Progression of Magnetization Transfer Ratio Changes Following Cerebral Hypoxia-Ischemia in Neonatal Rats: Comparison of Mild and Moderate Injury Models

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Introduction

Magnetization Transfer (MT) magnetic resonance imaging is considered sensitive for detecting injury and changes of myelination in cerebral white matter. MT imaging also detects tissue changes associated with ischemic brain injury . Although studies assessing MT imaging for detection of hypoxic-ischemic injury in immature brain are limited, there is some evidence that MT imaging is sensitive for the early detection of ischemic injury following cerebral hypoxia/ischemia in infants [1] as well as in adult rats [2]. Uncertain are the evolution of MT ratio (MTR) changes following an ischemic insult and the pattern of MT imaging changes that occur following different injury severities. We hypothesized that MT ratio maps would provide a more sensitive indicator of white than gray matter ischemic injury and would detect early white matter injury better than T2 imaging. The objective of the present study was to compare the progression of changes in the MT ratio following two different severities of a cerebral hypoxic-schemic insult in neonatal rats - a mild insult that tends to produce relatively selective white matter injury and a more severe insult that produces pannecrosis.

Materials and Methods

T2 and MT imaging was performed in 40 neonatal rats at 1hr, 24hr, 48 hr, 1 week or 4 weeks after an episode of unilateral cerebral hypoxia-ischemia at 7 days of age as described previously [3]. In this model, the right carotid artery was ligated under isoflurane anesthesia and the pups were subsequently exposed to a mild insult (8% oxygen for 40-45 minutes, with chamber temperature maintained at an average of 34.2ºC) or a moderate insult (8% oxygen for 70 minutes, with chamber temperature maintained at 35.5 ºC). MT imaging was performed using a 9.4T/21cm MR imaging system with proton density-weighted spin echo single-slice and multislice acquisition, with MT saturation on and off. The imaging parameters were TR=5000ms for 60 pulses of 6μT, TE=15 ms, FOV=2.0^2 cm for 1hr-1 wk and 2.5^2 cm for 4 weeks; 128x128 matrix, 5 slices 0.8 mm thick and 1500 Hz frequency offset. MTR was calculated as MTR= $((M_0-M_s)/M_0)$ x 100%, where M_s and M_0 were the signal intensities obtained with and without MT saturation, respectively. T2 maps were obtained using a multi-echo spin-echo sequence (TE=10ms between echos, TR=2500ms). Mean ROI's from ipsilateral and contralateral regions of white matter of the external capsule and gray matter of the parietal cortex were measured. Left-right differences were compared using Student's paired two-tailed t-tests.

Results

Cerebral hypoxia-ischemia produced variable changes in MTR or T2 ipsilateral to the hypoxia-ischemia depending on insult severity and time post-insult of the scans. Following a mild hypoxic-ischemic insult, there were initially no significant left-right differences in T2 in either cortical gray matter or white matter of external capsule but there were marked increases in T2 of white and cortical gray matter at 24 hr post-insult with no significant differences at 1 or 4 weeks post-insult. In contrast, the MTR (Fig 1 A-E, Fig 2) in white matter but not cortex was decreased at 1 hr post-insult and a difference remained at 24 hr and 48 hr post-insult. At 4 weeks post-insult, MTR scans either appeared normal or had obvious white matter lesions.

Following a more severe hypoxic-ischemic insult, T2 was increased ipsilaterally at all times post hypoxia-ischemia and for both gray and white matter regions with one exception. White matter was not increased ipsilaterally at 1 hr post-insult. This corresponds to the MTR decreases observed in the moderate hypoxic-ischemic injury group at 1 hr post (Fig 1F, Fig 2). With longer recovery times, there was a progressive decrease in the MTR ipsilaterally in both cortical gray and white matter of external capsule.

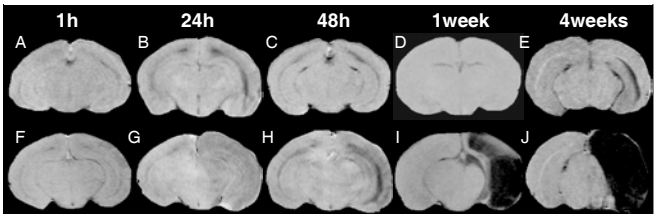

Fig. 1. MTR maps through posterior cerebrum at various times following unilateral transient cerebral hypoxia-ischemia in neonatal rats. Top Row – mild insult; Bottom Row – moderate insult.

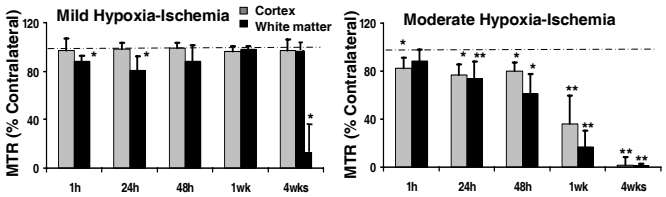

Fig. 2. MTR values as a % contralateral in white and cortical gray matter at various times following a mild (left) or moderate (right) hypoxic-ischemic insult. Regions shown are the white matter (external capsule) and gray matter (occipital cortex). *P<0.05 and **P<0.01.

Discussion and Conclusions

Both T2 and MTR imaging demonstrate progressive changes with a moderately severe insult whereas there is some normalization of MTR and T2 changes at 1 week following the mild insult. Only MTR was able to detect significant changes in white matter at 1 hr. post hypoxia-ischemia. Thus, MT imaging was sensitive for detecting the progression of hypoxic-ischemic changes particularly in white matter. The reduced MTR with hypoxia-ischemia is likely due to both edema and loss of cellular structure that differs in white and gray matter and with the severity of injury. The results support that MTR is a sensitive MR imaging method for detecting early pathological changes following HI, potentially allowing for early diagnosis and treatment for those infants affected by perinatal HI.

References

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