Alterations in water diffusion anisotropy indicate widespread cerebral white matter injury in premature infants

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Introduction: White matter injury is common in premature infants. MR studies of preterm infants at term-equivalent have shown diffuse excessive high signal intensity (DEHSI) in the white matter of the centrum semiovale on T1-weighted imaging. Further, these white matter abnormalities have been found to correlate with abnormalities of water apparent diffusion coefficient (ADC). Specifically, ADC values are reportedly higher in infants with DEHSI [1]. It has been postulated that these changes represent diffuse white matter injury in this population. In the present study, we have extended this analysis to include not only ADC values, but also relative anisotropy (RA). RA values increase with white matter maturation, particularly in association with myelination [2, 3]. Thus, diffusion weighted MR imaging (DWI) techniques offer highly-relevant information on white matter (WM) fibre tracts, providing clues on the process of myelination and the effect of white matter injury on microstructural brain development in premature infants.

Method: Diffusion tensor images (DTI) of the brain were acquired for 110 infants (19 full term and 91 preterm at term equivalent) using line scan protocol (5-6 mm thickness, axial slices, 0.5-1 mm gap, TE=78 ms, TR=2139 ms, FOV=22 cm, matrix=256x256, 2 images at b=5 s/mm^2, 6 images at b=700 s/mm^2). The diffusion gradients for b=700 s/mm^2 were oriented in six non-collinear directions. In addition, conventional T1-weighted and T2-weighted images were acquired. Quantitative measures of the water diffusion, such as apparent diffusion coefficient (ADC) and relative anisotropy (RA), were calculated from an axial image positioned above the lateral ventricles for 6 circular regions of interest (ROI) (area=15 mm^2, Fig.1). ROIs were chosen to minimize inclusion of voxels containing either cerebral spinal fluid (CSF) or gray matter (GM). A comparison of total and regional ADC and RA values was performed by dividing each hemisphere into 8 anatomical sectors (dorsal prefrontal, orbitofrontal, premotor, subgenual, sensorimotor, midtemporal, parieto occipital and inferior occipital with cerebellum), by reference to the axial plane enclosing the anterior commissure-posterior commissure (AC-PC) line and 3 limiting coronal planes [4]. The first coronal plane was positioned as a tangent to the genu of corpus callosum, the second passed through the anterior border of AC, and the third through the PC (Fig.2). A comparison of regional (dorsal, motor and parieto-occipital (PO) areas) volumes with the corresponding ADC and RA values for 27 preterm infants was performed. Student's t-tests were used to compare the ADC and RA values between the full term and the premature infants.

Results: ***ADC values*** within all regions of the white matter in the preterm group (n=85, mean ± SD, ADC=1.62 ± 0.19 μm^2/s) were significantly higher (p <0.001) than that in the full term (n=19, ADC=1.52 ± 0.16 μm^2/s) for all ROIs assessed. Specifically, the ADC values in frontal white matter (preterm: ADC=1.66 ± 0.17 μm^2/s; term=1.56 ± 0.13 μm^2/s; p<0.001), central white matter (preterm=1.53 ± 0.22 μm^2/s; term=1.41 ± 0.19 μm^2/s; p<0.001) and posterior white matter (preterm=1.66 ± 0.17 μm^2/s; term=1.58 ± 0.14 μm^2/s; p<0.005) were significantly higher for preterm infants at term equivalent compared to full term infants. ***RA values*** in the premature group (n=85, RA=9.4 ± 3.4%) were significantly lower than those in the full term (n=19; RA=11.0 ± 4.1%; p<0.005) when all ROIs were combined. On regional analysis RA was significantly lower only in the central white matter for preterm infants (preterm=11.5 ± 4.8%; term=14.9 ± 7.2%; p<0.01). The infants with white matter injury (WMI, n=6) had the highest ADC values (1.64 ± 0.21 μm^2/s) and the lowest RA values (8.6 ± 3.5%). Among the 27 preterm infants parcellated, the ADC values in the motor area were the lowest (1.49 ± 0.15 μm^2/s for the motor area *vs* 1.62 ± 0.19 μm^2/s for all parcellated areas combined, Fig.3). The RA values did not vary significantly between the regions, but the variance was high in the dorsal (9.3 ± 2.8%), motor (9.4 ± 2.3%) and PO areas (9.6 ± 2.1%).

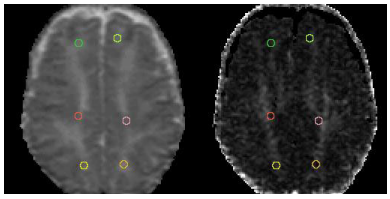

Fig. 1 ADC (left) and RA (right) showing ROIs

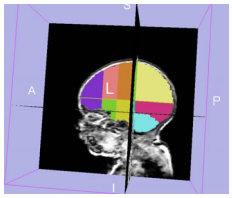

Fig. 2 Parcellation

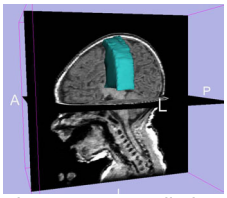

Fig.3 A parcellation volume (motor area)

Discussion: There are significant alterations of ADC and RA within the cerebral white matter of infants born prematurely at term equivalent in comparison to term born control infants. The premature infants demonstrated higher ADC values throughout the white matter, suggesting altered water content or fiber density and lower RA values that may indicate impaired white matter fiber tract development in association with prematurity. White matter injury resulted in significant alterations in white matter microstructure. Regional analysis revealed maximal alterations in the motor region.

Conclusion: This study confirms the finding that ADC values tend to be higher in white matter of preterm infants evaluated at term. In addition, RA values tended to be lower in preterm infants at term. Both higher ADC values and lower RA values are associated with more premature white matter [2, 3]. Whether these findings in this study reflect a delay in maturation versus outright brain injury can not be determined from these data. Overall, this study provides objective evidence of widespread white matter abnormality in this group of infants.

References:

[1] Counsell SJ, *et al. Pediatrics*. 2003, 112:1-7.
[2] Neil JJ, *et al. Radiology*. 1998, 209:57-66.
[3] Huppi PS, *et al. Pediatr Res*. 1998, 44:584-90.
[4] Peterson BS, *et al. J Am Medical Assoc*. 2000, 284:1939-47.