Title: The Creatine Transporter Deficiency Developmental History Questionnaire

Authors: Rebecca P Thomas, Amanda Bennett-Palladino, Can Ficicioglu, Whitney Guthrie, Robert J Davis, Aleksandra Bruchey, Simona Bianconi, Audrey Thurm, Judith S Miller

Introduction: Creatine transporter deficiency (CTD) is a rare, X-linked genetic disorder that causes intellectual disability and severe impairments in speech, motor skills, and adaptive skills (van de Kamp et al., 2013). A CTD diagnosis can be confirmed through genetic sequencing (SLC6A8) or magnetic resonance spectroscopy (MRS). Recent studies have begun to classify the phenotype of CTD in older children, but information about the first possible signs parents or physicians might notice are limited. Early diagnosis is important because signs of CTD may manifest before serious medical issues, such as seizures, appear. Furthermore, some children may respond (at least partially) to currently available treatments. As a first step to identifying earliest signs, parent recall of the child’s early development and path to diagnosis can be helpful.

Method: We conducted both an open-ended parent interview and medical record review with 17 families (n=20 distinct participants; n=3 with family history). This represents 13.3% of all known cases of CTD in the world. Diagnoses were confirmed with a documented SLC6A8 mutation, as identified through medical record review. We asked parents open-ended questions about the pregnancy, delivery, first years, first concerns as they arose, first concerns in hindsight, current concerns, and current strengths in their children. Several questions were modeled after items on the Autism Diagnostic Interview -Revised (ADI-R; Lord et al., 1994), in order to generate hypotheses about earliest signs and first referrals. We also reviewed medical records for any additional information about provider referrals, biological and genetic test results, and social histories. We used the combined data to create a standardized interview for future use with CTD or other rare disease populations.

Results: Children ranged in age from 1.2-20.11 years (M=9.6 years, SD=5.8 years). The CTD Developmental History Questionnaire included eight sections that cover development from early signs to current presentation: First Concerns, Pregnancy, Infancy, Physical Development, Feeding, General Medical, Language, and CTD Diagnosis. New information obtained that had not been well known in the literature included: 18 (90%) were the product of an uncomplicated pregnancy and birth; 8 (40%) had seizures before age 3; all showed significant delays before age 2. Diagnoses were made between the ages of 1-20 years, but only children with an older sibling with CTD were diagnosed before age 3. Most notably, in 10 cases (50%), the constellation of severe infantile projectile vomiting (not just reflux) and/or failure to thrive before age 12 months, along with significant delays in crawling or walking could have indicated a need for specialist referral earlier. In this group, actual diagnosis was made between ages of 3-11 years. Parents’ top behavioral concerns included: Language, challenging behaviors, independence skills, attention, and emotion regulation.

Discussion: Open-ended narrative histories from parents can provide information researchers may not have considered. In our sample, we found that the diagnosis of CTD was never made as early as the literature suggested, but that possible indicators exist that could help identify children at risk for CTD before age 12 months. This has generated hypotheses about how best to screen for and diagnosis CTD earlier. This open-ended, parent narrative approach could be helpful for identifying early signs of other rare diseases. Our developmental history form may also serve as a starting point for such an approach.

References/Citations: