Corpus Callosum Wallerian Degeneration in Unilateral Brain Tumors: Evaluation with Diffusion Tensor Imaging

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Introduction: Degeneration of white matter (WM) fibers at a distance from a primary lesion referred to as Wallerian degeneration (WD), is a common finding in many diseases of the central nervous system[1,2]. WD is characterized by a highly stereotypical course starting with the disintegration of axonal structures within days after injury, followed by degradation of myelin sheath and infiltration of macrophages with subsequent atrophy of the affected fiber tracts[3]. In ischemic stroke, WD of the corticospinal tracts is a well known phenomenon[2,4], however, only few studies have reported WD in the pyramidal tracts in brain tumors[1,2]. Corpus callosum (CC) is the largest commissural fiber that connects the homologous regions of both cerebral hemispheres and callosal axons exhibit a topographical distribution with different CC regions serving different cortical regions[5]. The white matter tracts of the CC are highly coherent which makes them well suited for study using diffsion tensor imaging (DTI). DTI is extremely sensitive to subtle differences in the architecture of white matter at the microstructural level[6]. CC white matter tracts are significantly influenced by cortical damage; a previous study demonstrated WD changes in different segments of CC in patients with large middle cerebral artery stroke using DTI at different time points[7]. The purpose of this retrospective study was to evaluate whether DTI can demonstrate water diffusivity changes in CC not visible on morphologic imaging in patients with grade IV gliomas and brain metatstases with no midline CC infiltration.

Materials and Methods: ***Subjects:*** Twenty-seven patients with treatment naïve unilateral grade IV gliomas and eleven patients with a solitary brain metastasis with no midline CC infiltration underwent DTI at 3.0 T scanner. Ten age-matched controls were also included. ***DTI data processing and segmentation of CC:*** For segmenting the CC, we used an automatic 3-dimensional level-set method that we previously introduced (Nazem-Zadeh MR et al. Segmentation of corpus callosum using diffusion tensor imaging: validation in patients with glioblastoma, submitted to JMRI 2010.) In this method, based on tensors, principal diffusion directions, anisotropy values of neighboring voxels, and prior information about the diffusivity pattern in CC, a similarity measure was proposed and used as a speed function in the level-set based algorithm. Besides, we considered two more thresholds on colinearity of the principal diffusion directions and similarity of FA values in the neighboring voxels. Subsequently, the CC was automatically divided into the Witelson subdivisions[5]. ***Statistical analysis:*** Two sample t-tests were done for the pairwise comparisons of controls, patients with GBM and metastases. P-values less than 0.05 were considered to be statistically significant and no adjustments were done for multiple testing. All data analysis was conducted using SAS (SAS version 9.2, SAS Institute Inc., Cary, NC).

Results: We observed significantly decreased FA values in all the regions of CC in patients with GBM and metastases compared to controls (Table 1). MD values showed a significant increase in all regions of CC except splenium in patients with GBM and isthmus in metastases compared to controls respectively (Table 2). However, no significant difference in FA and MD values for all the seven regions of CC was found in patients with GBM compared to metastases.

Table-1

Region	[a]Controls	[b]GBM	[c]Metastases	P values a vs b	a vs c	b vs c
CC1	0.53 ± 0.05	0.43 ± 0.11	0.42 ± 0.10	0.001	0.007	0.699
CC2	0.55 ± 0.02	0.50 ± 0.05	0.50 ± 0.05	<0.001	0.004	0.601
CC3	0.49 ± 0.04	0.40 ± 0.07	0.41 ± 0.08	<0.001	0.008	0.957
CC4	0.49 ± 0.05	0.38 ± 0.07	0.39 ± 0.09	<0.001	0.005	0.614
CC5	0.49 ± 0.04	0.39 ± 0.05	0.40 ± 0.07	<0.001	0.005	0.416
CC6	0.47 ± 0.05	0.39 ± 0.07	0.39 ± 0.08	0.003	0.015	0.884
CC7	0.58 ± 0.04	0.53 ± 0.05	0.52 ± 0.05	0.004	0.005	0.413

Table-2

Region	[a]Controls	[b]GBM	[c]Metastases	P values a vs b	a vs c	b vs c
CC1	0.70 ± 0.08	0.84 ± 0.22	0.89 ± 0.23	0.007	0.024	0.543
CC2	0.61 ± 0.05	0.67 ± 0.08	0.69 ± 0.09	0.028	0.022	0.583
CC3	0.67 ± 0.08	0.80 ± 0.15	0.82 ± 0.16	0.014	0.015	0.681
CC4	0.68 ± 0.08	0.86 ± 0.17	0.85 ± 0.16	<0.001	0.009	0.750
CC5	0.72 ± 0.09	0.89 ± 0.13	0.85 ± 0.15	<0.001	0.025	0.420
CC6	0.79 ± 0.11	0.90 ± 0.15	0.89 ± 0.16	0.041	0.116	0.799
CC7	0.64 ± 0.05	0.68 ± 0.07	0.70 ± 0.07	0.083	0.032	0.466

Descriptive statistics values (mean±SD) for FA (Table 1) and MD (Table 2) in controls, patients with GBM and metastases in seven different regions of the corpus callosum. CC1=rostrum; CC2=genu; CC3=rostral body; CC4=anterior midbody; CC5=posterior midbody; CC6=isthmus; CC7=splenium

Discussion: DTI provides information about water diffusivity within WM tracts which is based on a number of inter-related factors not just limited to tumor cell density, tumor cell invasion and edema but also includes a component of WD which has been mostly ignored by most of the researchers till now. Previous experimental studies on WD demonstrated that in WM, the anisotropy of diffusion mainly results from the axonal structures and myelin sheath[8,9]. Disintegration of the axonal structures and myelin sheath as occurs in WD, results in reduced anisotropy on DTI. In the current study, the observed decrease in the FA values is probably related to WD that results in the destruction of fiber structures within the tissue followed by gliosis and increase in extracellular matrix, disturbing the movement of water molecules parallel to the fibers rather than reduced FA seen with tissue destruction related to microscopic tumor infiltration as similar changes were seen in patients with GBM as well as in metastases. Our study showed a significant increase in MD values in all the regions of CC except splenium in patients with GBM and isthmus in metastases. This finding may be explained by a cumulative loss of cell membranes caused by the delayed damage of axons and proliferation of glial cells within the cerebral white matter. In our study, most of the patients had involvement of the frontal, parietal, parieto-occipital and temporal region secondary to a GBM and metastases.This suggests that the interhemispheric fibers from the frontal, parietal, occipital and temporal lobes that course through the rostrum, genu, rostral body, anterior midbody, posterior midbody, and splenium[10] are the most affected fibers secondary to the tumor related WD changes in these regions of CC. Our results indicate that DTI is more sensitive than morphologic MR imaging in the evaluation of changes within CC in brain tumors not infiltrating or directly involving the CC. However, these changes of DTI metrics in CC are due to WD rather than tumor infiltration as proven by our results showing similar changes in high grade gliomas as well as non-infiltrating metastases.

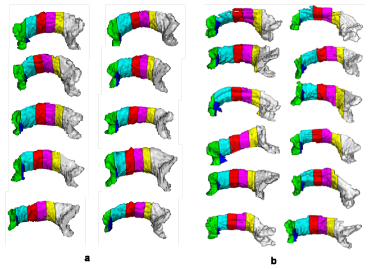

Figure 1. Segmentation results for the corpus callosum obtained by our proposed segmentation method for 10 control subjects (a) and 12 glioblastoma multiforme patients (b), not all the patients shown here.

References: [1] Lahrmann et al. J Neurooncol 2005;72:271-272 ; [2] Sawlani et al. J Neurol Sci 1997;146:103-108; [3] Johnson et al. Arch Neurol Psychiat 1950;64:105–121; [4] Matsusue et al. Acta Radiol 2007;48:690-694; [5] Witelson SF. Brain 1989;112:799-835; [6] Le Bihan D. Nat Rev Neurosci 2003;4:469–480; [7] Gupta et al. JMRI 2006;24:549-555; [8] Beaulieu C. NMR Biomed 2002;15:435–455; [9] Kreutzberg et al. Greenfield's neuropathology. 6th ed. London: Arnold; 1997. p 104-107; [10] de Lacoste et al. J Neuropathol Exp Neurol 1985;44:578-591.