CHARACTERIZATION OF MILD HYPOXIC-ISCHEMIC INJURY IN MULTIPLE WHITE MATTER TRACTS IN A NEONATAL RAT MODEL BY DIFFUSION TENSOR MR IMAGING

S. Wang[1,2], E. X. WU[3], H-F. Lau[3], J. Gu[1], J. Zhou[2], and P-L. Khong[1]

[1]Diagnostic Radiology, The University of Hong Kong, Hong Kong, Hong Kong, Hong Kong, [2]Radiology, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [3]Laboratory of Biomedical Imaging and Signal Processing, The University of Hong Kong, Hong Kong, Hong Kong, Hong Kong

INTRODUCTION: Perinatal hypoxic-ischemic encephalopathy (HIE) is an important cause of neonatal brain injury, which may result in cerebral palsy, learning disabilities, visual field deficits, and epilepsy[1]. It has been known that white matter (WM) is more sensitive to hypoxic-ischemic (HI) injury than gray matter (GM). One possible reason is that there is a lack of collateral circulation in WM, and the other is that oligodendrocytes progenitors in WM are sensitive to HI insults. Diffusion tensor MR imaging (DTI) is able to detect the microstructure of WM, which can be applied to evaluate path/physiological changes in WM. In this abstract, we show that the quantitative indices of DTI are able to reflect the severity of mild HI injury in different WM tracts in a neonatal rat model.

MATERIALS AND METHODS: Seven-day-old SD rats ($n = 7$) underwent the unilateral left common carotid artery (CCA) ligation, followed by the exposure to 8% oxygen-balanced nitrogen at 37°C for 50 minutes. The rats were imaged at Day1, 7, 14, 30 and 90 post-HI, using a 7T MRI scanner (Bruker, Germany) with a microimaging mouse brain coil (for D1, D7) or a rat brain coil (D14, D30 and D90). MRI sections were performed from 2mm anterior to the corpus callosum to the end of the cerebrum. The following imaging parameters were used: TR/TE = 3000ms/32ms, FOV = 32mm^2, thickness = 0.5mm, acquisition matrix = 256×256, b value = 0 and 1000 s/mm^2. FA values were created using DTIstudio v2.4 (Johns Hopkins University, USA). FA maps were analyzed by multiple ROIs, which were manually drawn over the WM tracts, including external capsule (EC), cerebral peduncle (CP), fornix (F), optical tracts (OT) and anterior commissure (AC) of each hemisphere, using Image J (NIH, USA) according to the rat brain atlas[2] **(Fig 1**). The difference between the injured/control DTI indices was computed as (injury-control)/control×100%. Paired t-test was used to detect statistical differences between injured and control WM tracts. Trends of DTI indices of WM tracts in both hemispheres were analyzed using linear mixed modeling.

RESULTS: ***Comparison of FA values between injured and control WM tracts (Fig 2):*** **EC:** A significant decrease of FA was found in injured EC from D1 to D90 post-HI, with a maximum decrease of 8% on D1 and a minimum decrease of 3% on D90. **CP and F:** There were significantly decreased FA values in injured CP and F from D1 to D30 post-HI, with a maximum reduction of 13% and 12% on D14 post-HI. **OT**: Significantly decreased FA value was only found at D30 post-HI in OT, with a reduction of 5%. In the other time points, FA values were similar in both sides of OT. **AC:** No significant differences were found among all time points, although slightly decreased FA values were detected in injury AC.

Longitudinal trend of DTI indices (Fig 2): Longitudinal trends were similar in all WM tracts in both sides with a significant increase in FA ($p < 0.01$).

DISCUSSION: (1) Significantly decreased FA values may reflect mild HI-induced dysmyelination in selected WM tracts (including EC, CP, F and OT)[3]. (2) Longitudinal increase of FA values in both the injured and control WM tracts consists with the changes of normal development and continual maturation of WM tracts. (3) It has been found that there was significantly reduced blood flow in ipsilateral medial cerebral artery (MCA) and anterior cerebral artery (ACA) following the ligation of one side of CCA, whereas there was no significantly changed blood flow in posterior cerebral artery (PCA)[4] **(Fig 3).** It is suggested that EC, CP and F have limited collateral circulation when ligation of ipsilateral CCA. Therefore, the injury is more severe than OT and AC which have major blood supply from PCA.

CONCLUSION: The different severity of WM tract injury was observed by DTI that may reflect mild HI induced dysmyelination in WM tracts and disturbances of cerebral blood supply in this ischemic model. Our results support the use of DTI as an imaging biomarker to non-invasively monitor the severity and longitudinal changes of mild HI-induced WM injury.

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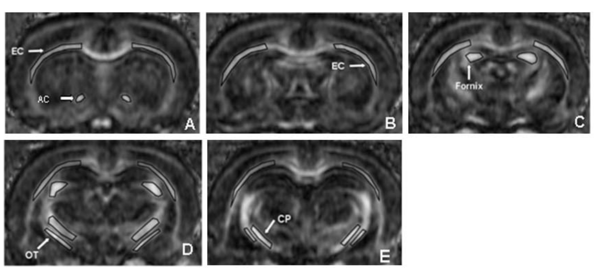

Fig 1. WM tracts and ROI location in FA maps (from anterior to posterior, A-E). External capsule (EC), cerebral peduncle (CP), fornix (F), optical tract (OT) and anterior commissure (AC).

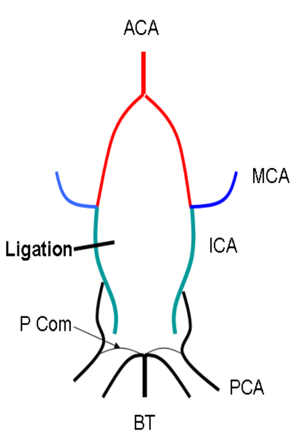

Fig 3. Circle of Willis in the rat brain. ACA: anterior cerebral artery (red line); MCA: middle cerebral artery system (blue line); ICA: internal carotid artery (green line). Ligation was performed in ipsilateral CCA; therefore, it suspended the blood supply in ipsilateral MCA and ACA. However, posterior cerebral artery (PCA) and posterior communicants (P Com) received blood supply from basilar trunk (BT); thus, WM tracts in this region were less affected.

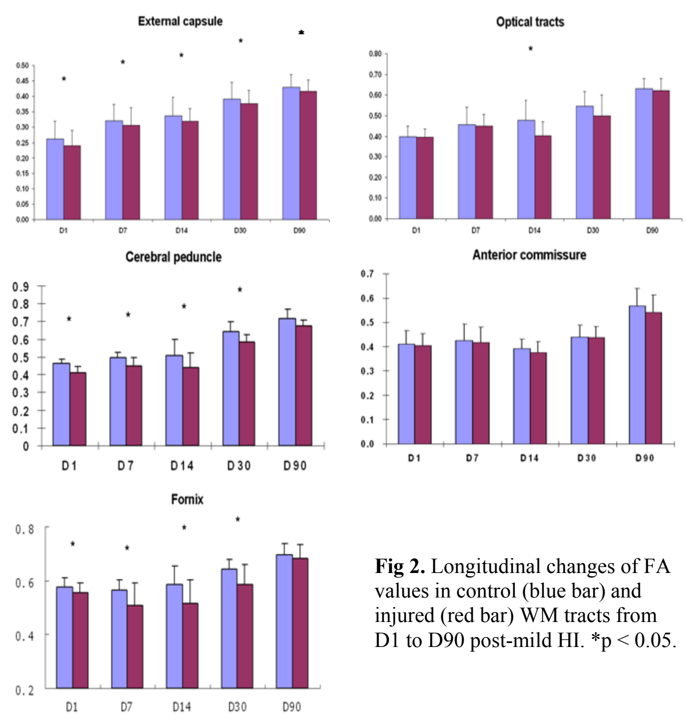

Fig 2. Longitudinal changes of FA values in control (blue bar) and injured (red bar) WM tracts from D1 to D90 post-mild HI. *p < 0.05.