Biochemical, Anatomical and Neuropsychological correlates in Hepatic Encephalopathy

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Introduction: Using one dimensional (1D) and 2D MR Spectroscopy (MRS), decreased myo-inositol (mI) and choline (Ch), and increased glutamate/glutamine (Glx) have been shown in selected regions of brain of hepatic encephalopathy (HE) patients (1) and globus pallidal (GP) hyperintensities have been reported on T1 weighted MR images (MRI). The relationship between these changes in MRI/MRS and neuropsychological (NP) impairment has also been explored (2-4). However most studies have used the single voxel approach with two voxels placed on the parietal and basal ganglia. Though majority of the NP tests involve frontal lobe function, MRI and MRS correlation has been shown with parietal lobe and basal ganglia. We performed two voxels [right frontal (Fr) and left occipital (Occ)] 2D localized correlated spectroscopy (L-COSY) with an aim to correlate the metabolites with the region specific NP tests. Another goal was to compare the diagnostic accuracy of the 2D MRS, GP signal intensities (SI) and NP tests, alone and in combination, in discriminating between minimal HE patients and controls.

Methods: 34 minimal HE patients (age: 50.5 ± 9.4 years) and 30 healthy volunteers (age: 48.9 ± 11.8 years) were investigated. A 1.5T MRI/MRS scanner (Siemens Medical Systems, Erlangen, Germany) with a body coil "transmit" and a dual surface coil "receive" assembly was used. **2D MRS**: 27 ml voxels were localized over right prefrontal dorsolateral white/gray and left visuo-occipital white/gray matter with TE=30ms, TR=2s and total scans=768 (1). The spectra were processed using Felix-2000 (Felix NMR Inc., San Diego, CA). The volumes under the diagonal and cross peaks in the 2D L-COSY spectra from both locations, and their respective ratios with the creatine (Cr) diagonal (_d) peak volume were calculated (1,2). **NP**: 25 patients and 27 controls also underwent a NP test battery on the same day of MRS and MRI. Test scores were converted to demographically-corrected T scores and grouped by different neurocognitive domains listed in Table 1.**MRI**: GP SI was measured in 19 patients and 20 controls. The MRS ratios, GP SI and NP domain scores were compared between patients and controls using t-test. Pearson's correlation was also performed. Selection of the variables that produced the best differentiation between patients and controls was done using the stepwise discriminant analysis as well as logistic regression analysis. Receiver operating characteristic (ROC) curve analysis was also performed. Significance level was set at $p < 0.05$.

Results and Discussion: In continuation with the pilot findings of this project (5), 2D MRS data showed significant decline of Ch_d, mICh and mI ratios in both locations and taurine (Tau)/Cr in the Fr region in patients. There was a significant increase of Glx ratio in both locations. The patients showed significantly lower domain scores than the controls for: motor function, cognitive speed, executive function and global scores. The mean GP SI in patients [left GP: 410.5 ($\pm$ 48.9), right GP: 413.6 ($\pm$ 49.1)] was significantly higher than that of controls [left GP: 350.5 ($\pm$28.5); right GP: 350.1 ($\pm$25.7)] (p < 0.0001). Fr Ch_d/Cr_d showed a significant positive correlation with cognitive speed, visuospatial and the language domain scores and Fr and Occ mICh/Cr_d positively correlated with motor and cognitive speed. Similarly, Fr and Occ Tau/Cr_d showed a positive correlation with the cognitive speed domain. Only Fr Glx/Cr_d and Occ Tau/Cr_d significantly correlated with the global domain scores, negatively and positively respectively (Table 1). Discriminant analysis with the significant variables is depicted in Fig 1. Fig. 2 shows the results of logistic regression analysis and ROC curves for each modality and their combinations. Combining both Fr and Occ MRS ratios correctly predicted 100% of the subjects by selecting Occ mICh/Cr_d and Fr mICh/Cr_d as the significant variables. mICh/Cr_d stands out as a powerful discriminant strengthening the role of myoinositol and choline in the pathophysiologic process of HE.

Table1. Pearson's correlation coefficients (r) of metabolite ratios and NP scores

NP Domain	Fr	r	Occ	r
Visuo-spatial	Ch_d	.587(*)	Tau	.639(*)
	Asp	.537(*)		
Language	Ch_d	.542(*)		
	Glx	-.700(**)		
Motor	mICh	.698(**)	mICh	.598(*)
	mI	.705(**)		
	Tau	.624(*)		
Cognitive Speed	Ch_d	.673(**)	mICh	.616(*)
	mICh	.704(**)	Tau	.539(*)
	mI	.751(**)		
	Tau	.745(**)		
Attention	NAA_d	.686(**)	Cr	-.631(*)
	ThrLac	-.707(**)	PCh	-.668(**)
			GABA	-.585(*)
			ThrLac	-.596(*)
Global	Glx	-.545(*)	Tau	.540(*)
Executive	NS		NS	
Memory	NS		NS	
Right GP#	NS		NS	
Left GP#	NS		NS	

NS- Not significant; * Significant at 0.05 level; ** Significant at 0.01 level; #- n = 7; Asp- Aspartate, PCh- Phosphocholine, ThrLac- Threonine and Lactate

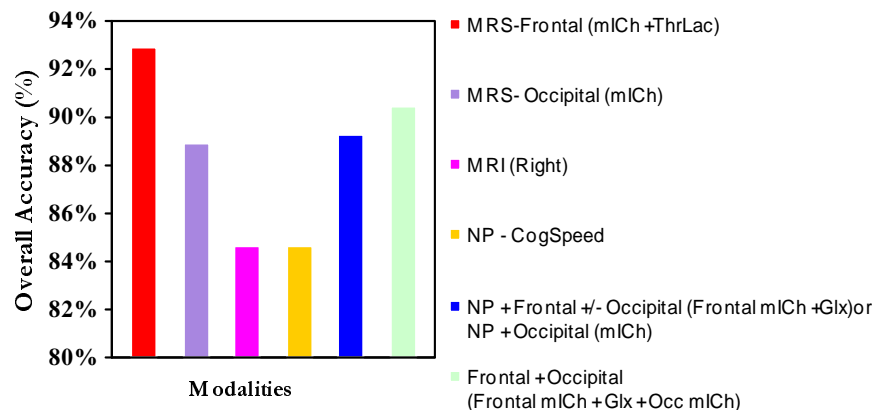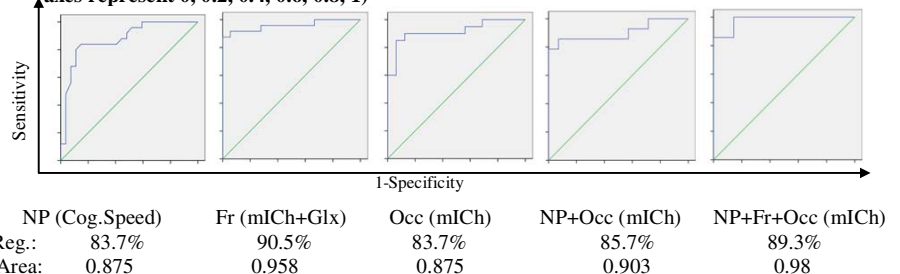**Fig.1.Results of Discriminant Analysis for the different modalities**

Legend:
- MRS-Frontal (mICh +ThrLac)
- MRS- Occipital (mICh)
- MRI (Right)
- NP - CogSpeed
- NP +Frontal +/- Occipital (Frontal mICh +Glx)or NP +Occipital (mICh)
- Frontal +Occipital (Frontal mICh +Glx +Occ mICh)

Fig.2. Results of Logistic Regression Analysis and ROC curve analysis (Tick marks on both axes represent 0, 0.2, 0.4, 0.6, 0.8, 1)

	NP (Cog.Speed)	Fr (mICh+Glx)	Occ (mICh)	NP+Occ (mICh)	NP+Fr+Occ (mICh)
Logistic Reg.:	83.7%	90.5%	83.7%	85.7%	89.3%
ROC Curve Area:	0.875	0.958	0.875	0.903	0.98

Conclusion: Our preliminary results so far indicate that 2D MRS ratios not only give pathophysiological information and correlate with neuropsychological impairment but also give the best diagnostic predictability in differentiating MHE patients from controls as compared to either NP tests or MRI alone, with mICh/Cr_d ratio being the most discriminant variable amongst all. Frontal MRS ratios show higher predictability than Occipital MRS ratios.

References:
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