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Creatine deficiency syndromes, which are inborn errors in brain metabolism of creatine, present clinically with various neurological symptoms that include extrapyramidal movement disorders, developmental regression, behavioral problems and intractable epilepsy. These congenital brain diseases, discovered and characterized within the past decade, are sorted into two major categories. The first category consists of deficiencies of enzymes, specifically guanidinoacetate methyltransferase (GAMT) and arginine-glycine-amidinotransferase (AGAT), which are vital to the endogenous synthesis of creatine. Patients with GAMT deficiencies, when treated with oral creatine, demonstrate improvement of clinical symptoms and biochemical abnormalities, yet complete normalization of the clinical condition is not observed (Schulze et al. 1997). Unlike in patients with GAMT deficiency, oral creatine supplementation nearly completely restores pre-treatment creatine levels, as well as significantly improves the existing developmental deficits, in patients with AGAT deficiencies (Items et al. 2001). The second category includes deficiencies in brain creatine transporter activity. Identified as a X-linked phenomena affecting male children (and oftentimes their female carriers as well), patients treated with oral creatine show negligible rates of creatine uptake and thus no clinical improvement or increased creatine/phosphocreatine signal when analyzed by magnetic resonance spectroscopy (MRS) (Cecil et al. 2001).

In this Summer Research Fellowship project, the goal was to develop an assay which could assess the lack of creatine transporter activity in patients with the creatine transporter defect. Existing data demonstrates that carriers and patients of the creatine transporter defect have altered levels of creatine in the blood, blood cells and urine when compared to normal, healthy controls. In order to quantify these differences, we sought to develop an assay that could assess the relative activity of the creatine transporter by comparing intracellular vs. extracellular RBC creatine concentrations. Our unique adaptation to the standard fluorometric assay used to measure total tissue creatine (Conn 1960) seems to allow the reliable quantification of this ratio in a set of controls, thus providing an index of creatine transporter activity. In the future, we will look to characterize the differences in creatine concentrations of blood, serum and urine samples taken from diagnosed patients and healthy volunteers. The potential elimination of the multiple modalities currently used to diagnose the condition (MRS, magnetic resonance imaging, Western blot, muscle biopsy), as well as the establishment of diagnostic controls (for expected [Cr] values) for pediatric patients, will ultimately ease the identification of the population with defect as well as the screening of those patients who demonstrate similar clinical symptoms. Along with the other ongoing projects in the laboratory and clinical settings, it is anticipated that the assay will help to demonstrate proof of principle that oral Cr supplementation will increase (and possibly normalize) brain Cr in the population carrying the transporter defect.