The \([\text{Ins}]/[\text{NAA}]\) ratio is highly correlated with clinical score in Huntington’s Disease, likely reflecting simultaneous astrogliosis and neuronal loss

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**Introduction**

Huntington’s disease (HD) is a neurodegenerative disorder characterized by abnormal movements (chorea), dementia, and preferential degeneration of the striatum. This pathology is associated with metabolic anomalies that might be detected using NMR spectroscopy. Up to now cerebral \(^1\)H spectroscopy of HD patients has revealed almost systematic decreases in N-acetyl-aspartate (NAA) in the striatum [1-3], occasional increases in lactate and glutamate+glutamine [1,4,5]. Only one report mentions an increase in myo-inositol (Ins) in the juvenile form of the disease [3]. Myo-inositol, which is considered as a glial marker, could be a potential marker of degeneration in HD. However the chemical shift of Ins is close to water (in the 3-4ppm region) and all resonances are J-coupled, making it difficult to reliably quantify this metabolite. In this context our purpose has been to test the hypothesis of elevated myo-inositol in HD. Short echo time \(^1\)H spectroscopy was performed in a large patient group and in age-matched healthy controls. Spectra were quantified using LCModel [6], revealing significantly elevated Ins in HD patients and strong correlation of Ins/NAA with clinical scores.

**Materials & Methods**

**Subjects and NMR acquisitions** \(^1\)H NMR spectra were acquired from 27 HD patients presenting an advanced stage of HD disease (length of disease: 9±4 years) and 6 healthy controls. Experiments were performed on a clinical whole-body 1.5 T Siemens system equipped with a 8-channels head coil, allowing simultaneous acquisition of 8 \(^1\)H PRESS spectra (striatal volume of interest ~8cm\(^3\), TE/TR=30/1500ms, NT=128). Another set of spectra was acquired for each subject using the same PRESS sequence at TE=135 for potential detection of lactate.

**Data processing**

Spectra averaging and phasing were performed using Matlab (The Mathworks Inc., Natick, MA). Spectra quantification was performed using LCModel software [6]. The concentrations of NAA, creatine (Cr), choline (Cho), Ins, Taurine (Tau), glutamate+glutamine (Glx) and lactate (Lac) were estimated for each subject.

**Results & Discussion**

**Metabolites concentrations**

In a first time, the concentrations of striatal metabolites were normalized relatively to Cr (see Table 1). Contrary to literature studies [Sanchez-Pernaute 1999], the [NAA]/[Cr] ratio does not present significant changes between HD patients and controls. However, the [Ins]/[Cr] ratio is increased by 77% in HD patients relatively to controls (0.76±0.26 vs 0.43±0.07, p=2.5×10\(^{-5}\), t.test) and the [Cho]/[Cr] ratio by 24% (0.26±0.04 vs 0.21±0.02, p=4.5×10\(^{-5}\), t.test). The other metabolite ratios ([Glx]/[Cr], [Tau]/[Cr], [Lac]/[Cr]) do not present significant changes (data not shown). The stability of the [NAA]/[Cr] ratio coupled with the increase of the [Cho]/[Cr] and [Ins]/[Cr] ratios is difficult to interpret because of the dependence on [Cr] variations. To simplify the analysis, the [Cho]/[NAA] and [Ins]/[NAA] ratios were estimated and shown to be increased by 28% (p=3×10\(^{-5}\), t.test) and 84% (p=9.2×10\(^{-5}\), t.test) respectively. Given the fact that the increase in [Ins] is mainly a marker of glial proliferation and that choline is a marker of membrane density, the coupled increase of [Ins]/[NAA] and [Cho]/[NAA] ratios could reflect an unbalance between glial and neuronal populations in the striata of HD patients, and more precisely an increase of glial contribution. This finding is in accordance with the fact that neuronal death in HD is generally coupled with astrogliosis. Finally, the [Cho]/[NAA] ratio and particularly the [Ins]/[NAA] ratio appear to be more relevant and discriminating than [Cho]/[Cr] and [Ins]/[Cr] ratios for HD patients.

**Correlation with clinical scores**

This part of the study was performed for 21 of the 27 HD patients for which clinical scores were available. As shown in figure 2, the [Ins]/[NAA] ratio was found to be highly correlated with the UHDRS (Unified Huntington Disease Rating Scale) score (p=2×10\(^{-4}\), Pearson test). Note that an increase of the UHDRS score means a decrease in motion capabilities of HD patients. Under the hypothesis of astrogliosis coupled to neuronal degeneration, this correlation can be the consequence of the striatal neuronal loss. To a lesser extent, the [Cho]/[NAA] ratio appears to be correlated with the duration of HD disease (p=1.1×10\(^{-3}\), Pearson test, data not shown). In conclusion, short echo time \(^1\)H spectroscopy combined with LCModel quantitation reveals strongly increased myo-inositol in the striatum of HD patients (77% increase). The [Ins]/[NAA] ratio is the most discriminating index between patients and controls (p=9.2×10\(^{-5}\)). This ratio presents the best correlation with the UHDRS score (p=2×10\(^{-7}\)), probably reflecting astrogliosis associated with neuronal loss.

**References**