Brain Phenylalanine Levels in Phenylketonuria using 2D Correlated Spectroscopy

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TARGET AUDIENCE: Researchers and clinicians interested in new methods of measuring phenylalanine in the brain in patients with phenylketonuria

BACKGROUND: Phenylketonuria (PKU) is an autosomal recessive disorder caused by mutations in the gene responsible for the liver enzyme phenylalanine hydroxylase, resulting in a block in the conversion of phenylalanine (Phe) to tyrosine and subsequently to elevated levels of Phe in blood and brain. The buildup of Phe in the brain results in progressive, neurological decline by 3 or 4 months of age. It has been suggested that the blood Phe level is not necessarily an indicator of neurological and neuropsychological deficits. Thus, robust measurement of the Phe concentration in the brain noninvasively would provide a more direct assessment of the severity of the disease in patients with PKU.

OBJECTIVE: The goal of this study was to improve the measurement of the *in vivo* concentration of Phenylalanine (Phe) using 2D Correlation spectroscopy (COSY) in the brains of subjects with Phenylketonuria (PKU).

METHODS: *Study Protocol.* Nine subjects with early treated classic Phenylketonuria (PKU) (pre-treatment/off-diet blood Phe concentration above 1200 µmol/L, Phe tolerance of less than 300 mg or genotype associated with classic PKU) were selected for this study. The MR imaging and spectroscopy protocol was performed in a 3T MR scanner (Siemens TIM Trio) using a 32-channel head coil. Structural MRI for localization of MRS voxels used the MP-RAGE sequence with TR/TE = 1800/3.4 ms, TI=1100, FA = 7º, FOV = 25.6cm2, 176 contiguous axial slices, voxel size 1x1x1 mm. Two MRS sequences were used: 1D MRS (PRESS; TR 2s, TE 30ms, 64 avgs) and 2D COSY (TR 1.5s, initial TE 30 ms, 64 increments of 0.8 ms, 8 avgs, 3x3x3 cm^3). MRS voxels were placed in the posterior central gyrus (PCG) and posterior white matter (PWM) as shown in Figure 1.

Data Analysis. The metabolite concentrations were estimated from the PRESS spectra LCModel [1]. For the 2D COSY spectra, metabolite concentrations were calculated from the volume of the peak and calibrated to the LCModel estimation. Felix NMR was used to measure the volume of Phe and Creatine (Cr) resonances from the 2D COSY spectra. LCModel was used to obtain the absolute Cr concentration. The ratio of the COSY Phe and Cr resonance volumes was scaled by the relative number of spins contributing to each resonance (5 and 3, respectively) and multiplied by the absolute Cr concentration estimated by LCModel.

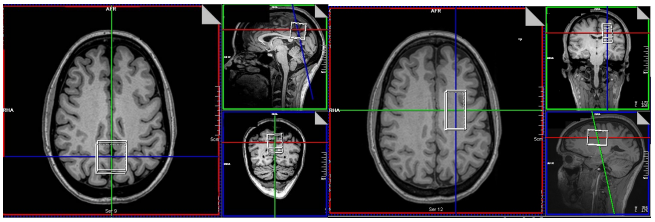

Figure 1: MRS Voxels: Left: Posterior Cingulate Gyrus (PCG) and Right: Posterior White Matter (PWM)

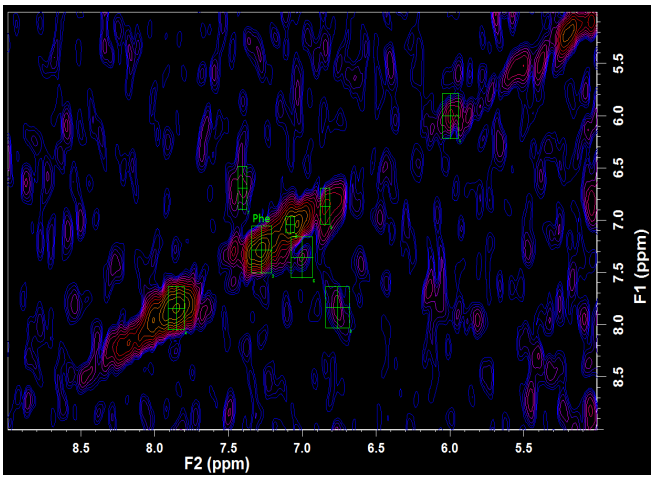

Figure 2: 2D COSY Spectrum (9-5ppm region) from the brain of a subject with PKU

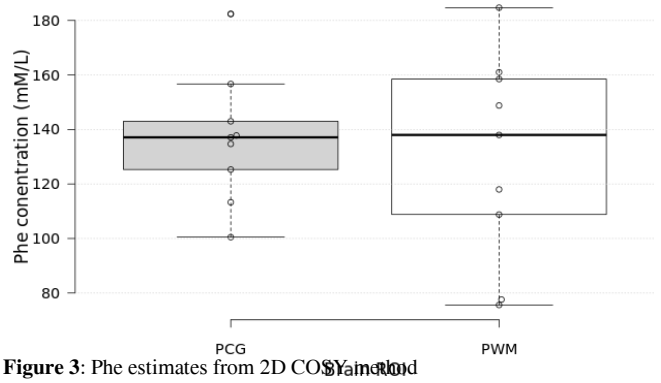

Figure 3: Phe estimates from 2D COSY method

RESULTS/DISCUSSION: The resulting estimates of the Phe concentrations are shown in Figure 3. The brain Phe concentrations estimated from 2D COSY are in the range of 0.075 to 0.2 mM/L. This is comparable to estimation with the PRESS sequence in literature [2, 3]. The Phe resonance is used from the COSY spectrum. Because this peak in a region of the spectrum where relatively few brain metabolites resonate, the Phe resonance is less likely to be contaminated by signal from another metabolites.

CONCLUSION: Since the Phe concentration can be very low even in persons diagnosed with PKU, the ability to separate the Phe signal from other brain metabolites in an MR spectrum would improve the estimation of the absolute Phe concentration in the brain. With a more robust estimation of Phe concentrations in the brain, MRS could prove to be a valuable tool for monitoring and assessing patients with PKU.

REFERENCES: [1] Provencher S. Automatic quantitation of localized in vivo 1H spectra with LCModel. NMR in Biomedicine 2001. [2] Koch R, et al. Blood-brain phenylalanine relationships in persons with phenylketonuria. Pediatrics 2000. [3] Moats RA, et al. M. Brain phenylalanine concentrations in phenylketonuria: research and treatment of adults. Pediatrics 2003.