

## CLINICAL REPORT

# Treatment efficacy of high-dose creatine supplementation in a child with creatine transporter (*SLC6A8*) deficiency

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## Abstract

**Background:** Creatine transporter deficiency is an inborn error of metabolism caused by a deficiency in the creatine transporter protein encoded by the *SLC6A8* gene. Previous treatment with creatine supplementation, either alone or in combination with creatine precursors (arginine or glycine), has been attempted; the efficacy of therapy, however, remains controversial.

**Methods and Results:** To analyze the treatment efficacy of high-dose creatine supplementation on creatine transporter deficiency, we reported a child diagnosed with creatine transporter deficiency, who was treated with a conventional dose of creatine (400 mg/kg/d) for 1 month, then twice the dose (800 mg/kg/d) for 2 months, and finally 3 times the dose (1200 mg/kg/d) for 3 months. The patient tolerated the treatment well and showed improvements in muscle mass and strength when the creatine dose was gradually increased to 1200 mg/kg/d. However, when assessed by proton magnetic resonance spectroscopy (H-MRS), the brain creatine concentration did not increase, and there was no improvement in speech and neurodevelopmental symptoms.

**Conclusion:** We conclude that high-dose creatine supplementation (1200 mg/kg/d) alone improved muscular symptoms, but did not improve cognitive symptoms and brain creatine concentration assessed using H-MRS. Therefore, new treatment strategies are required for the management of creatine transporter deficiency.

## KEY WORDS

cerebral creatine deficiency, creatine, H-MRS, *SLC6A8*

Creatine transporter deficiency is an inborn error of metabolism caused by a deficiency in the creatine transporter protein encoded by the *SLC6A8* gene. Previously treatment with creatine supplementation, either alone or in combination with creatine precursors (arginine or glycine), has been attempted; the efficacy of therapy, however, remains controversial. We conclude that high-dose creatine supplementation (1200 mg/kg/d) alone improved muscular symptoms, but did not improve cognitive symptoms and brain creatine concentration assessed using proton magnetic resonance spectroscopy. Therefore, new treatment strategies are required for the management of creatine transporter deficiency.

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## 1 | INTRODUCTION

Creatine transporter deficiency (CTD) is caused by pathogenic variants in *SLC6A8* (OMIM:300036), resulting in the lack of creatine transport into high energy-demanding organs such as the brain and muscles. Clinical characteristics of CTD include intellectual developmental disability, speech delay, autism, seizures, and muscle hypotonia. The diagnosis of CTD is based on clinical presentation and/or increased urine creatine/creatinine ratio, and reduction or absence of the creatine peak visualized by proton magnetic resonance spectroscopy (H-MRS). DNA analysis of the disease-causing mutations in *SLC6A8* or measurement of impaired creatine uptake in fibroblasts is used to confirm the clinical diagnosis of CTD (Dunbar et al., 2014).

In previous reports, treatment strategies were based on the hypothesis that correction of intracellular cerebral creatine deficiency would improve clinical outcomes (Stockler et al., 2007). Treatments for CTD include supplementation with creatine, either alone or in combination with L-arginine and glycine (triple therapy), and the addition of S-adenosyl methionine as an adjuvant therapy for CTD. However, the efficacy of therapy remains controversial (Jaggumantri et al., 2015; Stockler-Ipsiroglu et al., 2014; Valayannopoulos et al., 2012; Van de Kamp et al., 2012).

We previously reported a case of a Chinese girl with Brown-Vialetto-Van Laere syndrome (BVVLS), which was associated with defective riboflavin transporters encoded by the *SLC52A2* gene. Following high-dose vitamin B2 supplementation, her mental and motor function improved (Shi et al., 2019). Oral supplementation of creatine is intended to maximize creatine transport into the brain via the residual function of the creatine transporter or by potential alternative transport mechanisms (Stockler et al., 2007), as demonstrated by in vitro fibroblasts of patients with transporter deficiency (deGrauw et al., 2002). Creatine is relatively as safe as vitamin B2, so we report the safety and efficacy of oral supplementation of a high dose of creatinine in a child with CTD.

## 2 | CLINICAL REPORT

### 2.1 | Clinical history

The patient was a 5-year-old boy who was diagnosed with CTD at 3 years and 3 months of age based on intellectual developmental disability, speech delay, seizures, walking unsteadily, decreased brain creatine content on the H-MRS, increased urine creatine/creatinine ratio, and molecular analysis *SLC6A8* (NM\_005629.3 chrX:152959440-152959442 c.1222\_1224del p. Phe408del) (GeneBank Accession Number RefSeq NG\_012016.2). The proband's mother had heterozygous mutations. The proband's uncle carried

the same hemizygous mutation and had similar symptoms. Epileptic seizures were controlled with oral sodium valproate and topiramate for nearly 2 years.

### 2.2 | Treatment

Upon obtaining consent from the child's parents, creatine supplementation was administered at the age of 4.5 years. He was treated with a conventional dose of creatine (400 mg/kg/d) for 1 month, then twice the dose (800 mg/kg/d) for 2 months, and finally 3 times the dose (1200 mg/kg/d) for 3 months. All doses were taken three times a day. Renal and hepatic function were monitored regularly and were normal throughout treatment period. The gradual increase in creatine dose to 1200 mg/kg/d was well tolerated, and the patient had no side effects such as vomiting, abdominal pain, diarrhea, etc. The primary and secondary outcomes, as well as safety parameters before and after treatment are listed in Table 1. The muscular symptoms were improved after treatment, the urine creatine/creatinine ratio increased, indicating good compliance to treatment. However, there was no significant improvement in the cognitive function and brain creatine concentration on H-MRS.

## 3 | DISCUSSION

The reported prevalence of CTD is 0.4%–1.4% in males with intellectual developmental disability and 2% in patients with X-linked intellectual developmental disability (Jaggumantri et al., 2015). Given the high frequency of CTD, it is important to establish an adequate intervention strategy. Adriano et al. found that di-acetyl creatine ethyl ester, a compound that can cross biological membranes independently of a transporter due to its very high lipophilicity, offers hope as a treatment for the disease, but is still being tested in animals (Adriano et al., 2018). Reports of significant changes in brain creatine concentration and formal neuropsychological test performances are rare, whereas those of improvements in secondary outcomes (e.g., epilepsy, behavior, mood, attention, and muscle mass) are more frequent, suggesting the potential benefits of creatine supplementation. Furthermore, 90% of the patients who showed improvement in symptoms had initiated treatment before 9 years of age, indicating the benefits of early intervention (Dunbar et al., 2014). *SLC6A8* mutations may lead to a decreased number and impaired function of creatine transporters. The oral dose of creatine in children with cerebral creatine deficiency syndromes was usually 200–400 mg/kg/day in previous reports (Dunbar et al., 2014), but this showed poor efficacy in children with CTD (Stockler et al., 2007). We speculated that a higher dose of creatine may further increase the concentration of creatine

**TABLE 1** Changes in outcomes before and after creatine monotherapy in the patient

	Before treatment	After treatment (dose mg/kg/day)/duration		
		400 mg/kg/day/1 mon	800 mg/kg/day/2 mon	1200 mg/kg/day/3 mon
Current age/age at diagnosis/age treatment started	5 yrs/3 yrs 3 mon/4.5 yrs			
Safety <sup>a</sup>	No safety concerns	No safety concerns	No safety concerns	No safety concerns
Seizures	Seizures remained well controlled/ electroencephalograph was abnormal	No change	No change	No change
Speech	Just say "Mom" unconsciously, very rarely	No change	No change	No change
Neurodevelopmental testing <sup>b</sup>	Moderate	Not performed	Not performed	Moderate
Behavioral disturbances <sup>c</sup>	Attention deficit disorder	No change	No change	No change
Neuromuscular symptoms <sup>d</sup>	Walk unsteadily	No change	No change	Increase in muscular mass, strength, and coordination
Urine creatine-to-creatinine ratio (reference range 0.005–1.07 mmol/mmol creatinine)	3.903 mmol/mmol	Not performed	4.102 mmol/mmol	7.515 mmol/mmol
Brain Creatine (H-MRS)	The creatine peak of the right lateral ventricle anterior horn decreased significantly	Not performed	No change	No change

Abbreviations: H-MRS, proton magnetic resonance spectroscopy; mon, months; yrs, years.

<sup>a</sup>Safety (liver, kidney, complete blood count) was monitored with the following analyses in blood and urine: AST, ALT, GGT, BUN, creatinine, albumin, electrolytes, GFR, and plasma guanidinoacetate and creatine.

<sup>b</sup>Neurodevelopmental testing assessed using standardized psychometric scales (Gesell development schedules). Development quotient (DQ) was used to classify the severity: severe-profound DQ < 39; moderate DQ = 40–54; mild DQ = 55–75.

<sup>c</sup>ADHD Rating Scale IV; Behavior Assessment System for Children.

<sup>d</sup>Muscular strength analysis by clinically observed and physical exam. Muscle mass analysis by measuring the body composition using Bioelectrical Impedance Analyzer.

in the brain and further improve symptoms. The previous case report of the patient with BVVLS treated with high-dose vitamin B2 further confirms this possibility (Shi et al., 2019).

Creatine is one of the most popular nutritional ergogenic aids for athletes, and is even considered as a health food. In addition to athletic and exercise improvement, research has shown that creatine supplementation may enhance post-exercise recovery, injury prevention, and spinal cord neuroprotection, and that long-term supplementation is safe and well-tolerated in healthy individuals and in numerous patient populations ranging from infants to the elderly (Kreider et al., 2017).

We increased the patient's dose of creatine from a regular dose to a high dose (from 400 mg/kg/d at 1 month, to 800 mg/kg/d at 2 months, to 1200 mg/kg/d at 3 months), intending to maximize creatine transport into the brain via the residual function of the creatine transporter or by a potential alternative transport mechanism. There was improvement in muscular symptoms after treatment, related to the effect of creatine itself on the muscle, consistent with most previous reports.

The urine creatine/creatinine ratio increased, indicating good compliance to treatment. However, there was no significant improvement in the cognitive function and brain creatine concentration on H-MRS, and the reason for this is unclear. We speculate that the lack of *SLC6A8* in astrocytes around the blood–brain barrier limits the brain's capacity to import creatine from the periphery, suggesting that the central nervous system mainly relies on endogenous creatine synthesis, while the separate expression of *AGAT*, *GAMT*, and *SLC6A8* in different neurons leads to insufficient synthesis of cerebral creatine from precursors (Braissant et al., 2010). Due to the parents' refusal, we were unable to measure the creatine levels in the patient's CSF by a lumbar puncture. In addition, since the duration of treatment was only 6 months and the high-dose creatine treatment was only 3 months, a longer follow-up period may be required to verify the efficacy. Although the oral dose of creatine supplementation might not have been large enough, we did not further increase the dose due to the parents' refusal.

In conclusion, there is currently no effective treatment for CTD. We attempted to treat a patient with CTD based on theories and previous experience treating patients with similar conditions. However, in our patient, high-dose creatine supplementation (1200 mg/kg/d) alone only improved muscular symptoms, while there was no improvement in cognitive function and brain creatine levels on the H-MRS. Despite some limitations, this study provides further insight on the treatment of CTD. New treatment strategies are required, including creatine derivatives transported independently from the creatine transporter, or via alternative pathways and transporters.

## ETHICAL STATEMENT

The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and was approved by the ethic committee of Guangzhou Women and Children's Medical Center, China. Informed consent was obtained from parents of the proband.

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## CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS


Kaili Shi and Huimin Zhao interpreted the biochemical data, drafted the initial manuscript, and approved the final manuscript as submitted. Kaili Shi designed the intervention and methods. Kaili Shi also supervised all aspects of the study, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. Shuming Xu and Wenjuan Li interpreted the results of the MRS. Han Hong was responsible for the follow-up. All authors read and approved the final manuscript.

## DATA AVAILABILITY STATEMENT

The data used to support the findings of this study may be released upon application to the corresponding author who can be contacted at [kailihappy@126.com](mailto:kailihappy@126.com).

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