

# Anatomical and Neurochemical Changes in Minimal Hepatic Encephalopathy and their Neuropsychological Correlates

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## Synopsis

Patients with minimal hepatic encephalopathy (HE) and healthy controls were scanned by T1-weighted MRI, and had spectra recorded from their occipital white matter, frontal gray matter and basal ganglia regions. Both patients and healthy controls underwent various neuropsychological tests. Using normalized representative gray levels of the globus pallidus, HE patients could be distinguished from healthy controls. HE patients had significantly elevated ratios of combined glutamate and glutamine to creatine, as well as reduced ratios of choline to creatine and myo-inositol to creatine, compared to healthy controls. MRI abnormalities and neuropsychological deficits were correlated with various metabolic changes in HE patients.

## Introduction

Neuropsychological testing is the current gold standard in the diagnosis of minimal hepatic encephalopathy (HE). Magnetic resonance imaging (MRI) and spectroscopy (MRS) of the brain offer specific markers of HE. These methods were applied to HE patients and healthy controls, in conjunction with neuropsychological testing, in order to assess the presence of minimal HE and to understand its pathogenesis.

## Methods

Using a GE 1.5-T MRI scanner, axial brain images of 22 patients awaiting liver transplantation and 14 healthy controls were recorded over a 26-cm field of view, with an acquisition matrix size of 256x192 pixels, TR=800 ms and TE=8 ms. The slice thickness was 4 mm, without slice separation. Representative gray levels of the globus pallidus were calculated and normalized to representative gray levels of the thalamus (giving a "thalamus ratio") and corpus callosum (giving a "corpus callosum ratio"). Water-suppressed proton spectra were recorded in the frontal gray matter, occipital white matter and basal ganglia of all subjects. The PRESS sequence was used to localize an 8-ml voxel, and CHESS was used for water suppression.<sup>1</sup> Spectra were acquired with TE=30 msec, TR=3 sec and 64 averages. Spectra were processed using LC-Model (S.W. Provencher), which fit each spectrum to a curve. Metabolite peaks whose standard deviations exceeded 25% were excluded from statistical analyses.

Each subject underwent 18 neuropsychological tests, divided into six categories: Speed of Processing, Executive Function, Motor Function, Fluency, Verbal Memory, and Non-Verbal Memory. The average raw score from each category was correlated with MRI and MRS data, by calculating the Pearson correlation coefficients.

## Results

The two MRI-based measures, taken together, separated the patients and healthy controls into two groups with minimal overlap (Figure 1).

Patients had higher ratios of total glutamine and glutamate to creatine ((Gln+Glu)/Cr) in the basal ganglia than healthy controls ( $p < 0.017$ ). In the frontal gray matter, MRS results indicated that patients had reduced choline (Cho)/Cr ( $p < 0.002$ ) and myo-inositol (Ins)/Cr ( $p < 0.007$ ). The occipital white matter's (Gln+Glu)/Cr was significantly higher ( $p < 0.0004$ ), and its Ins/Cr lower ( $p < 0.01$ ), in patients than in healthy controls.

The thalamus ratio correlated negatively with the basal ganglia's Ins/Cr ( $r = -0.578$ ,  $n = 16$ ,  $p = 0.019$ ). In the frontal gray matter, Ins/Cr was correlated negatively with the thalamus ( $r = -0.629$ ,  $n = 14$ ,  $p = 0.016$ ) and corpus callosum ratios ( $r = -0.608$ ,  $n = 14$ ,  $p = 0.021$ ), and NAA/Cr correlated negatively with the corpus callosum ratio ( $r = -0.497$ ,  $n = 19$ ,  $p = 0.031$ ). The occipital white matter's ratio of Cho/Cr correlated negatively with the corpus callosum ratio ( $r = -0.560$ ,  $n = 22$ ,  $p = 0.007$ ). Ins/Cr in the occipital white matter correlated negatively with both the corpus callosum ( $r = -0.723$ ,  $n = 12$ ,  $p = 0.008$ ) and thalamus ( $r = -0.770$ ,  $n = 12$ ,  $p = 0.003$ ) ratios.

In the frontal gray matter, the ratio of Ins/Cr correlated positively with the Speed of Processing score ( $r = 0.540$ ,  $n = 14$ ,  $p = 0.046$ ). Executive Function correlated positively with both Gln/Cr ( $r = 0.599$ ,  $n = 14$ ,  $p = 0.024$ ) and (Gln+Glu)/Cr ( $r = 0.487$ ,  $n = 18$ ,  $p = 0.041$ ). Motor Function correlated positively with Gln/Cr ( $r = 0.667$ ,  $n = 14$ ,  $p = 0.009$ ) and (Gln+Glu)/Cr ( $r = 0.588$ ,  $n = 18$ ,  $p = 0.010$ ). In the occipital white matter, Glu/Cr and [Gln+Glu]/Cr correlated positively with Motor Function ( $r = 0.503$ ,  $n = 18$ ,  $p = 0.033$  and  $r = 0.678$ ,  $n = 20$ ,  $p = 0.001$ , respectively) and Executive Function ( $r = 0.567$ ,  $n = 18$ ,  $p = 0.014$  and  $r = 0.585$ ,  $n = 20$ ,  $p = 0.007$ , respectively). Gln/Cr and [Gln+Glu]/Cr correlated negatively with the Speed of Processing score ( $r = -0.757$ ,  $n = 11$ ,  $p = 0.007$  and  $r = -0.628$ ,  $n = 20$ ,  $p = 0.003$ , respectively) (Figure 2).

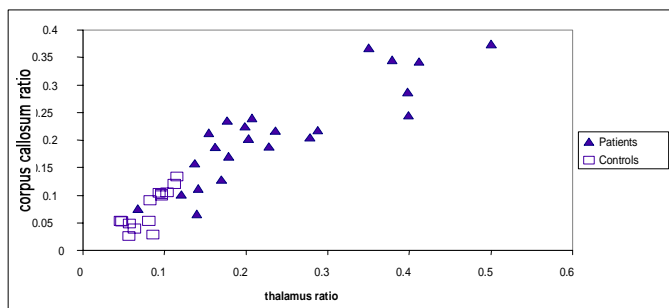
## Discussion

Hyperintensity of the globus pallidus is found to be an indicator of HE. The observed reduction of Ins/Cr in the frontal gray matter and occipital white matter of patients with minimal HE is consistent with a proposed mechanism of HE pathogenesis: the heightened synthesis of glutamine by brain glutamate and excess blood ammonia in astrocytes followed by a compensatory loss of myo-inositol to maintain astrocyte volume homeostasis.<sup>2</sup> In all three brain regions examined, there were negative correlations between Ins/Cr and the MRI measurements of the globus pallidus signal intensity. These correlations suggest that the globus pallidus hyperintensity of minimal HE patients may serve as an indication of the severity of HE. Cho/Cr and NAA/Cr were correlated negatively with the globus pallidus signal intensity. The roles of these metabolites in HE are not yet known.

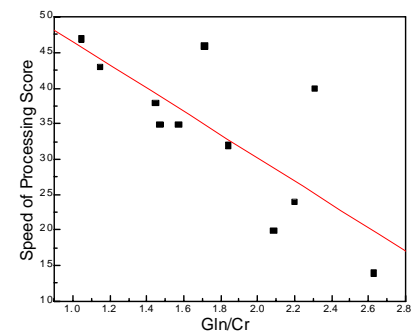
Executive Function and Motor Function scores are high for poorly performing subjects, as these tests quantify the time required to perform various complex tasks. Impairments of HE patients' motor functioning are linked to an excess of glutamine and total Gln+Glu in the frontal gray matter and an excess of glutamate and total Gln+Glu in the occipital white matter. Impairment of executive functioning corresponds to a surplus of glutamine and total Gln+Glu in the frontal gray matter, and an excess of glutamate and total Gln+Glu in the occipital white matter. Reduced speed of processing is associated with an excess of glutamine and total Gln+Glu in the occipital white matter.

## References

1. Bottomley P, U.S. Patent 4-480-228.1984
2. Cordoba J, Alonso J, Rovira A, Jacas C, Sanpedro F, Castells L, Vargas V, Margarit C, Kulisevsky J, Esteban R, Guardia J. The development of low-grade cerebral edema in cirrhosis is supported by the evolution of <sup>1</sup>H-magnetic resonance abnormalities after liver transplantation. *J Hepatology* 2001; 35:598-604



**Figure 1.** The T1-weighted MRI-based corpus callosum ratios and thalamus ratios of healthy controls and HE patients. This graph demonstrates a possible separation between the two groups using this pair of MRI-based measures.



**Figure 2.** Correlation between the Speed of Processing scores of HE patients and Gln/Cr ratios in their occipital white matter.