In-vivo Magnetization Transfer Brain MRI of Mice with Neonatal Hypoxia-Ischemia

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Summary: The objective of this study was to develop a quantitative in-vivo imaging technique for assessment of outcome in mice with perinatal brain injury. Magnetization Transfer (MT) Imaging was performed 3 weeks after a hypoxic-ischemic insult in CD-1 pups and showed decreased MTR values on the affected hemisphere as well as in the corpus callosum and internal capsule.

Introduction: Periventricular white matter disease is extremely common in extremely premature infants and often leads to cerebral palsy and severe neurocognitive disability[1]. Hypoxia-ischemia and perinatal inflammation are thought to be the leading causes of this condition. By performing unilateral carotid artery ligation followed by brief hypoxia in newborn mice we attempt to develop a mouse model mimicking this disease[2]. We conducted in-vivo quantitative magnetization transfer imaging to determine the severity of brain injury in these animals.

Methods: All experiments were performed in accordance with protocols approved by the institutional animal care and use committee. On day of life five, CD-1 pups from the Charles River Laboratories underwent right sided carotid artery ligation under Isoflurane anesthesia. This was followed with 15 minutes of hypoxic exposure by placing the pups in enclosed, vented chambers submerged in a 36 degree Celsius water bath and flushed with a humidified mixture of 10% oxygen. Thereafter, pups were returned to the dam and in-vivo imaging studies were performed at approximately 4 weeks of age under isoflurane anesthesia and compared to their control littermate.

Imaging studies were carried out on a Bruker 9.4 T horizontal bore spectrometer. A 30mm sawtooth imaging coil was used for both transmission and reception. First T2 weighted coronal images were acquired using the Fast Spin Echo sequence (4 averages, TR = 4s, effective TE= 24 ms, 4 echoes per TR, field of view = 1.8 x1.8 cm, 128 x 120 matrix,19 slices and a 9 minute scan time). In each animal, two single coronal MT weighted (MTw) images (2 averages, offset = 1.6 khz, saturation field strength = 2.2 μT, 5.5 min scan time per slice) were obtained, one at the level of the hippocampus and another image at the most anterior aspect of the corpus callosum. The same images were collected without an MT pre-pulse to obtain M_0 images at the same coronal level as the MTw.

Images were then reconstructed to 128x128 using Paravision 3 and MT ratio (MTR) maps, defined as $1 - MTw / M_0$ were calculated using software routines in matlab. MTR values were measured for each hemishphere and in 2 different ROIs (corpus callosum and internal capsule as shown in the left figure) in each slide using DTI studio.

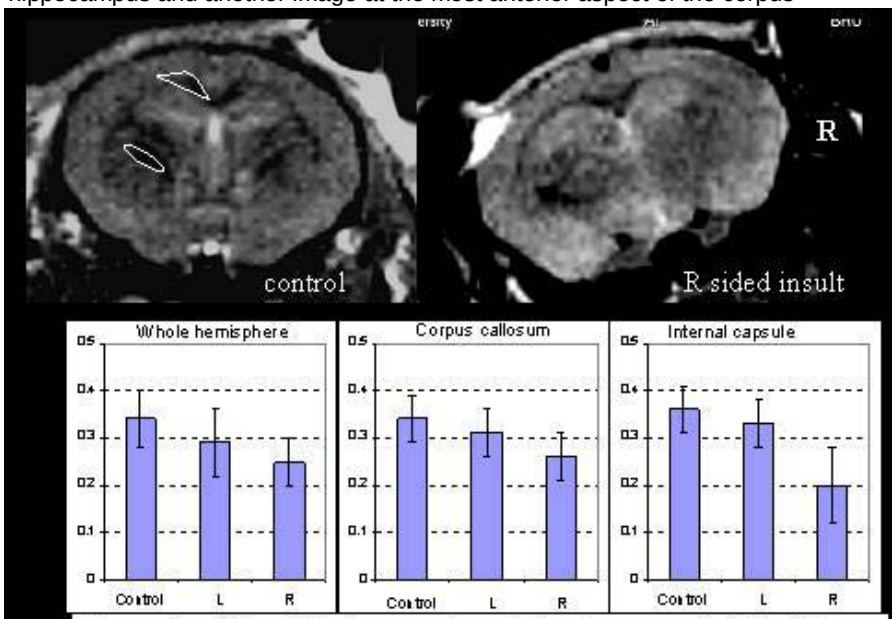

Figure: Top: MT weighted images of a control and a mouse with right sided neonatal injury as well as the ROIs selected for corpus callosum and internal capsule. Note the right sided thinning of the white matter in the internal capsule and the corpus callosum.
Bottom: MTR values (error bars: 1 STD) of the whole hemisphere, the corpus callosum and the internal capsule of the left and right side in injured mice

Results: A mild diffuse signal increase was seen in the T2 and MT weighted images in mice with neonatal brain injury compared to their unaffected littermate. In order to highlight these changes further and obtain quantitative information, we optimized the MT imaging sequence on a control mouse to maximize the white/grey matter contrast. Using this sequence, mean MTR values were lower in the white matter regions on the side of carotid artery ligation in the injured mice compared to the control. There was also a reduction of the mean right hemispheric MTR compared to the left hemisphere which was visible in the MTR maps.

Conclusion

This work is a first demonstration that perinatal brain injuries can be highlighted in mice using MT imaging. Our results suggest that MT Imaging allows a quantitative evaluation of the hypoxic-ischemic mouse brain in-vivo. This work is the first demonstration that perinatal brain injuries can be highlighted in mice using MT imaging. These images were then confirmed using histology, in both mild and severe cases. This method may therefore serve as a quantitative variable of outcome and help for monitoring of therapeutics.

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References:

1. Volpe JJ. Brain injury in the premature infant: neuropathology, clinical aspects, and pathogenesis. MRDD Res Rev 1997;3:3-12.
2. Johnston MV, et al. Models of Cerebral Palsy: Which Ones Are Best? J Child Neurol; 20; 984.