CLINICAL REPORT

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Improvement of Regressive Autism Symptoms in a Child with *TMLHE* Deficiency Following Carnitine Supplementation

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Disorders of carnitine biosynthesis have recently been associated with neurodevelopmental syndromes such as autism spectrum disorder (ASD). A 4-year-old male with autism and two episodes of neurodevelopmental regression was identified to have a mutation in the *TMLHE* gene, which encodes the first enzyme in the carnitine biosynthesis pathway, and concurrent carnitine deficiency. Following carnitine supplementation, the patient's regression ended, and the boy started gaining developmental milestones. This case report suggests that deficits in carnitine biosynthesis may be responsible for some cases of regression in individuals with ASD, and that testing for the respective biochemical pathway should be considered. Furthermore, this case suggests that carnitine supplementation may be useful in treating (and potentially preventing) regressive episodes in patients with carnitine deficiency. Further work to better define the role of disorders of carnitine biosynthesis in autism spectrum disorder is warranted. © 2015 Wiley Periodicals, Inc.

Key words: carnitine; autism spectrum disorder; developmental delay; regression; *TMLHE*

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INTRODUCTION

Carnitine is a naturally occurring amino acid metabolite of lysine and methionine, obtained from meat and dairy products in the diet, and produced endogenously in the kidneys, liver, and brain [Monfregola et al., 2005]. Carnitine plays an essential role in fatty acid catabolism by transporting long-chain fatty acids (LCFAs) into the mitochondrial matrix for use in beta-oxidation. Endogenous carnitine biosynthesis in humans proceeds through four enzymatic steps, of which the first occurs in peripheral tissue mitochondria and is catalyzed by the enzyme N-6-trimethyllysine dioxygenase (TMLD), which is encoded by the *TMLHE* gene at the Xq28 locus [Vaz and Wanders, 2002].

Disorders of carnitine biosynthesis and transport most commonly manifest clinically as cardiomyopathy with or without generalized skeletal muscle weakness [Stanley et al., 1991; Shibbani et al., 2014]. Primary systemic carnitine deficiency (OMIM # 212140) can also result in early episodes of life-threatening, Reye-like metabolic decompensation [Scaglia and Longo, 1999]. However, other presentations are less severe or even asymptomatic [El-Hattab et al., 2010], including reports of isolated gastrointestinal symptoms [Shoji et al., 1998], mild developmental delay [Wang et al., 2001; Magoulas et al., 2012], and asymptomatic mothers diagnosed by birth of an infant detected to have carnitine deficiency via newborn screening [El-Hattab et al., 2010]. Recently, we described a series of male probands with developmental delay and autism spectrum disorder (ASD) who were found to have deletions in the *TMLHE* gene, and showed through investigation of multiplex families that *TMLHE* mutation is likely a low-penetrance risk factor for non-syndromic or "idiopathic" ASD [Celestino-Soper et al., 2012]. Additional reports have confirmed the association of *TMLHE* mutations and decreased plasma carnitine levels in

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patients with ASD [Nava et al., 2012]. This finding of a metabolic aberration predisposing to ASD, with a metabolite that can be readily measured and supplemented clinically, is of unique interest for assessing the hypothesis that carnitine supplementation may improve autistic symptoms in these patients. However, there are no current reports of this potential response to carnitine supplementation in the literature.

We report here on a 4-year-old male with a previous diagnosis of ASD who was identified to have a *TMLHE* mutation upon presentation for developmental regression and whose regressive symptoms appeared to improve following carnitine supplementation.

METHODS

Clinical whole-exome sequencing (WES) and biochemical studies were performed at the Baylor College of Medicine Medical Genetics Laboratories using standardized protocols as previously described [Yang et al., 2013]. Briefly, a blood sample from the proband was obtained and genomic DNA was isolated, fragmented, and then ligated to Illumina multiplexing adapters. Massively-parallel sequencing was performed on an Illumina HiSeq platform with 100 bp paired-end reads and a mean coverage of target bases >100X. Illumina HumanExome-12v1 SNP array was also used to analyze the genomic DNA for quality control. Sanger sequencing was performed for confirmation of an identified potentially pathogenic mutation in the proband and on samples from both parents. Data analysis and interpretation were performed using Mercury 1.0 using the standard workflow previously described [Yang et al., 2013].

For trimethyllysine (TML), gamma-butyrobetaine (gBB), and free carnitine determination, patient plasma or urine samples were diluted and then mixed with 20 μl of internal standards (d3-L-carnitine, d9-gamma-butyrobetaine HCL, and d9-trimethyllysine). Next, methanol was added to the mixture for protein precipitation. The supernatant was then transferred to HPLC sample vials containing 0.1% heptafluorobutyric acid (HFBA) buffer before being injected into HPLC-MS/MS. Analysis was performed on a Waters Acuity TQD UPLC/MS/MS. Total carnitine was determined by a similar derivative MS/MS method as previously described [Smith and Matern, 2010].

CLINICAL REPORT

Developmental History

The patient was born at full term to a 29-year-old G1P1 mother by induced vaginal delivery following an uncomplicated pregnancy with appropriate prenatal care. He was otherwise healthy and meeting developmental milestones until approximately 12–18 months of age, at which time his parents reported hyperactivity, poor eye contact, lack of joint attention, and an interest in objects over people. The patient was originally given a diagnosis of pervasive developmental disorder- not otherwise specified (PDD-NOS) by an outside neurologist based on Childhood Autism Rating Scale (CARS) testing at age 2.5 years. At age 3 years, the patient was assessed using the ADOS (Autism Diagnostic Observation Schedule), module 2, administered by his school system's clinical psychologist as part of their comprehensive evaluation. He met criteria for ASD based on both his overall score (Communication + Social Interaction, patient scored 20, cut-off <12) and individual components of Communication (patient scored 7, cut-off <5) and Social Interaction (patient scored 13, cut-off <6). In addition, some unusual sensory interests and repetitive behaviors were noted.

At 2 years and 9 months of age, he experienced an episode of developmental regression while the family was traveling in Asia. Approximately two weeks prior to the regressive episode, he had been treated for a throat infection with antibiotics. The regressive episode was characterized initially by agitation and aggression, which developed into lethargy, poor arousal, and a profound loss of previously acquired developmental milestones, most notably speech. His regression also included previously acquired fine motor skills and social interaction. At the onset of this episode, his parents reported he had a concurrent gastroenteritis presumed to be viral in origin. The developmental regression occurred over a period of approximately two weeks, and lasted four months before he began to slowly recover lost skills. During these four months, his parents began a gluten and casein free diet in search of potential therapy, and they reported he began improving within 2 days after initiation of this dietary modification. No additional dietary/vitamin supplements were given at that time. He gradually regained all previous skills over a period of approximately 1.5 years and was maintained on the gluten/casein free diet. At the age of 4 years and 6 months, he was assessed by a developmental pediatrician and autism specialist. He was diagnosed with Autism Spectrum Disorder based on history, exam, previous positive ADOS assessment, and overall clinical impression.

He remained in his state of normal health and continued to develop along his trajectory until 4 years and 11 months of age (~2 years since first episode) when he again experienced an episode of profound developmental regression, at which time he presented to our clinic. This regressive episode also began with agitation and aggression, followed by lethargy, poor arousal, and loss of previously acquired skills. The patient's parents described this episode as very similar to the first. At the onset of this second episode, his parents began giving him vitamins B12, B6, folinic acid, and fish oil supplementation, based on empiric considerations. They reported initial improvement of the agitation/aggression, but developmental regression then began occurring again, prompting their presentation to our clinic. His parents denied any gastroenteritis at this time. At the time of this presentation, he had been maintained on the gluten/casein free diet since his first episode, but ate fish, chicken, and beef regularly.

Past Medical History

The patient had a previous diagnosis of PDD-NOS as described and anxiety disorder. His parents reported he had allergies to gluten, casein, egg, peanuts, and yeast. He had a history of chronic gastrointestinal discomfort that had been evaluated and followed at an outside hospital without identification of any organic process.

Family History

The patient's paternal first cousin had speech delay beginning at 1 year of age, but no other family members have had neuro-

FIG. 1. A 4-year-old boy with autism spectrum disorder and regressive episodes, found to have a TMLHE mutation.

developmental problems. His parents were otherwise healthy, there was no consanguinity and neither parent had a history of autism, developmental regression, or other neuropsychiatric disease. He has a biological sister who was 3 years old at time of presentation and healthy, without developmental delay or regressive episodes.

Clinical, Laboratory, and Genetic Evaluation

Physical exam was generally normal. He was non-dysmorphic and had normal height, weight, and head size parameters for his age (Fig. 1). His neurological exam was notable only for generalized hypotonia. MRI of the brain performed at an outside institution had been unremarkable 3 months prior to presentation, and the patient previously had a normal hearing evaluation.

Prior to presentation at our clinic, he had a series of metabolic diagnostic tests performed at an outside institution, all of which were within normal limits except for urine ketosis, low urine creatine (repeated at this presentation and found to be normal), and low total plasma homocysteine (repeated, and found to be normal). Chromosome microarray analysis (Baylor, version 9.1), and fragile X DNA testing were normal. Lactate, ammonia, plasma amino acids, urine organic acids, urine purines and pyrimidines, and urinary sialic acid were all normal. At the time of presentation, total plasma homocysteine and methionine levels were within normal limits. A carnitine biosynthesis panel (trimethyllysine, gamma-butyrobetaine, and carnitine), and acylcarnitine profile were ordered. Additionally, whole exome sequencing was initiated at this time in an attempt to identify underlying genetic causes of the patient's developmental regression.

Biochemical testing was notable for low C0 component of acylcarnitine (7 μM/L; normal range 28–56 μM/L), but all other components of the acylcarnitine profile were within normal limits (data not shown). Further assessment with a full plasma carnitine biosynthesis panel demonstrated low levels of gamma butyrobetaine (gBB) and free carnitine (Table I). WES identified a novel, hemizygous 2 bp deletion in exon 6 of the *TMLHE* gene (c.961_962del; p.I321fs; ChrX: 154736591) predicted to be deleterious according to ACMG guidelines [Richards et al., 2008]. Sanger sequencing confirmed this finding, and showed that the patient's mother is heterozygous for this deletion.

Clinical Course Following Carnitine Supplementation

Based on the laboratory and WES findings, the patient received supplemental L-carnitine at 200 mg/kg/day, titrated to higher doses but ultimately maintained at 200 mg/kg/day as the maximum tolerated dose. The supplementation started 8 days after first presentation to our clinic for his second regressive episode.

Four days after initiation of carnitine supplementation, his mother reported he was tolerating the treatment well and "seemed calmer." By two weeks after treatment had begun, his parents reported noticeable increases in language, non-verbal expression, and engagement with others. A general trend in improvement and recovery of his baseline interactive, language, gross, and fine motor skills continued over the subsequent month. By three months after

TABLE I. Carnitine Profile at Time of Initial Presentation

	Plasma concentration (μM/L) [normal range]	Urine concentration (mmol/mole creatinine) [normal range]
Trimethyllysine (TML)	0.40 [0.21–1.19]	116.07 [8.0–21]
Gamma butyrobetaine (gBB)	0.02 [0.35–1.43]	0.07 [0.0–1.1]
Free carnitine	2.0 [10–40]	1.0 [2–33]
TML/gBB ratio	20 [0.2–2.2]	1658 [0–242]

initiation of carnitine supplementation, his parents reported that all his previous milestones had returned; moreover, he had begun acquiring new milestones that he previously had not had. This included looking directly at his parents and smiling, more eye contact, joint attention, awareness, and interest in other people than before. His plasma levels of carnitine were now within the normal range (on carnitine supplementation, Table II).

At follow up in our clinic 4.5 months after initiation of carnitine therapy, his increased awareness and eye contact were notable, however, there was a new finding of hand flapping. The patient has since been maintained on L-carnitine at 200 mg/kg/day and is being followed closely for continued neurodevelopmental assessment. His parents report that symptoms appear to be dosage-sensitive, with better social interaction and language skills while on L-carnitine doses of 200 mg/kg/day and above and decreased language and social interaction whenever a dose decrease to less than 200 mg/kg/day was attempted. At the same time, doses of greater than 200 mg/kg/day were not very well tolerated, mostly due to gastrointestinal discomfort.

Follow Up in Family Members

A 13-month-old male cousin, son of the proband's maternal aunt, was tested following the proband's diagnosis, and found to carry the c.961_962del *TMLHE* variant. Subsequent biochemical analyses on plasma revealed a carnitine of 13 micromoles/liter [reference range 10–40], a trimethyllysine of 3 micromoles/liter [reference range 0.2–1.1], and a gBB of 0 [reference range 0.35–1.4], indicating true biochemical TMLD deficiency. His development up until that time had been normal, and he was preventively started on a low dose of L-carnitine (50 mg/kg/day).

DISCUSSION

In summary, we report on a patient with ASD who experienced two episodes of regression (one associated with viral illness), who then recovered developmental milestones upon initiation of carnitine supplementation, and was identified to have a maternally inherited frameshifting mutation in the *TMLHE* gene. This case illustrates important considerations for biochemical identification of carnitine deficiency and *TMLHE* mutation analysis, and suggests interesting hypotheses about the role of carnitine metabolic dysfunction in ASD.

First, in contrast to most previous patients with TMLD deficiency, plasma TML was not elevated in this patient. However, this patient's TML/gBB ratios were 6.8 and 9 times greater than the upper limits of normal in plasma and urine, respectively (Table I). Although TML was significantly elevated in urine in this patient, plasma TML was consistently within the normal range. In contrast, gBB was reduced in his plasma but within normal range in his urine. This biochemical phenomenon has been observed in two other patients with *TMLHE* mutations identified in our laboratory (data not shown). This suggests that the TML/gBB ratio may be a superior diagnostic marker for TMLD deficiency instead of TML or gBB levels in isolation, as it is likely that the plasma free carnitine concentration is influenced significantly by recent dietary intake. Similar to our case, a recent report describes a patient with a homozygous gene deletion of *BBOX1* (the last enzyme in the pathway for carnitine biosynthesis), in a girl with epilepsy, microcephaly, and intellectual disability, who had plasma carnitine levels in the low-normal range [Rashidi-Nezhad et al., 2014]. Furthermore, our case suggests that carnitine deficiency may not be readily evident from the acylcarnitine profile alone, which is commonly used in isolation to screen for defects in carnitine metabolism. Only the carnitine biosynthesis profile shows the deficiency of plasma carnitine in the context of its biochemical pathway, with normal or elevated trimethyllysine and decreased gamma-butyrobetaine. This suggests that an acylcarnitine profile alone may not be a sufficient screening test for TMLD deficiency.

TABLE II. Plasma Carnitine Profile After 2 Months of Carnitine Supplementation

	Plasma concentration (μM/L) [normal range]
Trimethyllysine (TML)	0.89 [0.21–1.19]
Gamma butyrobetaine (gBB)	1.48 [0.35–1.43]
Free carnitine	41.9 [10–40]
Total acylcarnitines	19 [5–18]

In addition, this case suggests a number of interesting hypotheses and implications for both the broad ASD phenotype and for specific cases of identified carnitine biosynthesis deficiency in children with neurodevelopmental disorders. First, this patient experienced two episodes of regression, which may have been triggered by viral illnesses. It is known that plasma carnitine levels are decreased following inflammation [Adlouni et al., 1988], bacterial infection, and in Crohn's disease [Demirkol et al., 1994]. Furthermore, carnitine levels decrease when there is increased energy demand in the system. Individuals with TMLD deficiency may therefore be particularly sensitive to such stressors. Second, in both situations, regression ceased following a change in diet or dietary supplementation: gluten-free diet in the first instance and supplementation with carnitine in the second. Interestingly, previous work on individuals with celiac disease has demonstrated that carnitine levels are increased in children on gluten-free diets alone (without supplementation) as compared to those on free diets [Ceccarelli et al., 1992; Curione et al., 2005]. While there is no biochemical testing available to document that the change to a gluten-free diet after the first episode of regression could have increased plasma carnitine levels, it is conceivable that direct or indirect increases of carnitine levels may have played a role in the recovery in both situations.

It is important to consider whether carnitine supplementation may improve autistic behaviors overall, or merely prevent or alleviate specific regressive episodes related to metabolic stress. Recent work suggests that there is only weak evidence that dietary modifications improve core autistic symptoms [Mari-Bauset et al., 2014]. However, this case suggests that children with identifiable deficits in carnitine biosynthesis may benefit from carnitine supplementation during periods of febrile illness or other acute

stressors in an attempt to prevent developmental regressive episodes. Furthermore, long-term supplementation of carnitine may be considered in individuals with identifiable mutations and biochemical testing demonstrating decreased carnitine levels at more than one time point.

More broadly, it is also of interest to consider if low carnitine levels during critical periods of neurodevelopment may contribute to neurocognitive dysfunction and/or the development of neurodevelopmental disorders such as ASD, in addition to prompting regression during acute episodes of metabolic stress. The previous significant association with mutations in carnitine biosynthesis enzymes and idiopathic ASD lends support to this notion [Celestino-Soper et al., 2012; Nava et al., 2012], as does the substantial body of research into metabolic and mitochondrial abnormalities in patients with idiopathic autism spectrum disorders [Rossignol and Frye, 2012].

The hypotheses suggested by this case need to be formally tested in large, blinded, placebo-controlled trials before routine supplementation of carnitine in such patients can be recommended. Furthermore, it is important to consider that the natural history of this patient's development may include regressive events followed by recovery that are completely independent of diet or carnitine supplementation. Following this patient further throughout his development and assessing other patients with *TMLHE* mutations will help to clarify this possibility. It will also be important to repeat formal psychiatric testing in this patient as he continues to develop to assess for improvement or stabilization of ASD symptoms.

In conclusion, we report a patient with ASD and regressive episodes identified to have a truncating mutation in *TMLHE*, who improved with dietary modification and carnitine supplementation. Further work to establish the role of carnitine metabolism in normal neurodevelopment, neurodevelopmental disorders like ASD, and in acute episodes of neurodevelopmental regression are necessary, as are more rigorous efforts to assess the efficacy of carnitine supplementation in children with identifiable mutations in carnitine biosynthesis.

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