Assessment of Disease Severity in Degenerative Brain Disorders Using Multiparametric MRI

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Introduction: We present here a generalized paradigm for evaluation of degenerative brain disease using MRI, with a specific application to late infantile neuronal ceroid lipofuscinosis (LINCL). LINCL is a uniformly fatal lysosomal storage disease resulting from mutations in the CLN2 gene that encodes for tripeptidyl peptidase 1, a lysosomal enzyme necessary for degradation of products of cellular metabolism. Neurological symptoms begin to appear at ages 2 to 4 years and progressively worsen with age, leading to death by the ages of 8 to 12 years. With the goal of -using quantitative, non-invasive imaging biomarkers sensitive to disease progression, we evaluated a five-component MRI metric, and tested its correlation with a clinically derived disease severity score. Previously, we reported preliminary results from a pilot study, and here report full details on a larger dataset (N=41) that includes principal component analysis in the derivation of an objective imaging based disease severity score.

Methods: Forty one MRI data sets were acquired from thirty subjects [2.5–8.4 yr, median 5.0 yr, 9 male/21 female]. Eleven subjects were scanned at two time points as part of a separate therapeutic trial for LINCL but were untreated at the time of the scans. MRI parameters were measured across the brain, including quantitative measures of the apparent diffusion coefficient (ADC), diffusion fractional anisotropy (FA) of white matter, nuclear spin-spin relaxation time (T_2) of gray matter, volume percentage of cerebrospinal fluid (%CSF), and N-acetylaspartate to creatine ratios (NAA/Cr). The total scan time for the complete imaging protocol was 75 minutes. Whole brain histograms were generated, and the mode (maximum) and mean values of the histograms were used to characterize disease severity. All subjects were evaluated using the Weill Cornell LINCL Disease Severity Scale by four observers.[1] The subjects' Clinical LINCL scores (0 – 12 scale) were 6.0 ± 2.5 on average and ranged from 1.5 to 11. Principal component analysis (PCA) was performed on the MRI dataset using MATLAB (Natick, MA). All possible combinations of n biomarkers were tested, with $n \leq 5$. We then defined an MRI based disease severity score to be equal to the linear combination of the n biomarkers weighted by the coefficients of the first principal component (PC1). This scoring system had a scale determined by minimizing the sum of squared differences with the clinical LINCL scores and was similar to the 0 to 12 range of clinical LINCL scale.

Results: Correlation of single MRI parameters against the clinical LINCL scale yielded linear regressions with R^2 ranging from 0.25 to 0.70. The best PCA combination of MRI biomarkers included ADC, %CSF, and NAA/Cr ($R^2 = 0.74$, $p < 0.001$).
The vector of coefficients for PC1 (0.56, 0.59, -0.58) was used to calculate the MRI disease severity score (MRIDSS) as:

$$\mathbf{MRIDSS \equiv -1.29 * \{0.56*[(ADC-0.94)/0.06] + 0.58*[(\%CSF-30.8)/4.4] - 0.60*[(NAA/Cr - 1.56)/0.24]\} + 5.8}$$

Note that the positive coefficients (ADC, %CSF) properly reflect those biomarkers that increase with disease severity while the negative coefficient (NAA/Cr) is applied to a biomarker that decreases with disease severity.

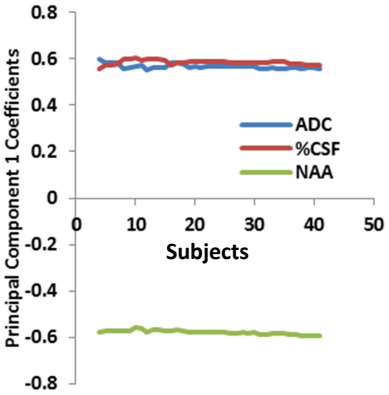

Figure 1

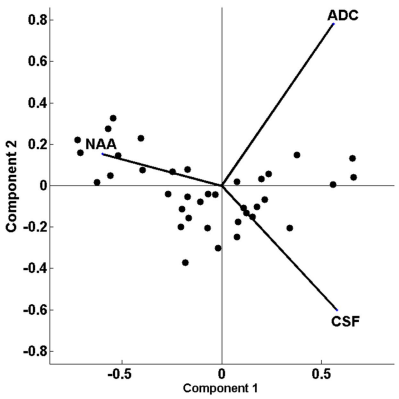

Figure 2

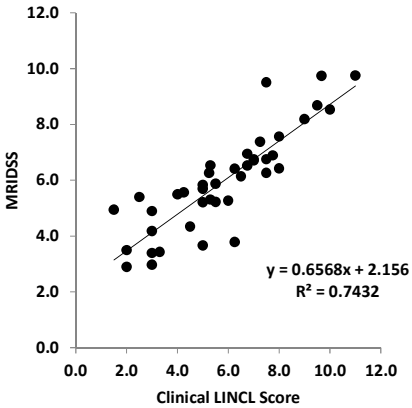

Figure 3

Figure 1 displays the robustness of the principal component analysis by repeating the calculation with the addition of each new subject. Figure 2 shows a plot of PC1 versus PC2 for all subjects along with the relative contribution of each MRI biomarker accounted for by these two principal components. The final correlation of the MRI disease severity score with the clinical LINCL score is shown in Figure 3.

Discussion: A quantitative, non-invasive MRI-based disease severity score for late infantile neuronal ceroid lipofuscinosis has been presented [2]. The metric combines data from brain water apparent diffusion coefficients, the volume percentage of cerebrospinal fluid, and N-acetyl aspartate to creatine metabolite ratios. The methods described herein are quite general and can be applied to a wide range of brain disorders.

References: 1) Worgall S, Kekatpure MV, Heier L, et.al. Neurology. 2007; 69: 521-535. 2) Dyke JP, Sondhi D, Voss HU, et.al. AJNR Am J Neuroradiol. 2012 Oct 4.