

Assessment of Disease Severity in Late Infantile Neuronal Ceroid Lipofuscinosis Using Multiparametric MRI

J. P. Dyke¹, D. Sondhi², H. U. Voss¹, D. C. Shungu¹, X. Mao¹, K. Yohay³, S. Worgall³, N. R. Hackett², C. Hollmann², M. E. Yeotsas², S. M. Kaminsky², B. Kosofsky³, L. A. Heier¹, R. G. Crystal², and D. Ballon¹

¹Radiology, Weill Cornell Medical College, New York, NY, United States, ²Genetic Medicine, Weill Cornell Medical College, New York, NY, United States, ³Pediatrics, Weill Cornell Medical College, New York, NY, United States

Introduction: Late Infantile Neuronal Ceroid Lipofuscinosis (LINCL), or Batten Disease, is a rapidly progressing, uniformly fatal lysosomal storage disease resulting from mutations in the CLN2 gene with largely neurological symptoms¹. Disease onset occurs at 2-4 years of age, with progression to death at age 8-12 years. The current standard of care includes T₁ and T₂ weighted magnetic resonance imaging (MRI) and a neurological rating system known as the Weill Cornell LINCL scale to assess disease severity, including assessments of feeding, gait, motor, and language functions². To improve the sensitivity to detect disease progression, we combined five quantitative MR imaging techniques in a completely objective, multi-parametric magnetic resonance panel to produce a single outcome metric.

Methods: The five MRI techniques were applied across the entire brain and yielded measures of 1) T₂ relaxation times, 2) apparent diffusion coefficients (ADC), diffusion fractional anisotropy (FA), percent CSF volume (%CSF), and N-acetyl aspartate to creatine ratios (NAA/Cr). Data were acquired from the first 10 subjects [5.1±0.8 yr, 4M/6F] under general anesthesia using a 3.0 Tesla General Electric MRI system with an 8-channel head resonator (over 100 MRI studies are planned on 32 subjects). A spin echo pulse sequence with echo times of 20,40,60 and 80 ms was applied for quantitative whole brain T₂ mapping. Echo planar isotropic (2x2x2 mm) diffusion tensor images (b=800 s/mm²) were acquired with 33 gradient directions. ADC's and FA values were calculated for the cortical region of the brain. A high-resolution isotropic 3D BRAVO GRE pulse sequence was used for volumetric analysis of %CSF. Proton spectroscopic imaging data were acquired with and without water suppression for assessment of NAA/Cr.

Quantitative T₂ values were fitted from the multi-echo sequence to produce whole brain T₂ histograms. Fractional anisotropy and cortical ADC maps were created on-line from the isotropic diffusion weighted echo planar data. The %CSF volume was calculated using segmentation algorithms from SPM5 and IBASPM. Peak spectroscopic areas were integrated for all voxels in the brain excluding the lateral ventricles. Whole brain histograms were created for each of the imaging biomarkers and fitted with Gaussian functions. A multivariate linear regression combined all five biomarkers into a single outcome metric.

Results: Regression analysis of single MRI parameters against the Weill Cornell LINCL scale yielded coefficients in the range R² = 0.53 to 0.87 [Table 1]. However, a multivariate linear regression that combined the five parameters compared to the Weill Cornell LINCL scale yielded R²=0.90, p<0.0001. Table 1 gives the values of individual MRI biomarkers at the extremes of the LINCL scale [0-12], where a score of 0 represents a nonambulatory gastrostomy tube-dependent subject with unintelligible or no speech, and 12 is normal. The resulting predictive value of the multivariate MRI metric is plotted against the LINCL Score in Figure 1 with representative images shown in Figure 2.

Table 1	Cortical ADC	CSF Volume	NAA/Creatine	FA Value	T ₂ Area	Multivariate
Pearson R ²	0.87	0.63	0.61	0.57	0.53	0.90
LINCL[0]	1.07E-3 mm ² /s	38.3%	1.25	0.057	0.026	
LINCL[12]	7.77E-4 mm ² /s	18.2%	2.02	0.086	0.039	

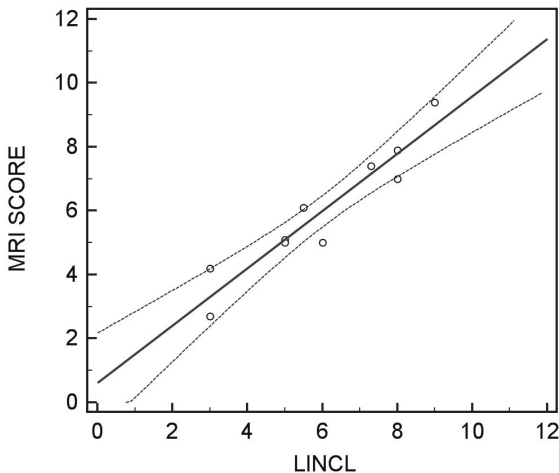


Figure 1: The Multivariate 5 component MRI biomarker metric is compared with the Weill Cornell LINCL Scale showing the 95% confidence intervals.

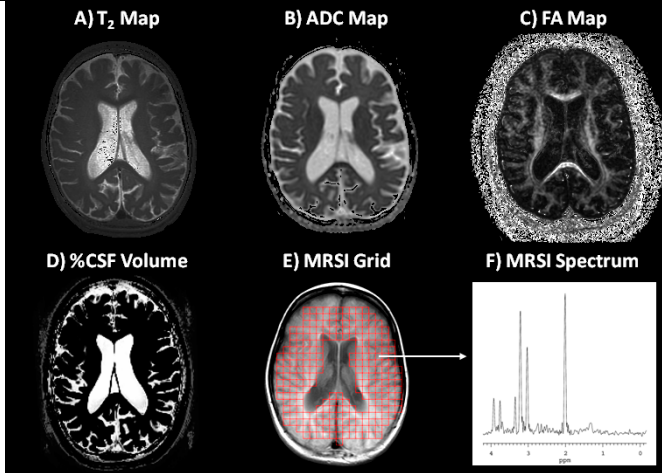


Figure 2: Example of the five component MRI panel. A) T₂ map, B) ADC map, C) FA map, D) %CSF map, and E,F) MRSI NAA/Cr map.

Discussion: The multiparametric metric obtained from the combination of T₂, ADC, FA, %CSF, and NAA/Cr whole brain magnetic resonance techniques resulted in a measure of disease severity that was well correlated with the discrete Weill Cornell LINCL score. The metric is a non-invasive, objective variable that correlated with clinical status independent of patient age, and may prove beneficial in future serial assessments of subjects undergoing treatment. Future work will focus on regional analysis of MRI biomarkers to assess specific areas of degeneration at various stages of disease progression.

1) Jalanko A, Brault T. Biochim Biophys Acta. 2009;1793:697-709. 2) Worgall S, et.al. Hum. Gene Ther. 2008;19: 463-474.