Longitudinal Magnetic Resonance Spectroscopy and T2 Measurements in a Mouse Model of Niemann-Pick Type C Disease

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Introduction

Niemann-Pick Type C (NPC) disease is a rare autosomal recessive neurodegenerative disease which involves impaired transport of intracellular lipids and accumulation of unesterified cholesterol in lysosomes and late endosomes in cells throughout the body [1]. NPC disease symptoms, including progressive ataxia, developmental dystonia, and dementia, often appear in the first decade of life, and the disease is often fatal by the end of the patient's teenage years. No effective treatments are currently available, but several have been proposed and are in various stages of development and testing in animal models. Reliable and quantitative non-invasive imaging techniques that can track the progression and response to treatment of NPC disease will be valuable in both preclinical animal model studies and clinical studies.

Abnormal myelination has been reported in a case study of clinical NPC disease using Diffusion Tensor Imaging (DTI) [2]. Dismyelination in a mouse model of NPC disease has been reported shortly after weaning at 23 days of age and quantified with DTI experiments [3], but required 3 hours of scan time. Magnetic resonance spectroscopy (MRS) has been used in studies of several mouse models of neurodegenerative diseases [4], and in clinical studies of Niemann-Pick Type C disease [5,6,7], but has not been reported in the NPC mouse model. In this work, a longitudinal study of T2 mapping and MRS measurements in a mouse model of NPC disease has been performed to examine T2 relaxation and brain metabolite levels as possible indicators of disease progression and response to therapy.

Methods

Age matched wild-type (WT) control mice and NPC disease model mice (NPC) were scanned at weekly intervals from 22-43 days of age, and again at 64 days of age. Experiments were carried out on a 7T Bruker Biospec equipped with a four element phased array receive-only surface coil. Animals were anesthetized with isoflourane gas and placed into an animal bed restraint system. Body temperature was monitored with a fiber-optic rectal probe and maintained at 37° C with circulating hot water.

T2-weighted datasets were collected with a 2D radial fast spin-echo sequence using imaging parameters: TR=5000 ms, ETL=8, 1024 radial lines with 170 data points collected per line, resolution=100x100x500 um^3, and a scan time of 10:40 (min:sec). A reconstruction method taking advantage of the oversampling of the center of k-space in radial sampling [8] was used to obtain eight images with varying TE values, and calculate T2 maps from 21 coronal slices within the brain. A region of interest analysis was used to obtain T2 values from the white matter areas of the external capsule, corpus callosum, and cingulum, while avoiding inclusion of ventricular spaces.

MRS datasets were collected with a point-resolved spectroscopy (PRESS) sequence, and the following acquisition parameters: TR=2500 ms, TE=20ms, 2048 points covering a spectral width of 4 kHz., and 250 averages for a scan time of 10:35 (min:sec). 3mm cubic voxels were placed in the cortex and cerebellum areas of the mice on which the FASTMAP shimming procedure was used. Spectra were analyzed by calculating the ratio of the metabolite peak signals to that of the unsuppressed water signal from the spectroscopic voxel.

Results and Discussion

Results from the T2 study are shown below in Fig. 1. T2 values in white matter differ significantly between the WT and NPC groups at all time points studied. T2 relaxation times in both NPC and WT mice decrease with age. Relative metabolite peak intensities are shown in Fig. 2 for the spectral peaks corresponding to the metabolites Choline (Cho), Creatine (Cre), N-Acetyl Aspartate (NAA), and lipid peaks at 1.3 and 0.9 ppm. None of the metabolite levels are significantly different between the two groups of mice. From these results, it is likely that quantitative T2 mapping could play a role in non-invasive evaluation of NPC disease and its response to therapy while MRS measurements appear to lack the sensitivity to the disease.
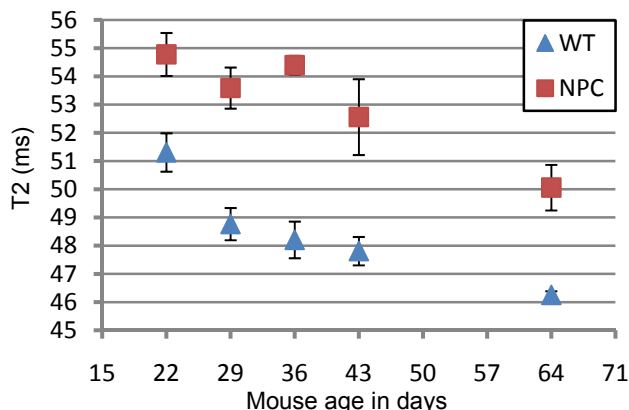

Figure 1. Values of T2 in white matter regions of groups of WT and NPC mice at 5 ages. T2 differences between the groups are significant at all timepoints (P<.005).
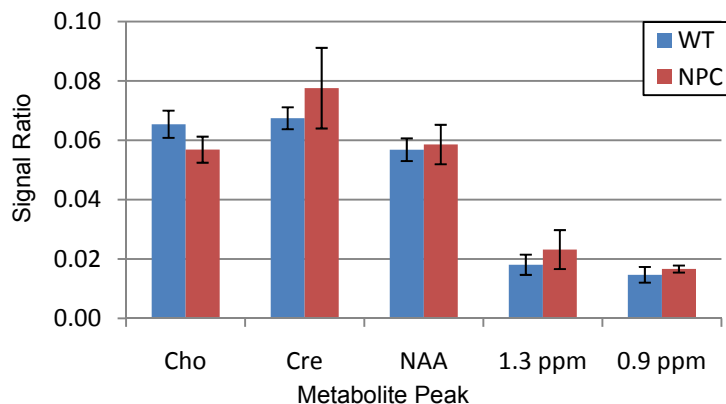

Figure 2. Relative metabolite measurements from 3mm cubic voxels in the cerebellum of 64 day old WT and NPC mice, differences between WT and NPC mice did not reach significance.

References

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