Published in final edited form as:

J Pediatr. 2019 March ; 206: 283–285. doi:10.1016/j.jpeds.2018.11.008.

Early Signs of Creatine Transporter Deficiency

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Abstract

Early identification is a goal for Creatine Transporter Deficiency (CTD), and will be critical for future treatment. Before the first birthday, half of this sample showed both a significant feeding/weight gain issue, and delayed sitting or crawling. Combined, these early indicators could have alerted providers to conduct a urine screen.

Keywords

Infant Vomiting; Failure to Thrive; Motor Delay

Introduction

CTD is a rare X-linked single gene disorder, and one of three cerebral creatine deficiency syndromes.¹ Children with CTD experience significant developmental delays, including minimal verbal development, intellectual disability, motor dysfunction, and seizures. Preliminary diagnosis is possible by measuring creatine and related metabolites in blood and/or urine, or by proton magnetic resonance spectroscopy.² Definitive diagnosis is made by sequencing *SLC6A8* and creatine uptake studies. CTD does not result in imminently life-threatening conditions early in life. There is no routine procedure in primary care that would identify CTD in infants. A recent review suggested most diagnoses would be made before age 3 years.³ However, there have been no studies yet of the actual age of diagnosis. We

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Financial Disclosure: Drs. Aleksandra Bruchey and Robert J Davis are employees of Lumos Pharma, Inc. The other authors have no financial disclosures relevant to this article.

Conflict of Interest: The authors have no conflicts of interest relevant to this article to disclose.

interviewed families and reviewed available medical records to determine 1) age of diagnosis in a retrospective sample; 2) developmental course and the earliest signs of CTD; and 3) the path to diagnosis experienced by families.

Methods

Twenty males with genetic confirmation of CTD based on pathological mutation in the SLC6A8 gene from 17 families participated (known cases range from 200–250 globally). Participants were age 1.2–20.11 years ($M=9.6$ years, $SD=5.8$ years). Racial and ethnic breakdown was: 75% White/non-Hispanic, 10% Asian, 10% Black, and 5% Hispanic. Parents participated in an extensive, open-ended interview about pregnancy, delivery, early development, first concerns, concerns in hindsight, and current functioning. Parents provided access to medical records for review, and home videos of participants at different ages. Seven participants were also evaluated in person. Content from the interviews and medical records informed the creation of a CTD Developmental History Interview for ongoing research (available from the authors). Families were also interviewed with the Vineland Adaptive Behavior Scales Survey Form, Second Edition.⁴ The Institutional Review Boards at The Children's Hospital of Philadelphia and NICHD approved this study.

Results

Age of diagnosis.

The only CTD diagnoses made before age 42 months were in children with a known family history at birth (2 of the 3) or an early seizure (2 of 6 with seizures) or early change in balance and coordination ($n=1$). When they occurred, seizures prompted an earlier diagnosis in general (average age of 68 v. 111 months). See Table 1 for age of first signs, diagnosis, and the time span between them for each participant.

Pregnancy and delivery.

Complications were rare and minor. The most significant was mild heart rate decelerations during labor in one participant, later attributed to an anomalous insertion of the umbilical cord into the placenta.

Development from 0–11 months of age ($n=20$).

Ten of the 20 participants had both a feeding or weight gain issue (eight with projectile vomiting and very slow weight gain, two with slow weight gain and very low energy) as well as an early delayed milestone (sitting up or crawling). Four more children had either one or the other. One had a seizure without other early signs. Six families tried prescription-based formulas, with limited success. Eight children would eventually be diagnosed with failure to thrive or had a feeding tube placed. While the benefit of hindsight suggests that 15 children had at least one early indicator, parents of only eight were significantly concerned at the time, and only three children were referred to Early Intervention (EI). The two children diagnosed before the first birthday had a known family history.

Development from 12–24 months of age (n=19).

Vomiting resolved in all but two children by 12 months of age. However, 18 of 19 children failed to walk on time (15 walked at 24 months). Seven children had their first apparent seizure (by parent report or neurological exam) between 12 to 24 months; five of these had shown both early vomiting and motor delays. By 24 months, all parents were significantly concerned about delays in motor milestones, lack of babbling or speech sounds (n=12), persistent feeding problems but no longer vomiting (n=9), seizures (n=6) or activity level (n=2). However, only seven children enrolled in EI during this time period, for a cumulative total of 10/20 children in EI. No children were diagnosed between 12–24 months of age.

Development from 24–36 months of age (n=18).

All children were walking by age 36 months, but at least one child had ataxia and at least one had a very unusual gait, and other motor delays were present. Only one child continued to experience significant vomiting (which has continued through childhood). All 18 continued to show no or minimal language development. Four children were referred to EI for the first time, for a cumulative total of 14/20 in EI. Two children had their first seizure and a third had a sudden change in coordination which prompted immediate evaluation (but no seizure activity was detected); two of these received the CTD diagnosis during this period.

Pathway to a CTD diagnosis.

Of the 20 children, three had a family history which prompted testing, and one was found through a research study specifically screening for CTD in children with autism or intellectual disability.⁵ Six had a seizure and one had a sudden change in balance that led to a specialist referral. Otherwise, six had parents who actively sought specialty care despite a reported lack of concern from primary care providers; and four had a provider refer for specialty care based on developmental concerns. Specialty providers included neurology, genetics, and developmental and behavioral pediatrics, with each discipline associated with some catches and some misses.

Current presentations.

Current ages ranged from 14 months to 20 years. While still severely impaired, the individuals in our sample continued to learn new skills. The two adults both developed *phrase speech for the first time in late adolescence*. However, across the sample verbal skills remained limited: four used some phrase speech, nine used only single words, and seven had no expressive language. Home videos and parent report indicated that children understood at least some aspects of complex conversations happening around them. Independent daily living skills remained very low, with all standard scores on the Vineland ranging between 28–69 (population mean=100; standard deviation=15). With regard to behavior, nine families reported current behavior challenges, including self-injury (n=8), throwing objects (n=7), tantrums (n=7), and aggression toward other children (n=5). Six had a community diagnosis of Autism Spectrum Disorder. With regard to medical issues, four used feeding tubes, and one continued to have significant seizures. We did not gather systematic information about current use of medications or supplements.

Current parent concerns and child strengths.

Parents reported relative strengths in receptive language, and a generally happy mood in young children (n=13). The parents of adults (n=2) indicated significant emotional dysregulation in adolescence, which subsided in adulthood. Top concerns were independence (n=14) and communication (n=10). Almost all still need assistance with basic self-help skills such as toileting, dressing, and bathing. Challenging behaviors were a concern for some (n=5), followed by seizures (n=5) and vomiting (n=1).

Discussion

When presenting together, very early feeding or weight gain issues (significant vomiting or failure to thrive) and motor delays (sitting or crawling) could have potentially alerted providers to seek a specialty referral and/or conduct a urine screen for half of the study participants. Urine screens are not perfect, but can be effective as early as age 1 month; see recent ACMG guidelines.² However, most of our participants were diagnosed after a seizure or only after years of delayed development. While this study is limited to retrospective parent report and medical record review, it is informative since the sample comprises possibly ~10% of all known cases, and it presents the first in-depth look at the sequence of events that ultimately led to an accurate diagnosis.

While feeding issues and delayed milestones are not very specific indicators, clinical guidance available across widely respected entities (www.medlineplus.gov; www.healthychildren.org; www.uptodate.com) does not alert families or primary care providers to consider a rare metabolic condition in infancy. Online information about infant emesis or vomiting points to reflux, illness, allergy, or pyloric stenosis, although vomiting is known to occur in other neurometabolic conditions.⁶⁻⁸ Furthermore, parents and providers could use more tools to reach a consensus on what constitutes vomiting v. reflux, such as showing videotapes of the behavior to a physician.

Current guidance about failure to thrive⁹ also does not alert families or providers to consider a rare metabolic condition. Widespread guidance is still based on a landmark study from 1978¹⁰ which concluded any medical explanation for FTT will be identifiable from the history and physical examination, with no extra value provided by laboratory screening tests. Our data suggest that considering the possibility of rare metabolic disorders could lead parents and providers to an earlier diagnosis. Similar calls have been proposed to view early life epilepsy as a possible signal of a genetic disorder rather than a separate condition.¹¹

Finally, to our knowledge we are the first to report a metabolic condition where infant vomiting may resolve with the introduction of solid food. Specialists evaluating an older child might not even ask about vomiting in early infancy if it has resolved, since solid foods reduce reflux for many babies, but combined with other early delays significant infant vomiting may be diagnostically relevant and suggest a metabolic condition. Further research should examine possible mechanisms of vomiting in these patients, particularly including whether it could be due to hypotonia since there are often other motor delays in CTD. Other possible considerations include esophageal sphincter dysfunction, or delayed gastric emptying, but we have not examined those specifically. More generally, gastrointestinal

problems could be added to the section on metabolic testing in guidelines for genetic testing in children with intellectual disability or developmental delay.^{12–14}

We encourage pediatricians to closely monitor children with delayed basic milestones, significant feeding or weight gain issues, vomiting, or failure to thrive and consider a urine screen or genetics referral. CTD is a rare condition, but complacency may significantly delay diagnosis. We also recommend information about CTD for pediatricians be included on prominent websites and within AAP resources.

Acknowledgments

Funding source: This study was supported by Lumos Pharma, Inc., and the Intramural Research programs of NCATS, NICHD and NIMH.

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Table 1.

Ages and time spans between first signs and diagnosis.

Child	Positive Family History	Signs age 0–12 mos	Signs age 12–24 mos	Age of first seizure (Y:M)	Approximate age of CTD dx (Y:M)	Time from first sign to diagnosis
A		V, M	X	1:11	2:6	1–2 years
B		V, M	X	3:0 ^a	2:5	1–2 years
C		V, M	X	1:7	5:2	3 years
D		V, M	X		3:6	2–3 years
E	X	V, M	X	1:6	0:3	n/a
F		V, M	X	1:8	6:0	6 years
G	X	V, M	X		0:1	n/a
H		V, M	X	2:0	4:0	2 years
I			X		9:0	7 years
J			X	4:0	4:7	3–4 years
K		V	X	2:0	11:6	9 years
L		M	X		3:6	2–3 years
M	X		X		5:0	n/a
N		S	X	0:8	9:0	8 years
O		V, M	X		11:0	9 years
P		V	X	2:2	4:0	2 years
Q			X	2:0	7:0	5 years
R			X		20:0	18 years
S		V, M	X	4:6	5:0	4–5 years
T		M	X	3:0	8:0	7–8 years

V = Vomiting or significant feeding issue

M = Early delay in sitting or crawling

S = Seizure

^aThis patient had a noticeable change in balance at age 2:5 which is what led to the CTD diagnosis.