diffusion is isotropic whereas a value of 1 represents extremely anisotropic conditions, which suggests that water molecules only diffuse along one axis. Compared with the control group, the FA values in the mTBI group for the genu and the body of the corpus callosum, the internal capsule, and the thalamus decreased significantly for the injured side and the non-injured side, as did those for the injured side in the frontal and temporal lobes ($P < 0.05$).

FAK is similar to the FA, in that they both reflect the anisotropy of kurtosis tensor. Compared with the control group, the FAK values in the thalamus and putamen of the mTBI group decreased significantly for the injured side and the non-injured side, and the FAK values for the genu and body of the corpus callosum, the anterior limb of the internal capsule, and the injured side of the frontal lobe also significantly decreased ($P < 0.05$).

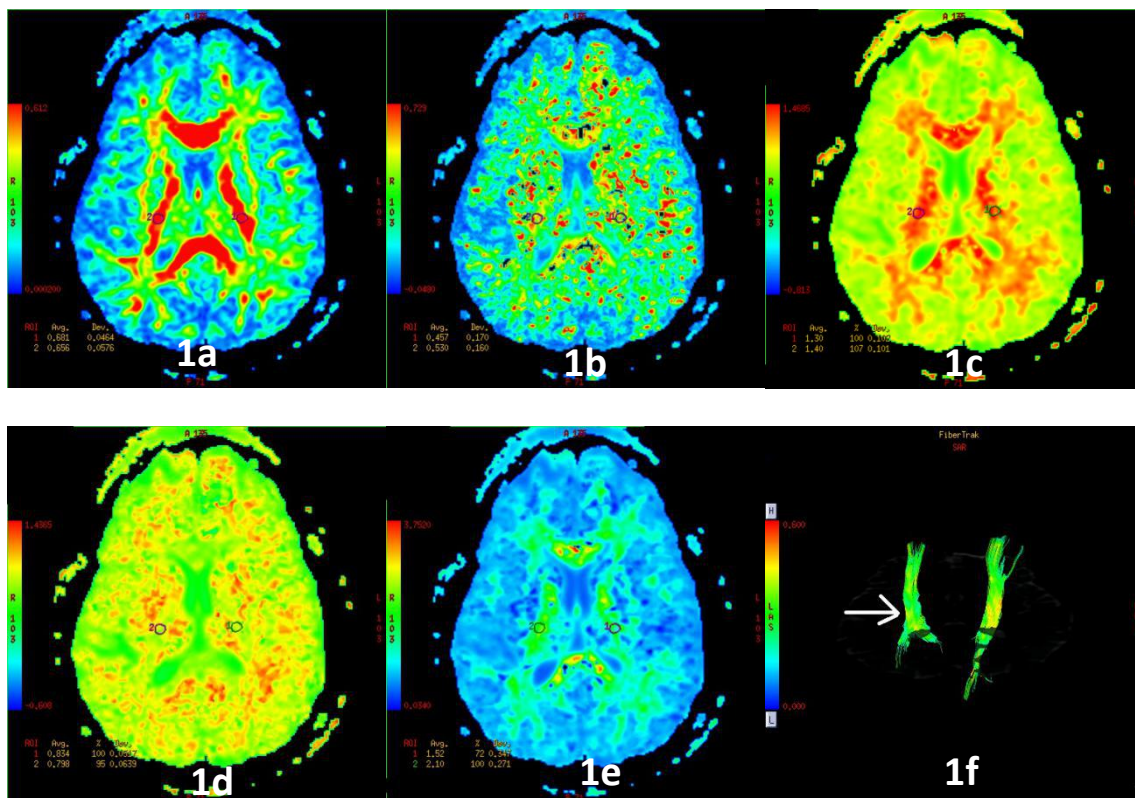


Figure 1 A 33-year-old man with the left frontal and parietal injury presented with transient confusion of unconsciousness, headache and dizziness after traffic accident. The selected region of interest in bilateral internal capsule. **a**, (FA pseudo color map) left 0.681 right 0.656; **b**, (FAK pseudo color map) left 0.457 right 0.530; **c**, (MK pseudo color map) left 1.30 right 1.40; **d**, (AK pseudo color map) left 0.834 right 0.798; **e**, (RK pseudo color map) left 1.54 right 2.13. **f**, (DTT) compare to the right side of the corticospinal tract, the color of the left side become light (arrow).

Table 1 Parameter values and statistical results in the control group and mild TBI patients group at different observation periods

Location		FA	FAK	MK	AK	RK
Genu of corpus callosum	Control group	0.783 ± 0.009	0.625 ± 0.030	1.341 ± 0.191	0.750 ± 0.008	2.321 ± 0.478
	The injured side	0.757 ± 0.049	0.589 ± 0.068	1.121 ± 0.169	0.767 ± 0.036	1.854 ± 0.384
	The mirror region	0.764 ± 0.040	0.603 ± 0.122	1.144 ± 0.247	0.752 ± 0.033	1.878 ± 0.460
	<i>P</i> Value	$P_a = 0.024$	$P_a = 0.037$	$P_a = 0.000$	$P_a = 0.041$	$P_a = 0.001$
		$P_b = 0.047$	$P_b = 0.443$	$P_b = 0.006$	$P_b = 0.742$	$P_b = 0.004$
Splenum corporis callosi	Control group	0.795 ± 0.018	0.610 ± 0.026	1.368 ± 0.015	0.721 ± 0.018	2.318 ± 0.188
	The injured side	0.734 ± 0.059	0.557 ± 0.088	1.187 ± 0.163	0.730 ± 0.053	1.914 ± 0.602
	The mirror region	0.745 ± 0.077	0.590 ± 0.069	1.213 ± 0.173	0.727 ± 0.084	2.054 ± 0.572
	<i>P</i> Value	$P_a = 0.000$	$P_a = 0.013$	$P_a = 0.000$	$P_a = 0.471$	$P_a = 0.007$
		$P_b = 0.008$	$P_b = 0.238$	$P_b = 0.000$	$P_b = 0.764$	$P_b = 0.056$
D anterior limb of internal capsule	Control group	0.647 ± 0.058	0.494 ± 0.022	1.093 ± 0.046	0.961 ± 0.011	1.594 ± 0.113
	The injured side	0.496 ± 0.086	0.441 ± 0.093	1.030 ± 0.112	0.980 ± 0.054	1.400 ± 0.354
	The mirror region	0.519 ± 0.107	0.456 ± 0.110	1.069 ± 0.097	0.962 ± 0.044	1.409 ± 0.416
	<i>P</i> Value	$P_a = 0.000$	$P_a = 0.019$	$P_a = 0.021$	$P_a = 0.131$	$P_a = 0.024$
		$P_b = 0.000$	$P_b = 0.140$	$P_b = 0.318$	$P_b = 0.898$	$P_b = 0.061$
Posterior limb of internal capsule	Control group	0.757 ± 0.012	0.595 ± 0.035	1.249 ± 0.111	0.776 ± 0.035	2.286 ± 0.343
	The injured side	0.722 ± 0.036	0.566 ± 0.063	1.159 ± 0.734	0.799 ± 0.053	1.908 ± 0.438
	The mirror region	0.737 ± 0.038	0.584 ± 0.046	1.185 ± 0.069	0.791 ± 0.053	2.010 ± 0.443
	<i>P</i> Value	$P_a = 0.000$	$P_a = 0.077$	$P_a = 0.003$	$P_a = 0.104$	$P_a = 0.004$
		$P_b = 0.023$	$P_b = 0.394$	$P_b = 0.029$	$P_b = 0.306$	$P_b = 0.030$
Thalamus	Control group	0.358 ± 0.044	0.455 ± 0.027	1.056 ± 0.082	0.938 ± 0.072	1.138 ± 0.187
	The injured side	0.314 ± 0.052	0.404 ± 0.102	0.891 ± 0.161	0.988 ± 0.068	0.840 ± 0.217
	The mirror region	0.323 ± 0.050	0.409 ± 0.089	0.910 ± 0.149	0.963 ± 0.072	0.885 ± 0.245
	<i>P</i> Value	$P_a = 0.005$	$P_a = 0.034$	$P_a = 0.000$	$P_a = 0.026$	$P_a = 0.000$
		$P_b = 0.020$	$P_b = 0.035$	$P_b = 0.000$	$P_b = 0.352$	$P_b = 0.001$
Putamen	Control group	0.257 ± 0.038	0.589 ± 0.041	0.881 ± 0.128	1.037 ± 0.066	0.820 ± 0.297
	The injured side	0.229 ± 0.061	0.511 ± 0.138	0.746 ± 0.108	1.076 ± 0.101	0.627 ± 0.150
	The mirror region	0.240 ± 0.040	0.527 ± 0.122	0.791 ± 0.088	1.064 ± 0.079	0.637 ± 0.179
	<i>P</i> Value	$P_a = 0.090$	$P_a = 0.020$	$P_a = 0.001$	$P_a = 0.159$	$P_a = 0.010$
		$P_b = 0.085$	$P_b = 0.036$	$P_b = 0.011$	$P_b = 0.246$	$P_b = 0.019$
Cortex of frontal lobe	Control group	0.369 ± 0.026	0.328 ± 0.035	1.136 ± 0.035	1.016 ± 0.049	1.230 ± 0.025
	The injured side	0.338 ± 0.049	0.291 ± 0.071	1.007 ± 0.079	1.067 ± 0.080	1.132 ± 0.139
	The mirror region	0.361 ± 0.047	0.315 ± 0.073	1.021 ± 0.081	1.024 ± 0.063	1.169 ± 0.203
	<i>P</i> Value	$P_a = 0.014$	$P_a = 0.042$	$P_a = 0.000$	$P_a = 0.018$	$P_a = 0.004$
		$P_b = 0.487$	$P_b = 0.475$	$P_b = 0.000$	$P_b = 0.647$	$P_b = 0.194$
Cortex of temporal lobe	Control group	0.384 ± 0.014	0.350 ± 0.035	1.062 ± 0.081	0.944 ± 0.056	1.253 ± 0.099
	The injured side	0.361 ± 0.040	0.321 ± 0.112	0.945 ± 0.138	1.015 ± 0.101	1.040 ± 0.222
	The mirror region	0.382 ± 0.055	0.344 ± 0.082	0.962 ± 0.134	0.995 ± 0.080	1.065 ± 0.207
	<i>P</i> Value	$P_a = 0.016$	$P_a = 0.272$	$P_a = 0.002$	$P_a = 0.008$	$P_a = 0.000$
		$P_b = 0.847$	$P_b = 0.758$	$P_b = 0.006$	$P_b = 0.980$	$P_b = 0.001$
Cortex of Parietal lobe	Control group	0.369 ± 0.020	0.345 ± 0.058	1.174 ± 0.074	0.943 ± 0.066	1.420 ± 0.174
	The injured side	0.353 ± 0.033	0.305 ± 0.081	1.088 ± 0.078	0.966 ± 0.078	1.228 ± 0.193
	The mirror region	0.368 ± 0.020	0.331 ± 0.093	1.110 ± 0.213	0.949 ± 0.111	1.285 ± 0.189
	<i>P</i> Value	$P_a = 0.067$	$P_a = 0.069$	$P_a = 0.001$	$P_a = 0.307$	$P_a = 0.002$
		$P_b = 0.894$	$P_b = 0.564$	$P_b = 0.201$	$P_b = 0.825$	$P_b = 0.021$

Note: P_a = compared between the injured side and the control group; P_b = compared between the mirror regions and the control group. Compared with the control group, in the study group FA values of bilateral genu of corpus callosum, splenium corporis callosi, internal capsule and thalamus were significantly reduced, and FAK values of bilateral thalamus and putamen were significantly reduced, and the differences were statistically significant ($P < 0.05$). Compared with the control group, in the study group MK and AK values of bilateral genu of corpus callosum, posterior limb of Internal capsule, thalamus, putamen and cortex of temporal lobe were significantly reduced, while RK values in the genu of corpus callosum, thalamus, cortex of frontal lobe, temporal lobe at the injured side were increased, and the differences were statistically significant ($P < 0.05$).

MK refers to the mean value of diffusion kurtosis, on the gradients in all directions, which is positively related to the complexity of the tissue structure. Compared with the control group, the mTBI group had significantly lower MK values in the genu and the body of the corpus callosum, the posterior limb of the internal capsule, the thalamus, putamen, frontal lobe, and temporal lobe for the injured side and the non-injured side. The MK values were also significantly decreased in the anterior limb of the internal capsule and on the injured side of the parietal lobe ($P < 0.05$).

RK refers to the average value of all diffusion kurtosis, perpendicular to the main eigenvector direction, which reflects the kurtosis information perpendicular to the axon direction. Compared with the control group, in the mTBI group, the RK values at the genu of the corpus callosum, the posterior limb of the internal capsule, the thalamus, putamen, temporal lobe, and bilateral parietal lobes significantly decreased for the injured side and the non-injured side, as did those at the body of the corpus callosum, the anterior limb of the internal capsule, and the injured side of the frontal lobe ($P < 0.05$).

AK refers to the largest diffusion eigenvalue of kurtosis in the main diffusion eigenvector, which reflects the kurtosis information along the axon direction. Compared with the control group, in the mTBI group, the AK values at the genu of the corpus callosum, the thalamus, and the injured side of the frontal and temporal lobes significantly increased ($P < 0.05$).

According to the Youden index that was identified by the principle of maximization of the Sensitivity and specificity, the Youden index about the MK, AK, and RK of the thalamus were 1.621, 1.621, 1.635, and 1.724, respectively, and the corresponding optimal limits were 0.959 and 0.956, 0.914, respectively. The ROC curve analysis is shown in Figure 2. The AUC of AK was 0.820, and its sensitivity and specificity were 68.2% and 95%, respectively; the AUC of RK was 0.809, and its sensitivity and specificity were 63.6% and 95%, respectively; and the AUC of AK was 0.775, and its sensitivity and specificity were 68.2% and 80%, respectively.

Discussion

Today, the practical value of DTI in mTBI diagnosis

has been well-recognized. A reduced FA value is generally believed to be associated with damage and the loss of white matter integrity, and may also reflect the lesioning or damage to the myelin sheath and axon membrane, reductions in the density of the axon assembly, or reduced connectivity and consistency of axons [3]. In this study, we found that the FA values of the corpus callosum and the internal capsule in the mTBI group were significantly reduced. Meanwhile, the FA values of some gray matter regions (the thalamus, frontal lobe, and temporal cortex) were also reduced, indicating that the FA value is significantly more sensitive to the damage in white matter than in gray matter. FAK is a new parameter that has been proposed in recent years. It is similar to the FA value for DTI and reflects the anisotropy of the kurtosis tensor [6]. Rune [7] found that, during the acute phase, FA is more commonly reduced compared to FAK, whereas, after 3 months, FAK is more commonly reduced than FA. FAK is thought to depend only on the peak tensor. Compared with the diffusion tensor, the kurtosis tensor can better reflect diffusion in biological tissues. In this study, we found that in the mTBI group, the FA values of the corpus callosum and the anterior limb of the internal capsule, as well as some gray matter (thalamus, putamen, and frontal lobe), were significantly decreased. These results indicated that the FAK value can better reflect the early damage to white matter but is less sensitive than the FA value. DKI scans can obtain DTI-related parameters, as well as fiber bundle imaging, which can display more complex structures, such as fiber bundle intersections and bifurcations. Thus, DKI can provide more realistic and rich information regarding the direction and connection of fiber bundles, allowing the visualization of the reduced white matter fiber bundle density, as a lighter color, and other minor changes in mTBI patients (Figure 1f).

The MK value is the most representative parameter in DKI, is not dependent on the spatial orientation of the tissue structure, and can be used for both the gray and white matter structures. This study demonstrated that the MK values of the gray and white matter were significantly reduced, reflecting neuron atrophy, changes in the densities of neurites and myelin sheaths, astrocytes hyperplasia, damage to the normal structures of neurites, and demyelination [8]. In addition, the RK values for both gray and white matter in the brain were also significantly reduced, whereas the AK value of

some gray matter increased. These results indicated that the presence of cerebral edema after trauma. The water molecules had limited and reduced axial diffusion ability, whereas diffusion movements in the vertical direction increased significantly. In addition, contrecoup injuries may occur during brain trauma, although previous studies have primarily focused on the injured side. Although mTBI only causes quite mild injuries, the possibility of contrecoup injuries cannot be excluded. Fan et al. [9] studied mTBI patients within 3 days of injury and identified damage in the bilateral temporal cortex, the genu of the corpus callosum, and the thalamus. Our data is consistent with their findings and revealed that the genu of the bilateral corpus callosum, the posterior limb of the internal capsule, the thalamus, putamen, and both sides of the temporal lobe of mTBI patients demonstrated significantly reduced MK and RK values. Thus, in mTBI patients, damage can occur to the tissues of the bilateral cerebral hemispheres.

The thalamus is the largest gray matter mass in the diencephalon. As the subcortical center and relay station for sensory information, it is extensively interconnected with the cerebral cortex, closely influencing the activities of the motor system, limbic system, ascending reticular system, and cerebral cortex. Increasing studies have shown [10, 11] that the thalamus plays a special role in prognosis after mTBI. Mild brain trauma can cause significant changes in the thalamus, which are closely related to neurological dysfunctions, such as headache, sleep disorders, and fatigue. Therefore, most studies have focused on the thalamus after mTBI. This study revealed that the MK, AK, and RK values in the thalamus changed significantly, suggesting the presence of thalamic injury. The AUC of MK was 0.820, and its sensitivity and specificity were 68.2% and 95%, respectively, which were all higher than those for either the AK or RK. These findings indicated that the thalamus plays an important role in the onset and development of mTBI and that DKI, especially the MK value, showed considerable significance for the evaluation of changes within the thalamus microstructure.

In summary, DKI can provide more abundant information regarding white matter microstructure, and it can supplement the insufficiencies associated with DTI for the description of gray matter structures. DKI generates more sensitive and specific parameters than DTI [12] and can provide a further imaging basis for the early diagnosis, treatment, and prognosis of mTBI.

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