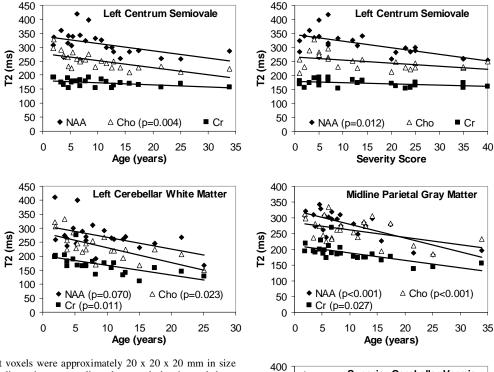# Measurement of Metabolite T2 at 3T in Niemann-Pick Disease Type C

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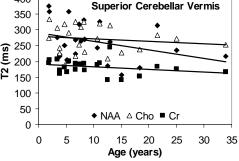
Introduction: Niemann-Pick disease, type C (NPC) is an autosomal recessive neurovisceral lipid storage disorder that leads to progressive neurodegenerative symptoms (1). Onset of symptoms is usually in childhood; the rate of progression is reported to be variable, and patients can survive into adulthood. Because brain imaging findings are nonspecific (and are often normal until late in the course of the disease) and because the MRI abnormalities that appear late in the disease (atrophy and white matter signal changes) are not easily quantified, we are seeking a more readily quantifiable MR-based method to enable monitoring of therapy. Previously we reported a correlation between relative metabolite levels in certain locations in the brain and symptom severity scores (2). Accurate quantitation of metabolite levels (i.e., in molar or molal units rather than relative units) requires knowledge of T1 and T2 of the metabolites *in vivo*. Information on the variation of metabolite T2 with location, age, and disease state is sparse; thus, we report our measurements of metabolite T2 at the locations we have studied.

Methods: *Subjects.* 24 patients with NPC (11 M, 13 F; age range 2-34, median 8 years) were studied. Patients or their guardians signed IRB-approved consent to participate in this ongoing longitudinal study. *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 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, 140ms, and 280ms; TR=2000ms; 128 NEX; same prescan settings for all 3 echo times). 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 6.1 – 10.4 cm^3, mean 8.0 cm^3), although the dimensions were adjusted to match the size and shape of the targeted anatomical area. Voxels having poor SNR or poor linewidth were excluded from further analysis. *Processing.* We used the Philips MRS processing package that is part of the scanner software. Initial phase adjustment was automatic, followed by manual correction if needed. 9 metabolite peaks were fit after 10-term initial baseline subtraction. Peak areas were exported to a spreadsheet for further processing. T2 of 3 peaks (NAA 2.0 ppm, Cr 3.0 ppm, and Cho 3.2 ppm) was calculated using a 3-point logarithmic model. Linear regression analysis (using SPSS) was performed to examine for correlation between metabolite T2, age, and clinical severity scores.

Results: Because there is a statistically significant correlation between age and severity score (p=0.008), age and severity score were used as covariates in the linear regression analysis. In the left centrum semiovale, Cho T2 correlated with age, while NAA T2 correlated with severity score. In the left cerebellar white matter and midline parietal gray matter, the T2 of all 3 metabolites correlated with age but not with severity score. In the superior cerebellar vermis, the metabolite T2 did not correlate with either age or severity score (plots are shown in the figures).

Discussion: Choline T2 varied with age at 3 of the 4 locations studied, while creatine T2 and NAA T2 varied with age at 2 locations. This suggests that when correction for T2 decay is applied for the most accurate reporting of metabolite levels (molar or molal units), both the age of the subject and the voxel location have to be considered in the calculation. Presumably, the T2 of the metabolites is being influenced, at least in some locations, by some ongoing process associated with brain maturation. Multiple normal processes exist that could contribute to changes in relaxation times, including progression of myelination, changes in tissue water content, and deposition of minerals and metals. We also found that at one location NAA T2 varied with symptom severity score, an estimate of disease severity; thus, at least for NPC, disease severity may need to be taken into account in these calculations. As few reports of metabolite T2 in children are available, and as our numbers varied with age and location rather than disease severity, these numbers we report may be more widely applicable to normal children and to children diseases other than NPC, at least until more specific results are reported for other situations.

References:
1. Vanier MT, Millat G. "Niemann-Pick disease type C" Clin Genet. **64**(4):269-81 (2003)
2. Baker EH, Yanjanin NM, Porter FD. "MRS Measurement of Disease Severity in Niemann-Pick Disease Type C" ISMRM 2008:2059