Original Article

Demystifying White Matter Injury in the Unconscious Patients with Diffusion Tensor Imaging

Abstract

Background: Diffusion tensor imaging (DTI) and diffusion tensor tractography (DTT) provide a noninvasive window to study the neural connectivity and reconstruct the tracts. Detection of white matter injury (WMI) by DTT is a recent application being used in stroke, diffuse axonal injury, and neurodegenerative disorders. Fiber tracking in patients with brain hemorrhage can detect loss of fibers and anatomical disruption of the tracts, which can be useful in the prognostication of patient outcome. **Materials and Methods:** DTI and fiber tracking was done in four patients admitted at Fujita Health University Banbuntane Hospital, Japan, with decreased consciousness following brain hemorrhage (3 patients with aneurysmal subarachnoid hemorrhage and one patient with bifrontal hemorrhage), and WMI was analyzed. We also reviewed the literature on tractography in patients with brain hemorrhage and its correlation with consciousness. **Results:** We found significant frontal WMI in the form of thinning and anatomical disruption in all four cases. The frontal white matter tracts form an important component of the limbic system and ascending reticular activating system and frontal WMI correlated with the poor conscious level and cognitive dysfunction. Structural damage to the fiber tracts demonstrated as thinning, reduction in the volume or absence on tractography with corresponding reduction in the mean fractional anisotropy values in the frontal white matter of the affected side. **Conclusion:** DTI can be useful as a critical tool for revealing the anatomical basis for the cognitive dysfunction and unconsciousness and can be possibly used to prognosticate patient recovery. Early detection of WMI by DTI can also help in tailored rehabilitation. The authors believe that DTT could have a crucial role in the future for detecting structural changes which lead to cognitive dysfunction and further studies are needed to arrive at a specific protocol for detecting WMI.

Keywords: *Brain hemorrhage, diffusion tensor imaging, diffusion tensor tractography, fiber tracking, unconsciousness, white matter injury*

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Introduction

Diffusion tensor imaging (DTI) and fiber tracking by diffusion tensor tractography (DTT) are the modalities of noninvasive imaging of the white matter and used for the reconstruction of the trajectory of the tracts. It is presently being primarily used as a preoperative imaging tool that assists in planning surgical procedures to avoid damage to the major tracts, especially in intrinsic brain tumors and epilepsy surgery. Fiber tracking by tractography is a recent application which is gaining interest in the study of white matter injury (WMI). DTT can be used to analyze the course, integrity, anatomical connectivity, or possible disruption of the white matter fibers. It has been so far used in traumatic diffuse axonal brain injury, cerebral ischemia, and neurodegenerative disorders. We present our preliminary experience where DTI and DTT were used to analyze the reason for poor conscious level in patients with intracerebral hemorrhage (ICH) and aneurysmal subarachnoid hemorrhage (SAH) and also review the literature available. All the patients in our study had white matter changes detected on the DTT which correlated with the altered consciousness. The authors believe that DTT could have a crucial role in the coming years for explaining the white matter injuries, which lead to cognitive dysfunction.

Materials and Methods

DTI and fiber tracking were done in four patients admitted at Fujita Health University

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Banbuntane Hospital, Japan, with decreased conscious level and cognitive dysfunction following cerebrovascular accident (3 patients with aneurysmal SAH and one patient with bifrontal hemorrhage), and DTI changes in the frontal white matter were analyzed. The Glasgow coma scale (GCS) and Mini-Mental State Examination were used to assess the cognitive changes. 3 Tesla magnetic resonance imaging (MRI) was used for image acquisition using the standard protocols' region of interest (ROI) for the fractional anisotropy (FA) values, and fiber tracking was manually fixed over the bilateral frontal white matter. MRI (Vantage Centurian; Canon, Ingenia 3T; Philips) and DTI specifications used were Sequence = SE-EPI, TR = 8059, TE = 49, ets = 1.0 ms BW = 1302 Hz/pixel, FOV = 23 cm × 23 cm, MTX = 208 × 208, slice thickness = 2.0 mm, Gap = 0, number of slice = 82, MultiBand SPEEDER = 2, PE-SPEEDER = 3, B = 1000 (12 axis), Fatsat = ON, ime = 2:09.

Case 1

A 45-year-old female presented with sudden-onset headache. Her GCS was E4V4M6 (14/15) with no focal neurological deficit. On evaluation, the patient was found to have ruptured anterior communicating artery aneurysm with Fisher's Grade 4 SAH and left frontal ICH [Figure 1a]. The patient underwent emergency left pterional craniotomy and clipping of aneurysm [Figure 1b]. She also underwent a decompressive craniectomy and ventriculoperitoneal (VP) shunt in the postoperative period. Patient's GCS remained at E2VaM5. DTI and DTT were done at 6 weeks in which the cingulum and the fornix on the left side could not be delineated and left frontal connectivity was decreased [Figure 2a-d]. The patient progressed gradually to GCS E4VAM5 and tailored neurorehabilitation was initiated.

Case 2

A 55-year-old hypertensive male patient had a fall and sustained head injury. His GCS was E1V1M5, pupils were equal and reacting, computed tomography (CT) brain revealed bifrontal contusion with bifrontal thin acute subdural hematoma [Figure 3a]. The patient was treated with anticerebral edema measures, and he gradually showed improvement in his GCS to E4V4M6 on day 7 after injury, but he continued to have confusion and cognitive dysfunction. MRI showed resolving bleed with edema [Figure 3b]. Diffusion-weighted imaging (DWI) and tractography done after 1 week revealed discontinuation and reduction of fibers in the bilateral frontal white matter tracts along with reduced FA values and thinning of right cingulum [Figure 4a and b].

Case 3

A 56-year-old male patient presented with sudden-onset altered sensorium. His GCS was E3V3M5, and imaging revealed ruptured right middle cerebral artery (MCA)

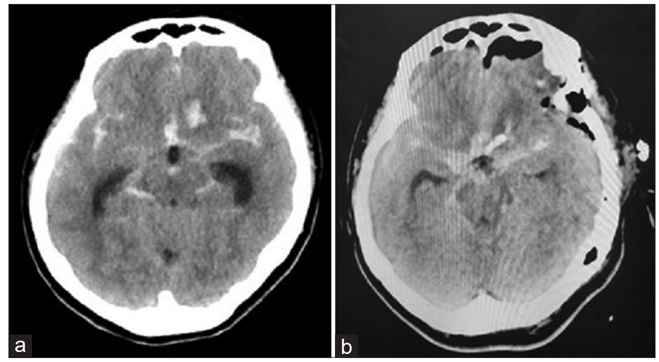

Figure 1: (a) Computed tomography brain showing Fisher's Grade 4 subarachnoid hemorrhage with left frontal intracerebral hemorrhage from ruptured ACOM aneurysm. (b) Computed tomography brain showing postcraniotomy changes and clip *in situ*

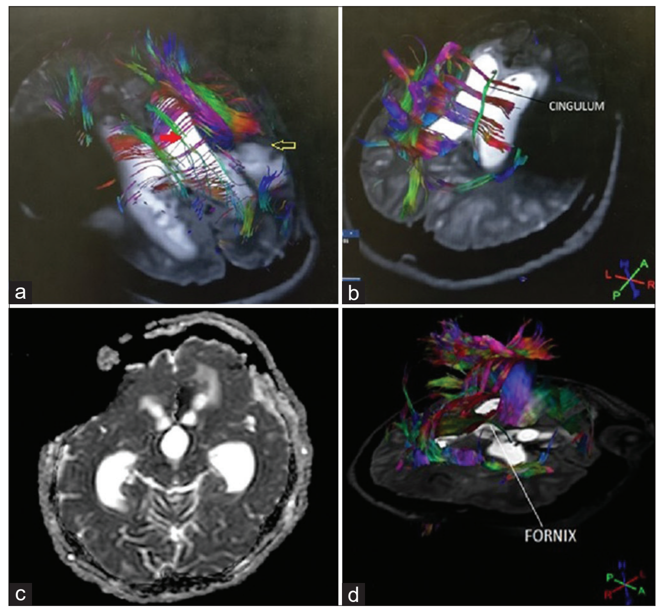

Figure 2: (a) Diffusion tensor tractography showing thinning of left cingulum (red arrow) and disconnection in the left frontal fibers (yellow arrow). (b) Diffusion tensor tractography demonstrating normal cingulum on right with shunt-related black artefact. (c) Magnetic resonance imaging showing the white matter changes in the left frontal region. (d) Diffusion tensor tractography showing fornix on the right. It was absent on the left side

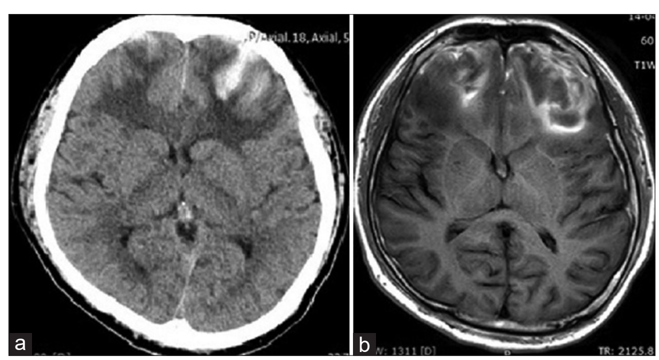

Figure 3: (a) Plain computed tomography brain showing bifrontal contusion (left>right). (b) Magnetic resonance imaging T1 weighted showing white matter edema surrounding the contusion

aneurysm with Fisher's Grade 4 SAH. During the surgery, the aneurysm re-ruptured, and clipping,

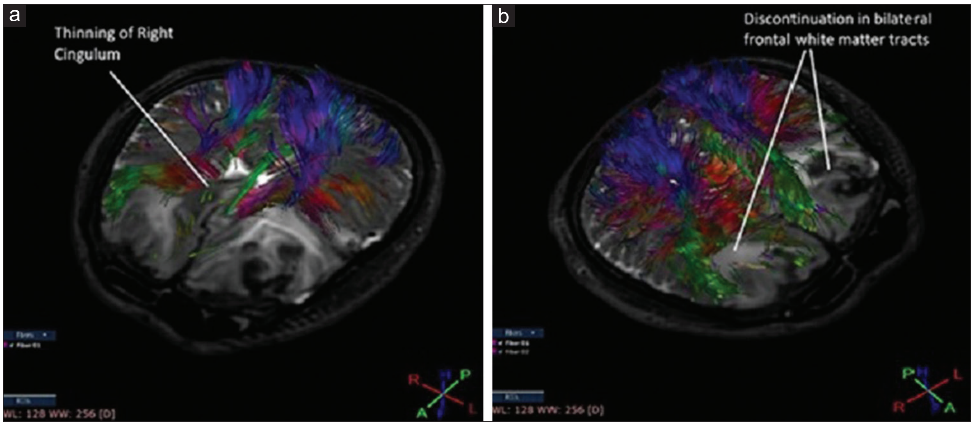

Figure 4: (a) Tractography showing thinning of right cingulum. (b) Diffusion tensor tractography showing discontinuation in bilateral frontal tracts

external ventricular drainage, and a decompressive craniectomy were done at another center. Postoperative imaging revealed right frontal ICH. He also underwent VP shunt and cranioplasty 4 weeks later. The patient's postoperative GCS continued to remain E4VTM5 after 1 year, and he was referred to our center for neurorehabilitation. CT brain revealed right frontal damage and gliosis [Figure 5a]. MRI with DWI and DTT showed severe reduction in connectivity from the right frontal lobe and reduced FA values in the right frontal white matter [Figures 5b, 6a and b].

Case 4

A 64-year-old male presented with Fisher's Grade 4 SAH due to ruptured basilar artery tip aneurysm [Figure 7a and b]. The patient's GCS was E4V4M6 with no motor deficit. Coiling and external ventricular drainage were done. Postoperatively, his GCS remained the same. He continued to have confusion and memory deficit. Postoperative MRI revealed a small right frontal bleed at the external ventricular drain insertion site [Figure 8a]. MRI DWI and tractography done 4 weeks later showed reduced FA values in the right frontal region and discontinuation in the frontal fiber tracts [Figure 8b].

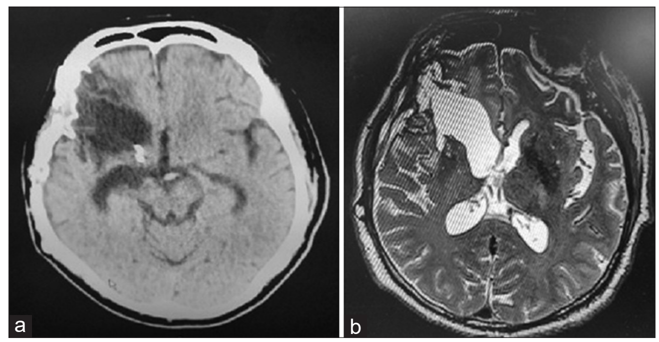

Figure 5: (a) Postoperative computed tomography after 1 year showing right frontal gliotic change. (b) Magnetic resonance imaging T2 image showing extensive white matter damage right frontal region

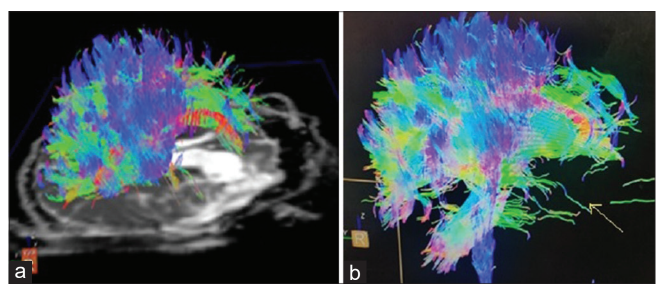

Figure 6: (a) Diffusion tensor tractography showing reduction and disruption of the right frontal white matter tracts (yellow arrow). (b) Diffusion tensor tractography showing discontinuation of the right frontal white matter tracts (yellow arrow)

Results

The variations in FA values of the bilateral frontal white matter and the tractography findings in the cases are summarized in Table 1.[1] The normal reference value of FA in the frontal white matter in a healthy adult was taken as above 0.35. We found WMI with significant frontal white matter damage in the form of thinning and anatomical disruption of the tracts in all the cases, and this correlated with the cognitive status of the studied patients. Our preliminary study results have shown that DTI can possibly reveal the anatomical basis for the cognitive dysfunction and unconsciousness following brain hemorrhage and can be used as a critical analytical tool in explaining the disintegration of the neural circuits. The results can in turn be useful for the prognostication of the clinical outcome.

Discussion

Neural circuits in consciousness and memory

Limbic system

The limbic system is a complex part of the nervous system consisting of both cortical and subcortical structures and plays a crucial role in the conscious level of the patient. Cognition, emotions, behavior, and memory are among its many functions. The intricate structural anatomy includes the cingulum, hippocampal formation (dentate gyrus, hippocampus, and subicular complex), amygdala, septal area, and the hypothalamus.

Papez circuit and mamillothalamic tract

Shah *et al*.[1] have very elegantly presented the fiber dissection technique of the limbic system by the Klingler technique, which provided the anatomical visualization and basis for the voxel placement and ROI study in the DTI [Figure 9a and b]. Papez circuit begins with the hippocampus and reaches the mammillary body via the fornix. The mamillothalamic tract (MTT) then continues to the anterior nucleus of the thalamus, which in turn is projected to the hippocampus by the cingulum which completes the circuit [Figure 10]. Structurally, the MTT is a solid white matter band of fibers running along and parallel to the forniceal columns and anterior bodies.[2] It is a major direct communication pathway of the thalamus with the mammillary bodies of the hypothalamus, and the damage to it causes severe memory impairment, resulting in amnesia and cognitive dysfunction. The amnestic syndrome or impairment of recent memory was originally

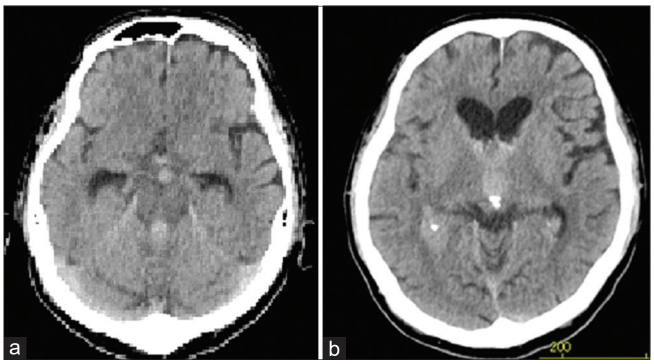

Figure 7: (a) Plain computed tomography brain showing subarachnoid hemorrhage and intraventricular hemorrhage Fisher's Grade 4. (b) Plain computed tomography brain showing subarachnoid hemorrhage and intraventricular hemorrhage Fisher's Grade 4

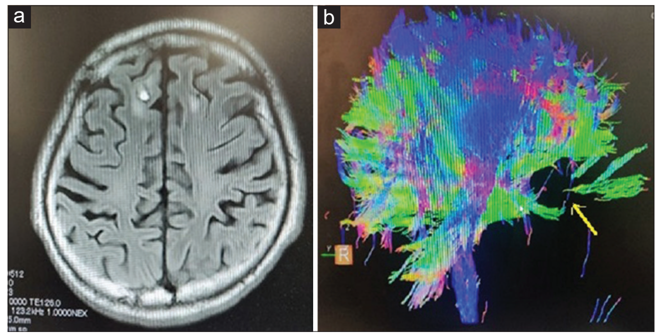

Figure 8: (a) Magnetic resonance imaging showing right frontal bleed. (b) Diffusion tensor tractography showing disruption in the right basal forebrain tract (bold yellow arrow)

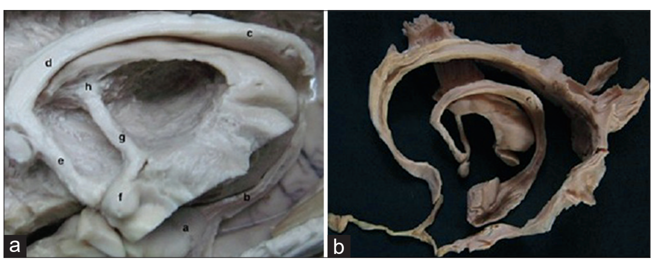

Figure 9: (a and b) The anatomical dissection of Papez circuit and limbic system and its connections by Kingler technique done by Shah *et al*. a-hippocampus, b-fimbria, c-crus of fornix, d-body of the fornix, e-column of the fornix, f-mammillary body, g- mamillothalamic tract, h-anterior nucleus of thalamus

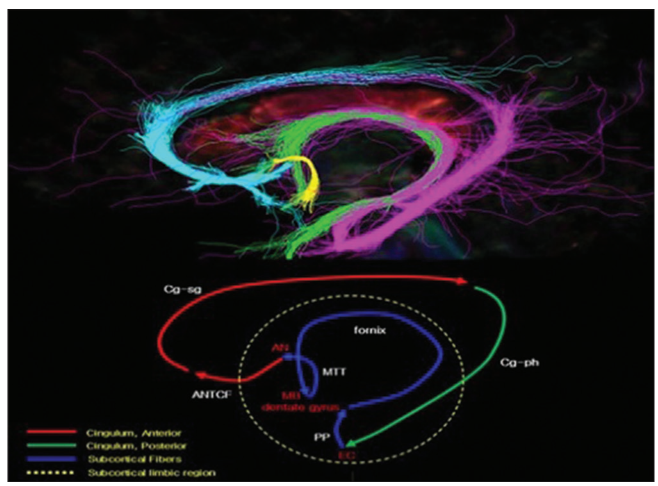

Figure 10: Tractography of Papez circuit and mamillothalamic tract using 7 Tesla magnetic resonance imaging. Image for reference from paper by Choi *et al*. 2019[4]

Table 1: Summary of results with the fractional anisotropy values of frontal white matter and diffusion tensor tractography finding

Case number	Diagnosis	FA values Frontal WM	Tractography finding
1	ACOM aneurysm SAH, ICH	R 0.31 L 0.15	Absent left cingulum and fornix, reduced left frontal WM tracts
2	Bifrontal contusion, ICH	R 0.13 L0.08	Thinning of right cingulum and bilateral reduced frontal WM tracts - left > right
3	MCA aneurysm SAH, ICH	R 0.19 L0.30	Gross reduction of right frontal WM tracts
4	Basilar top Aneurysm SAH, IVH	R 0.30 L 0.47	Reduction of smaller WM fibers in right frontal

SAH – Subarachnoid hemorrhage; IVH – Intraventricular hemorrhage; WM – White matter; ICH – Intracerebral hemorrhage; MCA – Middle cerebral artery; FA – Fractional anisotropy; ACOM – Anterior communicating artery

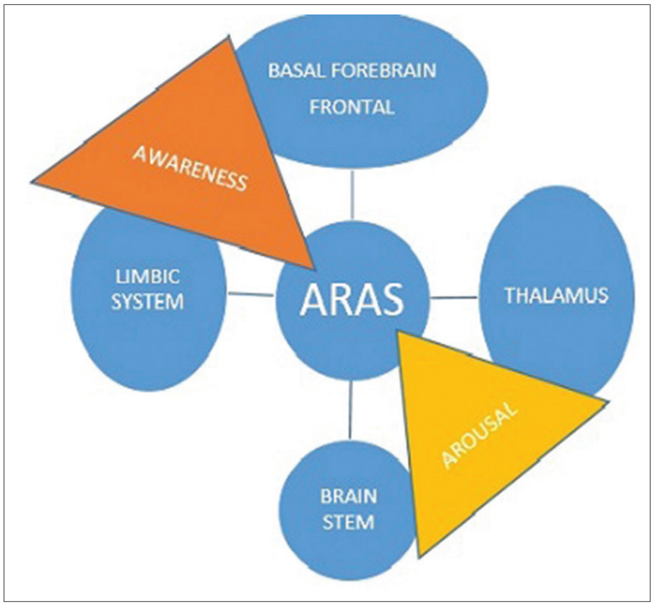

Figure 11: Neural circuits in consciousness

described by Korsakoff in alcoholics. Similar presentations have also been described in head trauma, cerebrovascular disorders, and hypoxic brain injury. The MTT is therefore one more important site of damage in the complex memory circuit of the hippocampal–limbic system.[3,4]

Ascending reticular activating system

The ascending reticular activating system (ARAS) or the reticular activating system is a complex reticulum of neurotransmitter-specific synapses and interconnections with cell bodies in the tegmentum of brainstem, basal forebrain, and thalamus. Also called as the extrathalamic modulatory system, it is a crucial structure serving as the center for control of consciousness and arousal. Human consciousness can be simplified as consisting of two main components – arousal and awareness. Arousal pathways originating in the brainstem reticular network activate the awareness networks in the cortex via synapses in the thalamus and the frontal cortex or may project directly to the basal forebrain circuits [Figure 11]. The pathway consists of the ventral and dorsal tegmental tracts projecting from the thalamic nuclei to the basal forebrain and the middle forebrain bundle [Figure 12]. Several studies have demonstrated tractography and DWI changes in ARAS in patients with decreased conscious level.[5-9]

Diffusion tensor imaging and diffusion tensor tractography for evaluation of white matter injury

Diffusion MRI of the brain was first adopted for the evaluation of acute ischemic stroke during the early 1990s. The advent of 3 Tesla MRI and advanced software for DTI and fiber tractography has opened an entirely new noninvasive window on the white matter connectivity of the human brain. Based on the principles of Brownian motion, imaging molecular water diffusion

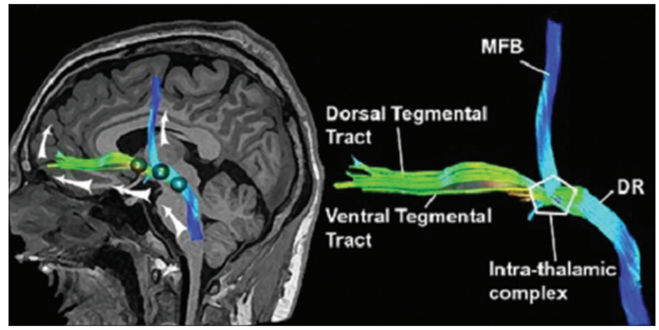

Figure 12: Tractographic reconstruction of the ascending reticular activating system by Ordóñez-Rubiano *et al.*[9] (ROI: 1 midbrain, 2 thalamus, 3 hypothalamus)

confers the ability to probe the microstructural properties of biologic tissues and diffusion ellipsoids are derived from three-dimensional Eigen vectors.[1] Fiber tracking is derived from the diffusion ellipsoids in the voxels in the ROI. Noise, patient movement, and distortion from imaging artifacts such as aneurysm clip and coil can disrupt the imaging.

Current applications of diffusion tensor imaging and fiber tractography

DWI is primarily being used as a diagnostic tool in ischemia, infection, tumors, demyelinating disease, and diffuse axonal brain injury. It is also a useful for the presurgical mapping of white matter pathways for planning the operative approach to avoid injury to the tracts. Fiber tracking in the recovery period and assessment of cognitive and motor outcome following brain hemorrhage is an evolving application of DTI.

White matter injuries in subarachnoid hemorrhage

Cognitive dysfunction is the most common morbidity after SAH, and it could be a complete loss of consciousness, Vegetative State (VS), Minimally Conscious State (MCS), amnestic state, behavioral changes, or impaired memory. Early brain injury following SAH can occur both in the white and gray matter region. Several studies have indicated that undetected WMI could be the reason for cognitive decline in these patients. WMI could be focal or global and may result from blood–brain barrier disruption, neuroinflammation, or ischemic and oxidative stress.[10,11]

Recent studies have shown disruptions in the MTT and Papez circuit following SAH. Jang *et al.* retrospectively studied 16 patients with SAH and found 62.5% of them to have injury of the MTT (decrease in FA values and reduction in volume of tract) in at least one hemisphere, which correlated positively with the cognitive dysfunction. They hypothesized that the injury could be at the point where the tract is closest to the cistern.[12] Jang *et al.* in another paper have also reported injury of the precommissural fornix in a patient with ruptured

MCA aneurysm. They observed bilateral discontinuation of the forniceal cruses and reduction in fiber volume and FA values on DTI.[13] Another study by Jang and Kim has reported reduction in the number of fibers and injury of the lower portion of the ARAS in patients with SAH.[7] Further, there is another study by Jang and Seo that evaluated multiple injuries in the dorsal and ventral ARAS in a patient with ruptured ACOM aneurysm who had intraventricular hemorrhage, SAH, and frontal ICH who underwent clipping and continued to have depressed conscious level (GCS 10). DTT done at 6 weeks revealed narrowing of the right ventral lower ARAS and decreased neural connectivity from the thalamic interlaminar nuclei to both prefrontal cortices and basal forebrains.[14] This paper highlights how multiple sites of injury must be considered in patients with decreased consciousness following aneurysmal SAH. Ordóñez-Rubiano *et al*. demonstrated damage to the tegmental tracts and middle forebrain bundle in a patient with decreased consciousness and bilateral frontal contusion following trauma.[9]

Hong *et al*. have done fiber tracking and DTI for 11 patients with ACOM aneurysm rupture who had sustained memory impairment and found decreased FA values and absent trajectory of the cingulum and the fornix in 54.5% and 63.6%, respectively, and they attributed it to perforator infarct or mechanical injury caused by the hemorrhage.[15] A case report by Jang and Yeo demonstrated damage to the Papez circuit with injury in the fornix and thalamocingulate tract in a patient who had provoked confabulations and memory impairment after ACOM rupture.[16]

White matter injury in frontal hemorrhage

With basifrontal contusions and frontal ICH, there is a definite mechanical compression of the basal forebrain tracts by the hemorrhage or disruption of the connecting fibers. Structural damage to the fiber tracts demonstrated as thinning, reduction in the volume, or absence on tractography with corresponding reduction in the mean FA values in the frontal white matter of the affected side correlated with the poor conscious level and cognitive dysfunction in our patients. Results in our paper were consistent with the literature published so far. A summary of the sites of WMI and the neurological dysfunction caused by it is given in Table 2.

White matter fiber tracking: A novel tool to predict the outcome and prognosis

Can we predict the cognitive recovery of patients with DTI? The answer is possibly yes. Although the application of DTI as a prognostic tool is still in the early phase, very promising results are being reported worldwide. By detecting the exact site of white matter disruption in the tractography, it may be possible to predict the recovery in patients with impaired consciousness and cognitive dysfunction. Identification of the WMI by fiber tracking could pave way for novel and targeting therapeutic mechanisms to prevent and repair WMI in the future. For example, the early detection of ARAS injury in SAH by DTI could play a crucial role in in early initiation of neurorehabilitative measures.[7] A recent study by Tsung *et al*. in 22 patients with brain injury showed that the DTI had a distinct advantage over the conventional CT in assessing the tract injury and can be used in formulating the treatment and rehabilitation plan.[17] More studies will be needed to arrive at a protocol-based tractography in detecting circuit and tract-specific WMI in the unconscious patient.

Table 2: Summary of the sites of white matter injury and outcome

Site of WMI	Outcome
Fornix	Memory disturbances
Commissural fibers	Memory disturbances
Cingulum	Memory disturbances
Mamillothalamic tract	Memory disturbances, amnestic syndrome
Ascending reticular activating system	Decreased arousal, minimally conscious state, vegetative state
Frontal connecting fibers and basal forebrain bundle	Cognitive disturbances, confusion

WMI – White matter injury

Conclusion

DTT is a powerful noninvasive anatomic imaging tool for the demonstration of gross fiber architecture and white matter injuries. Early recognition of WMI by fiber tractography can help in tailored pharmacologic and electrophysiologic (e.g., deep brain stimulation) treatment and neurorehabilitation program. It can also help in prognosticating the patient outcome. The limitation of our study is that only few cases were studied and a larger study would be required to conclusively prove the efficiency and specificity of DTI as a diagnostic and predictive tool. The authors plan to follow-up the cases studied at 6 months and study the recovery of WMI. In conclusion, the tractography technology and imaging software programs are rapidly evolving, and with the advent of 7 Tesla MRI machines, we could be soon looking at DTI which could precisely localize the microstructural injuries even in the smaller fibers of the white matter. WMI-targeted therapeutics could well be the future to prevent and repair the brain injury.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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