Quantitative diffusion tensor imaging and T1 relaxometry in Niemann-Pick C Disease

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Introduction. Niemann-Pick C (NPC) disease is an autosomal recessive neurovisceral lipid storage disorder characterized at the cellular level by accumulation of unesterified cholesterol and glycolipids in the endosomal/lysosomal system. Brain imaging findings include atrophy of the cortex, brainstem, cerebellum, and sometimes the corpus callosum, without obvious signal abnormalities on MRI(1). As atrophy is not easily monitored, we sought a more readily quantifiable imaging method to enable therapeutic monitoring. We are attempting to develop MR based quantitative measurements for the assessment of disease severity using quantitative diffusion tensor imaging (DTI) and T_1 relaxometry, measuring the fractional anisotropy (FA), apparent diffusion coefficient (ADC), and T_1 relaxation times in NPC patients, correlating the results to each patient's symptom based severity score.

Methods. 14 patients (age 3 – 32 yr., mean 10) with NPC were studied. Symptomatic severity scores of these patients ranged from 2-35, mean 17. Patients were imaged with informed consent under an IRB approved protocol. The MR studies were performed on a 3.0T Philips MR system with a SENSE head coil. Diffusion tensor imaging was performed using a single-shot, spin echo, echo planar DTI sequence. 32 directions (max b factor = 1000) were used. Matrix = 128 x 128; FOV = 240 mm; slice thickness 2.5 mm; TR = 6000 ms; TE = 76 ms; # of averages = 1; acquisition time 3:36 min. The DTI sequence was repeated 3 times, and registered to 1 set of data set using Philips PRIDE tool. The same tool was used to compute the FA and ADC maps. Regions of interest (ROIs) were drawn in 19 different regions of the brain, including in the brainstem, cerebellum, cerebral white matter, and deep grey nuclei, to measure the FA and ADC. T_1 relaxation times were calculated using Deoni's dual flip angle technique(2). We used 2 SPGRE images (TR = 8.1 ms; TE = 3.9 ms; FOV = 240 mm; matrix = 256 x 256; slice thickness = 3 mm, acquisition time 4:12 minutes) with 2^o and 12^o flip angles, and made T_1 maps using our own software. ROIs were drawn in 30 different regions including cortical grey matter, deep nuclei, white matter, brainstem, and cerebellum. To maintain consistency, the ROIs were drawn by a single radiologist. The Pearson correlation test was used to correlate severity scores to FA, ADC, and T_1 relaxation times in the various regions of the brain.

Results. For the quantitative DTI measurements, a statistically significant correlation ($p<0.05$) was found between severity scores and FA in the superior cerebellar vermis, fornix, globus pallidus, cingulum, inferior fronto-occipital fasiculus, and genu and splenium of the corpus callosum; and between severity scores and ADC in the superior cerebellar vermis, forceps minor, fornix, and inferior fronto-occipital fasiculus. For T_1 relaxation time, a statistically significant correlation ($p<0.05$) was found between severity scores and T_1 relaxation time in the superior cerebellar vermis and genu of the corpus callosum.

Conclusion. This preliminary study demonstrates correlation of MR based measurements of FA, ADC, and T_1 relaxation times in certain locations in the brain to an established symptomatic severity measure for NPC. FA and ADC measurements appear to be correlated to symptoms in more regions of the brain than T_1 relaxation times, suggesting that they may be sensitive to more subtle changes. These measurements were made as part of a longitudinal study following the evolution of symptoms in detail and evolution of quantitative MR parameters throughout the brain. Establishment of a reliable quantitative measurement related to disease severity could be useful as an objective means of monitoring progression of the disease and monitoring response to treatment.

References. (1) Sevin, M, G Lesca, *et al*. (2007) Brain 130 (Pt 1): 120-33. (2) Deoni, SC, BK Rutt, *et al*. (2003) Magn Reson Med 49(3): 515-26.

Figure 1. Correlation of FA and ADC to severity score in **a**) superior cerebellar vermis **b**) inferior fronto-occipital fasiculus **c**) fornix.
Figure 2. Correlation of FA to severity score in cingulum, globus pallidus, genu and splenium of corpus callosum.
Figure 3. Correlation of ADC (x 10^{-3}mm^2/s) to severity score in forceps minor.
Figure 4. Correlation of T_1 relaxation time (msec) to severity score in the superior cerebellar vermis and genu of the corpus callosum.

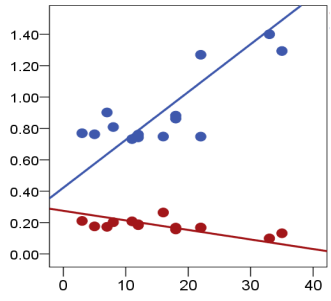

Figure 1a

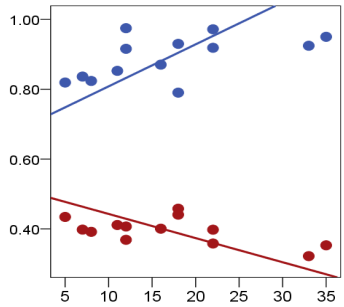

Figure 1b

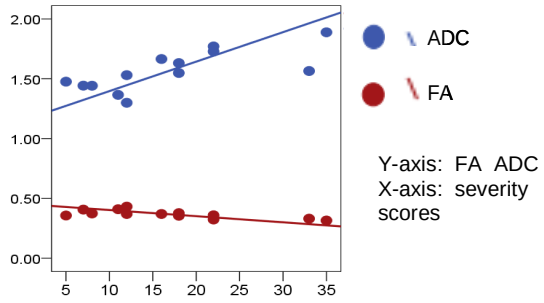

Figure 1c

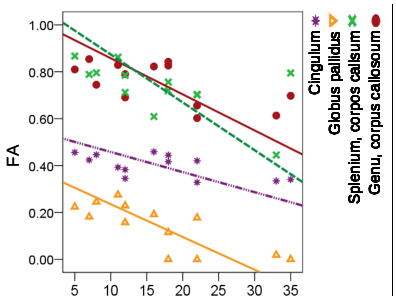

Fig. 2

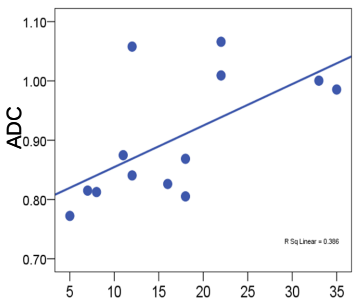

Fig. 3

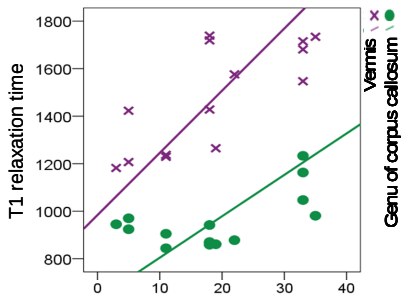

Fig. 4