Differences in the Vulnerability of Gray versus White Matter to a Mild or a Moderate Hypoxic-Ischemic Insult Assessed with MR Imaging

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Introduction

Periventricular leukomalacia is the predominant form of white matter injury seen in pre-term infants and is the major cause of cerebral palsy associated with developmental deficits in motor, perceptual, visual or cognitive functions in later life [1]. To understand the mechanisms underlying periventricular leukomalacia and to develop optimal diagnostics or beneficial interventions, a reliable animal model for periventricular leukomalacia or white matter injury is important. Unfortunately, perinatal rodent models of cerebral hypoxia-ischemia often produce extensive neuronal injury in the gray matter without selective white matter injury [2]. Considering the fact that white matter in immature brain is quite poorly perfused compared to gray matter and immature brain has a less efficient blood flow autoregulation, we hypothesized that a relatively mild cerebral hypoxic-ischemic insult could produce more extensive injury to white than gray matter.

Material and Methods

Cerebral hypoxia-ischemia was produced in 7-day-old rats as described previously (3). Briefly, the right carotid artery was occluded under isoflurane anesthesia with subsequent exposure to 8% oxygen for either 1.5 hr at a body temperature of approx. 37-38^{o}C (moderate insult) or for 45-50 minutes at a body temperature of 36-37^{o}C (mild insult) (chamber temperature of 35.5 or 34.5 ^{o}C, respectively). At 24hrs following hypoxia-ischemia, magnetic resonance imaging with a 9.4T magnet (Magnex) equipped with an Avance console (Bruker) was performed to acquire T_1 and T_2 maps. T_2 maps were collected from a set of T_2 weighted spin echo images (32 echoes, TR=1200ms, 10ms between echoes, FOV=3cm^2, 128×128 matrix) and T_1 maps were acquired with an inversion-recovery Snapshot-FLASH imaging technique (TR=3.55 ms, TE=2.1 ms, increasing time of inversion delays of 234, 503, 831, 1233, 1751, 2480, 3728, 9226 ms). Software developed within the Inst. for Biodiagnostics was used to measure relaxation times within the regions of corpus callosum, cortex and striatum in the hemispheres contralateral and ipsilateral to the carotid artery occlusion. Changes in relaxation times were presented as ipsilateral/contralteral ratios. Tissue damage was also assessed histologically within hematoxylin and eosin stained sections to identify the region of infarct in the moderate group or cellular damage at 24 hrs in the mild group.

Results

At 24 hours after hypoxia-ischemia, neonatal rats with a mild insult had white matter regions that appeared markedly brighter than those of gray matter in T_1 and T_2-maps, whereas animals with a moderate insult tended to have brighter gray than white matter regions (Fig.1). The quantitative analysis demonstrated that during mild hypoxia-ischemia, a significant increase in the ratios of ipsilateral/contralateral T_1 and T_2 within periventricular white matter such as corpus callosum and less of an incease within gray matter such as cortex and striatum (Fig 2). Conversely, following moderate hypoxia-ischemia, the increases in ipsilateral/contralateral T_1 and T_2 were greater in magnitude in gray than white matter.

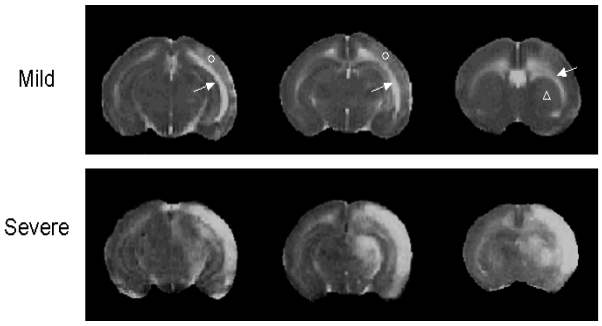

Fig1. T_2-maps obtained at 24hrs. post cerebral hypoxia-ischemia from rats with either a mild or severe hypoxic-ischemic insult. Differences in the vulnerability of gray versus white matter to a mild or a severe hypoxic-ischemic insult are apparent. Regions of interest: corpus callosum (arrow); cortex (circle); striatum (triangle).

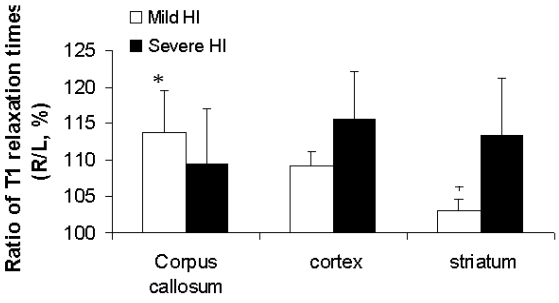

Fig 2. Analysis of gray-white matter differences as a Right (R) / Left (L) ratio of T_1 relaxation times at 24hrs. after either a mild or severe cerebral hypoxia-ischemia (HI). *p <0.05, different from striatum (gray matter) response.

Conclusions

Following an episode of cerebral hypoxia-ischemia in neonatal brain, the damaging effects within white matter as detected with MR imaging are dependent on the severity of the insult. Surprisingly, we found that a mild insult, consisting of a short duration of hypoxia-ischemia at a slightly lower body temperature, produces enhanced damage in white matter and a relative sparing of gray matter compared to a more severe hypoxic-ischemic insult. This neonatal rodent model of mild cerebral hypoxia-ischemia should prove useful for the investigation of improved methods of diagnosis, management or treatment of periventricular leukomalacia. *(Funded by the Robertson Fund for Cerebral Palsy).*

References

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