Impaired white matter development in extremely low birth weight infants with previous brain hemorrhage

Xiawei Ou[1], Raghu Ramakrishnaiah[1], Charles Glasier[1], Sarah Mulkey[1], Zhaohua Ding[2], and Jeffrey Kaiser[3]

[1]*Unversity of Arkansas for Medical Sciences, Little Rock, AR, United States,* [2]*Vanderbilt University, TN, United States,* [3]*Baylor College of Medicine, TX, United States*

INTRODUCTION Preterm birth and associated low birth-weight remains a prevalent condition despite tremendous advancement in healthcare in recent decades. Of particular concern are infants born with extremely low birth-weight (ELBW, birth weight < 1000g). White matter abnormalities are common in ELBW infants. These abnormalities can range from macroscopic injury such as cystic periventricular leukomalacia (PVL) which can be detected by ultrasound to microstructural abnormalities that can be measured by sensitive MRI methods such as diffusion tensor imaging (DTI). Intraventricular hemorrhage (IVH) is the main form of brain hemorrhage in preterm infants and mostly happens within a few days after birth. While the adverse neurodevelopmental consequence of severe IVH is recognized, the consequence of low grade IVH is less clear. We speculate that even low grade IVH is associated with white matter injury which is a known risk factor of poor neurodevelopmental outcome. Our hypothesis is that any form of hemorrhage in the brain, including all grades of IVH would be associated with white matter abnormalities at term-equivalent age.

METHODS ELBW infant were recruited for MRI examinations. Informed consent was obtained from parents, and all procedures complied with the local IRB regulations. The medical records of the ELBW infants were reviewed for cranial ultrasound diagnosis of IVH. Thirty-three ELBW infants were included in this study. Among them, seven had grade 3 or 4 IVH, eight had grade 1 or 2 IVH, nine had no ultrasound diagnosis of IVH but showed blood product deposition on MRI at term-equivalent age, and another nine had no ultrasound diagnosis of IVH and also no blood product deposition on MRI. In addition, 10 full-term healthy newborn infants were recruited to serve as controls to the ELBW infants. All ELBW infants had MRI examinations without sedation at term-equivalent age. The MRIs were performed on a 1.5 Tesla Achieva MRI scanner (Philips Healthcare, Best, the Netherlands) with a pediatric 8-channel SENSE head coil. Sagittal T1-weighted 3D reconstructed to 3 planes, axial T2-weighted, axial diffusion weighted, and axial T2*-weighted gradient echo or SWI sequences were used. In addition, a single shot spin echo planar imaging sequence with diffusion weighting gradients (b = 700 s/mm^2) uniformly distributed in 15 directions was used to acquire DTI data. The control infants had similar MRI at postnatal age of about 2 weeks.

The conventional MRI was evaluated by two experienced neuroradiologists who were blinded to the grouping information of the ELBW infants. They independently determined whether there was blood product deposition and scored the white matter for each infant. The scoring method consisted of six components: white matter signal intensity on T1 and T2, volume of periventricular white matter, presence of cysts, ventricular dilation, abnormality on DWI, and corpus callosum thickness, with each component scored from 1 to 4, corresponding to normal, mildly, moderately, and severely affected, respectively. A normal brain would have a total score of 6, while a brain with white matter injury would have a higher score. The average white matter score for each ELBW group were calculated and compared to controls by Wilcoxon rank-sum test.

The DTI fractional anisotropy (FA) maps were exported to a workstation with FSLfor tract-based spatial statistics (TBSS) analysis. Randomization with Threshold-Free Cluster Enhancement (TFCE) was used to perform voxel-wise comparison of FA values in each ELBW group vs. control infants.

RESULTS There was no difference in birth gestational age and the postmenstrual age at MRI between the ELBW infant groups. The postmenstrual age at MRI was similar in control infants and the ELBW infants. White matter scores for the control and ELBW infants are reported in Table 1. Compared to control infants, the white matter score was not significantly different in ELBW infants without blood deposition on MRI (p=0.17), but was significantly different in other ELBW infant groups (p=0.02, 0.003, 0.0001, respectively). Figure 1 shows the DTI TBSS results for the ELBW and control infants. Compared to controls, ELBW infants without blood deposition on MRI at term-equivalent age did not show any white matter region with significantly lower FA values (p<0.05, corrected). ELBW infants with old blood on MRI but no IVH diagnosis showed a few regions with significantly lower FA values (p<0.05, corrected). These regions are limited mostly to the splenium and body of the corpus callosum. ELBW infants with grade 1 or 2 IVH had widespread regions with lower FA values (p<0.05, corrected). These regions include the optic radiation, the genu, body, and splenium of the corpus callosum, the corona radiata, and the longitudinal fasciulus. ELBW infants with grade 3 or 4 IVH had even more extensive white matter regions with decreased FA (p<0.05, corrected), including most of the association, projection, and callosal fibers.

	White matter score	P-value (compared to controls)
Controls	6.0 ± 0.0	N/A
ELBW without blood on MRI	6.2 ± 0.3	0.17
ELBW without blood on MRI and no IVH	6.7 ± 0.9	**0.02**
ELBW with Grade 1 or 2 IVH	7.5 ± 1.7	**0.003**
ELBW with Grade 3 or 4 IVH	8.6 ± 1.3	**0.0001**

Table 1: White matter scores for the control and ELBW infants

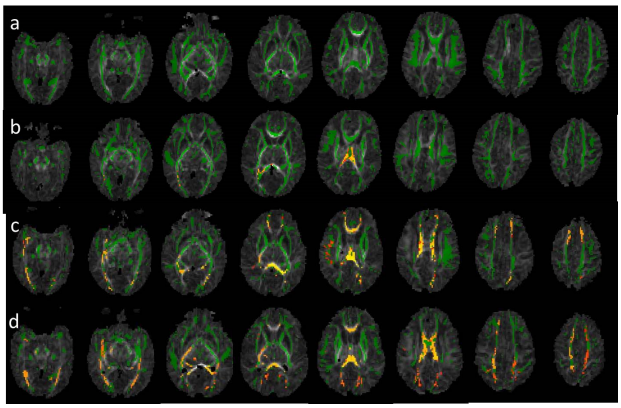

Figure 1: DTI TBSS results. Green represents the average white matter skeleton overlaid on FA images, orange/yellow represent white matter regions with significantly lower FA values (p<0.05, corrected) when compared to control infants in a) ELBW infants with no blood product deposition on MRI, b) ELBW infants with blood product deposition on MRI but no ultrasound IVH, c) ELBW infants with grade 1 or 2 IVH, and d) ELBW infants with grade 3 or 4 IVH.

DISCUSSION Our results showed that all degrees of previous hemorrhage in the brain had significant effects on white matter development in ELBW infants at term-equivalent age. Compared to term control infants, ELBW infants with no blood product deposition in the brain did not have a significant difference in white matter score or microstructural development measured by DTI, while ELBW infants with signs of previous brain hemorrhage had significantly worse white matter scores and lower FA values in many regions in the brain.

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