Evidence of Altered High-Energy Phosphate and Membrane Phospholipid Metabolism in Pelizaeus-Merzbacher Patients with PLP1 duplications using ^{31}P Magnetic Resonance Spectroscopy

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Background: Pelizaeus-Merzbacher disease (PMD) is an X-linkedrecessive leukodystrophy of the CNS caused by mutations affecting the major myelin protein, proteolipid protein 1 (PLP1). The clinical spectrum that describes the severity of PMD expresses vast heterogeneity that depends on the nature of the PLP1 mutations and altered gene expression.To better understand the cellular pathogenesis caused by *PLP1* duplications, the most common form of PMD, ^{31}P magnetic resonance spectroscopy (^{31}P MRS) was used to assess high-energy phosphate and membrane phospholipid (MPL) metabolism. Specifically, it is unclear to what extent high-energy phosphate and MPL metabolites are altered in cortical, subcortical and white matter (WM) areas of PMD patients compared to healthy individuals.

Methods: 15 PMD patients with *PLP1* duplications (mean age: 17.9 ± 7.2 yrs; range: 9 to 30 yrs; 15 males) and 25 healthy individuals (mean age: 15.6 ± 5.9 yrs; range: 9 to 29 yrs; 25 males) participated in the study. A 3D whole-brain, multi-voxel ^{31}P MRS measurement was collected on a 3T Siemens Verio system using a dual-tuned ^{31}P/^{1}H head coil. The acquisition parameters were: 3D FID_CSI sequence modified with a pre-acquisition delay of 1.4 ms, FOV=340×340×170mm, slab thickness=120mm, acquisition matrix=14×14×8, zero-filled=16×16×8 (nominal voxel dimension=2.125×2.125×2.125 cm^3), TR=0.54 sec, bandwidth=3.3 kHz, 64 averages (weighted-average k-space), elliptical k-space sampling, with ^{1}H-decoupling and acquisition time 23 min. T_1-weighted MRI images were also collected during the ^{31}P MRS session, which was used to co-register the subject space of the ^{31}P MRS to the high-quality T_1-weighted images collected using a single-tuned ^{1}H volume coil.

The ^{31}P signals of different right and left anatomical voxel locations were systematically extracted and quantified [100% automated (1)]. These voxel locations of interest were pre-defined anatomically on a template brain (cortical, sub-cortical and white matter areas) and were co-registered and re-mapped to the subject space. These same voxel locations were also mapped on the tissue-segmented images to determine the tissue fraction within each voxel. The ^{31}P metabolites [PE, PC, Pi, glycerophosphoethanolamine (GPE), glycerophosphocholine (GPC),phosphocreatine (PCr), dinucleotides (DN) and ATP (two doublets and a triplet)] were modeled in the time-domain with 21 Gaussian-damped sinusoids and with a 5H Gaussian apodization (right figure) and expressed as a mole %relative to the total quantified ^{31}P signal. A generalized linear regression model (PROC GENMOD; SAS Institute Inc.) with subject group, age, gender, grey matter tissue fraction and side (right and left) as the main effects, was used to test group differences.

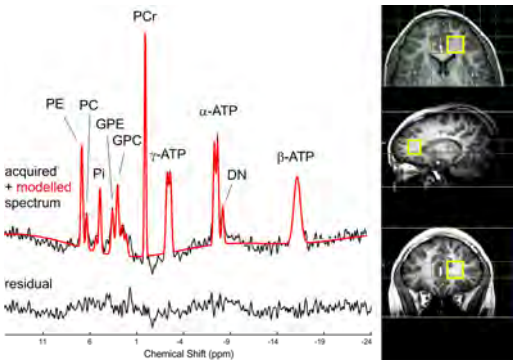

Figure: An example of a quantified ^{31}P spectrum from the anterior frontal white matter.

Results: Results showed significant and widespread increased PCr in the anterior and posterior white matter (AWM and PWM), anterior and posterior cingulate cortex (ACC and PCC), hippocampus (HIP), occipital cortex (OCC), caudate (CAU) and thalamus (THA)of PMD patients compared to controls (all $p<0.05$). There was also a significant decreasein β-ATP in the PCC among PMD patients. Additionally, results showed significant and widespread decreases of the MPL breakdown product, GPC, in the AWM, PWM,OCC, CAU, THA, and dorsal prefrontal cortex (dPFC) of PMD patients compared to controls ($p<0.05$), while GPE levels were significantly increased in the ACC and PCC ($p<0.05$).

Discussion: For the first time, alterations in ^{31}P metabolites in PMD patients are being reported. The widespread increase in PCr, a highly-mobilized high-energy phosphate store, may indicate an environment of decreased utilization of energy in the CNS among PMD patients. Though no significant differences were noted with the precursors of MPLs, the decrease in breakdown products of MPLs may relate with the degeneration of the phospholipid bilayer content in the CNS as a mechanism of PMD pathogenesis, perhaps contributing to the lack of energy demand. ^{31}P MRS has provided us insight into the cellular pathogenesis of PMD both in terms of phospholipid metabolites as well as energy expenditure for the first time, and serves as a way to identify potential surrogate biomarkers to follow treatment of patients in the future.

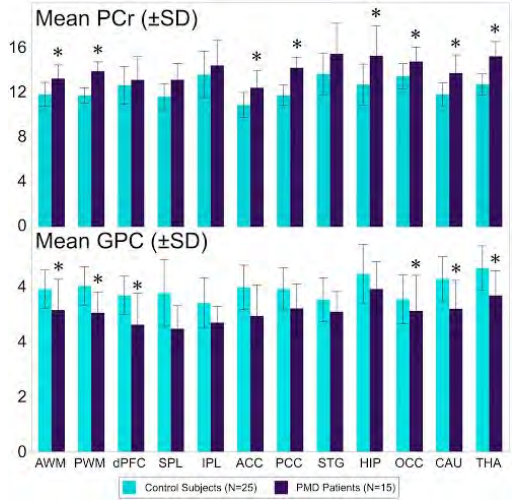

Figure: Widespread increase in PCr and decrease in GPC in PMD patients compared to controls.

1. Wu H*, Goradia DD, Stanley JA. A Fully Automated and Robust Method of Extracting CSI voxels from Precise Anatomical Locations: An Application to a Longitudinal 31P MRS Study. Proceedings of the 22nd Annual meeting of the International Society for Magnetic Resonance in Medicine 2014.