MILD HYPOXIC-ISCHEMIC BRAIN INJURY IN NEONATAL RATS USING DIFFUSION TENSOR MR IMAGING: A LONGITUDINAL STUDY

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INTRODUCTION: Selective white matter (WM) injury has been found in mild hypoxic-ischemic (HI) neonatal rat brain injury (1). We evaluate the longitudinal changes in the WM of a mild HI rat brain injury model using diffusion tensor image (DTI) and correlate the findings with histology.

METHOD AND MATERIAL: Seven-day-old rats underwent unilateral left common carotid artery ligation followed by exposure to 8% oxygen-balanced nitrogen at 37°C for 50 minutes (n=9). All rats were included in the longitudinal MRI scanning at the D1, D7, D14, D30 and D90 post surgery. DTI and T2WI were performed using a 7T animal MRI scanner (Bruker, Germany) with a microimaging mouse brain coil (for D1, D7) or a rat brain coil (D14, D30 and D90). Coronal MRI sections were performed from 2mm anterior to the corpus callosum to the end of the cerebrum. Following imaging parameters of DTI were used: TR =3000ms, TE=32ms, FOV = 32mm (for D1 and D7), 40mm (for D14, D30, D90), thickness = 0.5mm (for D1 and D7), 0.7mm (for D14, D30, D90), acquisition matrix = 128 x 128 (zero filled to 256 x 256), acquisition time=8 min, b value =0 and 1000 s/mm^2. T2WI images were obtained by using the following parameters: TR=11189ms, TE=20ms, FOV=256mm, acquisition matrix=128 x 128, slice thickness=1.0 mm. FA, trace, $\lambda_{//}$ and $\lambda_{\perp}$ were created for quantitative analysis using DTIstudio v2.4 (Johns Hopkins University, U.S). Signal intensity of FA, trace, $\lambda_{\perp}$ and $\lambda_{//}$ maps were analyzed using ROI manually drawn over the external capsule (EC) of each hemisphere on 5 consecutive slices at every time point by Image J (NIH, U.S) (Figure 1). Rats (n=5) were randomly selected for histological evaluation of WM brain injury after the last scan using H&E and luxol fast blue (LFB) staining. Optical densities (OD) of LFB were measured in both symmetrical EC at 200 histological digital images by Image J for quantitative analysis. Paired t-test was used to detect statistical differences in the DTI indices and OD of LFB between two sides of EC.

RESULTS: Abnormal high signal intensity regions were demonstrated at T2WI in the ipsilateral cortex and along the WM in all rats at D1. One rat was found to have persistent abnormal signal in the cortex but not in WM at D7, and this disappeared at D30. Figure 2 shows longitudinal indices of FA, trace, $\lambda_{//}$ and $\lambda_{\perp}$ in ipsilateral (■, dashed line) and contralateral EC (▲, solid line) (★, $p<0.05$, ★★, $p<0.001$). Significant decrease in FA was found in ipsilateral EC from D1 to D30 after HI (with maximum decrease of 10.3% in D1). Apart from significantly increased ipsilateral trace at D1, similar trace was found in both sides of EC in other time points. Significantly elevated $\lambda_{\perp}$was found in ipsilateral EC in every time point with maximum increase of 13.2% on D1. Meanwhile, similar $\lambda_{//}$ was found in both sides of EC at all time-points. When evaluating the longitudinal changes of DTI indices, we found similar longitudinal trends in both sides of EC from D1 to D90; an increase in FA,a decrease in trace , a decrease of $\lambda_{\perp}$ and stable $\lambda_{//}$. Figure 3 shows sections of EC (a-f) stained with H&E (a-c) and LFB (d-f). Normal tissue morphologies were demonstrated in both EC (a-c). For LFB (d-f), ipsilateral sides of EC (f) shows decreased LFB staining density compared to contralateral EC (e). The mean OD of LFB for ipsilateral/contralteral EC was 0.39 ±0.12 vs 0.44±0.12, (p=0.043).

Figure 1

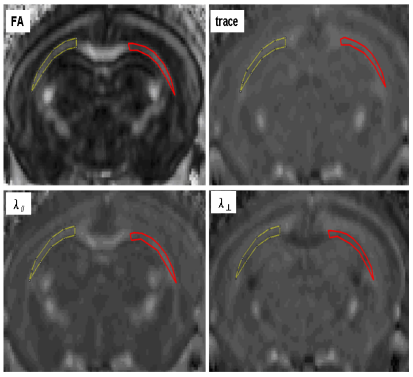


Figure 2

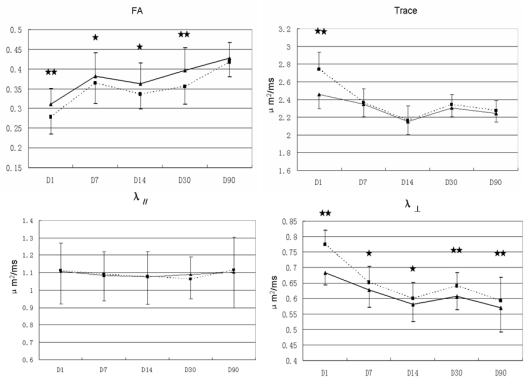
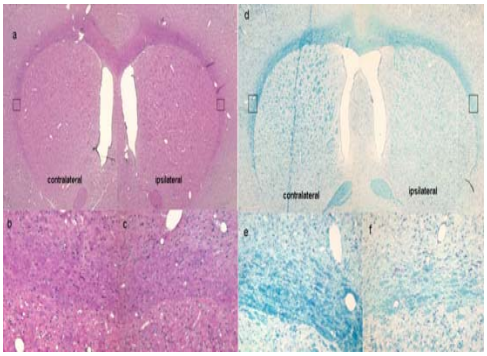


Figure 3



CONCLUSION: Significantly elevated $\lambda_{\perp}$ with no change in $\lambda_{//}$ in the ipsilateral WM suggests reduced myelination (2) in the ipsilateral WM compared to the contralateral WM as a consequence of mild HI injury. This was confirmed by LFB stain, which showed impaired myelination in the injury side. Transient elevation in trace on D1 is likely due to vasogenic edema. The longitudinal changes of decrease in $\lambda_{\perp}$, increase in FA and decrease in trace on the ipsilateral WM which parallels changes of normal development on the contralateral WM suggests continual maturation processes after HI injury although there was no catch up in $\lambda_{\perp}$ even in D90. Our findings demonstrate that DTI indices are able to reflect these processes in vivo and could provide critical diagnostic information to non-invasively monitor myelination and WM damage in mild HI.

REFERENCES: 1. Qiao M, et al. Neurosci Lett. 2004; 368:332-336. 2. Song SK, et al. Neuroimage. 2002; 17:1429-1436.