Longitudinal magnetic resonance spectroscopy in premanifest and early Huntington disease.

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Introduction

Huntington disease (HD) is a neurodegenerative disease that currently has no cure and leads to severe cognitive and physical impairment which requires full-time care as the disease progresses, ultimately leading to death[1]. The purpose of this study was to examine brain metabolites using ^{1}H magnetic resonance spectroscopy (MRS) as possible biomarkers for disease progression. A previous study using a single timepoint, compared metabolite concentrations in the putamen between controls and pre-manifest HD (subjects possessing genetic predisposition to HD) and early-HD subjects[2]. This study found decreased N-acetyl aspartate (NAA) and glutamate (Glu) and increased myo-inositol (mI) in early HD compared to premanifest HD. Another MRS study at 7T found significantly decreased NAA and creatine (tCr) in the putamen of manifest HD patients[3]. The current study longitudinally examines changes in putamen metabolites across 36 months to assess the ability of MRS metabolites to be used as biomarkers and to compare the metabolite concentrations to control. It is the first study of its kind and is a part of the Track-HD cohort.

Methods

All subjects, early (n=30), pre-HD (n=25) and control (n=30), were recruited for TrackHD[2]. However, only subjects that had been scanned at all four timepoints (0, 12, 24, 36 months) were included in the longitudinal analysis lowering the analyzed subject groups to: early (n=15), pre-HD (n=19) and control (n=22). A 3T MRI (Philips Healthcare) was used to collect a single voxel MR spectra on the left putamen were obtained (3.5cm x 1cm x 1.5 cm) with TR=2000ms, TE=35ms, 1024 samples and 128 averages. The spectra were analyzed using LCModel[4], and were normalized to the unsuppressed water spectral area as well as water concentration. Metabolites that could be fitted with a %SD of <20% were included. Seven metabolites (total NAA (tNAA), NAA, tCr, glutamate (Glu), choline (tCho), (mI), and Glu + glutamine (Glx)) were examined for each subject group and compared over the four visits. A Student's t-test was used to compare the metabolite concentrations between subject groups within each visit, a $p<0.05$ was considered to be significant.

Results

The average metabolite concentrations for four metabolites over the four visits are shown in Figure 1 for all three patient groups. tNAA was significantly lower in early-HD at all four time points compared to controls and pre-HD. NAA showed a similar trend to tNAA (not shown). tCr was lower in early-HD vs controls at all time points. tNAA and tCr showed the same pattern of concentrations at all time points: [Control] > [pre-HD] > [early-HD]. Glu (not shown) also showed this pattern across the four visits, but Glx was not as consistent across the timepoints (not shown). mI was found to be significantly increased compared to controls for Visits 2-4 and significantly increased from pre-HD for Visits 1-3 but not Visit 4. No significant differences in tCho concentration could be found between the three subject groups at any of the time points.

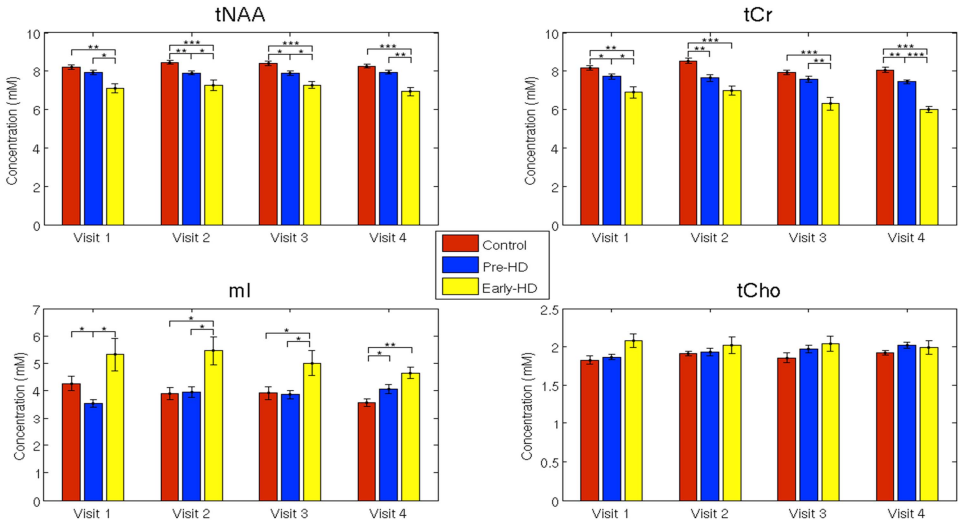

Figure 1: Error bars are the standard error of the mean. Asterisks indicate level of significance using a Student's t-test: *p<0.05, **p<0.01, ***p<0.001

Discussion

Here we present longitudinal results from early- and pre-HD subject groups in comparison to controls. The most significant changes in metabolite concentrations between the subject groups were seen in tNAA, tCr and mI. tNAA is thought to be a more reliable measure than NAA, and though its exact role is poorly understood, it is thought to be a marker for the integrity of neurons and is decreased in many pathologies. The initial pattern in Visit 1 (decreased tNAA as disease progressed) was seen at all four timepoints. tCr is often assumed to be consistent across different brains and pathologies and is thus used as a standard for other metabolites. However, here it is shown that in HD tCr is significantly lower in early-HD (this was also previously found in a 7T study[3]). The observed decreases in tCr may have been affected by the known decrease in putamen size with disease progression in HD[5]; therefore, when examining HD, the common MRS practice of looking at metabolite ratios to Cre may give misleading results Changes in glial cells may be reflected in changes in [mI]. Increased mI has also been been seen in Alzheimer disease[6,7]. mI was increased for early-HD at all timepoints, although at Visit 4 pre-HD [mI] was not significantly different than early-HD. mI is a possible biomarker not only for disease identification but also disease progression. It was found in an earlier study of Visit 1 that early-HD [mI] correlated with the clinical motor score UHDRS.

Conclusion

This study presents the first long term results of MRS in HD and presents possible biomarkers. Further examination of the relationship between clinical scores and these metabolites will be needed, however, mI , tNAA and tCr show potential as biomarkers of disease and disease progression from premanifest- to early-HD.

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