Effect of Gender on Cerebral Hypoxic-Ischemic Injury in Neonatal Brain: A Magnetic Resonance Imaging Perspective

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Introduction

Evidence in adults indicate that female sex hormones such as estrogen confer some degree of neuroprotection against damage caused by cerebral hypoxia-ischemia or stroke (1). The influence of gender in neonates differs from that in adults in that damage in neonatal males and females can be similar following a hypoxic-ischemic insult, although there are reports in studies in vivo and in vitro of gender-related differences in apoptotic pathways or differences in neuroprotection observed (2,3). Whether there are gender related differences in infants clinically is uncertain but magnetic resonance imaging (MRI) is an essential diagnostic tool that can be used to investigate this possibility. To date MRI has not been used in neonatal models to examine potential sex related differences in damage caused by cerebral hypoxia-ischmeia We hypothesized that there would be gender-differences in the extent, distribution or degree of vasogenic edema detected with MRI following a transient cerebral hypoxia-ischemia in neonatal rats. This was investigated using a 7 day old rat model and T2 imaging to determine infarct size and a measure of edema.

Material and Methods

Seven day old Wistar rat pups (n=20) 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). At 48 to 72 hours following the hypoxia-ischemia, animals were anesthetized with isoflurane and T2 images of the brain were acquired using a 9.4T MR system. T_2 maps were determined from a set of T_2 weighted spin echo images (32 echoes, TR=2500ms, TE=10ms between echoes, FOV=3cm^2, 128×128 matrix). Infarct volume was calculated as a sum of the infarct area within each of the slices in T2 images multiplied by slice thickness and expressed as a % of the volume of the contralateral normal hemisphere. T2 was measured at 72 hr post insult within the lesion of the ipsilateral parietal cortex. Differences between groups were compared using a Students t-test and considered significant at $p<0.05$.

Results

All the pups subjected to unilateral cerebral hypoxia-ischemia demonstrated regions of hyperintensity within their MRI scans involving the cortex, striatum, hypothalamus and thalamus ipsilateral to the occlusion (Fig. 1). Distribution and extent of ischemic injury detected with T2 was similar in male and female pups resulting in equivalent volumes of infarct (Fig. 2A). However, measurement of T2 values within parietal cortex in the ischemic territory demonstrated significant increases ipsilaterally ($P<0.01$) that were less in female than male rat pups (Fig, 2B).

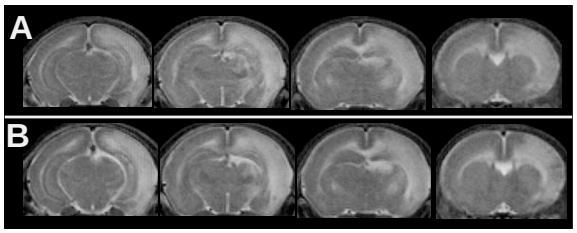

Fig. 1. Representative T2-weighted images from a female (A) and a male (B) rat pup 48 hrs after being subjected to transient unilateral cerebral hypoxia-ischemia.

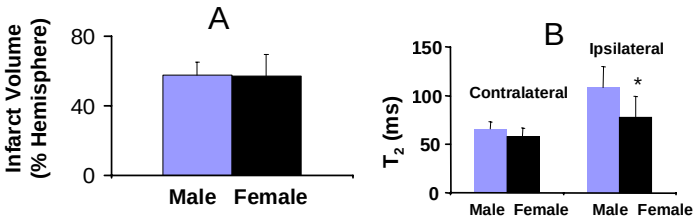

Fig. 2. Comparison of infarct lesions in male and female pups 48-72 hr after a transient episode of unilateral cerebral hypoxia-ischemia. Infarct volume (A) and T2 values (B) in the lesion were similar irrespective of gender.

Conclusions and Discussions

The present results demonstrate that in immature rats there are similar distributions and overall volumes of hypoxic-ischemic injury as detected with MRI in either male or female rats. This suggests that the vascular anatomy and areas of ischemia produced by right carotid aretery occlusion and exposure to hypoxia are similar irrespective of gender in this well established model of neonatal cerebral hypoxia-ischemia. In contrast, there was a dependence on gender of the T2 values determined in the ischemic areas indicating a greater degree of cerebral edema in males than females. This supports sex-related differences in the cellular responses to ischemia or mechanisms of cell injury or death. Is consistent with studies in neonates that have demonstrated a sexual dimorphism regarding apoptotic cell death mechanism and effectiveness of neuroprotection in immature brain (2,3). MRI can provide an important imaging modality to investigate gender influences on hypoxic-ischemic mechanisms of injury and neuroprotection in neonates.

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References

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