Progression of MRI Changes and their Correspondence with Histological Changes in the Descending Corticospinal Tract following Neonatal Hypoxic-Ischemic Infarction.

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Introduction

Recent clinical magnetic resonance imaging (MRI) studies have demonstrated the presence of diffusion weighted imaging (DWI) changes that are particularly evident in the cerebral peduncle of the descending corticospinal tract (DCST). The DCST includes motor fibres of the posterior limb of the internal capsule, cerebral peduncle, basis pontis and medullary pyramid (1,2). Such imaging changes were proposed to be related to Wallerian degeneration following infarction in the cortex, although direct histological confirmation in clinical studies is difficult. Furthermore, the variability of both lesion size and location and time post insult have made it difficult to identify the progression of axonal changes following stroke in human neonates. We demonstrated recently that an animal model of unilateral cerebral hypoxia-ischemia has MR imaging changes at 1-2 days post insult consistent with those seen clinically (3). In the present study we investigate 1. both the *acute and chronic* changes in T2 and diffusion weighted images containing the DCST following a unilateral cerebral hypoxic-ischemic insult in neonatal rats and 2. the corresponding axonal changes detected histologically to provide direct evidence for Wallerian degeneration.

Methods

Seven day old Wistar rat pups (n=49) were subjected to either sham surgery or unilateral cerebral hypoxia-ischemia produced by occlusion of the right common carotid artery under isoflurane anesthesia followed by exposure to 65 minutes of hypoxia (8% O_2) (4). At 1,2,3,7 or 28 days following the hypoxia-ischemia, the rats were anesthetized with isoflurane and MR imaging scans of the brain (multiple spin-echo and multiple DWI) for determination of T2 and Apparent Diffusion Coefficient (ADC) maps were acquired using a 9.4T Bruker Biospin (Magnex) MR system with an Avance II console. Subgroups of animals were euthanized immediately post MRI and perfusion fixed brains were processed for histological assessment at various levels of the DCST. Sections were stained with hematoxylin and eosin to detect cellular changes with SMI 31 immunohistochemistry to detect axonal phosphorylated neurofilament changes and with Bielschowsky's silver stain to detect axonal fibre changes. T2 and ADC values were measured in ipsilateral and contralateral selected regions of the DCST and also within ischemic or normal contralateral parietal cortex or non-ischemic ipsilateral and contralateral pontine nuclei.

Results

Quantitation of the T_2 and ADC changes demonstrated significant changes ipsilateral to the ischemia at times as early as 1 day post-insult. Ipsilateral-contralateral differences in ADC along the DCST demonstrated early decreases, normalization and later increases by 1 and 4 weeks post insult (e.g. within cerebral peduncle and internal capsule) (Figure A). Ipsilateral T_2 was greater than that contralaterally at all time points within regions of the DCST and ischemic cortex. SMI-31 staining of neurofilaments within axons generally showed reduced intensity of staining ipsilaterally which was confirmed in Bielschowsky silver stained sections (Figure B). By one and four weeks post insult there was also a decrease in number of stained fibres indicative of a loss of axons associated with Wallerian degeneration (Figure C).

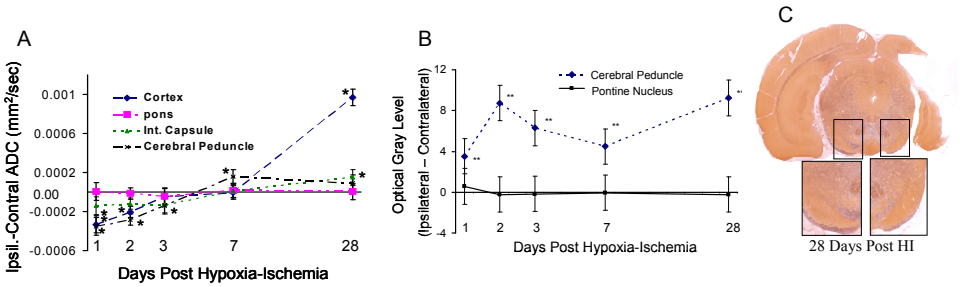

Figure. Progression of Ipsilateral (Ipsil.)-Contralateral (Contral) changes in ADC within regions of the DCST (Internal capsule and cerebral peduncle) (A). These generally corresponded to changes in axonal neurofilament staining (B) and silver staining (C).

Conclusions

This study provides the first demonstration of the progression of MR imaging changes in the DCST following cortical infarction in neonatal brain. T_2 and Diffusion weighted/ADC imaging changes occur within the DCST at either acute (1-3 days) or chronic (7-28 days) times following unilateral cerebral hypoxia-ischemia in neonatal rats. Histological staining demonstrates early loss of neurofilament staining acutely and reduced number of fibres at more chronic time points consistent with Wallerian degeneration in this model of neonatal hypoxia-ischemia. Diffusion weighted and T_2 increases and ADC decreases occur at relatively acute times post hypoxia-ischemia whereas both T2 and ADC are increased more chronically. These results should assist in the diagnosis and timing of MR imaging changes detected clinically in human neonates following stroke.

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