Quantitative Evaluation of Cortico-callosal Wallerian Degeneration with Diffusion Tensor Imaging in Moderate Traumatic Brain Injury

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Introduction: Traumatic brain injury is a major cause of death and one of the most frequent neurological disorders. It is known to affect physical abilities and cognitive functions (1). TBI may result in either focal or diffuse pathology or in many cases a combination of both. These pathologies are not static but may evolve with time. In contrast to focal injury, diffuse injury is usually less evident on conventional imaging. Given the widespread interhemispheric connections that course through the corpus callosum (CC) and its primary function in mediating interhemispheric communication, callosal pathway disruptions can have a profound impact on cognitive functioning (2). Patients with TBI often demonstrate slowed information processing on neuropsychological testing. Atrophy of the CC is a documented consequence of moderate-to-severe TBI, which has been expressed as volume loss using quantitative magnetic resonance imaging (MRI). Recent studies have demonstrated the sensitivity and utility of diffusion tensor imaging (DTI) in identifying and characterizing microstructural pathologies including those occurring from TBI. In brain white matter, the principle diffusion direction corresponds well with orientation of major fiber in each voxel. Diffusion tensor tractrography (DTT) gives 3-dimensional information of white matter fiber tract. We hypothesized that the callosal FA values from the ipsi-lateral (injured) hemisphere would be lower compared to contralateral CC in the same patient and also to the CC of age/sax matched controls. Further, we hypothesized that the callosal FA values from contra-lateral normal appearing hemisphere would be lower at follow-up study compared with controls as a result of either the disruption of a normal developmental trajectory or continued degeneration.

Materials and Methods:
In this study we have included five patients (3 male, 2 females; median age, 20 years; age range, 15 to 25 years) with moderate unifrontal lobe TBI. The patients underwent both unenhanced head CT and MRI, including DTI within 7 days and again after 3 months of injury. All patients had a history of loss of consciousness at the time of injury. The severity of injury was assessed by using Glasgow Coma Scale (GCS) (3). Seven age/sex matched healthy controls (5 males and 2 females; median age 20 years, age range from 16-26 years) with no known history of neurological abnormality and with normal MR imaging were also recruited. The study protocol was approved by the Institutional ethics committee.
Conventional MRI images were acquired in the axial plane on a 3 Tesla MRI scanner (Megnetom, Skyra, Siemens). The protocol included T2-weighted, T1-weighted, Inversion recovery, SWI, and DTI sequence. DTI data were acquired using a single-shot echo-planar dual SE sequence with ramp sampling. Diffusion-weighted acquisition parameters were: b-factor= 0 and 1000 s/mm2, slice thickness=3 mm with no interslice space, number of slices=45, FOV=240 mm×240 mm, TR=8 sec, TE=100 ms, and NEX=2. Fiber assignment by continuous tracking (FACT) algorithm was used for reconstruction of fibers. Sub-regions of corpus callosum (CC) were generated and quantified by using in-house developed JAVA based software. The white matter fiber tracts were generated as described in detail elsewhere (ref). CC was further divided into the callosal fibers corresponding to injured hemisphere and contralateral normal appearing CC using in-house developed JAVA based software **(fig.1).**
Statistical analysis: Student's paired t-test was used to see the difference in mean fractional anisotropy (FA) and mean diffusivity (MD) values at base line (with in 7 days of injury) and at 3 months after injury in patients. Independent sample t test was performed to see the difference in FA and MD values between controls and patient group. A p value ≤ 0.05 was considered to be significant.
Results:
Baseline Vs Follow-up study: A significant decrease in FA value was observed in genu and rostral body of CC corresponding to injured hemisphere at follow-up study compared with baseline study **(fig.2)**. In CC contra-lateral to injured hemisphere significant decrease in FA was observed in rostral body at follow-up study compared with baseline study. In callosal fibers corresponding to injured side, an increasing trend in MD values was observed at follow-up as compared to baseline study in genu, rostral body and anterior mid body, however it did not reach at the level of statistical significance.
Control Vs Patient: At the time of baseline study only genu of injured hemisphere showed significantly decreased FA compared to controls. At the time of follow-up study significantly decreased FA with increased MD was observed in rostrum, genu and rostral body of injured hemisphere compared to controls. Significantly decreased FA in rostrum and genu contra-lateral to injured hemisphere was observed at follow-up study compared with controls. Significantly increased MD was observed in rostrum contra-lateral to injured hemisphere compared with controls at follow-up study.

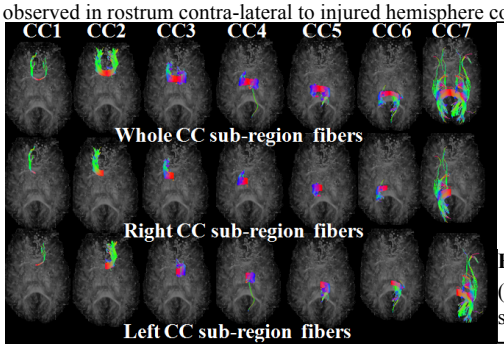

Fig.1: Demonstration of division of callosal sub-regions in right and left using automated approach.

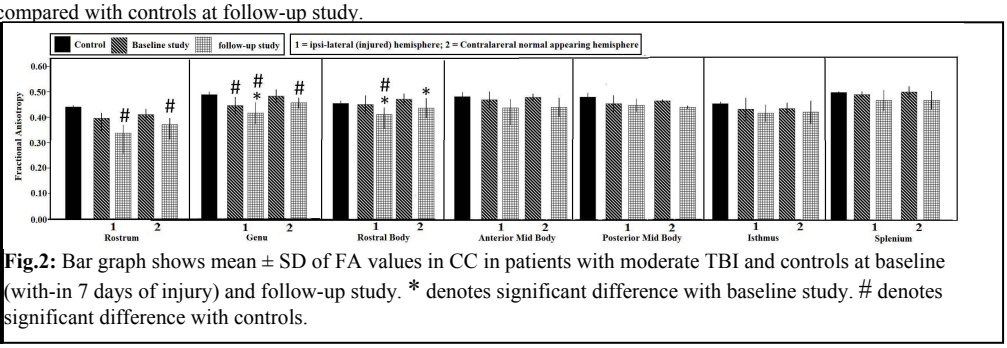

Fig.2: Bar graph shows mean ± SD of FA values in CC in patients with moderate TBI and controls at baseline (with-in 7 days of injury) and follow-up study. * denotes significant difference with baseline study. # denotes significant difference with controls.

Discussion: This study demonstrates the potential of DTT to quantify cortico-callosal wallerian degeneration at three months following closed head injury. A trend of reduced FA and increased MD values was observed in all the subregions of anterior CC corresponding to the injured hemisphere compared to both contralateral normal appearing CC sub-regions as well as controls. In addition, callosal FA values in normal appearing contralateral CC at three month of the follow-up showed decreased FA with modest change in MD values as compared to controls suggesting continued axonal degeneration. The observed decrease in FA values in the current study is presumably related to WD that results in the loss of ordered structures within the tissue, restricting the movements of water molecules, and may reflect the progressive axonal damage and/or myelin loss with time. In a histopathologic study, De Lacoste et al (ref) reported that WM fiber bundles from the inferior frontal and anterior inferior parietal regions course through the rostrum and genu of the CC; and fibers from the superior frontal and anterior parietal regions course through the anterior two-thirds of the body of CC. Reduced FA in subregions of CC suggests damage to the fronto-callosal connections in patients with isolated frontal lobe injury. Increased callosal MD values in rostrum, genu and rostral body of injured hemisphere at the time of follow-up study correspond to an increase in the extra-cellular space (vasogenic oedema). We conclude that DTT based quantification in frontal lobe injury may be useful for wide spread assessment of DAI in callosal fibers and help in prognosticating disease outcome.

References: (1) Scheid R, et al. Arch Neurol 2006;63:418-424; (2) Aukema EJ, et al. Int J Radiat Oncol Biol Phys 2009;74:837–843; (3) Teasdale G and Jennett B. Lancet 1974;2:81-84; (4) Trivedi R, et al. Pediatr Res 2009;66:636-641; (5) De Lacoste MC, et al. J Neuropathol Exp Neurol 1985;44:578–591.