Quantification of DTT metrics in various fiber bundle in patients with frontal lobe injury and its correlation with Neuropsychological tests

M. Kumar[1], D. Pal[1], R. K. Rathore[2], B. K. Ojha[3], A. Chandra[3], R. Kumar[3], and R. K. Gupta[1]

[1]Radiodiagnosis, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India, [2]Mathematics and Statistics, Indian Institute of Technology, Kanpur, Uttar Pradesh, India, [3]Neurosurgery, Chhatrapati Shahuji Maharaj Medical University, Lucknow, Uttar Pradesh, India

Introduction: Traumatic brain injury (TBI) results from an outside force traumatically injure the brain secondary to falls, vehicle accidents and violence (1). It is known to affect cognitive, physical and psychological skills (2). MRI studies have shown that frontal lobe is most prone to injury following mild to moderate TBI. Frontal lobes play an essential role in attention, long term memory and executive functions. Conventional MRI techniques are poor in characterizing diffuse axonal injury (DAI) in patients with TBI (3). Diffusion tensor imaging (DTI) has been proposed as a noninvasive method to quantify DAI in these patients as these studies have shown white matter (WM) microstructural abnormalities, not observed with conventional MRI (4). Most of the quantitative DTI studies are based on region of interest (ROI) analysis and may not represent the true extent of DAI in these patients. Diffusion tensor tractography (DTT) helps to demonstrate structural abnormality of the whole fiber tracts and is proposed for DAI quantification in patients with frontal lobe injury to assess DAI in various fiber bundles and to look for correlation of these fiber bundles measures with various neuropsychological tests (NPT).

Materials and methods:

Human subjects: Conventional MRI and DTI was performed within 7 days and after 6 months of injury in 21 TBI patients (15 male; age range from 15-45 years) showing unilateral/or bilateral frontal lobe injury. All patients had a history of loss of consciousness at the time of injury. 21 age/sex matched healthy controls (17 males; age range from 15-50 years) were also included. Study protocols were approved by Institutional ethical committee.

Imaging protocol: T2, T1, T2-FLAIR, T2* GRE and DTI data was acquired on 1.5 T GE unit. DTI was acquired by using a single-shot echo planar dual spin-echo sequence with ramp sampling. The b-factor was set to 0 and 1000 s/mm^2; TR=8s; TE=100ms; and NEX=8. Total 36 axial sections were acquired with a slice thickness of 3mm, with zero spacing, FOV of 240mm. Fiber tracking was performed using in-house developed java based software, described in detail elsewhere (5).

Data quantification: The mouse clicks were made on mid sagittal stable fiber mass maps on corpus callosum (CC) at the level of massa intermedia. CC was divided into seven segments [rostrum, genu, rostral body, anterior mid body (AMB), posterior mid body (PMB), isthmus, splenium (SPL)] according to Witelson classification (6). The mouse clicks were made on right and left superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), limbic tracts [fornix and cingulum (CNG)] and inferior fronto-occipital fasciculus (IFO), tapetum (TP), anterior, posterior and superior thalamic radiation (ATR, PTR and STR), on those coronal stable fiber mass map where the thickness of respective fiber bundle was maximum.

NP Tests: NPT were performed in controls and patients at 6 months following injury. NPT included number connection tests (NCT A and B), figure connection tests (FCT A and B) and performance subset of modified Wechsler Adult Intelligence Scale (WAIS-P, modified for Indian population) (6).

Statistical analysis: Multiple comparisons using Bonferroni, Post Hoc tests were performed to determine the changes in DTI indices among controls, baseline and follow-up patients. Pearson correlation was also performed between DTI indices and NPT scores in follow-up patients.

Results: We found reduced fractional anisotropy (FA) and increased mean diffusivity (MD) values in all WM tracts in TBI patients compared to controls, even though the changes were statistical significant in some of the fiber bundles. We observed significantly reduced FA in CNG and IFO in patients with right frontal injury (RFI); However ILF show significant reduced FA in patients with RFI as well as left frontal injury (LFI). Increased MD was observed in SLF in patients with RFI; however STR shows significant increase MD in patients with RFI as well as LFI. We observed a significant decrease in FA in AMB, and Isthmus along with decrease in MD in AMB and PMB in patients with unifrontal injury compared to controls. We observed a significantly decreased FA in CNG, IFO, SLF, genu and SPL along with decrease in MD in TP and IFO in patients with bifrontal injury compared to controls. NPT scores were found to be significantly impaired on follow-up in patients compared to controls and some of these tests showed significant correlation with DTI indices of different WM tracts.

Discussion: The possible reasons for reduced FA in WM tracts in TBI patients are, loss of structural order or integrity of WM fiber, edema, axonal deterioration, or fiber disruption (7).We observed abnormal DTI indices in CNG and IFO in patients with right frontal lobe injury (RFI); However ILF was affected in patients with RFI as well as left frontal lobe injury (LFI). Lack of significant change in DTI indices in all WM tracts may be due to the variation in structural organization, thickness of fibers, vicinity from skull or softness of the tissue. In TBI patients, some of the WM tract shows significant difference in DTI indices between baseline study compared to control suggesting DAI. However some of the WM tracts did not show any change in DTI indices in baseline which became significant in follow-up study compare to control suggesting Wallerian degeneration. It has been shown that water diffusion in biological tissue is greater in the extra-cellular than intra-cellular space. Increased MD values correspond to an increase in extra-cellular space in these patients (8).

Patients with LFI show significant correlation of ILF with OAT (r=0.814, p≤.026) and NCTA (r= -0.627, p=.005) imply that left frontal lobe involved in attention and controlling language related movement while RFI patients show significant correlation of CNG with NCTA (r= -0.529, p=.001), NCTB(r= -0.681, p=.027) and FCTB(r= -0.953, p=.047) suggest that the right frontal lobe plays a role in non-verbal abilities. Genu and splenium were significantly correlated with NCT A (r=-0.613, p=.034 and r= -0.579, p=.049) and B (r=-0.814, p=.026 and r=-0.582, p=.047), FCT A (r=-0.582, p=.047 and r= -0.596, p=.032.), reflects the mental attention and visuo-spatial skills. SLF showed significant correlations with those NPT [BDT (r=0.560, p=.046), OAT (r=0.669, p=.012) and DST (r=0.615, p=.033)] which are responsible for motor behaviour, working memory, language articulation. The neuropsycho--logical changes were found to be more impaired in patients with bifrontal injury compared to unifrontal injury, supports that patients with bifrontal injury have more severity and more neurocognitive deficits. We conclude that DTT based approach may be more realistic in DAI assessment in TBI patients with frontal lobe injury.

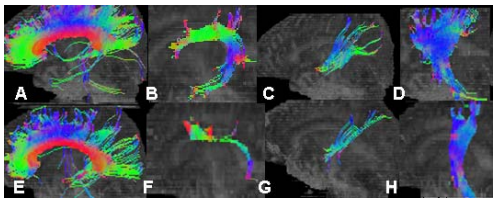

Fig: Representative fiber tractography results from a control subject (upper row) and a patient with traumatic brain injury (TBI) (lower row). Fig. A and E (CC), B and F (SLF), C and G (PTR), D and H (STR) in control and TBI patient, respectively

References:

1. Goldstein M, et al. Ann Neurol 1990; 27:327-332.
2. Fork M, et al. Brain Inj. 2005; 19:101-108.
3. Jian XU, et al. J Neurotrauma; 2007; 24:753-765.
4. Voss HU, et al. J Clin Invest. 2006; 116:2005-2011.
5. Trivedi R, et al, Pedia Res, 2009 (In press).
6. Dhiman RK, et al. J Gastroenterol Hepatol.1995; 10: 14-23.
7. Arfanakis K, et al. AJNR; 2002;23:794-802.
8. Wieshmann UC, et al, Lancet 1999; 353: 1242-1243.

Table: Bonferroni post hoc analysis of DTI indices (FA) in control and patients with frontal lobe injury (base line and follow-up)
R=Right; RA= Right affected; RNA= Right not affected; L=Left; LA=Left affected; LNA=Left not affected; FU=Follow-up

Variable	(I) group	(J) group	(I-J)	Sig.
		Unifrontal injury		
CNG	control R	baselineRIA	.026824	.036
	FU RTA	control R	-.033824	.003
IFO	control L	Baseline RA	.029596	.007
	FU RA	control R	-.023106	.482
ILF	control R	FURA	.039200	.001
	control L	Baseline RA	.031982	.015
		Baseline LA	.036057	.025
		FU RA	.046857	.000
		FU LA	.037857	.014
	Baseline RA	FU RA	.039875	.004
	FU RA	baseline LNA	-.039875	.004
		FULNA	-.032750	.046
	FU LNA	control R	-.006450	1.000
AMB	Control	FU	0.069	0.029
Isthmus	Control	Baseline	0.047	0.027
		Bifrontal injury		
CNG	Control	Baseline	.0177000	.049
IFO	Control	Baseline	.0248286	.042
SLF	Control	Baseline	.0398190	.001
	Baseline	FU	.0372357	.016
Rostrum	Control	FU	.1079714	.0359
	Control	Baseline	-.1079714	.0359
SPL	Control	Baseline	.0941933	.0293