Delayed diffusion abnormalities in white matter following perinatal hypoxia-ischemic injury to central grey matter: a late therapeutic window?

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Introduction: Following severe perinatal hypoxia-ischaemia at term the most common pattern of brain injury seen on magnetic resonance imaging (MRI) is bilateral damage to the basal ganglia and thalami (BGT), which is associated with later motor impairment. However even if initial white matter (WM) appearances are normal, infants with BGT lesions often develop WM atrophy, which relates to additional cognitive impairment. We postulate that this atrophy occurs consequent on injury to the central grey matter.
Aim: This study used diffusion weighted MR imaging (DWI) to address the question: is there evidence of delayed onset microstructural abnormality in WM of infants with BGT injury and initially normal WM after perinatal hypoxia-ischaemia at term?
Methods: Ethical approval for this study was obtained from the Hammersmith Hospitals Trust Research Ethics Committee. MR imaging was performed using a 1.5 Tesla Philips Eclipse Scanner. Images were obtained with conventional T1 and T2 weighted sequences. DWI was acquired using single shot echo planar imaging (EPI) at multiple levels. Fifteen slices of 5mm thickness were obtained (TR 6000ms, TE 110ms, FOV 24cm, b values of 0 and 1000 s/mm2) in three orthogonal directions. The total acquisition time was 37 seconds. Analysis of the DWI was undertaken using in house software, and apparent diffusion coefficients (ADC) were measured using the diffusion trace maps.
Results: 28 infants with BGT lesions following perinatal asphyxia and 15 term born control infants were studied. The median gestational age for the patients was 40 (range 37-42) weeks and for the controls was 38.5 (36-43) weeks. Median age at scan was 6 days for both groups. Five infants had repeat scans On scans acquired during the first week in patients with BGT lesions the WM was visually normal on conventional MR imaging and the ADC values in WM were similar to controls. In control infants ADC values decreased with increasing postnatal age but this did not reach significance. In infants with BGT lesions ADC values increased significantly with postnatal age. In scans performed after the first week ADC values in anterior WM and posterior WM were significantly higher than both those infants imaged during the first week and from controls. $p<0.05$ In infants with repeated scans the ADC values for both anterior and posterior WM regions were increased significantly on their follow up scan ($p= 0.009$) performed after 7 days.

Region	Controls imaged <7 days N=9	Controls imaged >7 days N=6	BGT imaged < 7 days N=18	BGT imaged > 7 days N=10
Anterior white matter	1.65 (1.46-1.7)	1.6 (1.5-1.63)	1.47 (1.33-1.7)	1.73(1.57-1.85)*
Posterior white matter	1.55 (1.35-1.85)	1.53 (1.4-1.6)	1.5(1.2-1.7)	1.63 (1.45-1.85)*

Table 1. ADC x10 -3 mm2/sec values in the white matter of controls and patients * $p<0.05$

Discussion: ADC values in WM normally decrease with increasing age postnatally [1,2] We have shown an increase in ADC values in WM with postnatal age following perinatal hypoxia-ischaemic injury to the BGT. The initial ADC values in the WM were not significantly reduced compared with normal controls which, implies that there was not a direct ischaemic effect, giving rise to WM infarction which would in turn have led to increased ADC values after the first week. The delayed abnormalities within the WM may be secondary to axonal degeneration and or an effect on the neighbouring oligodendrocytes. In addition the evolution of the ADC values from normal to increased is against a primary necrotic process but would however, be consistent with apoptosis within the WM [3]. This delayed process may be amenable to interventions in the first week following perinatal hypoxia-ischaemia. These interventions would need to be targeted at WM rescue. Such interventions have the potential to alleviate the severe cognitive deficits seen in children with perinatally acquired basal ganglia and thalamic injury.

References: 1) Forbes KP et al Radiology 2002;222:405-409 **2)** Lovblad KO et al Neuroradiology 2003;43:400-403 **3)** Brauer M . Progress in Neuropsychopharmacology and Biological Psychiatry. 2003:27 323-331