Measurement of Disease Severity in Niemann-Pick Disease Type C Using 3T MRS

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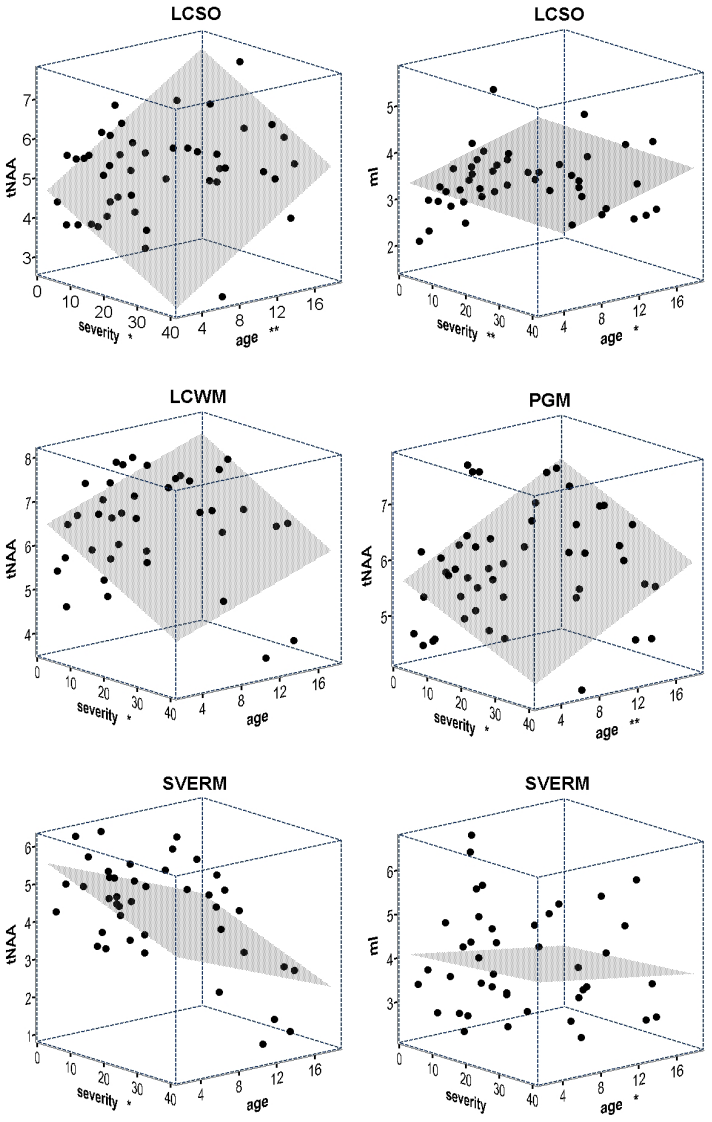
Introduction: Niemann-Pick disease, type C (NPC) is an autosomal recessive neurovisceral lipid storage disorder, involving liver, spleen, lungs, and brain, characterized at the cellular level by accumulation of unesterified cholesterol and glycolipids in the lysosomal/late endosomal system (1). Onset 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 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*. 23 patients with NPC (12 M, 11 F; age range 1-20, median 8 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 1-5 visits per patient, for a total of 49 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 – 10.4 cm^3, mean 7.7 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 (tNAA), Glu+Gln, and lactate using LCModel (2). Referencing to the unsuppressed water peak allowed relative quantitation of metabolite levels. The levels were corrected for CSF partial volume according to the method in reference 3; however, correction for T1 and T2 decay was not performed due to lack of available relaxation times for the metabolites *in vivo*. ANCOVA analysis (using SPSS) was performed to examine for correlation between metabolite levels, age, and severity scores.



Results: Statistically significant ($p<0.05$) correlations were found at several locations: in the left centrum semiovale (LCSO), both age and severity score correlated with myo-inositol and tNAA ($p<0.001$ for all 4 correlations); in the left cerebellar white matter (LCWM), there was a correlation between severity and tNAA ($p=0.019$); in the midline parietal gray matter (PGM), there was a correlation between tNAA and both age ($p=0.005$) and severity score ($p=0.046$); in the superior cerebellar vermis (SVERM), there was a correlation between age and myo-inositol ($p=0.014$), and a correlation between severity score and tNAA ($p=0.012$). Plots are shown in the figures. Significant negative correlations are marked * and significant positive correlations are marked ** on the axis label.

Discussion: NAA is contained almost exclusively within neurons and is generally taken to be a marker of neuron health. Our finding of a negative correlation between tNAA and severity at all 4 locations fits with the understood mechanism of injury of this disease, which is progressive neuron loss due to injury by lipid deposition. In the cerebrum, NAA normally increases rapidly in early childhood, then gradually as it approaches adult levels (4). This explains the positive correlation between tNAA and age in the cerebrum (LCSO and PGM), despite the positive correlation of severity score with age ($p=0.008$). Correlation of myoinositol rising with severity implies inflammation or glial cell proliferation; the latter could be simulated by the relative increase in concentration of glial cells after loss of neurons. Establishment of a reliable quantitative measurement related to disease severity, such as levels of tNAA or myoinositol, could be useful as an objective means of monitoring progression of the disease and monitoring response to treatment.

References:

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