DTI assessment of sensory-motor pathways in children with cerebral palsy

Anastasiya Batrachenko[1,2], Arnaud Guidon[1,3], Jessica Sun[4], Mohamad Mikati[5], Joanne Kurtzberg[6,7], and Allen W Song[1,8]

[1]Brain Imaging and Analysis Center, Duke University, Durham, North Carolina, United States, [2]Medical Physics, Duke University, Durham, North Carolina, United States, [3]Biomedical Engineering, Duke University, Durham, North Carolina, United States, [4]Pediatrics, Pediatric Oncology, Duke University, Durham, NC, United States, [5]Pediatric Neurology, Duke University, Durham, North Carolina, United States, [6]Pediatrics, Pediatrics Blood & Marrow Transplantation, Duke University, Durham, NC, United States, [7]Pathology, Duke University, Durham, NC, United States, [8]Radiology, Duke University, Durham, North Carolina, United States

INTRODUCTION: Cerebral palsy (CP) is a non-congenital sensory-motor disorder that affects 2-3 out of 1000 children in the US and is one of the most socially costly pediatric disorders [1,2]. Corresponding brain MRI abnormalities include white matter thinning, stroke edemas, and ventricular malformations. Particularly affected are the periventricular white matter and the corticospinal tract (CST) [3,4]. Cord blood stem cells have demonstrated promise for significant improvement of sensory-motor function in human and animal subjects with stroke and spastic hemiparesis [5, 6]. However, the exact regenerative and compensatory biological mechanisms have not yet been fully characterized in human patients. Diffusion tensor imaging (DTI) is currently the most direct method to image the strength of white matter (WM) connectivity [3, 7, 8] to assess developmental progress of the affected pediatric brain before and after the stem cell infusion. In this work, we present our recent results employing DTI to investigate CST integrity in children with CP and further correlate diffusion connectivity metrics with neurological behavioral scores in these children. Through this preliminary analysis, we demonstrate that DTI will be a valuable technique in characterizing white matter integrity in CP and could help investigate the treatment outcome during the course of cord blood stem cell therapy.

MATERIALS AND METHODS: Thus far, we scanned 19 pediatric patients diagnosed with spastic cerebral palsy (ages 1-6yrs, 9 hemiplegic, 5 diplegic, 5 quadriplegic), under sedation (in compliance with institutional IRB protocol) on 3 Tesla GE scanner. A DTI protocol with a 25-direction gradient encoding scheme was used at b =1000s/mm^2. The TE was 70.5ms, TR was 12000ms, and all images were acquired at 2mm isotropic resolution. Fiber tracking was performed in MedINRIA with FA threshold of 0.2 and smoothness factor of 20 out of 100. From the JHU MNI single subject FA template [1], standard ROIs used to determine the CST pathway were warped to each patient's image space via the LDDMM algorithm pipeline [9], and were subsequently used to delineate the CST in each patient. Total CST volumes were plotted for diplegic and quadriplegic patients against the neurological symptom severity score, and fiber volume asymmetry fractions (calculated as a ratio of affected to unaffected CST volumes to normalize for total fiber volume differences due to age) were plotted for hemiplegic patients.

RESULTS: Figure 1 compares CST distributions in a representative hemiplegic and quadriplegic patient. As shown on figure 2, there is an apparent and inverse correlation of total CST volumes and the diagnosed disease severity score in diplegic and quadriplegic subjects (r^2=0.967). In hemiplegic subjects, the CST asymmetry between healthy and affected brain hemispheres is expected to be greater in more severe cases of the disease, indicated by smaller proportion of affected CST with respect to the healthy tract volume. The observed hemiplegic asymmetry trend, however, is more complex. While most of the more severely affected subjects indeed have greater CST asymmetry than those with milder cases of CP, one of the less affected patients (subject 15) is showing unusually low affected CST volumes. Such high CST asymmetry, but in presence of advanced sensory-motor functionality, may be indicative of functional compensation of the affected body side within the ipsilateral brain CST.

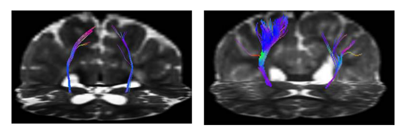

Figure 1: CST in quadriplegic (left) and hemiplegic (right) patient, color-coded by local fiber orientation

DISCUSSION: We present preliminary correlation of white matter connectivity integrity with neurological functionality scores in pediatric cerebral palsy patients undergoing cord blood stem cell treatment. Of the conventional diffusion metrics, fiber volumes of the corticospinal tract correlated with disease severity most significantly, with total diplegic and quadriplegic CST volumes showing an inverse linear relationship with increasing CP severity score. Because of the lack of normal CST within the subject for control, the diplegic and quadriplegic CST volumes were not normalized to remove the age effect. However, the decreasing trend is expected to remain due to the similar age range distribution of these patients with each CP sub-type. Hemiplegic CST asymmetry, on the other hand, seems to have similar inverse correlation with severity of the disease, but with one noticeable outlier (subject 15). A potential explanation for this observation is the possible mechanisms for ipsilateral sensory-motor functionality compensation, which would benefit from an fMRI confirmation (as a follow-up scan). In summary, as the study progresses, we anticipate that our standardized and quantitative DTI will help characterize potential causes of cerebral palsy symptoms and mechanisms of functional improvement during the course of stem cell treatment.

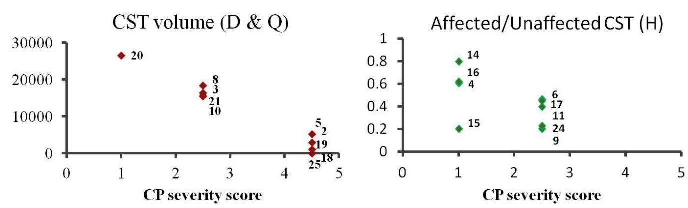

Figure 2: *Left:* Total CST volumes (left+right mm^3) vs. CP severity in diplegic and quadriplegic subjects. *Right:* Ratio of affected to unaffected CST volume in hemiplegic subjects. Numerical labels represent subject IDs in the study.

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