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Cerebral creatine deficiency syndrome – A treatable cause of developmental delay - A case series and review of literature

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Abstract

The cerebral creatine deficiency syndromes are inborn errors of creatine metabolism, which include two creatine biosynthesis disorders: guanidinoacetate methyltransferase (GAMT) deficiency and L-arginine: glycine amidino transferase (AGAT) deficiency, as well as creatine transporter deficiency (CTD, SLC6A8 deficiency). They may present with a combination of symptoms such as global developmental delay, cognitive impairment, language disorder, behavioral problems, seizures, hypotonia, myopathy, and movement disorder. A high index of suspicion is necessary to identify these disorders at the earliest, as they are potentially treatable. Herewith, we present five cases of cerebral creatine deficiency syndromes.

Keywords: Creatine deficiency disorders, Global developmental delay, absent creatine peak in magnetic resonance spectroscopy

INTRODUCTION

Cerebral creatine deficiency syndromes (CCDS) are a group of potentially treatable neurometabolic disorders with a primary defect in the synthesis or transport of creatine to the brain.[1] These are inborn errors of creatine metabolism which include the two creatine biosynthesis disorders- L-arginine:glycine amidino transferase (AGAT) deficiency, and guanidinoacetate methyltransferase (GAMT) deficiency and a Creatine Transporter Deficiency (CRTR due to SLC6A8 mutation). The clinical features include global developmental delay, cognitive dysfunction, and behavioral problems in all three CCDS, and seizures and movement disorders are common in GAMT and CRTR deficiencies. As there are no specific clinical features to suspect these disorders, they are often missed or diagnosed late. Knowledge about these disorders is essential for diagnosing and treating them early, along with the use of creatine supplementation, to achieve a better outcome. Here, we present a case series of CCDS.

METHODS

This retrospective study was conducted in the Department of Pediatric Neurology at Institute of Child Health & Hospital for Children, Madras Medical College, Chennai, India. A retrospective chart review of children diagnosed with creatine deficiency syndrome between July 2019 and June 2025 was conducted. During this period, 34,028 new patients attended our outpatient department. Global developmental delay was the reason for referral in 13,800 patients, of which, on further evaluation, five patients were diagnosed with CCDS. Data regarding clinical features, biochemical investigations, neuroimaging findings, electroencephalographic findings, and exome sequencing results were retrieved. The ophthalmologist's opinion regarding vision and fundus examination, and hearing evaluation reports were collected. The child psychologist's opinion, regarding the Vineland Social Maturity Scale (VSMS) scores for assessing intelligence, was obtained. Social Quotient scores of 55-69 were classified as mild intellectual disability,

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scores between 36 and 54 as moderate, 21 and 35 as severe, and below 20 as profound disability.

RESULTS

Five children were diagnosed with CCDS during this period – three with GAMT deficiency, one with AGAT deficiency, and one with CRTR deficiency. There were three males and two females. The mean age of onset was 1.3 ± 0.31 years, and the mean age at diagnosis was 4.9 ± 3.5 years. The history of consanguinity was noted in four of the five children (80%); there was no history of similar illness among the family members. Pedigree charts were not available for perusal.

Patient 1

A six-year-old female child, firstborn of third-degree consanguineous parents, with a normal perinatal history, presented with two episodes of generalized seizures at 4 years of age. She experienced a delay in acquiring milestones in all domains, more so in language and social milestones. She walked by the age of 2, could speak only two words, and recognize her parents, but could not identify body parts or colors. She had a minimal face-to-face context with a poor attention span. There was generalized hypotonia, retained deep tendon reflexes, gait, appendicular ataxia, and microcephaly. She was severely thin built with severe wasting and stunting.

Patient 2

A five-year-old female child presented with recurrent myoclonic seizures, about 10-15 episodes a day for the last six months. She was the second child of third-degree consanguineous parents, with a normal neonatal period. Her motor milestones were normal; however, she had a severe language delay, as she could only speak bisyllables. She was unable to express her needs, distinguish between caregivers and strangers, or identify common objects. She had poor eye-to-eye contact, did not obey commands, or respond to calls. There were no neurocutaneous markers, skin /hair changes, or microcephaly. There were no involuntary movements or cerebellar signs.

Patient 3

A seven-year-old male child, firstborn of second-degree consanguineous parents, was brought in with a history of recurrent generalized and myoclonic seizures past 6 months. History of recurrent febrile seizures from 1 year of age, and was on antiseizure medications. His developmental milestones were delayed, as he attained head control by 8 months of age, sat by 1 year of age, stood by 1 year and 6 months, and walked by 2 years of age. At the age of seven, he could speak only two words and recognize his mother. He could not express his toilet needs, and he would often play alone. His anthropometry showed that he had severe wasting and stunting with a weight of 12kg(<-3z), height of 98cm(<-3z), and a BMI of 12.4. He had autistic features with minimal face-to-face contact. His vocabulary was only two words. He was unable to identify common objects, colors, or body parts. His vision and hearing were normal. He had difficulty getting up from a sitting position. Deep tendon reflexes were preserved, and plantar reflexes were flexor.

Patient 4

A two-year-old male child, second born of non-consanguineous parents with a normal perinatal history, was brought for evaluation of developmental delay. He achieved independent walking at the age of 2, could speak only bisyllables, and recognized her parents and strangers. Distal hypotonia in all four limbs with preserved reflexes was noted.

Patient 5

Two years and six months old, firstborn of fourth-degree related parents, presented with seizures for the past nine months, unprovoked generalized seizures. He also had global developmental delay in that he stood by himself at 2 years, and walked alone by two years and five months. He could speak only 3 words. He recognized his parents. He was hyperactive and neither responding to calls nor obeying commands. Generalised hypotonia was noted.

All of them presented with global developmental delay (100%). Four had behavioral problems in the form of autistic features (80%). Seizures were present in four children, all with GAMT deficiency and one with AGAT deficiency. One child with GAMT deficiency had generalized and myoclonic seizures, and the other two had generalized seizures. The child with AGAT deficiency had recurrent febrile seizures. One child with GAMT deficiency showed choreoathetosis. Proximal weakness in

the lower limbs in the form of difficulty in rising from the floor was noticed in the child with AGAT deficiency. The clinical features, imaging results, and genetic findings of these children are presented in Table 1. All were treated with oral creatine monohydrate. A protein-restricted diet was followed in children with GAMT deficiency. All underwent physiotherapy, occupational therapy, and speech therapy as well. One child was not under follow-up after the first three years. The mean duration of follow-up was 21.5± 15.7 months with a range of 8-48 months. There was good seizure control with one or two antiseizure medications. Repeat assessments showed a mild improvement in socio-cognitive skills in all. They started showing interest in the surroundings, began playing with peers, began comprehending spoken language, and started obeying simple commands.

DISCUSSION

CCDS are a group of inborn errors of creatine metabolism that present as global developmental delay, impairment of expressive speech, intellectual disability, autistic features, and epilepsy. GAMT and AGAT deficiency are autosomal recessive disorders, and CRTR deficiency is X-linked recessive.[2]

The prevalence of CCDS in patients with neurological disease of unknown origin is 0.25%[3], mild-to-severe intellectual disability is 2.7%[4] and autism is less than 7 per 1000.[5]

In humans, approximately 50% of creatine is derived exogenously from food, and the remaining half is synthesized in the body primarily in the liver, kidneys, and pancreas. In the first step, guanidinoacetic acid (GAA) is formed from arginine and glycine, catalyzed by L-arginine: glycine amidinotransferase (AGAT).[6] In the second step, catalyzed by guanidinoacetate N-methyltransferase (GAMT), methylation of GAA in the presence of S-adenosylmethionine results in the formation of creatine and S-adenosylhomocysteine.[6,7] Creatine is then transported through the bloodstream to the muscle and brain, where it is taken up via sodium and chloride-dependent creatine transporter (CRTR) and plays a pivotal role in energy availability in these tissues.[7] Creatine and creatine phosphate are nonenzymatically converted into creatinine and excreted in urine. (Figure 1)

The clinical features include global developmental delay, cognitive dysfunction, and behavioral problems in all three creatine deficiency disorders, and seizures and movement disorders in GAMT and CRTR deficiencies. Females with CRTR deficiency can be asymptomatic carriers or can present with a phenotype similar to males. The clinical phenotype in each syndrome is depicted in Table 2.

Global delay (100%), movement disorder, and proximal weakness (20%) each were noticed in our cohort, which was in accordance with other studies. Epilepsy was observed in 80% of our cases, in agreement with Kinhal *et al*, whereas it was reported in all cases by Passi *et al.*[10] and in about 50% of cases by others.[13,14] Autistic features were noted in four of our children (80%), whereas all patients with CCDS had autism or attention deficit in other studies.

A distinct lack or profound diminution of the combined creatine and phosphocreatine peak on proton MRS is a hallmark of cerebral creatine deficiency syndromes.[8] Biochemically, GAMTD is identified by elevated levels of guanidino acetic acid (GAA) in body fluids such as urine, serum, and cerebrospinal fluid. In contrast, GAA levels are low in AGATD and normal in CRTR defects. An elevated urine creatine/creatinine ratio is seen in CRTR deficiency. In GAMT-D and AGAT-D, plasma creatine levels are usually low. The diagnosis is confirmed by genetic testing.[9]

Guanidinoacetate methyltransferase deficiency (GAMT-D) was first described in 1994 by Stockler *et al*. as the first inborn error of creatine metabolism[1] with an estimated incidence of 1:2,50,000. It is the second most common CCDS disorder, with approximately 110 patients reported worldwide. Speech delay is considered a hallmark of this disease. Seizures occur in 75%–90%, and movement disorders in 40% of patients.[14] Intellectual disability may range from mild to severe. Behavioral problems such as hyperactivity and autistic features are common.[9] The pathophysiology of GAMTD involves a combination of cerebral energy deficiency due to a depletion of brain creatine/ phosphocreatine and neurotoxic action of GAA, a partial agonist at GABAA receptors.

MRI brain may be normal or may show bilateral hyperintensities in globus pallidus, which may resemble mitochondrial encephalopathy. Nearly half of the patients had T2 signal hyperintensities of the globus pallidus at the time of diagnosis, with reversal in 90% on treatment. One of our patients had bilateral globus pallidi lesions. (Figure 2)

Table 1: Clinical features and investigations of children with CCDS

Parameters	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age of onset(yrs)	1	1.4	1.3	1.5	1.4
Age at diagnosis(yrs)	5	4	7	2	2
Motor delay	Yes	Yes	Yes	Yes	Yes
Language delay	Yes	Yes	Yes	Yes	Yes
Cognitive dysfunction	Yes	Yes	Yes	Yes	Yes
Autistic features	Yes	Yes	Yes	No	Yes
Epilepsy	Yes	Yes	Yes	No	Yes
Movement disorder	Yes	No	No	No	No
Proximal weakness	No	No	Yes	No	No
Failure to gain weight	Yes	Yes	Yes	Yes	Yes
Dysmorphism	No	No	No	No	Yes
Consanguinity	Yes	Yes	Yes	No	Yes
Family history	No	No	No	No	No
Ophthal opinion	Normal	Normal	Normal	Normal	Normal
Hearing evaluation	Normal	Normal	Normal	Normal	Normal
SQ/IQ	Moderate ID	Moderate ID	Moderate ID	Moderate ID	Mild ID
Serum creatinine (0.7-1.2mg/dl)	0.26mg/dl	0.35mg/dl	0.34mg/dl	0.44mg/dl	0.46mg/dl
MRI brain	Hyperintensities in globus pallidi	Normal	Normal	Normal	Normal
MRS	Absent creatine peak	Absent creatine peak	Not done	Not done	Absent creatine peak
NCS	Normal	Normal	Normal	Normal	Normal
EEG	Sharp waves in both temporo parietal regions	Normal	Normal	Normal	Generalized epileptiform discharges
Whole Exome Sequencing	homozygous missense variant c.432G>A in exon 4 of GAMT gene	Homozygous base pair deletion in c.164_171del in exon 1 of GAMT gene	Homozygous missense variant c.1237C>T in exon 9 of GATM gene	Hemizygous frameshift mutation in c.626_627del in exon 3 of SLC6A8 gene	Compound heterozygous mutations in c.424_426delGAG in exon 4, c.122T>A in exon 1 of GAMT gene
Diagnosis	GAMT def	GAMT def	AGAT def	CRTR def	GAMT def
Oral Creatine	400mg/kg/d	400mg/kg/d	400mg/kg/d	200mg/kg/d	400mg/kg/d
Others	Protein restriction	Protein restriction	-	Arginine 400mg/kg/d	Protein restriction
Duration of follow-up	For the first 3 years, no follow-up past 3 years	4 years	1.5 years	One year	8 months
Outcome	No seizures for 1.5years with two ASMs ; mild improvement in cognition, behavioural problems -improvement in SQ from 38 to 42	No seizures for 1.5 years with two ASMs; mild improvement in cognition, behavioural problems -improve ment in SQ from 40 to 48	No seizures for 8months with single ASM ; improvement in motor, cognitive, and language milestones, - improve ment in SQ from 40 to 46	Improvement in motor, cognitive, and language milestones – improvement in SQ from 38 to 40	No seizures for 6 months with two ASMs; improvement in cognition. Repeat psychological assessment is planned.

ASM – anti-seizure medication

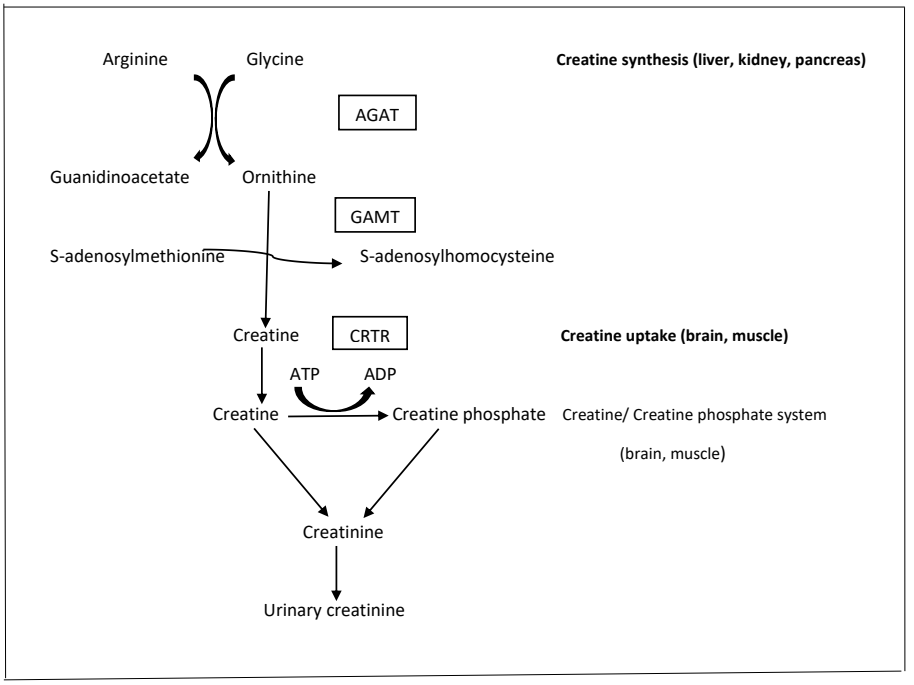

Figure 1. Synthesis and transport of creatine in the body

Table 2: Clinical, biochemical, imaging features, and management of creatine deficiency syndromes

Clinical features	**GAMT-D**	**CRTR-D**	**AGAT-D**
Global developmental delay	100%	100%	100%
Intellectual disability	100%	85%	80%
Epilepsy	86%	59%	10%
Movement disorder	40%	40%	Not reported
Behavioral issues	>75%	85%	25%
Other neurological features	Hypotonia in 40%	Absent	muscle weakness in 50%
Non-neurologic features	Absent	dysmorphism in 45% GI symptoms in 35% cardiac features in 39%	Absent
Investigations			
Urine, plasma, CSF GAA	Elevated	Normal	Low
Urine creatine-creatinine ratio	Normal	Elevated	Normal
Plasma creatinine	Low	Normal	Low
Creatine peak in ^{1}H-MRS	Absent	Absent	Absent
Management			
Creatine	(400–800 mg/kg /day)	(100–200 mg/kg/day)	(400–800 mg/kg /day)
Ornithine	(400–800 mg/kg/ day)	----	----
Arginine	----	400 mg/kg/day	----
Glycine	----	150 mg/kg/day	
Diet	Protein- or arginine-restricted diet	----	----

Table 3: Comparison of our study with other studies

Variables	Passi *et al.*[10] n=13 Multicentric 2015-2021	Kinhal *et al.*[11] n=7 Single centre 2020-2023	Sun *et al.*[12] n=14 Single centre 2017-2022	Kaufman *et al.*[13] n=6 Single centre 2015-2023	Our study n=5 Single centre 2018-2025
Gender ratio	11:1	4:3	2:5	2:1	3:2
Mean age at presentation & diagnosis	--	1.5 & 9.3yrs	1-2 & 3.75yrs	1.1&4.4yrs	1.3 & 4.9yrs
Developmental delay	100%	100%	100%	100%	100%
Autism	100%	100%	21%	NA	80%
Epilepsy	100%	70%	57%	50%	80%
Movement disorder	15%	30%	NA	33%	20%
Myopathy	15%	30%	NA	NA	20%
MRI brain, MRS	GP changes in 4, absent creatine peak in 10	Cerebellar atrophy in 1, absent creatine peak in 4	White matter changes in 3, cerebral atrophy in 1, thin CC in 3, reduced / absent creatine peak in all	NA	GP changes in 1, Absent creatine peak in 3
EEG abnormal	64%	40%	NA	NA	40%
Urine GAA	Not done	Elevated in 2	Elevated in 6	NA	Not done
GAMT AGAT CRTR	2/13(40%) Nil 8/13(60%)	3/7(43%) 1/7(14%) 3/7(43%)	6/14(43%) 0 8/14(53%)	2(33%) 0 4(67%)	3/5(60%) 1/5(20%) 1/5(20%)
Improvement with creatine supplements	N=11 5/11(45%)	N=3 Partial response in all	N=14 8/14(53%)		N=5 Partial response in all

Creatine Transporter 1 (CRTR1) Deficiency, the commonest form of CCDS, accounts for nearly 70% of all CCDS. The prevalence of creatine transporter deficiency in males with intellectual disability is between 0.4 and 1.4 % and approximately 2 % in males with X-linked intellectual disability. The clinical features include intellectual disability, epileptic seizures, developmental delay, autistic features, attention deficit hyperactivity disorder (ADHD), failure to thrive, and gastrointestinal problems.[15] Most of these patients require significant support for all daily activities and have limited verbal capacity. Heterozygous females can present with mild-moderate intellectual disability, learning difficulties, behavioral problems, and seizures, and the phenotype can vary from normal to abnormal depending on X-inactivation pattern. Affected males typically have a more severe phenotype, owing to the presence of a second copy of *SLC6A8* in females, which can compensate for heterozygous mutations depending on X-chromosome inactivation. Other neurologic features include hypotonia, joint laxity, and strabismus. Non-neurologic features include gastrointestinal findings such as vomiting, constipation, gastric ulcers, hiatal hernia, and cardiac involvement in the form of long QT disorder.

AGAT deficiency, described in 2001 by Item *et al*, is the least common of the three. Less than 20 patients have been reported in the literature. Apart from global delay, cognitive dysfunction, behaviour problems, myopathy was observed in approximately half of the patients.

GAMT deficiency was the commonest CCDS

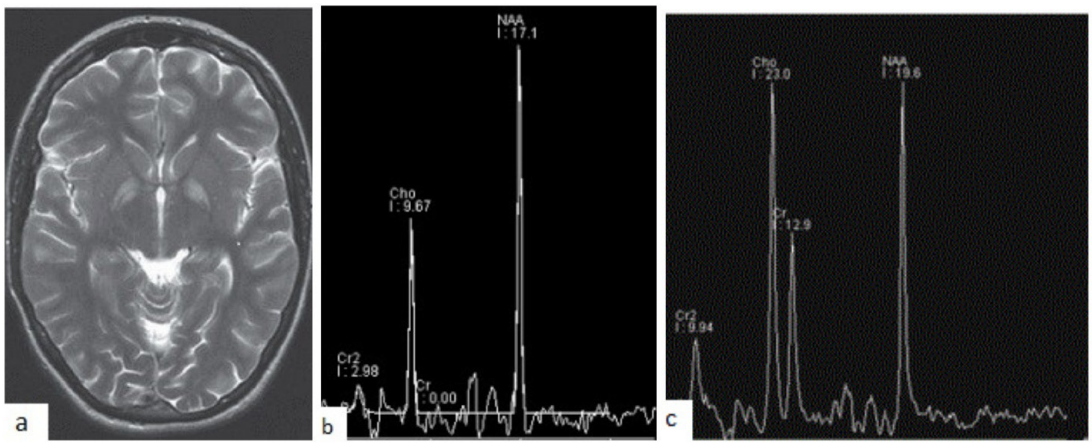

Figure 2. a. MRI brain axial T2W image showing bilateral hyperintensities in globus pallidi. b. MRS showing absent creatine peak. c. normal MRS for comparison

in our cohort, in contrast to CRTR deficiency reported by others.[10,12,13] Kinhal *et al*. have reported equal distribution of GAMT and CRTR deficiencies.[11]

All creatine deficiency disorders are treated with supplementation with creatine monohydrate to replenish cerebral creatine levels. Creatine monohydrate of 400–800 mg/kg/day should be given in three to six divided doses. GAMT deficiency is treated with ornithine supplementation to decrease the accumulation of neurotoxic GAA in the central nervous system and a protein- or arginine-restricted diet. Ornithine supplementation decreases GAA accumulation by competitive inhibition of AGAT enzyme activity. Ornithine supplementation of 400–800 mg/kg/day, administered in divided doses, is beneficial.[9] Sodium benzoate conjugates glycine and inhibits GAA production via substrate deprivation. CRTR deficiency is treated with arginine and glycine supplementation in addition to creatine[16], which may reduce the associated behavioral problems such as anxiety and aggressiveness. Occupational, speech, physical therapies, behavior therapy, and genetic counseling regarding the risk of recurrence in future pregnancies are important.

Treatment results in improvement of epilepsy and movement disorder, whereas intellectual disability and speech impairment persist.[14] All our patients had good seizure control and mild improvement in cognition and behaviour. The targeted early intervention of metabolic pathophysiology provides for the opportunity to significantly impact the outcome and prognosis of an otherwise severe intellectual disability.[9] Pre-symptomatic treatment is effective in achieving a good neurodevelopmental outcome.[6] Annual assessment of glomerular filtration rate for assessment of kidney function while on creatine supplementation therapy is essential.

GAMT deficiency is a candidate disorder for newborn screening, as elevated guanidinoacetate can be detected on dried blood spot with no false-positive results using liquid Gas Chromatography-Mass Spectrometry.[17]

In conclusion, cerebral creatine deficiency syndromes should be considered in any child with global developmental delay, epilepsy, autistic features, and a normal neonatal period. Magnetic resonance spectroscopy should be included in the imaging schedule to look for an absent creatine peak. Early identification and creatine supplementation with protein restriction are associated with neurodevelopmental gains.

DISCLOSURE

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Conflict of interest: Nil.

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