Age Dependent Differences in Photothrombotic Ischemic Injury Detected Using Quantitative MR Imaging

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Purpose: To determine whether there are differences in immature compared to adult brain in photothrombotic ischemic insults and their MR detection.

Background: Ischemic stroke due to thrombotic emboli is a major cause of stroke in both adults and infants. Although neonatal and adult brain have different susceptibilities to ischemic injury in white matter, few report remarkable differences in gray matter. Recently, we modified the photothrombosis method to produce varying severities of insults in adult rats with a mild lesion being associated with modest T_2 changes and scattered cell death. We hypothesized similar effects in immature brain and compared MR imaging following mild and moderate photothrombotic insults in neonatal and adult rats.

Methods: MR slices with various severities of photothrombotic ischemic lesions were produced in anesthetized neonatal (postnatal day 5) or adult rats. For the photothrombosis procedure, the skull was exposed and in adult rats the thicker skull was thinned prior to placing a mask for rectangular spot illumination. Rose Bengal was administered IV (10mg/kg) or IP (60mg/kg) in adults and neonates, respectively with similar concentrations being achieved in blood after a delay in neonates. The cortex was illuminated with white light for 5 min in adults and commonly from 5-15 min in neonates. MR scans were acquired the next day using a 9.4T Bruker MR system consisting of a T_2 spin echo sequence (10ms echo spacing, 32 echoes) and an echoplanar diffusion sequence (5 b values) allowing the determination of T_2 and Apparent Diffusion Coefficient maps. Regions of interest were identified using the hyperintense lesion area in DW images. T_2 was measured within this lesion area, in regions of adjacent deeper cortex and within normal control cortex.

Results: The modified photothrombotic model produced lesions of mild and moderate severity. Previous studies found that the mild lesion in adult rats was associated with complete or partial cortical reperfusion. Mild lesions in neonatal cortex routinely consisted of small hyperintense regions of DW increase that corresponded spatially to marked increases in T_2 (Fig). In contrast, mild lesions in adults had a hyperintense region on DW corresponding to a marked T2 increase accompanied by modest T_2 increases beyond the DW lesion border. When lesions were grouped into moderate and mild, with mild lesions consisting of hyperintense DW lesions of <1mm^2 area with a T_2 change of <50% greater than control, the groups consisted of DW lesions in neonates and adults of respective similar mean size for mild lesions (0.5 ± 0.4(n=4) ; 0.5 ± 0.3 mm^2 (n=5)) and moderate lesions (1.3 ± 0.4 (n=8);1.7 ± 0.5 mm^2 (n=8)) mm^2. Quantitatively, there were marked T_2 increases (mean >40%) above control regions within the DW lesion area of the mild group irrespective of age. In contrast adjacent cortex had elevated T_2 only in mature brain (Fig I). Similar differences in the neonatal and adult animals in T_2 changes within cortex adjacent to the DW lesion region were observed in the moderate lesion size groups.

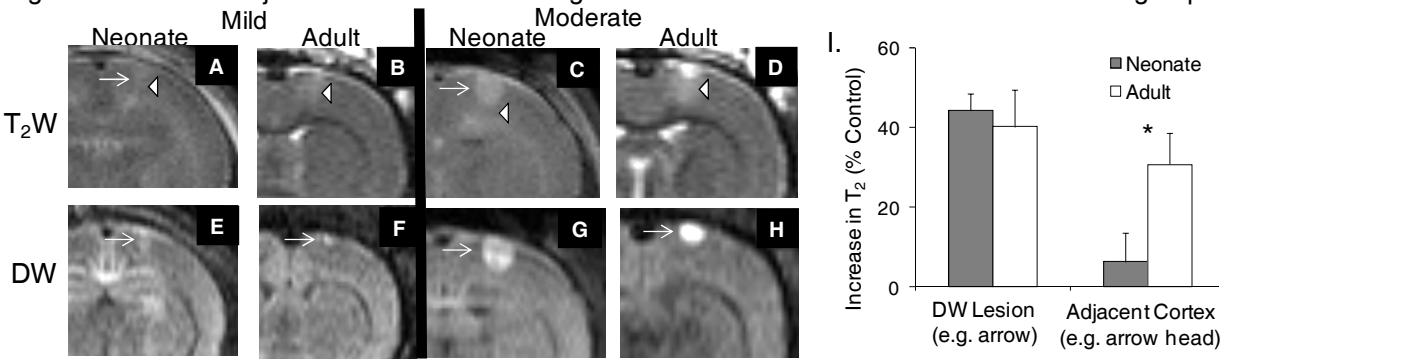

*Fig. Mild and Moderate Photothrombosis lesions in neonatal and adult rats. Representative T_2 weighted(A-D) and Diffusion Weighted (DW, E-H) images of a mild lesion (A,B,E,F) and a moderate lesion (C,D,G,H) one day post insult. The lesion core (arrow) is readily observed as hyperintense areas in DW images. Modest T_2 increases adjacent to the hyperintense DW area in deeper cortex is commonly observed in adult and not neonatal brain. This was confirmed by differences in quantitative measures of T_2 in neonates compared to adults(I). *P<0.006, Neonatal different from adult. Bonferroni corrected Student's t-test.*

Discussion: The results demonstrate that there are differences detectable with MRI regarding the ischemic injury produced by photothrombosis depending on the maturity of the subject with T2 imaging being more sensitive for detecting ischemic injury in mature adults. The reason is unclear but may reflect developmental differences including: 1. that immature animals have a much lower resting cerebral blood flow and blood pressure than adult s, 2. that there is less spontaneous lysis of the thrombotic clots in neonates representing permanent occlusion whereas there is reperfusion injury in adults and/or 3. there are different endothelial effects of Rose Bengal on the formation of thrombus. Irrespective, this model provides a promising approach to study thrombotic occlusion and reperfusion injury and its MR diagnosis; the use of quantitative T2, DW and ADC and their histological correlates deserving further investigation. The histological changes that underly these MR differences will be of interest and relevance considering the increasing efforts to treat more patients with thrombolytics or endovascular therapy not only in the elderly but also in pediatric stroke patients.

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