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REVIEW ARTICLE

Primary creatine deficiency syndrome as a potential missed diagnosis in children with psychomotor delay and seizure: case presentation with two novel variants and literature review

Parastoo Rostami[1] · Sareh Hosseinpour[2] · Mahmoud Reza Ashrafi[2] · Houman Alizadeh[3] · Masoud Garshasbi[4] · Ali Reza Tavasoli[2]

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Abstract

Creatine is the main source of energy for the brain. Primary creatine deficiency syndromes (PCDSs) are inborn error of metabolism of creatine synthesis. Symptoms of central nervous system involvement are the most common clinical manifestations in these disorders. We reviewed medical records of all genetically confirmed patients diagnosed by whole exome sequencing who were referred to Myelin and Neurodegenerative Disorders Clinic, Children's Medical Center, Tehran, Iran, from May 2016 to Dec 2018. A literature review was conducted on clinical and genomic variability of PCDS to compare our patients with previously reported cases. We report two patients with creatine deficiency among a cohort of 550 registered cases out of which 200 patients had a genetically confirmed neurodegenerative disorder diagnosis. The main complain in the first patient with creatine transporter (CRTR) deficiency was seizure and genetic study in this patient identified a novel hemizygote variant of "c.92 > T; p.Pro31Leu" in the first exon of *SLC6A8* gene. The second patient with guanidinoacetate methyltransferase (GAMT) deficiency had an unknown motor and speech delay as the striking manifestation and molecular assay revealed a novel homozygote variant of "c.134G > A; p.Trp45*" in the first exon of *GAMT* gene. PCDSs usually are associated with nonspecific neurologic symptoms. The first presented case had a mean delayed diagnosis of 5 years. Therefore, in children with unexplained neurologic features including developmental delay and/or regression, mental disability and repeated seizures without any significant findings in metabolic studies, PCDSs can be considered as a differential diagnosis and molecular analysis can be helpful for the precise diagnosis and treatment.

Keywords Creatine deficiency · Developmental delay · Seizure · Inborn error of metabolism · GAMT deficiency · CRTR deficiency

✉ Masoud Garshasbi
masoud.garshasbi@modares.ac.ir

✉ Ali Reza Tavasoli
a_tavasoli@sina.tums.ac.ir; alirezatavasoli236@gmail.com

[1] Division of Pediatric Endocrinology and Metabolism, Growth and Development Research Center, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

[2] Myelin Disorders Clinic (Iranian Neurometabolic Registry), Pediatric Neurology Division, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

[3] Division of Pediatric Radiology, Department of Pediatrics, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

[4] Department of Medical Genetics, Faculty of Medical Sciences, Tarbiat Modares University, Teheran, Iran

Introduction

Creatine metabolism

Creatine is the main source of energy for brain, heart, and muscle [1]. About 50% of the diurnal creatine requirement in the body achieves through the diet and the rest is provided by endogenous production. Creatine is biosynthesized through two sequential steps. In the first step arginine and glycine are combined together to form guanidinoacetic acid and ornithine. This stage is catalyzed by arginine glycine acyltransferase (AGAT). During the second step, guanidinoacetic acid converts to creatine by guanidinoacetic acid methyltransferase (GAMT) (Fig. 1) [2]. The main organs for endogenous synthesis of creatine are kidneys, pancreas (with high AGAT activity) and liver (with high GAMT activity).

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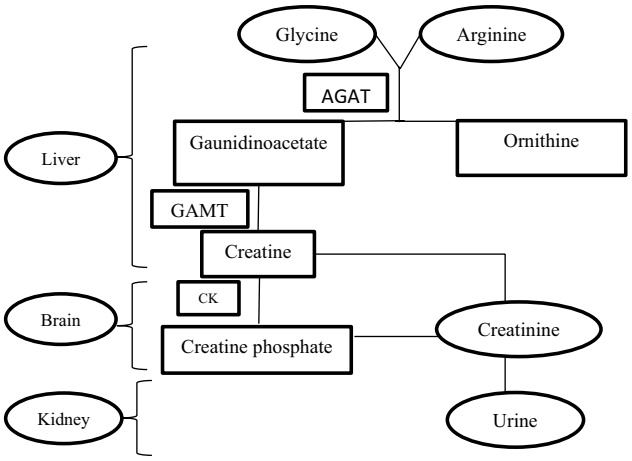

Fig. 1 The pathway for metabolism of creatine. *GAMT* guanidinoacetic acid methyl transferase, *AGAT* arginine glycine acyltransferase, *CK* creatine kinase

The liver can produce about 1–2 g of creatine per day in the human body and decreases with age [2]. Creatine enters into the bloodstream and then will be picked up by cells through sodium and chloride-dependent creatine transporter (CRTR, SLC6A8) [3]. The brain needs to pick up creatine through CRTRs that are located at the blood–brain barrier, as it can only make a small amount of creatine. Some part of the intracellular creatine transforms into crearine phosphate by creatine kinase (CK) which has a high energy content [3]. Finally, creatine and creatine phosphate will be converted to creatinine and excreted into the urine [4].

Creatine deficiency syndromes

Primary creatine deficiency syndromes (PCDSs) are inborn errors of metabolism of creatine synthesis and they are classified into three categories: (1) arginine-glycine amidinotransferase deficiency; (2) guanidinoacetate methyltransferase deficiency; (3) CRTR deficiency [1]. The brain is the principal affected organ in creatine deficiency disorders so, the clinical manifestations of PCDSs are mainly neurologic involvements such as; intellectual disability, developmental milestones delay (speech, motor and cognitive delay), early onset seizures and autistic behaviors in some patients [1]. Prominent physical and neurological examination findings in affected patients are failure to thrive, microcephaly, muscular hypotonia, movement disorders and extrapyramidal signs [4]. The secondary creatine deficiency occurs due to ornithine aminotransferase (OAT) deficiency and along with a high level of ornithine leads to the suppression of AGAT enzyme activity. Progressive chorioretinal degeneration, myopia, loss of peripheral vision and night blindness are the most important clinical features in OAT deficiency which present during the first decade of life but finally lead to the blindness during the third or fourth decades of life. In contrast to PCDSs, majority of patients with secondary creatine deficiency have normal intelligence [5]. The mainstay treatment of PCDSs is creatine supplement (as creatine monohydrate) that could lead to a considerable improvement or sometimes remedy of delayed developmental millstones in AGAT deficiency, control of seizures and amelioration of movement disorders in GAMT deficiency [6]. This treatment has not been effective in patients with CRTR deficiency [7] but high-dose L-arginine and L-glycine supplementation in some patients with CRTR deficiency have been associated with increased muscle mass, improved motor function, decreased frequency of intractable seizures and to some degree improvement in cognitive function [8]. Also sodium benzoate, high dose of L-ornithine and dietary arginine restriction can reduce the serum level of guanidinoacetic acid in GAMT deficiency [9]. Herein we report two novel variants in two patients with creatine deficiency.

Materials and methods

Participants

We reviewed recorded medical documents of all the 550 patients with main clinical manifestation of neurologic regression registered at Myelin and Neurodegenerative Disorders Clinic, Children's Medical Center, Tehran, Iran between May 2016 and Dec 2018. Around 200 of them had a genetically confirmed diagnosis for different types of neurodegenerative disorders by molecular studies such as single gene study, clinical and or whole exome sequencing (WES) methods. Here we report two cases of PCDS with clinical manifestations of unknown developmental delay or neurologic regression. Both of them were diagnosed by WES. Informed consent was obtained from the parents of the two cases to take part in this study. Local ethical committee of children's medical center approved our study.

Case presentation

Case 1

A 6.5-year old boy was referred to Myelin and Neurodegenerative Disorders Clinic at the age of 27-month because of repeated seizures and neurologic regression. He was the first child of a consanguineous marriage, born with a birth weight of 3400 g, length of 51 cm, and a head circumference of 35.5 cm. His seizures started at 2 months of age after his routine vaccination followed by recurrent mixed type seizures (infantile spasm during the first months of life and then focal seizures) accompanied with cognitive, speech and motor delay and neurologic regression. He was

unable to hold his neck, sit and speak at the time of referral. In examination, the patient had few abnormal facies including; large and low set ears and high arch palate. Some demographic features, clinical and paraclinical findings of the patient at the age of 27 months are shown in Table 1. Laboratory tests including plasma and urine amino acids profile, serum ammonia and lactate, serum acylcarnitine profile and urine organic acids were normal. During the following 2 years, his seizures were relatively under control with anti-seizure medications and rehabilitation programs were continued to improve his motor and swallowing abilities. Feeding was made by nasogastric tube and a normal diet. Three brain MRI series (at the ages of 4, 5 and 6 years) were available which revealed significant cerebral atrophy, abnormal deep white matter and dentate nucleus signal changes and large subdural effusions in frontoparietal and temporal areas (Figs. 2, 3). Ultimately, at the age of 6 years, WES was performed for this patient which revealed a novel hemizygote variant of "c.92 > T; p.Pro31Leu" in the first exon of *SLC6A8* gene. His mother was carrier for this variant but his father was normal (Fig. 4a). The mother is healthy and she had completed her school and has normal social skills as an adult person. After diagnosis of PCDS in him, creatine supplement was started with a dosage of 100 mg/kg/day divided in three doses for him but he became lethargic after taking the creatine monohydrate. So, we decreased the dose of creatine supplement to 25 mg/kg/day divided in three doses. Our plan was to increase the dose gradually up to 100–200 mg/kg/day (suggested therapeutic dose) to increase patient's tolerability to drug but unfortunately, the patient could not tolerate the doses higher than 25 mg/kg/day. In addition, arginine hydrochloride with a dosage of 400 mg/kg/day in three doses was started for him. Now, the patient has 6.5 years old. During the past 6 months, he has been seizure-free by anticonvulsant drugs (levetiracetam, lamotrigine, liskantin) and creatine and arginine hydrochloride are continued. Gross motor function classification system score (GMFCS) has regressed from 4/5 at the age of 6 years (time or starting creatine and arginine hydrochloride treatment) to 5/5 at the age of 6.5 years and the latest brain MRI at this age revealed diffuse cerebral and cerebellar atrophy. At the last visit, he had truncal hypotonia and was unable to sit or roll (GMFCS: 5/5) and also had severe intellectual disability, four limbs spasticity, poor swallowing, failure to thrive and constipation.

Case 2

A 30-month-old male was referred to Myelin and Neurodegenerative Disorders Clinic at the age of 13-month because of motor and speech delay. He was the second child of consanguineous parents, born through cesarean section with the weight of 3290 g, length of 52 cm, and a head circumference

Table 1 Demographic features, physical examination and paraclinical data in patients at first visit

Patient	Age of diagnosis (m)	HC (cm)	Weight (kg)	GMFCS	Seizure	Deep tendon reflex	Spasticity	Truncal hypotonia	Extrapyramidal movement	Eye examination	ABR	EMG/NCV	BrainMRI	EEG
Case 1	60	47	10	4/5	Tonic spasm, focal	Increased	+	+	+	Normal	Normal	Normal	Supratentorial atrophy, mild cerebellar atrophy	Burst attenuation, multifocal sharp activity
Case 2	22	48	10	3/5	–	Normal	–	+	–	Normal	Normal	Normal	Normal	Scattered sharp activity

GMFCS motor ability based on gross motor function classification system, *HC* head circumference, *ABR* auditory brainstem response, *EMG/NCV* electromyography/nerve conduction velocity, *EEG* electroencephalography

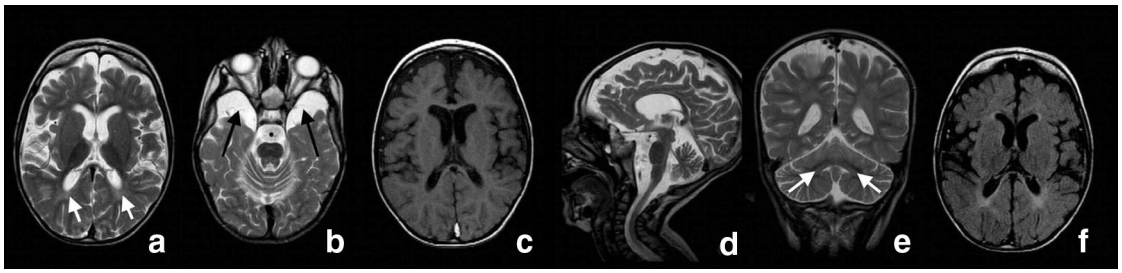

Fig. 2 Brain MRI of case 1 at age 5 years, spin echo T2 WI-images, axial at the level of basal ganglia and superior cerebellar peduncle (**a**, **b**), axial T1 WI at the level of basal ganglia (**c**), sagittal T2 WI (**d**), coronal T2 WI at the level of ventricular trigone and FLAIR sequence at the level of basal ganglia(**e**, **f**) revealed widening of Sylvain fissures and sulci (**a**, **c**) with bilateral large amount of extra-axial fluid in anterior temporal fossae reflecting diffuse brain volume loss (**b** black arrows). Mild bilateral abnormal increased signals in T2 WI-images were also seen in deep periventricular white matter and dentate nuclei (**a**, **e** white arrows). Some atrophy of both thalami was noticed furthermore (**f**)

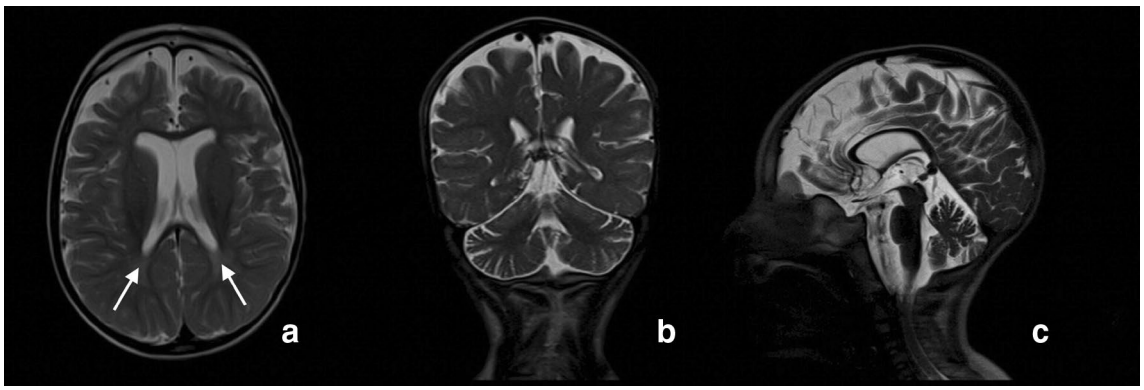

Fig. 3 Brain MRI of case 1 at age 6 years, spin echo T2 WI-images, axial at the level of basal ganglia (**a**), coronal at the level of ventricular trigone (**b**) and mid sagittal (**c**) showed diffuse brain volume loss, almost stable from last MRI in 1 year ago. Faint bilateral peritrigonal deep white matter signal changes mildly high in T2 WI-images (**a** white arrows), were noticed as well

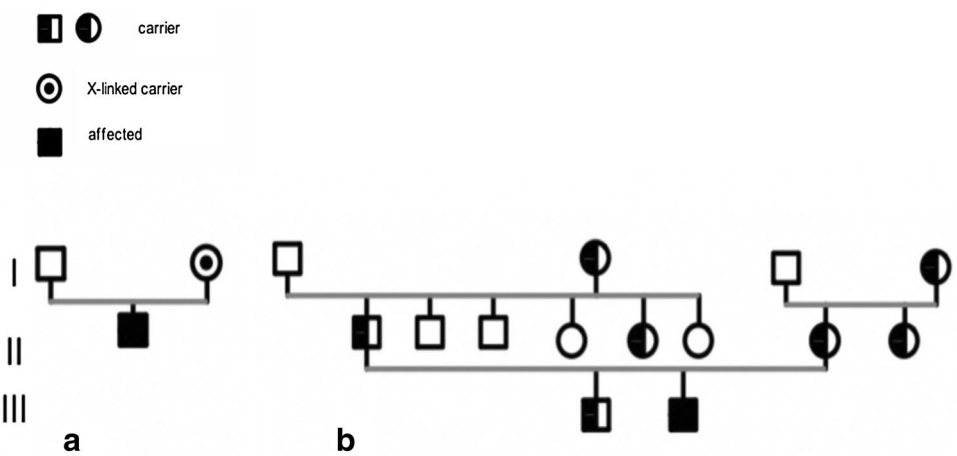

Fig. 4 **a** Pedigree of case 1, **b** pedigree of case 2

of 35 cm. At the 6 months of age, parents noticed that their child is hypotonic and not able to hold his neck. He had no history of seizure. Their parent stared rehabilitation program for him but no significant improvement was found in motor milestones. Therefore, the patient was referred to a pediatric neurologist at the age of 13 months. Available data of neurologic examination and some paraclinical findings at the first visit (at the age of 13 months) are shown in Table 1.

All metabolic studies and initial brain MRI at the age of 22 months were normal. Due to persistence of poor motor and speech developmental progression despite 10 months of rehabilitation programs, WES was performed on the patient. WES identified a novel homozygote variant of "c.134G > A; p.Trp45*" in the first exon of *GAMT* gene. This variant was studied in the other sibling and the first-degree relatives. All his family members including mother, father, brother, one of his aunts, maternal and paternal grandmothers were carrier for this variant but maternal and paternal grandfathers, uncle, and another aunt were normal (Fig. 4b). After confirming the PCDS, creatine monohydrate supplement with a daily dose of 200 mg/kg/day divided into three doses and low protein diet (1 g/kg/day) was started for him at the age of 24 months. After 6 months of treatment he showed significant improvements in his motor movement and speech domains, so that he was able to sit and walk few steps without help at the age of 30 months. Although his range of words to speak increased but is still limited and he can not make two words sentences. GMFCS has been improved from 3/5 at age of 24 months to 1/5 at the age 30 months.

Discussion

PCDSs are a group of diseases with nonspecific neurologic features and they usually will be misdiagnosed. We presented here two cases with PCDS and also did a mini-review on PCDSs. Mutations in three genes are responsible for PCDSs. PCDS due to CRTR deficiency is the most common type that was described in 2001 in a patient with neurologic symptoms and mental disability [1]. To date about 118 patients with CRTR deficiency have been reported. Although our knowledge has significantly increased about this disorder but some of these patients will be diagnosed with delay due to absence of characteristic symptoms [1, 2, 4, 8, 10–17]. The patients presented here like other reported patients had nonspecific neurologic symptoms including developmental delay, intellectual disability, dysmorphic features, frequent seizures, pyramidal tract signs and extrapyramidal movements. The first case was diagnosed with a delay of around 4 years. The range of brain MRI findings in this disorder varies from nearly normal to cerebral atrophy, delayed myelination, white matter hyperintensities, enlarged ventricles and thin corpus callosum [6]. Our first case had bilateral large amount of extra-axial fluid in anterior temporal fossae, progressive cerebral atrophy and non-specific white matter and dentate nucleus abnormal signals on sequential brain MRIs from age of 4–6 years. Therefore, clinical features and brain MRI findings were not conclusive for any specific diagnosis [4]. In patients suspected to PCDs, the measurement of some biochemical markers such as; levels of creatine and guanidinoacetate (GAA) and creatinine in urine, plasma and cerebrospinal fluid can be helpful for diagnosis [13]. The CRTR is encoded by the *SLC6A8* gene which encodes 13 exons and is located on Xq28 [18]. Up to now, 56 missense/nonsense variants have been reported in the *SLC6A8* gene (The human gene mutation database). We found the "c.92 > T; p.Pro31Leu" variant in the first exon of this gene in the first case which has not been reported so far. Some treatments have been used for CRTR deficiency such as glycine, creatine monohydrate and L-arginine supplementations [7]. None of them were effective in the first patient after at least 6 months of treatment. The second common type of PCDSs is GAMT deficiency which first was described in 1994 [2]. To date, about 121 patients with GAMT deficiency have been reported with an incidence of 1:2,640,000–1:550,000 [19–24]. The first clinical manifestations in the second patient reported here was motor developmental delay, language deficits without any seizure, behavioral changes and sever intellectual disability similar to other previously reported cases [22]. Brain MRI in these patients are either normal or reveal nonspecific basal ganglia signal intensities in T2-weighted images [8]. Up to now, 31 Missense/nonsense variants have been identified in *GAMT* gene (The human gene mutation database). We found a novel homozygote variant "c.134G > A" in the first exon of *GAMT* gene. In this patient treatment with the creatine monohydrate supplementation and protein restriction started at the age of 2 years for 6 months resulted to the significant improvements in the motor developmental domain (improvement of GMFCS from 3/5 to 1/5) but we could not justify similar effects on language and probably cognition domains as has been reported in another report [22]. The most common clinical manifestation in patients with AGAT deficiency is intellectual disability. Other reported symptoms are seizure, hypotonia, failure to thrive and movement disorders [25, 26].

In conclusion, PCDSs are associated with nonspecific neurologic symptoms, so pediatrician should consider PCDSs as one of the differential diagnoses in children with unexplained neurologic features especially developmental delay from mild to severe, developmental regression and frequent poorly controlled seizure episodes without any significant findings in metabolic studies. In these situations, the molecular analysis can be helpful for precise early diagnosis of PCDSs and starting treatments.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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