Absolute brain metabolite concentrations in non-acute Maple Syrup Urine Disease

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INTRODUCTION: Maple Syrup Urine Disease (MSUD) is a rare inborn error of metabolism with high prevalence in the Old Order Mennonites of rural Lancaster County, Pennsylvania. Deficiency of branched-chain 2-ketoacid dehydrogenase blocks the degradation of leucine, isoleucine, and valine and their 2-keto and 2-hydroxyacids (Fig,1). Cerebral accumulation of leucine and 2-keto-isocaproic acid are associated with mental status changes, ataxia, hallucinations, and progressive encephalopathy[1]. Regardless of effective dietary treatment, patients are at risk for episodic metabolic intoxication during infectious illnesses and may also suffer from chronic mental disability. The prevalence of chronic depression, anxiety, and attention deficit disorder is increased in patients even during periods of good dietary control[2]. Patients have lower mean IQ scores, which may be a result of acute and chronic biochemical disturbances in the brain[3-5]. Our research provides a unique neurochemical profile of medically managed MSUD patients free of acute illness and novel insights into the underlying mechanisms of chronic cognitive and behavioral sequelae of this complex disorder.

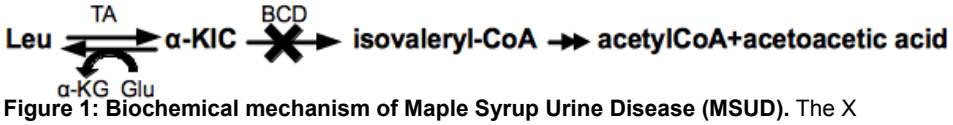

Figure 1: Biochemical mechanism of Maple Syrup Urine Disease (MSUD). The X designates the mutated branched chain amino acid dehydrogenase (BCD) in MSUD patients. No longer able to metabolize leucine (Leu), isoleucine, and valine. Buildup of keto acids causes a reversal in the direction of the transaminase (TA) reaction, resulting in buildup of branched chain amino acids and possibly also depleting glutamate (Glu) in the formation of a-ketoglutarate (a-KG).

MATERIALS AND METHODS: Neurochemistry was evaluated in MSUD patients and unaffected sibling controls using single voxel proton magnetic resonance spectroscopy (MRS; TE = 30 ms, relaxation time, TR = 2000 ms) using the Point Resolved Spectroscopy (PRESS) pulse sequence on a Siemens Magnetom Trio 3 Tesla MRI scanner. Three regions of interest were selected using a structural 3D T1-weighted image: anterior cingulated gray matter (ACC, 5.6 cc), left basal ganglia (BG, 6.8 cc), and right parietal white matter (3.4 cc). LCModel software was used to identify and quantify compounds by modeling the supposition of peaks of known metabolites onto the raw data[6]. Data was analyzed using an ANCOVA with age, partial voxel volume (% gray matter for left BG and ACC, % white matter for right parietal region of interest), and plasma leucine concentration as covariates.

RESULTS: Sixteen sibling controls and fifteen MSUD patients were recruited for this study, however data collected with an individual standard deviation above 30% was not included in the analysis. Decreased NAA was found in patients with MSUD, indicating decreased neuronal mitochondrial energy production (Fig. 2A shows left BG, left BG: $F = 15.98$, $p < 0.001$; ACC: $F = 10.77$, $p < 0.01$). Creatine levels in the right parietal white matter were decreased in the MSUD group (Fig. 2B, $F = 10.04$, $p < 0.01$). Glutamate was also decreased in patients with MSUD compared to controls (Fig. 2C shows left BG, left BG: $F = 35.07$, $p < 0.0001$ ACC: $F = 27.28$; $p < 0.0001$), possibly due to reverse transaminase function.

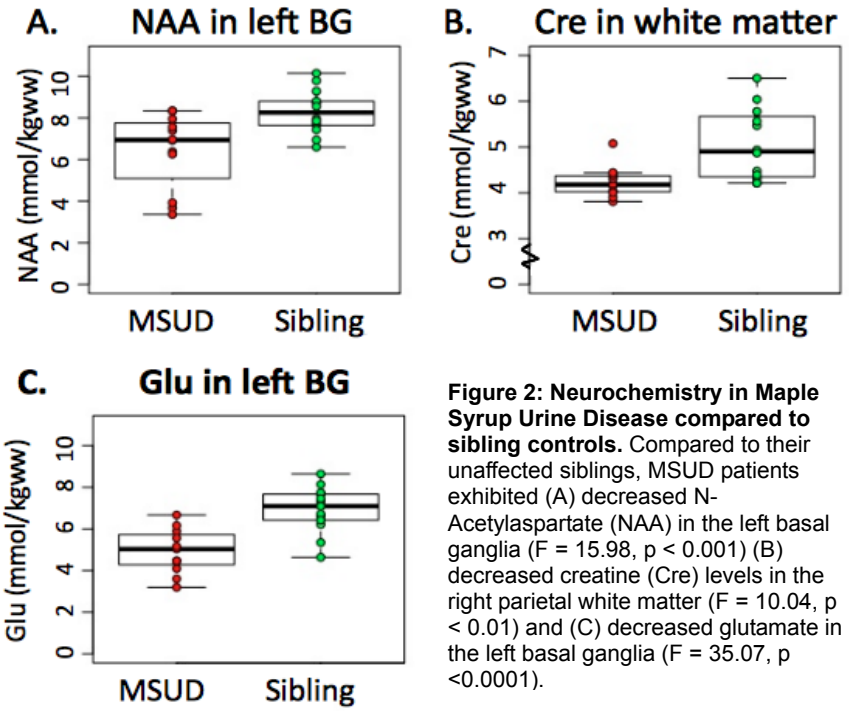

Figure 2: Neurochemistry in Maple Syrup Urine Disease compared to sibling controls. Compared to their unaffected siblings, MSUD patients exhibited (A) decreased N-Acetylaspartate (NAA) in the left basal ganglia ($F = 15.98$, $p < 0.001$) (B) decreased creatine (Cre) levels in the right parietal white matter ($F = 10.04$, $p < 0.01$) and (C) decreased glutamate in the left basal ganglia ($F = 35.07$, $p < 0.0001$).

CONCLUSION: Previous case reports of brain MRI and MRS in MSUD patients have focused on findings during acute crisis and have reported that neurochemical profiles return to baseline in recovery. However, in the chronic state, plasma amino and keto acid concentrations fluctuate and give rise to significant disturbances in amino acid transport into the brain. We report low cerebral glutamate, creatine, and NAA levels in alert MSUD patients, which suggests chronic impairments in neuronal mitochondrial function and neurotransmitter metabolism. Brain glutamate depletion occurs through reverse transamination, decreasing as 2-ketoisocaproic levels increase, which may depress the level of consciousness but also provide neuroprotection from glutamate-mediated damage. Parallel studies of MSUD brains after liver transplant are underway to assess the effects of this curative therapy upon brain chemistry and structure. We will report about the relationship between neurochemical profiles and neuropsychiatric outcomes. This work will help inform decisions about liver transplantation and provide insights into the neurochemistry of neuropsychiatric illnesses.

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