MRS Measurement of Disease Severity in Niemann-Pick Disease Type C

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Introduction: Niemann-Pick disease, type C (NPC) is an autosomal recessive neurovisceral lipid storage disorder, involving liver, spleen, lungs, and brain, characterized at the cellular level by accumulation of unesterified cholesterol and glycolipids in the lysosomal/late endosomal system (1). Onset of symptoms is usually in childhood; rate of progression is reported to be variable, and patients can survive into adulthood. Neurologic findings follow a progressive degenerative course. Brain imaging findings are nonspecific; scans are often normal, or may demonstrate atrophy of the cortex or cerebellum. Severe cases can have MRI signal abnormalities in the white matter (1). As atrophy and white matter signal changes represent late stages of organ injury and are not easily quantified, we sought a more readily quantifiable MR-based method to enable therapeutic monitoring. We are attempting to develop MR based quantitative measurements for the assessment of disease severity using magnetic resonance spectroscopy (MRS), correlating the results to each patient's symptom based severity score.

Methods: *Subjects*. 18 patients with NPC (11 M, 7 F; age range 3-51, median 10 years) were studied. Patients or their guardians signed IRB-approved consent to participate. As part of an ongoing longitudinal study, the current report includes data from 1-3 visits per patient, for a total of 31 patient visits. *Clinical evaluation.* At each visit, patients underwent history and physical examination, with particular attention to neurological findings. Objective tests included evaluations of hearing, cognition, and eye movement. We generated a severity score for each patient that was based on clinical findings and symptoms, to combine the results of 17 different evaluations. *MRI and MRS*. Scanning was performed on a 3T Philips Intera scanner, with 6- or 8-channel SENSE head coil. Most of the patients required sedation with propofol. Clinical MRI examination included T1-weighted, T2-weighted, FLAIR, and high-resolution MP-RAGE images, without intravenous contrast material. Single voxel spectroscopy was performed on voxels graphically prescribed from the MP-RAGE images (PRESS localization; CHESS water suppression; TE=38ms; TR=2000ms; 128 NEX). An unsuppressed water spectrum (TR=5000ms, TE=38ms, 16 NEX) was also acquired for each voxel. 4 voxels were acquired for each patient: superior cerebellar vermis, left cerebellar white matter, left centrum semiovale, and midline parietal gray matter. Most voxels were approximately 20 x 20 x 20 mm in size (range 5.6 – 9.5 cm^3, mean 7.5 cm^3), although the dimensions were adjusted to match the size and shape of the targeted anatomical area. In order to correct for CSF included within the voxels, we acquired a heavily T2-weighted image with location and slice thickness corresponding to the location of each spectroscopic voxel (FSE; ETL=8; TE=500ms; TR=3000ms). A phantom containing water was placed beside the head and included in the field of view. *Processing*. We estimated concentrations of myo-inositol, total choline containing compounds, creatine, NAA+NAAG, Glu+Gln, and lactate using an automated fitting routine, LCModel (2). Referencing to the unsuppressed water peak and correction for T1 and T2 decay allowed absolute quantitation of metabolite levels. The levels were corrected for CSF partial volume according to the method in reference 3. Linear regression analysis (using SPSS) was performed to examine for correlation between metabolite levels and clinical severity scores.

Results: Statistically significant ($p<0.05$) correlations were found between severity score and NAA+NAAG (tNAA) in the superior cerebellar vermis and in the left cerebellar white matter (plots are shown in the figures). Although tNAA had a declining trend at the other two locations, the correlation was not strong enough to reach statistical significance.

Discussion: NAA is contained almost exclusively within neurons and is generally taken to be a marker of neuron health. That, of the metabolites studied, only NAA is affected fits with the understood mechanism of injury of this disease, which is neuron loss due to injury by lipid deposition. The mouse model of this disease shows that affected mice have smaller brains than controls, with atrophy of the cerebellum and midbrain. Progressive neuronal loss, particularly of Purkinje cells, is a prominent feature. Demyelination is also present (1). Lack of correlation of the other metabolites is consistent with lack of certain other features (such as glial cell proliferation, inflammation, depletion of energy stores, or derangement of glucose metabolism), which if present, would cause derangements of other metabolites. Establishment of a reliable quantitative measurement, such as tNAA levels, related to disease severity could be useful as an objective means of monitoring progression of the disease and monitoring response to treatment.

References:

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