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Title: Altered fractional anisotropy caused by neonatal hypoxia ischemia is a result of increased radial diffusivity in injured white matter.
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Background: Diffusion tensor imaging (DTI) provides superior white matter (WM) contrast in the developing brain compared to standard MR sequences and demonstrates WM injury as early as 24 hours post neonatal HI. Prior work in our laboratory and from others has shown that DTI reveals progressive systems-based, connectivity mediated neurodegeneration following neonatal HI. Paired histological studies reveal loss of axonal neurofilaments responsible for structural support of the axon as an important component of HI WM injury. The WM damage following neonatal HI includes injury to both oligodendroglia (myelin forming cells) and direct axonal damage. The most common DTI index, fractional anisotropy (FA) reflects a ratio of the diffusivity along fiber tracts (axial diffusivity-Da) to diffusivity across fiber tracts (radial diffusivity-Dr) and has been used to separate direct injury to axons from injury to myelin sheaths in adult studies.

Objective: To determine the presence of abnormalities in Da and Dr in injured WM tracts following neonatal HI and the histopathologic basis for those abnormalities.

Methods: We used the Rice-Vannucci model to cause brain injury in p7 C57B6 mice and performed ex-vivo DTI and histopathology at p8, p11, p15, p21, p28, and p42 ($n \geq 4$/time point). Measures of FA, Dr and Da of the fimbria fornix (FF) and anterior commisure (AC) were calculated using in-house DTI Studio Software. Post imaging, brain tissue was sectioned and stained for either neurofilament-M (NF-M) expression or luxol fast-blue.

Results: In the contralateral FF, FA increases from p8 to p28 ($p<0.001$). Dr decreases ($p=0.002$) with no significant change in Da. By p11 and at subsequent time points there is loss of Neurofilament M and at p42 there is markedly diminished Luxol fast-blue staining in the ipsilateral FF. From p15 through p28 the FA of the ipsilateral FF is lower than the contralateral FF ($p<0.05$), Dr is increased in the ipsilateral FF (p11-p28 ($p=0.06$) , and there is no difference in Da. In comparison, the AC exhibits neither histologic nor DTI evidence of injury. Both ipsilateral and contralateral AC exhibit increasing FA values from p11 through p42 ($p=0.02$), no change in Da and decreasing Dr ($p=0.05$) consistent with normal development.

Conclusions: This study illustrates that neonatal HI blocks the normal developmental increase in FA in the injured FF during the weeks following HI, causes a loss of major neurofilament axonal structural proteins and results in loss of myelin at p42 in the ipsilateral FF. Despite histopathologic evidence for axonal injury, HI in the immature brain does not alter Da; rather it results in an increase in Dr. These results are consistent with those found in a fetal model of hypoxic brain injury, but in contrast to results in

adult models of HI. More studies are required to determine the neuropathologic substrate of alterations in FA and Dr in the developing brain following neonatal HI.