White Matter Injury Correlates with Hypertonia in a Cerebral Palsy Model

A. Drobyshevsky[1], M. Derrick[1], L. Ullman[1], I. Englof[1], X. Ji[1], A. M. Wyrwicz[2,3], S. Tan[1]

[1]Pediatrics, Evanston Northwestern Healthcare, Evanston, IL, United States, [2]Radiology, Evanston Northwestern Healthcare, Evanston, IL, United States, [3]Center for Basic MR Research, Evanston Northwestern Healthcare, Evanston, IL, United States

Introduction

Perinatal brain injury results in one of the highest index of burden of disease in view of the lifelong consequences and cost to society. Many neurodevelopmental deficits, such as cerebral palsy, are believed to be a result of prenatal hypoxia-ischemia in humans. Our laboratory has modeled *in utero* sustained and repetitive hypoxia-ischemia in the pregnant rabbit to mimic the insults of abruptio placenta and labor, respectively. Postnatal survivors exhibit multiple motor and sensory deficits, including hypertonia and postural deficits in all limbs, similar to cerebral palsy in humans.

Hypothesis

White matter injury following global hypoxia-ischemia in premature rabbit fetuses causes motor deficits in postnatal pups.

Methods

Animal surgery. In vivo global hypoxia–ischemia of fetuses was induced by uterine ischemia in timed pregnant New Zealand white rabbits at 70% (E22) gestation as described previously (Derrick et al., 2004). Briefly, a balloon catheter was introduced via the femoral artery into the descending aorta. Uterine ischemia was achieved by balloon inflation for 40 min. The balloon was then deflated and catheter removed. The dams were allowed to deliver in a nest box at term (31.5 d).

MRI imaging. Pups at postnatal ages P1 (E32), and P5 (E36) were sedated and imaged in 4.7T Bruker BioSpec scanner with custom made surface coil used for excitation and reception, inner diameter of 28 mm. DTI acquisitions were performed on 10 oblique coronal brain slices consisting of 6 non-collinear diffusion weighted spin echo images, TR/TE 2000/35 ms, with b=780 mm/s^2 and one reference image with b=0 mm/s^2; matrix size 128x64, 8 averages. Slice thickness/in-plane resolution were 1/0.156 mm for P1, 1.2/0.179 mm for P5 pups. Apparent diffusion coefficient (ADC) and fractional anisotropy (FA) indexes maps were calculated.

Results

We compared P1 pups with and without hypertonia following hypoxia-ischemia (H-I) to control pups (n=7-11/group). We found white matter injury by ADC and FA in white matter tracts in hypertonic pups compared to controls (ANOVA, $p<0.05$), while the pups without hypertonia were not different from controls. ADC was higher and FA lower in corpus callosum, internal capsule, corona radiate, and external capsule in H-I + hypertonia group (fig 1A). The hypertonic pups were then sub-analyzed on the basis of the presence of ventriculomegaly on MRI. FA decreased even further from P1 to P5 in those hypertonic pups that exhibited ventriculomegaly compared to recovery of FA in those hypertonic pups without ventriculomegaly (fig 1B).

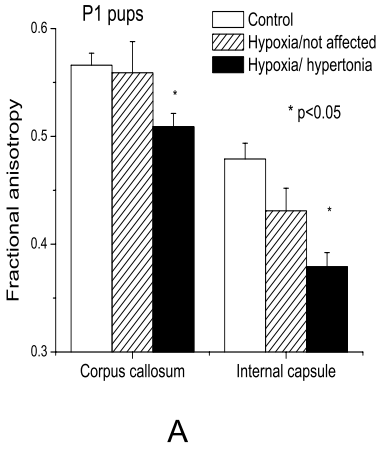
Conclusions

1) There is evidence of white matter injury by increased ADC and decreased FA following hypoxia-ischemia. The white matter changes depended upon whether there was hypertonia.
2) The continued decrease of FA with time showed that pups with ventriculomegaly failed to recover from the white matter injury. Thus the response of FA with time may be a good indicator of the plasticity of the postnatal developing brain.

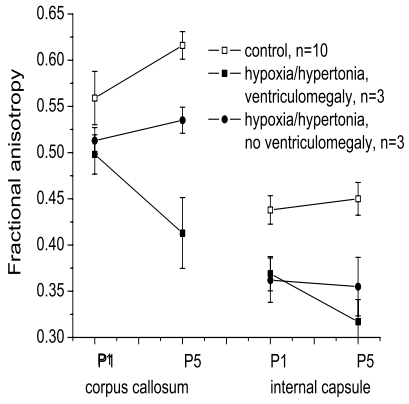
References

Derrick M, et al (2004) Preterm fetal hypoxia-ischemia causes hypertonia and motor deficits in the neonatal rabbit: a model for human cerebral palsy? J Neurosci 24:24-34.

Acknowledgements: NIH NS 43285,1 S10 RR15685



A



B