Non-invasive Monitoring of Niemann Pick type C Disease in Mice with Diffusion Tensor Imaging

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Introduction

Niemann-Pick Type C (NPC) disease is a presently untreatable, homozygous recessive disorder in the intracellular trafficking of low density lipoprotein derived cholesterol [1]. Patients with this disease accumulate excessive amounts of unesterified cholesterol in several organs, including the brain, and usually die before puberty. Many potential therapies are under development which necessitates a method by which drug response can be monitored. Because of the significant neurodegeneration associated with this disease, we have begun evaluating diffusion tensor imaging (DTI) as non-invasive tool to monitor the progression of NPC in a mouse model. For this initial study we carried out DTI experiments in eight mice (four NPC and four wild-type) and compared quantitative measures of anisotropy between them.

Methods

Npc1^{NIH} mutant mice from the BALB/cJ background were maintained by brother-sister mating of heterozygous animals. Animals were maintained at the University of Arizona Animal Care Facility on mouse chow containing 6% fat (or 10% for breeding mothers) and water *ad libitum*. At weaning (about 21 days of age), tail tips were removed from mice and genotypes were identified using polymerase chain reactions (PCRs) at the *Npc1*^{NIH} locus. MRI was carried out on wild type and late stage NPC mice, 69-74 days old, using a Bruker Biospec 4.7T instrument with 200 mT/m shielded gradients. Animals were anesthetized by isoflurane gas and placed into a homemade mouse holder which fit snuggly into a 24 mm volume RF coil (Doty Scientific Inc.). Body temperature was monitored using a fiber optic rectal probe and maintained using a circulating water bath. DTI was carried out in the axial plane using a diffusion-weighted radial FSE sequence [2] with the following parameters: TR = 1 s; TE_{ave} = 52 ms, echo spacing = 13 ms, ETL = 2, matrix 256 × 256, FOV = 2.56 × 2.56 cm^2, slice thickness = 1 mm, slice gap = 1mm. A total of seven images sets were collected, one without diffusion weighting and six with diffusion weighting (b = 1010 s/mm^2, Δ = 30 ms, δ = 5 ms) along 6 non-colinear gradient directions [3]. The total scan time was 2 hours. Diffusion anisotropy parameters, RA, FA and ADC were calculated using standard algorithms on a pixel-by-pixel basis using programs written in IDL.

Results

Fig.1 shows a T2 weighted image and ADC, FA and colorized directional diffusion maps from the brain of a NPC mouse. A high level of anisotropy is measured in several areas of the brain including the corpus callosum, external capsule, cerebral peduncle and cingulum. Histograms of the DTI parameters (FA, RA, ADC) for all the slices indicated that WT mice had values of RA and FA higher than the NPC mice. Pixels with FA > 0.6 have been shaded red and are overlaid onto T2 images of WT and NPC mice in Fig. 2. There are an insignificant number of pixels with high FA in NPC mice compared to WT mice, which could indicate demyelination /degeneration of white matter structures. Furthermore, the regions of abnormality are primarily in the cerebral peduncle and corpus callosum. However, it is also apparent that, for the same age mouse, the brain sizes of NPC mice are smaller than WT mice.

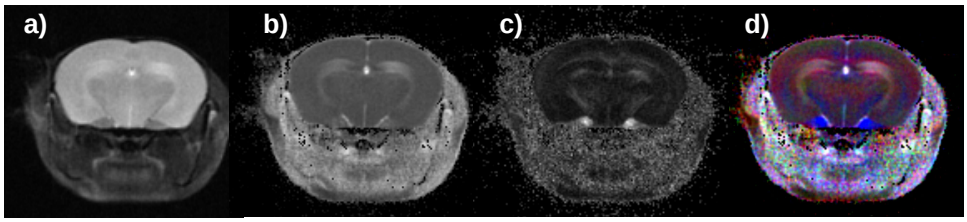

Fig. 1. (a) T2 weighted image and DTI maps: (b) ADC, (c) FA, and (d) directional diffusion (red:green:blue = R/L:A/P:C/R-direction) of an NPC mouse brain.

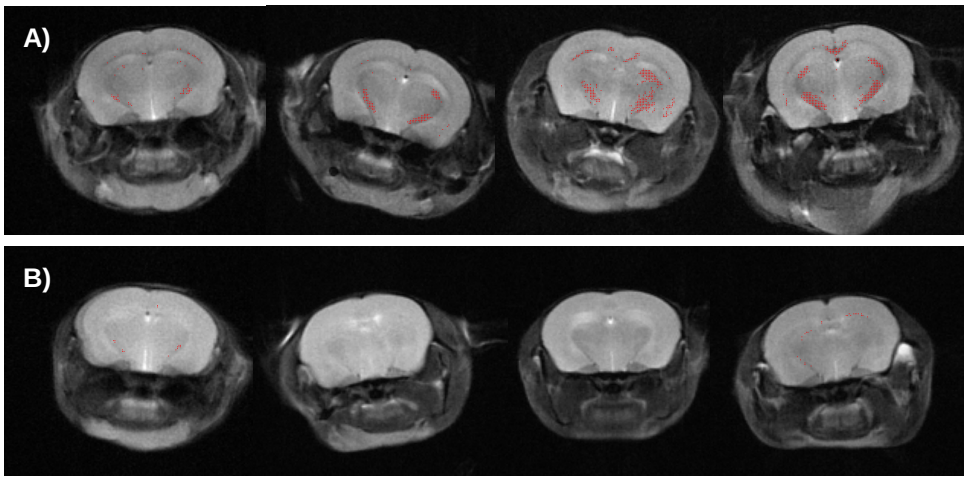

Fig. 2. FA maps of A) wild type mice and B) NPC mice. Pixels with FA > 0.6 are shown in red, overlaid on T2-weighted anatomical images.

Conclusions

These results, although preliminary, indicate that DTI has the sensitivity to quantitatively monitor changes in the brain of NPC mice. Because DTI methodology is readily transportable to human studies, these results have significant clinical importance.

References

[1] German et al., J Comp Neurol 433:415 (2001), [2] Trouard et al., *MRM* 42:11 (1999) [3] Hasan *et al*., *JMRI* 13:769 (2001).

Acknowledgement

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