

Guanidinoacetate Methyltransferase (GAMT) Deficiency, A Cerebral Creatine Deficiency Syndrome: A Rare Treatable Metabolic Disorder

Sir,

The prevalence of cerebral creatine deficiency syndrome (CCDS) has been estimated as 2.7% in children with unexplained mental retardation.^[1] The prevalence of CCDS in children with autism spectrum disorder has been reported to be less than 7 per 1000.^[2] CCDS encompasses guanidinoacetate methyltransferase deficiency (GAMT-D), L-arginine:glycine amidinotransferase deficiency (AGAT-D), and creatine transporter (CRTR) deficiency. Here, we report a 29-month-old boy with socio-adaptive and language delay, autistic traits and hypotonia. GAMT-D was diagnosed based on the elevated urinary excretion of guanidinoacetate (GAA), and identification of a novel pathogenic variant in *GAMT*, the gene encoding guanidinoacetate methyltransferase. There are only few reports of genetically confirmed GAMT-D cases from the Indian subcontinent.

A two year and five months old boy, second born to non-consanguineous parents, was brought for the evaluation of global developmental delay, predominantly involving socio-adaptive and language milestones. There were no antenatal or perinatal risk factors. Family history was non-contributory.

Microcephaly, plagiocephaly, low set ears, poor eye contact, inconsistent response to name call, poor attention span, hypotonia and hyporeflexia were observed on examination. Nerve conduction parameters, serum creatine kinase, and serum creatinine (patient value: 0.20 mg/dL; normal 0.03-0.5 mg/dL) were normal. Urine organic acid analysis revealed non-diagnostic elevation of aconitate, ethylmalonate, and glutarate. Tandem mass spectrometry revealed no abnormalities. Brain magnetic resonance imaging (MRI) at presentation showed symmetrical hyperintensity involving central pontine tegmental tracts and bilateral globus pallidi [Figure 1a and b]. Magnetic resonance spectroscopy (MRS) revealed an absence of creatine peak [Figure 1c]. Brain CT revealed calcification involving the bilateral globus pallidi [Figure 1d]. Given the findings of cerebral creatine deficiency by MRS, metabolite testing in urine was undertaken and urine testing showed increased excretion of GAA (1202 mmol/mol creatinine; normal <200 mmol/mol creatinine), most consistent with a diagnosis of GAMT-D. The GAA level also was increased in plasma (13.3 micromol/L; normal: 0.26–1.88), although this analysis was done after the initiation of creatine supplementation.

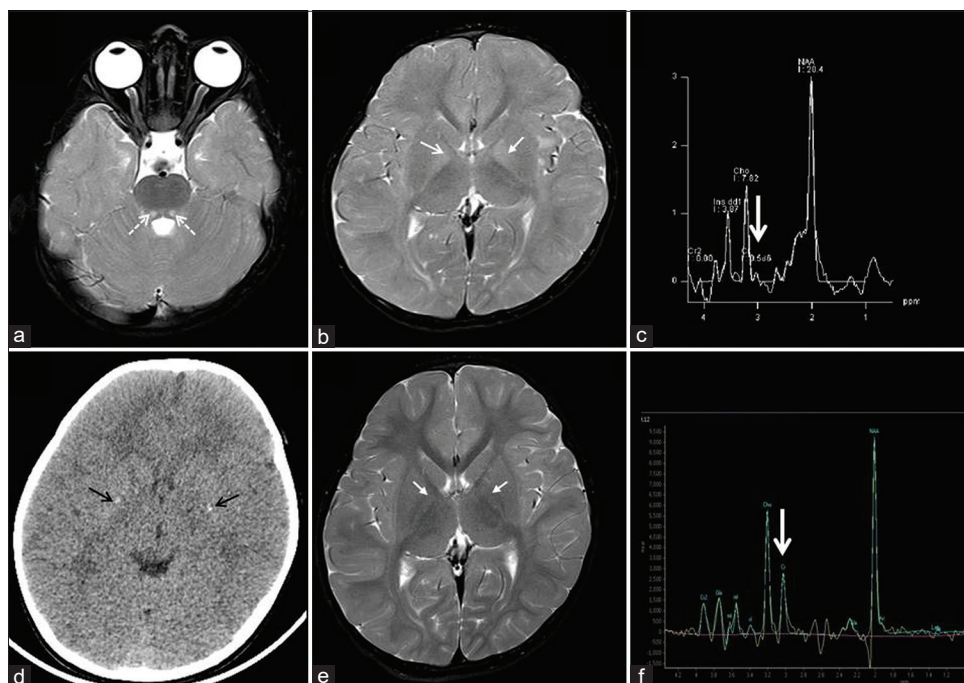


Figure 1: MRI brain showing symmetrical T2 hyperintensity involving bilateral central pontine tegmental tracts (white dash arrows in a) and globus pallidi (white arrows in b) and absent creatine peak at 3.0 ppm in MR spectroscopy (white bold arrow in c). CT brain (d) shows calcification involving bilateral globus pallidi (black arrows in d). Post-treatment MRI brain shows near complete resolution of signal changes in the globus pallidi (white arrows in e) and MR spectroscopy shows a small creatine peak (white bold arrow in f)

Sanger sequencing of *GAMT* identified a novel homozygous variant c.235C>T, in exon 2 [Transcript ID: ENST00000252288 transcribed from reverse strand; Genomic coordinate chr19:1399884G>A; GRCh37/hg19 build] leading to change in amino acid Glutamine to a premature stop codon [p.Q79Ter]. The resultant mRNA will either be shunted to NMD pathway or, if translated, will result in a truncated protein. This variant has not been reported in ExAC gnomAD or the 1000 Genome database and in silico analysis tools predict this variant as disease causing. Further, the phenotype is matching with the genotype. All evidences indicate that this variant is pathogenic.

Our patient was treated with creatine monohydrate at 500 mg/kg/d divided in three doses, low protein diet (0.5 gm/kg/d) to restrict arginine and also sodium benzoate that facilitates a reduction in GAA by decreasing serum glycine. Rapid improvement in socio-cognitive skills was observed and follow-up imaging nine months after the initiation of therapy showed near complete resolution of signal changes in the globus pallidi and a presence of small creatine peak on MRS [Figure 1e and f]. Child has been under regular follow-up with periodic neurodevelopmental assessment and appropriate biochemical investigations to exclude the treatment-related adverse effects.

In humans, creatine is derived exogenously from food and endogenously by creatine synthesis which occurs primarily in the liver, kidney and pancreas. *GAMT*-D was first described in 1994 by Stockler *et al.*^[3] The incidence of this disorder in the general population has been estimated to be approximately 1 in 2,640,000.^[4] In the first step of creatine synthesis, GAA is formed from arginine and glycine, catalysed by *AGAT*.^[5] In the second step catalysed by *GAMT*, methylation of GAA in the presence of S-adenosylmethionine results in the formation of creatine and S-adenosylhomocysteine.^[5,6] Creatine is transported through the bloodstream to muscle and brain, where it is taken up via sodium and chloride-dependent creatine transporter and plays a pivotal role for energy availability in these tissues.^[5-7]

Developmental delay or regression of milestones, seizures, autistic traits, and speech and language dysfunction are observed in patients with CCDS.^[5] A more severe phenotype is usually associated with *GAMT*-D while a milder phenotype is observed in patients with *AGAT*-D.^[5] Our patient had a predominant delay in socio-adaptive and language milestones, autistic traits and hypotonia. Although overlapping clinical features are described in all CCDS subtypes, seizures and extrapyramidal involvement are more commonly seen in children with *GAMT*-D and the clinical symptoms are thought to result from GAA accumulation.^[5] However, seizures and extrapyramidal signs were not observed in our case, suggesting that there is a range of phenotypic presentation in this disorder.

Diagnosis of *GAMT*-D is based on the demonstration of elevated GAA in body fluids, as seen in our patient, while the GAA level is low in *AGAT*-D. In both these disorders, plasma creatine levels usually are low. *CRTR* deficiency is

diagnosed based on the identification of an elevated urine creatine/creatinine ratio. The plasma GAA and creatine levels are normal in patients with *CRTR* deficiency. All patients with CCDS show evidence of small or absent creatine peak by MRS. Pathogenic variants in *GAMT*, *GATM*, and *SLC6A8* have been identified in patients with *GAMT*-D, *AGAT*-D and *CRTR* deficiency, respectively.^[5,8] Biochemical and molecular studies were consistent with a diagnosis of *GAMT*-D in our patient. As there are no reported clear genotype-phenotype correlations, it may be difficult to predict the severity based on the type of mutation alone.^[9] The phenotype was not severe in our case despite premature termination codon.

This report highlights the need to screen for inborn errors of metabolism, in the evaluation of children with syndromic autism as reported previously.^[10] Oral creatine supplementation is the main modality of treatment for patients with *GAMT*-D and *AGAT*-D. In patients with *GAMT*-D, arginine restriction and administration of ornithine and sodium benzoate have been tried to decrease the plasma GAA levels.^[5] Oral creatine monohydrate, L-arginine, L-glycine and S-adenosyl methionine have been tried in the management of creatine transporter defect, as it increases the endogenous synthesis of cerebral creatine.^[11] Although there is an appreciable benefit that occurs from creatine supplementation in CCDS, the outcome is variable among the subtypes. The efficacy of treatment is measured not only by the clinical outcomes such as developmental gains, seizure control and improvement in behaviour and muscle mass but also by MRS that gives an estimation of the brain creatine content.^[7] Children with CCDS have to be monitored periodically for effects related to the underlying disease and treatment with liver function test, renal function test, estimation of urine and plasma GAA, estimation of urine creatine, blood folate and homocysteine levels.^[7] Regular urine analysis must be planned in children with CCDS on treatment with high doses of creatine to monitor the formation of urinary creatine crystals and to exclude urinary tract infection.^[12]

Screening for CCDS must be considered in children with unexplained neurodevelopmental disorders with comorbidities such as autism, seizures, movement disorders or muscle weakness. MRS is an important tool in the evaluation of these children to diagnose CCDS. Pediatricians and Neurologists must be aware of this inherited treatable group of metabolic disorders, as establishing a diagnosis is often needed not only for initiation of treatment but also to counsel the family regarding the risk of recurrence and the options of prenatal diagnosis. We suggest that the estimation of GAA levels in urine and urinary creatine/creatinine ratio must be included in the evaluation of patients with unexplained intellectual disabilities or neurodevelopmental disorders.

Author's Note

The magnetic resonance imaging of brain of this case was included in "Pediatric bilateral basal ganglia lesions: A pattern based approach" that was presented as an electronic poster in an educational exhibit in the Radiological Society of North

America (RSNA) annual conference- 2017, held in Chicago, United States. This case was one among the cases presented as “Cerebral creatine deficiency syndrome: An underdiagnosed treatable cause of autism” in the Annual scientific day of Indian Journal of Pediatrics as a part of competitive grand rounds by senior residents on 2nd September 2018 held in All India Institute of Medical Sciences, New Delhi, India. This case was also one among the cases presented in the CME on rare diseases in the “4th International conference on birth defects (ICBD- 2018) and 5th Annual conference of the society of Indian Academy of Medical Genetics, on 15th December 2018 held in Christian Medical College, Vellore, Tamil Nadu, India.

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Conflicts of interest

There are no conflicts of interest.

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