Cerebral hypoxia-ischemia in neonates as a model of ischemic injury to study MR diagnosis of descending corticospinal tract degeneration

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Introduction

Recently, following neonatal cerebral hypoxia-ischemia, the descending corticospinal tract (DCST), which includes the motor fibers of the posterior limb of the internal capsule, cerebral peduncle, basis pontis and medullary pyramid have been shown to undergo acute Diffusion Weighted (DW) imaging signal changes in the paediatric human population (1,2). This may be attributed to possible early central nervous system (CNS) Wallerian or pre Wallerian degeneration detectable with acute magnetic resonance (MR) imaging. However, the tissue changes underlying the MR imaging changes in the DCST remain speculative. Indeed, we currently lack a comparable animal model to investigate such MR findings directly. We routinely perform MR imaging of cerebral changes in neonatal rats following cerebral hypoxia-ischemia and hypothesized that DW changes in the DCST similar to those observed clinically following cerebral ischemic injury would also be present in this animal model.

Material and Methods

Seven day old Wistar rat pups (n=14) were subjected to transient unilateral cerebral hypoxia-ischemia produced by occlusion of the right common carotid artery under isoflurane anesthesia followed by exposure to 65 minutes of hypoxia (3). Sham animals (n=7) underwent identification and isolation of the right common carotid artery and closure of the incision. At 24 and 48 hours following the hypoxia-ischemia, animals were anesthetized with isoflurane and T2 images of the brain were acquired using a 9.4T Bruker Biospin (Magnex) MR system. T_2 maps were determined from a set of T_2 weighted spin echo images (32 echoes, TR=5000ms, TE=10ms between echoes, FOV=2cm^2, 128×128 matrix). A set of diffusion weighted echoplanar images were acquired using five different b values (TR=5000ms, TE=40ms, FOV=2cm^2, 128×128 matrix). T2 relaxation times and apparent diffusion coefficients were calculated for each region of interest along the descending corticospinal tract in the right hemisphere ispilateral to the insult and in the left contralateral hemisphere. Left-right differences were compared using a paired t-test. Brains were processed and stained with hematoxylin and eosin (H&E) and immunohistochemically with SMI 31 antibody for axonal phosphorylated neurofilaments.

Results

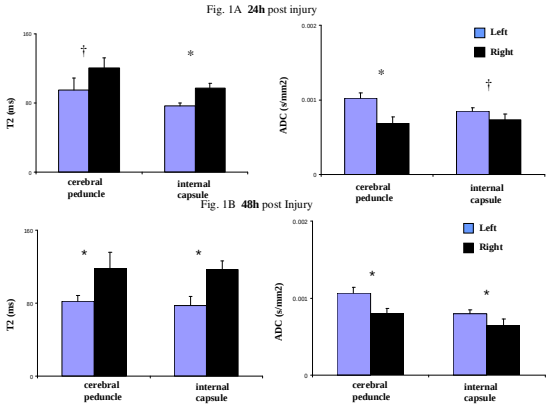

Figure 1A and 1B: Mean T2 or ADC in regions of the Descending Corticospinal Tract (Left to Right difference) to a unilateral cerebral hypoxic-ischemic insult. Values are either at **24 h** or **48 h** post hypoxia ischemia at the level of cerebral peduncle and internal capsule . (* p<0.001, † p<0.01)

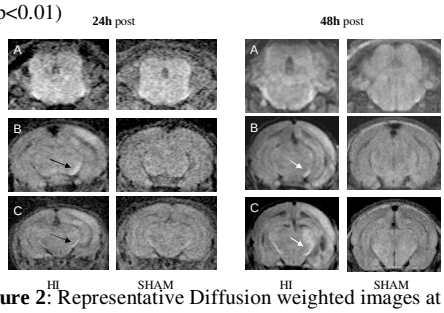

Figure 2: Representative Diffusion weighted images at the given times post surgery at medullary (A), pontine (B) and midbrain (C) levels. Arrows show cerebral peduncle and internal capsule of the DCST in B and C respectively.

T2 values in the selected regions of interest along the DCST, notably at the level of cerebral peduncle and internal capsule were significantly higher than their corresponding contralateral regions (Fig. 1 A). Likewise, their ADC values showed a significant left to right difference with lower ADC values of the DCST along the infarct side in the DWI images (Fig. 1B and 2). The shams did not show any Left-Right differences in either T2 or ADC. Histopathological analysis showed alterations in staining consistent with axonal degeneration along the DCST including ipsilateral reductions in neurofilament staining with SMI 31.

Discussion and Conclusion

CNS Wallerian degeneration is a progressive anterograde degeneration of the axon distal to the site of injury (trauma, inflammatory, hypoxic-ischemic, toxic or metabolic). Although the degenerative tissue changes may take months to years to become evident, cellular or molecular changes following neuronal injury may occur more acutely (eg. within 24 hours) (4). In our study, the increases in DWI and T2 and decrease in ADC detected are consistent with pre-Wallerian degeneration changes along the descending corticospinal tract, notably at the level of cerebral peduncle and internal capsule. These DWI and ADC changes are comparable to those observed in clinical studies. Our finding should provide a model for detailed future investigation of MR imaging as a diagnostic tool for detecting wallerian degeneration studying the underlying tissue correlates, in addition to defining its extent and progression with time. (*Supported by the Heart and Stroke Foundation of Alberta and the Alberta Heritage Foundation for Medical Research.*)

Reference: 1. Kirton A, Shroff M, Visvanathan T, deVeber G, *Stroke*, (2007); 38(3):974-80; **2**. Domi T, Kirton A, deVeber GA, Shroff M, Kouzmitcheva E, and MacGregor D; (2007); *Stroke* **3.** Meng S, Qiao M, Scobie K, Tomanek B, **Tuor UI**, *Pediatr Res*.(2006) 59: 554-9**; 4**. Vargas ME and Barres BA, *Annual Rev Neuroscience* (2007); 30:153-179.