Treatment-Induced Plasticity in Central Motor Pathways in Cerebral Palsy: Diffusion Tensor Imaging

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Introduction: Cerebral palsy (CP) is a heterogeneous disease and is associated with various types and degrees of motor impairment. This permanent and non-progressive disorder caused by damage to the developing brain manifests early in life.[1] Physical, occupational and constraint induced therapies are used in CP to improve the quality of life. Botulinum toxin is a treatment of choice in the clinical management of spasticity.[2] The temporary benefit of botulinum treatment can be significantly extended through activity-based rehabilitation programs.[3] We hypothesize that this treatment regimen induces plastic changes in corticospinal tracts (CST), an important part of the motor system for controlling movements.

Magnetic resonance imaging (MRI) is useful to investigate the cause and timing of injury in children with CP.[4] Diffusion tensor imaging (DTI) is a non-invasive MRI technique with the potential to probe subtle changes in the microstructural organization of white matter fiber tracts in-vivo. DTI has been used to study the plasticity of the CST in early blind patients.[5]The aim of this study is to investigate the role of DTI derived metrics to determine the clinical effectiveness of the combined therapy on motor function in children with spastic CP and determine if the improved motor function following intervention is associated with improved DTI measures of CST.

Materials and methods: The present study was carried out on 10 (male = 8, mean age = 7.2 year) healthy controls and 8 patients (male = 7, mean age = 6.13 years) with CP. All the eight patients had spastic quadriparesis with no sensory involvement on clinical examination. There was a history of perinatal hypoxic insult in all these children. Children were recruited after the age of 2 years, when the diagnosis of CP could be firmly substantiated.[6] Video gait analysis was done to resolve any intra observer discrepancies.

All patients were assessed by standard clinical examination (by a trained pediatric orthopedic surgeon), video gait examination, gross motor function classification system (GMFCS) scale [7] and modified Ashworth scales [8] (to measure spasticity) prior to and six months following intervention (botulinum injection followed by physiotherapy. The static component was treated with serial plaster for 6 weeks followed by botulinum A toxin injection (6-12 units /kg body weight depending on muscle bulk DYSPORT, IPSEN, UK). Post intervention, all patients were put on intensive neurodevelopmental therapy. All patients were sedated by intramuscular injection of ketamine (5mg/kg) and midazolam (0.1mg/kg). Oxygen supplement was given with face mask and propofol was started (1 mg/kg/hour) using MRI compatible syringe infusion pump. In controls, the MRI scans were performed without any sedation.

Conventional MRI (T1, T2, FLAIR) and DTI was performed on a 1.5 Tesla GE MRI scanner at two times – at baseline before starting any intervention and after six months of treatment. Normal healthy controls were scanned only once. All imaging was performed in the axial plane and had identical geometrical parameters: field of view (FOV) = 240 × 240 mm^2, slice thickness = 3 mm, inter slice gap = 0 and number of slices = 36. DTI data were acquired using a single-shot echo-planar dual spin-echo sequence with ramp sampling. The diffusion weighting b-factor was set to 1000 s mm^{-2}, TR ~ 8 sec, TE ~100 ms and number of excitations = 8. The diffusion tensor encoding used was a dodecahedral scheme with 10 uniformly distributed directions. The DTI data were processed using JAVA based software as described in detail elsewhere.[9] The DTI-derived maps were displayed and overlaid on images with different contrasts to facilitate the region-of-interest (ROI) placement. ROIs were placed on CST [at the five levels: upper medulla, pons, midbrain (MB), posterior limb of internal capsule (PLIC), and corona radiata (CR)] (Fig. 1). A Student's independent *t* test was performed to evaluate the differences in DTI metrics between age/sex matched controls and patients (before and after 6 months treatment) in brain parenchyma. $P < 0.05$ was considered to be statistically significant.

Results: At the time of base line study four out of eight children were classified in grade IV and after 6 months of treatment these patients were in grade III. Remaining four children were in grade II at the time of baseline study and were in grade I after 6 months of treatment.
Significantly decreased FA values in CST at all the levels were observed in baseline study compared to controls. Increased MD values were observed in CR in patients' baseline study compared to controls. On 6 month follow-up following combination therapy, significantly increased FA values were observed in CST at the level of CR, PLIC, and MB compared to baseline study (Fig. 2, 3). No change in MD values was observed in any region on follow-up compared with baseline study.

Discussion: There is a general agreement that increased FA is indicative of restoration of the integrity of white matter tracts. Therefore the increased FA in CST along with improved GMFCS score suggests that combined therapy restores the fiber tract integrity in motor pathway in these patients. Our studies demonstrate increased FA and improved motor score in all patients following the combined therapy relative to the baseline values. The observed increase in FA along with improved clinical motor scores suggests treatment induced plasticity of the central motor pathway in pediatric patients with CP after botulinum injection followed by physiotherapy.

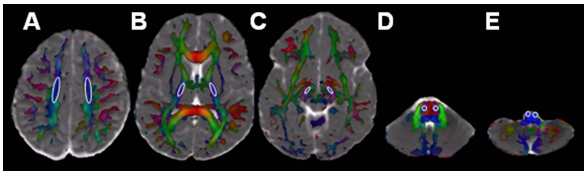

Fig.1: Color coded FA fused with MD maps from a 8-years-old healthy control showing ROI placement at the level of corona radiata (CR) (A), posterior limb of internal capsule (PLIC) (B), mid brain (MB) (C), pons (D), and medulla (E).

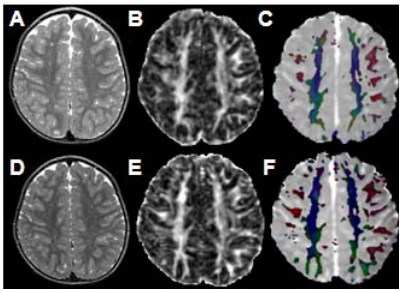

Fig. 2: T2 (A) from a 9-year-old child with spastic quadriparesis at the level of corona radiata do not show any visible abnormality. FA (B) and color coded FA fused with MD (C) shows FA distribution at base line study. After six months of botulinum injection followed by physiotherapy in the same patient. T2 (D) again shows no obvious changes compared to baseline study. FA map (I) shows increased FA values in corona radiata compared to baseline image (B). The difference is more clearly visible on colorcoded FA (F) fused with MD map.

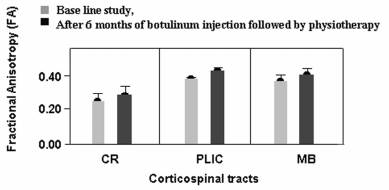

Fig. 3: FA values for different regions [CR, corona radiata; PLIC, posterior limb of internal capsule; and MB, mid brain] for patient group showing increase FA values after 6 months of treatment.

References:
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