Longitudinal Study of Metabolite Levels in Niemann-Pick Disease Type C

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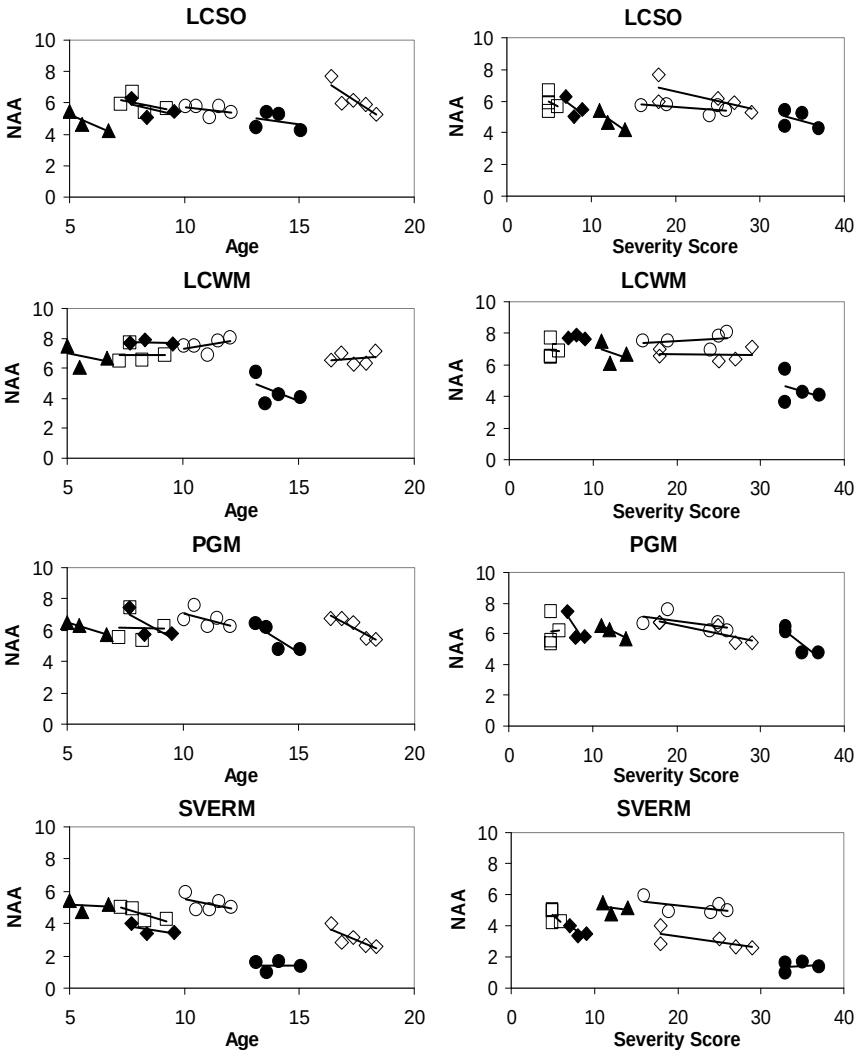
Introduction: Niemann-Pick disease, type C (NPC) is an autosomal recessive neurovisceral lipid storage disorder, involving liver, spleen, lungs, and brain, characterized at the cellular level by accumulation of unesterified cholesterol and glycolipids in the lysosomal/late endosomal system (1). Onset 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 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*. 6 patients with NPC (5 M, 1 F; age range 5-18 years) were studied. Patients or their guardians signed IRB-approved consent to participate. These patients represent a subset of 30 patients participating in an ongoing longitudinal study that includes MRI and MRS studies at 6 – 12 month intervals. The 6 patients selected for this report are the ones who have been scanned 3 or more times. *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*.



Results: NAA levels for each patient are plotted in the figures. Each figure represents one of the voxel locations. Each patient is represented by a different symbol. Plots versus age and plots versus severity score are shown. For most individuals at most locations, the plots show a decrease in NAA over time and a decrease in NAA with increasing severity score. The few exceptions to this pattern occur in the left cerebellar white matter, which was the location with lowest SNR and therefore greatest uncertainty in the measurements. (LCSO = left centrum semiovale, LCWM = left cerebellar white matter, PGM = midline parietal gray matter, and SVERM = superior cerebellar vermis).

Discussion: NAA is contained almost exclusively within neurons and is generally taken to be a marker of neuron health. In NPC, the understood mechanism of injury is that neurons are lost progressively due to injury by lipid deposition, which would be expected to lead to decreasing NAA levels. We have previously reported that in the larger cohort of the 30 patients in our study there is a correlation between relative metabolite levels in certain locations in the brain and symptom severity scores (3). The longitudinal results in these 6 patients demonstrate that this trend can also be followed in individuals over time. This trend is contrary to the expected increase in NAA that would be occurring in healthy children of the same age due to normal maturation of the brain (4). Establishment of a reliable quantitative measurement related to disease severity, such as levels of NAA, could be useful as an objective means of monitoring progression of the disease and monitoring response to treatment; this study suggests that the principle can be applied to individuals as well as to the cohort as a whole.

References:

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