Assessing Disease Severity in Late Infantile Neuronal Ceroid Lipofuscinosis Using Quantitative Magnetic Resonance Diffusion-Weighted Imaging

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Introduction: Late Infantile Neuronal Ceroid Lipofuscinosis (LINCL), a form of Batten disease, is a fatal neurodegenerative genetic disorder affecting approximately 200 children in the United States at any one time. Diagnosis of the disease is determined via DNA testing that identifies genetic mutations specific to LINCL. There are no known treatments for LINCL other than symptom management. Currently, disease progression and severity is assessed via a modified clinical disability scale (1). This study was conducted to evaluate whether quantitative data derived by diffusion-weighted MRI (DWI) techniques can supplement clinical disability scale information to provide a more refined evaluation of neurodegeneration, as well as disease progression and severity in the same patient.

Materials & Methods: This study prospectively analyzed 32 DWI-MRI exams from 18 patients (9M/9F; 3.4-13.8 years) having confirmed LINCL at various stages of disease. Disease severity was clinically monitored throughout the study using a modified CNS disability scale that ranked speech, language and seizure activity on a scale from 0 to 3 summing the results to produce the severity index. All image data was acquired on a 3.0 Tesla GE MRI system including T_1-weighted, T_2-weighted, and fluid-attenuated inversion recovery (FLAIR) sequences. A spin-echo diffusion-weighted (DWI) echo-planar imaging (EPI) sequence was implemented over the entire brain using a slice thickness of 5 mm with a field of view of 22 cm, a matrix size of 128 x 128, a TR of 8.2 s, a TE of 70-80 ms and 2 averages. Diffusion weighting (DWI) was acquired using b=1000 s/mm^2 in three orthogonal directions for a total scan time of 65 s. Figure 1 shows a diffusion-weighted image and an image acquired without diffusion weighting from a representative LINCL patient. A whole brain apparent diffusion coefficient (ADC) histogram was produced and fitted with a dual Gaussian function combined with a function designed to model voxels containing a partial volume fraction of brain parenchyma versus CSF (Figure 2). The partial volume function was modeled under the assumption that voxels that consist of brain matter and CSF contain both components in all possible and equally likely fractions (2). The global maximum of the model fit of the parenchymal compartment eliminating partial volume and CSF was used to characterize the whole brain ADC value. This value was then correlated with patient age, disease severity and duration.

Results: Figure 3 plots whole brain ADC values against patient age for all untreated patients showing an increasing trend over time. Serial studies are connected by lines and the CNS disability score is color coded for each patient as shown in the legend. Published whole brain ADC values from age matched controls are plotted for comparison (3). ADC values were linearly correlated with patient age (R^2=0.71, p<0.0001), disease duration (R^2=0.68, p<0.0001) and CNS disability scale (R^2=0.27, p=0.002). The average age at diagnosis for all LINCL patients was 3.9 ± 1.0 years (n = 18) which approximately corresponded to the point at which the regression fit of the whole brain ADC values in the LINCL population crossed that of the published age-matched controls.

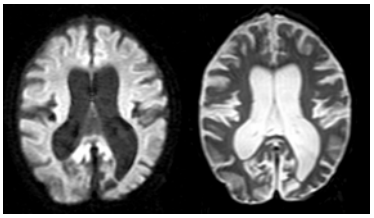

Figure 1

Discussion: Traditionally, DWI-MRI has been used to assess isotropic restriction of water molecules in stroke or white matter diseases of the brain. DWI has rarely been used to examine neurodegenerative diseases of the brain which primarily affect grey matter. This study examined the water diffusivity of the entire brain through the use of DWI. Whole brain ADC histograms included all voxels in the brain having signal intensities greater than a pre-defined threshold. This method eliminated user subjectivity required to place regions of interest on the images.

Our study showed a strong correlation between whole brain ADC values and age along with both disease severity and duration in LINCL patients. This indicates that brain ADC values acquired using DWI-MRI may be used as an independent measure of disease severity and duration in LINCL. Additional studies of patients undergoing various treatment protocols for LINCL and related disorders using DWI-MRI may supplement information gained from other clinical and diagnostic imaging measures to assess future treatment efficacies.

References: 1) Crystal RG, Sondhi D, Hackett NR, et.al. Hum Gene Ther 2004;15:1131-1154. 2) Laidlaw DH, Fleischer KW, Barr AH. IEEE Trans Med Imag 1998;17:74-86. 3) Ulug, AM. Develop Science 2002;5:286-292.

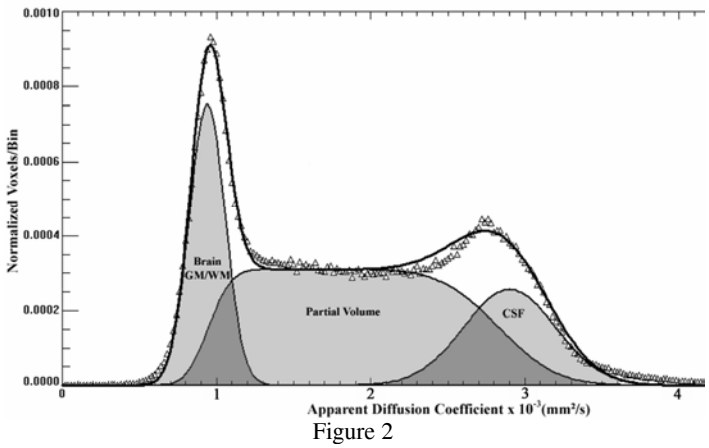

Figure 2

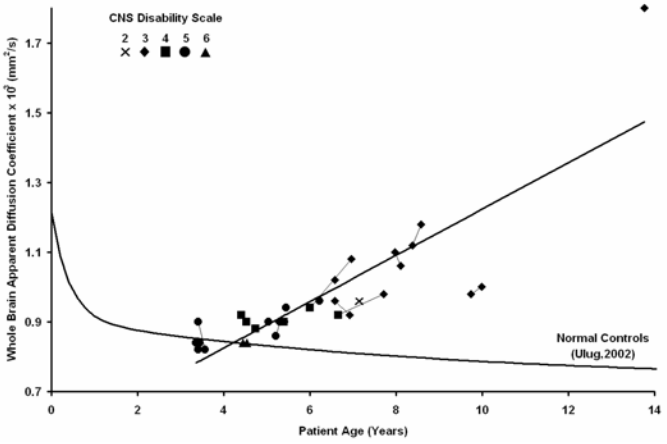

Figure 3