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 and 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 to participate were followed with increasing severity scores (3). The longitudinal results in these 6 patients 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.

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. (LCWM = 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: