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Case Report

Guanidinoacetate N-methyltransferase deficiency: Case report and brief review of the literature ☆

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ABSTRACT

Guanidinoacetate N-methyltransferase (GAMT) deficiency is a rare autosomal recessive disorder characterized by a decrease in creatine synthesis, resulting in cerebral creatine deficiency syndrome (CCDS). GAMT deficiency is caused by mutations in the GAMT gene located on chromosome 19, which impairs the conversion of guanidinoacetic acid (GAA) to creatine. The resulting accumulation of the toxic metabolite GAA and the lack of creatine lead to various symptoms, including global developmental delays, behavioral issues, and epilepsy. The gold standard for diagnosis of GAMT deficiency is genetic testing. Treatment options for GAMT deficiency include creatine supplementation, ornithine supplementation, arginine restriction, and sodium benzoate supplementation. These treatment options have been shown to improve movement disorders and epileptic symptoms, but their impact on intellectual and speech development is limited. Early intervention has shown promising results in normalizing neurological development in a minor subgroup of patients. Therefore, there is a growing need for newborn screening techniques to detect GAMT deficiency early and prevent permanent neurological delays. Here we report a case of GAMT deficiency with emphasis on imaging presentation. Our case showed reduced brain parenchyma creatine stores on MR Spectroscopy, which may provide an avenue to aid in early diagnosis.

Introduction

Guanidinoacetate N-methyltransferase (GAMT) is an enzyme that functions to create creatine (Cr), a substance used in the body to transfer and contain energy in the form of phosphate [1]. The process of creatine generation begins with the amino acids glycine and L-arginine. These substrates are trans-aminated to create guanidinoacetic acid (GAA) using the

Abbreviation: GAMT, Guanidinoacetate N-methyltransferase; Cr, Creatine; GAA, Guanidinoacetic acid; AGAT, L-arginine:glycine amidinotransferase; CK, Creatine Kinase; PCr, Phosphocreatine; ATP, Adenosine Triphosphate; CCDS, Cerebral Creatine Deficiency Syndrome; Cho, Choline; NAA, N-Acetyl Aspartate.

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enzyme L-arginine:glycine amidinotransferase (AGAT), after which GAA is transported to the liver or other tissues where GAMT uses S-adenosyl-L-methionine to add a methyl group to form creatine [1,2]. Creatine Kinase (CK) is then used to create phosphocreatine (PCr) which functions as an excellent energy storage source for the formation of adenosine triphosphate (ATP), both of which are used in muscle activity and exercise [3–6]. The energy stored in creatine is also utilized in the nervous system for signal transduction via neurotransmitter release, nerve growth, and membrane potential maintenance [7–10]. In cells with a high energy demand such as muscles, creatine transport is facilitated by the Na^+-Cl^- dependent creatine transporter, known as SLC6A8 [6,10]. Astrocytes forming the blood-brain barrier lack this creatine transporter, limiting the amount of creatine that enters the CNS [10,11]. It is thought that most of the brain's creatine supply is formed from endogenous synthesis with AGAT and GAMT [6,10,11].

Cerebral creatine deficiency syndromes (CCDS) are metabolic disorders characterized by an abnormally low amount of creatine in the brain. There are 3 known CCDS; an autosomal recessive GAMT deficiency, an autosomal recessive AGAT deficiency, and an X-linked creatine transporter deficiency [2,12,13]. GAMT deficiency is the most common disorder of creatine synthesis, but X-linked creatine transporter deficiency is the most common CCDS [6,12,13]. Located on chromosome 19, the gene that encodes GAMT has had a variety of mutations reported. Many patients have a silent mutation of c.327G>A, which occurs at the second exon splice site, causing the insertion of 44 nucleotides [5,14,15]. A lack of GAMT halts the transformation of GAA into creatine, which causes a buildup of GAA in bodily fluids and a decrease in total body creatine [13]. When functioning normally GAMT containing cells also uptake GAA to maintain low extracellular concentrations [16]. In high levels, GAA is neurotoxic and epileptogenic, and when combined with low creatine levels a multitude of symptoms occur [2,7,9,13,14,17–19]. The most common symptoms of GAMT are global developmental delays, behavioral issues, and epilepsy [14]. There are approximately 130 patients with reported GAMT deficiency with an estimated incidence of 1:250,000 newborns, however, these may be underreported due to nonspecific symptoms and lack of universal screening [7,17]. One study reports that among the general population, 0.123% are carriers [20]. The prevalence of CCDS in patients with intellectual disability is 2.7 %, which demonstrates a considerable occurrence within that population [8]. MR Spectroscopy also shows potential in screening for CCDS due to its ability to measure the low creatine levels in the brain, however, more evidence is needed to support its clinical use in diagnosis. Diagnosis of GAMT deficiency is confirmed by genetic testing.

Here we present a case of a 17-year-old male with confirmed GAMT deficiency.

Case report

A male child was born from nonconsanguineous parents at 40 weeks gestation via vaginal delivery with a birth weight of 2.8 kg. Pregnancy was complicated by anemia, mild use of alcohol until 6 weeks gestation, and tobacco use of around 7-10 cigarettes a day. Ultrasound and fetal movement throughout pregnancy were reported to be normal. Newborn screening for phenylketonuria, congenital hypothyroidism, galactosemia, cystic fibrosis testing, and chromosome testing was unremarkable. At 6 months of age, the patient was diagnosed with failure to thrive, as they were unable to gain adequate weight despite formula supplementation. The patient was able to sit at 10 months, but unable to crawl or pull to stand, and had minimal babbling. Laboratory values of the patients comprehensive metabolic panel, creatine phosphokinase, and thyroid stimulating hormone were normal. Serum ammonia and lactic acid levels were mildly elevated, and aldolase was mildly lowered. They were found to have low muscle tone and developmental delay and later began crawling around 14-15 months of age. The patient also had strabismus. At 19 months, they began to cruise, most often walking on the insides of their ankles. They were noted to have a small throat and a receding chin, weight/height less than the third percentile, and a head circumference in the 50th percentile. Workup including a brain MRI and at the time was normal. It was thought that the delayed development was improving so the patient was told to follow up at a later age for monitoring.

Table 1 – Age of symptom and diagnosis onset in a patient with GAMT deficiency.

Age of onset	Symptom/Diagnosis
6 mo	Failure to thrive
10 mo	Low muscle tone
	Developmental delay
15 mo	Strabismus
19 mo	Cruising using the inner ankles
	Dysmorphic facial features (Small throat, Receding chin)
3 y	Early Learning Accomplishment Profile (Global Developmental Delay)
	Gross motor = 18 mo
	Fine motor = 12 mo
	Cognitive = 13 mo
	Language = 13 mo
	Self help = 15 mo
	Social = 14 mo
	Short attention span
	Hair pulling
	Biting
5 y	Autism
	ADHD
5-12 y	Seizures
12 y	GAMT deficiency diagnosis

At 3 years of age, the patient was evaluated using the Early Learning Accomplishment Profile, and the patient was diagnosed with multiple developmental delays (Table 1). The patient showed a very friendly and happy demeanor with good eye contact and would spend time but not engage in play with others. They exhibited a very short attention span and had behavioral issues such as hair pulling and biting. The patient continued to have poor weight gain and had many food aversions. Genetic testing performed at 3 years of age showed no abnormalities.

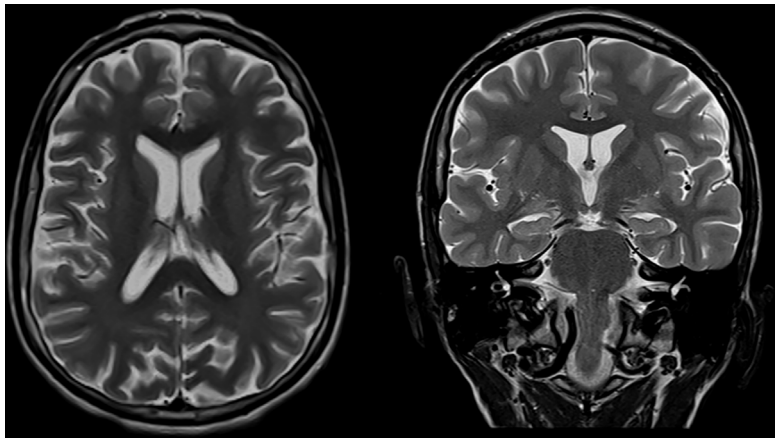

Fig. 1 – T2 MRI Brain, axial view (left) and coronal view (right) displaying greater than expected brain parenchymal volume and increases prominence of the ventricles and sulci in a 17-year-old male with recurrent seizures and global developmental delay.

Due to the patient's multitude of symptoms as they aged, repeat genetic testing at age 12 was obtained. Results showed a homozygous pathogenic variant of c.327G>A silent mutation was found in the GAMT gene, diagnosing the patient with pathogenic GAMT deficiency, a cerebral creatine deficiency syndrome. The patient had also been experiencing shaking episodes thought to be seizures, but an EEG was unable to be obtained due to compliance issues. Multiple seizure medications were trialed, however none proved effective. After continued seizures despite medication, at the age of 14 the patient was started on creatine monohydrate at 800 mg/kg of body weight per day, and ornithine supplementation at 800 mg/kg of body weight per day. Despite supplementation, the patient continued to have almost daily seizures, but reported that behavior, movement, and social abilities had improved with time.

At age 17, MRI brain and MR Spectroscopy were performed. Pertinent findings included generalized parenchymal volume loss with greater than expected prominence of the ventricles and sulci for patients age (Fig. 1). Interestingly, MR Spectroscopy analysis with voxel placed over the normal-appearing white matter of right centrum semiovale and gray matter (right basal ganglia) showed reduced Creatine peak, in keeping with a clinical diagnosis of GAMT deficiency (Figs. 2 and 3). Synthetic MRI Brain with quantitative analysis showed a brain parenchymal fraction of 84.1%, which falls below the 95th confidence level of brain parenchymal fraction measured with synthetic MRI in healthy patients [21] (Fig. 4). This correlates with the subjective assessment of brain parenchyma volume loss (Fig. 1).

The patient has since continued to supplement creatine and ornithine at the same rate as it previously showed clinical improvement. The patient opted not to restrict arginine from the diet.

Discussion

The most common symptoms of GAMT deficiency are epilepsy and global developmental delay, often affecting cognitive, speech/language, and behavioral functioning [2,4,8,12–14,17,22,23]. Many reports have also reported that epilepsy is resistant to treatment, likely due to the high levels of GAA accumulation [4,12,24]. Neurological manifestations can also include attention-deficit/hyperactivity disorder, impulsive behavior, and autistic traits [4,12,13,17,22]. Other symptoms noted are constipation and extrapyramidal movement disorders including but not limited to hypotonia/dystonia, rigidity, and impaired reflexes [2,4,8,12,14,17,22,23]. In accordance with these movement symptoms, brain MRI can show T2 hyperintensity of the bilateral globus pallidi, and CT imaging can show calcification of the same region, however, this is not always present [4,12–14,18,22]. After ruling out other genetic causes, 1 study reported a patient with recurrent bone fractures which was attributed to the sedentary nature of the disease due to their motor symptoms [17]. GAMT deficiency differs from the other CCDS as it has a higher rate of movement disorders, MRI changes, and treatment-resistant epilepsy [4,12]. Due to the rarity of the disease, and the numerous but nonspecific symptoms of GAMT deficiency, it is possible to misinterpret the diagnosis for a more common disorder. Therefore, an adequate history, physical, and diagnostic testing must be performed to catch the deficiency early.

Initial steps in diagnosis may include serum and urine testing for GAA and Creatine levels. Typically GAA is found in high levels in both serum/urine and Creatine is low in both serum/urine, however, due to variations in testing and patient deficiencies, sometimes the levels can be on the low-normal end [13,17,22]. Currently in patients with high clinical suspicion for GAMT deficiency, genetic testing showing altercation of the GAMT gene on chromosome 19p13.3 is the gold standard for confirming the diagnosis. While effective, this process can be difficult to obtain and has the caveat of long wait times for results.

MR Spectroscopy further confirmed the diagnosis in our case by showing a reduced creatine peak within the brain parenchyma. Multiple other studies have shown GAMT-deficient patients with decreased creatine levels on MR spectroscopy [2,6,18]. In GAMT-deficient patients, body fluids can

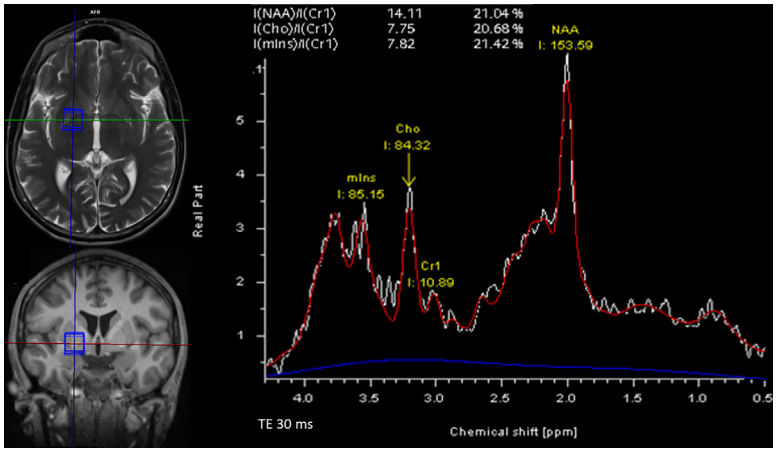

Fig. 2 – MR Spectroscopy, at echo time of 30 ms with voxel placed over the right Basal Ganglia (Posterior putamen, globus pallidus, and posterior limb of the internal capsule). Normal choline (Cho) and N-Acetyl Aspartate (NAA) peak. There is a substantially decreased creatine (Cr) peak at 10.89, with increased NAA/Cr and Cho/Cr ratios.

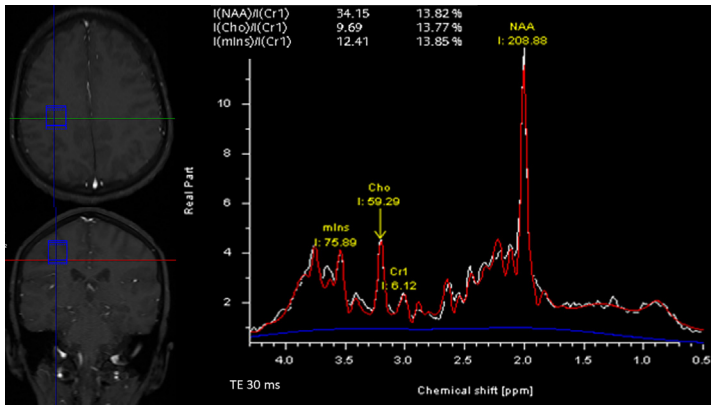

Fig. 3 – MR Spectroscopy, at echo time of 30 ms with voxel placed over the right centrum semiovale normal appearing white matter. There was normal choline (Cho), and N-Acetyl Aspartate (NAA) peak, with substantially decreased creatine (Cr) peak at 6.12, and increased NAA/Cr and NAA/ Cho ratios.

also show increased levels of GAA on MR spectroscopy [6,25]. MR spectroscopy in AGAT deficiency patients shows low levels of GAA, and the x-linked creatine transporter deficiency shows a normal to high level of GAA [2,8,22,26,27]. AGAT deficiency may also show a decreased creatine level on MR spectroscopy, similar to GAMT deficiency [6,26]. Due to these abnormal findings on MR spectroscopy, they may serve as useful markers to diagnose GAMT deficiency prior to genetic testing. Since MR spectroscopy measures levels of metabolites, there is potential to track treatment response based on changes in creatine and GAA, which would serve as a good prognostic tool. However, more supportive evidence may be needed due to the low prevalence of the disease. The relatively quick and noninvasive nature of MR spectroscopy is also beneficial, as it doesn't require techniques such as blood draws, tissue samples, or CSF samples, which can be difficult to obtain in younger patients. Brain imaging is often obtained in tandem with metabolic information, which allows you to evaluate for parenchymal volume and other pathologies within a single study.

Creatine may be used as a monotherapy to treat GAMT deficient patients, and the blood-brain barrier's restricted creatine permeability necessitates administering high doses to effectively supply the central nervous system [6,9–11]. Creatine is typically supplemented at a rate of 400-800 mg/kg/d and typically decreases plasma GAA concentrations around 40%-50% [4,14]. As a monotherapy, creatine monohydrate supplementation has been shown to improve epilepsy and movement disorder symptoms with minimal side effects, however monotherapy has less of an effect on behavioral and developmental delay symptoms [14,28].

Other treatment modalities include GAA reduction techniques such as ornithine supplementation, arginine restriction, and sodium benzoate supplementation. L-Ornithine at 400-800 mg/kg/d lowers plasma GAA an additional 36%-50% due to a competitive reduction in AGAT, the enzyme that synthesizes GAA [13,14]. While sometimes difficult to achieve due to behavior and dietary preferences of GAMT patients, arginine restriction with a total protein intake of 0.3-0.4 g/kg/d has been also shown to reduce GAA levels, lowering symptom

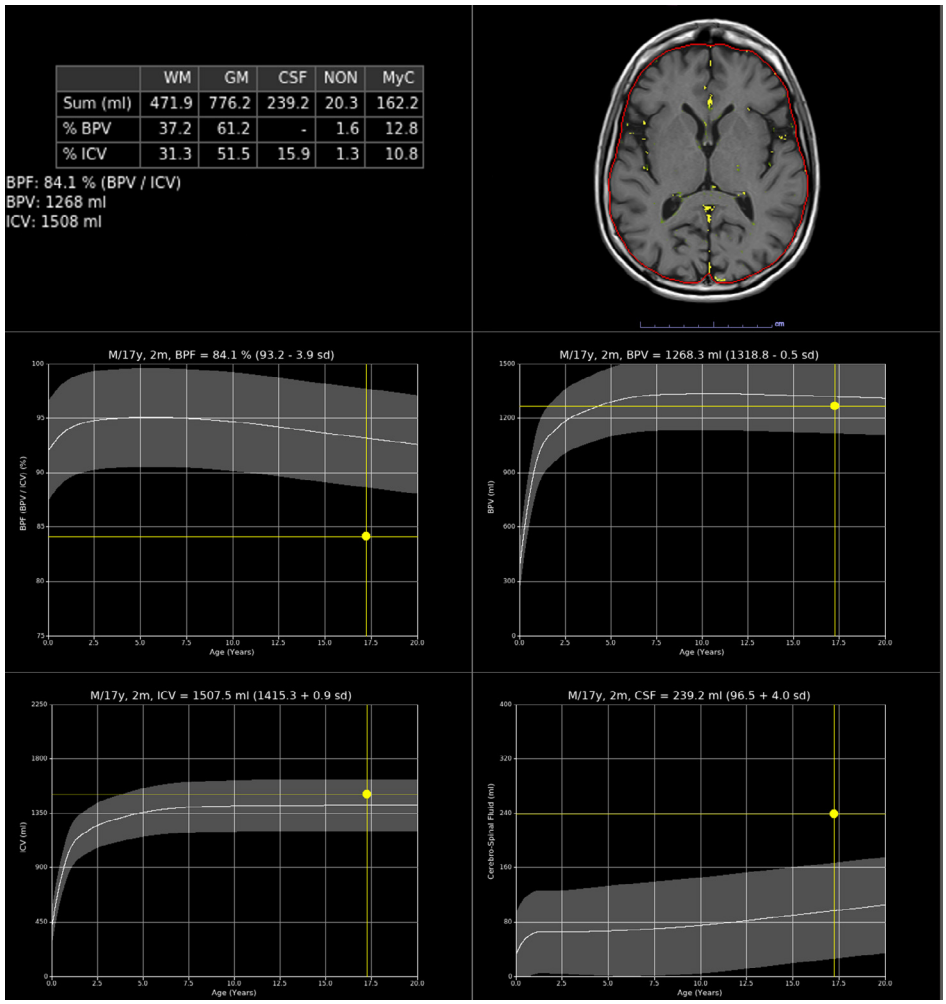

Fig. 4 – Synthetic MRI Brain with quantitative analysis showing a total brain parenchymal volume of 1268 mL, a total intracranial volume of 1508 mL, and a brain parenchymal fraction of 84.1% in a 17-year-old male with diagnosed GAMT deficiency.

burden [14]. Sodium benzoate is also used to decrease the substrate glycine, further reducing GAA levels [14].

A combination therapy including both creatine replacement and GAA reduction has been shown to improve seizure burden and motor disorders, with varying improvement of behavioral and speech symptoms [4,14,29,30]. In some cases, combination therapy is needed to decrease seizure frequency, as creatine monotherapy did not suffice [14]. While these therapies have no known major side effects, challenges may occur due to cost of treatment, administration difficulties due to behavior, and dietary preferences limiting the restriction of arginine. In our patient, seizure frequency did not decrease, but behavioral abilities and speech improved. After treatment, MR spectroscopy of the brain may show decreased GAA levels and increased creatine levels [4,14,19,22]. The MRI lesions in the globus pallidus previously mentioned have also been reported to be absent post treatment [13].

Some evidence may point to the benefit of early intervention, as 3 patients with a family history of GAMT deficiency that were treated in the early neonatal period were able to achieve normal neurological development [19,29,31]. The presence of a symptom free period in newborns also urges early detection to prevent any significant permanent neurological delays from forming [13]. Due to the high prevalence of CCDS in patients with intellectual disabilities, newborn screening has been proposed to establish an early diagnosis. One study suggests screening for GAMT deficiency using measured guanidinoacetate levels in dries blood spots obtained at birth [19,29]. Currently in the United States, both New York and Utah screen for GAMT deficiency using a similar method [32].

GAMT plays a crucial role in creatine synthesis, a process vital for energy transfer and nervous system function. CCDS, such as GAMT deficiency, lead to a range of clinical manifestations, including developmental delays, epilepsy, movement disorders, and behavioral issues. Treatment approaches, including creatine supplementation and other GAA reduction strategies, offer promise in ameliorating symptoms and improving the quality of life for affected individuals. Early diagnosis is pivotal in enabling appropriate interventions to prevent any permanent neurological dysfunction. MR spectroscopy has the potential to aid in the diagnostic workup of GAMT deficiency, as many patients have shown low creatine

levels and high GAA levels in the brain. Further studies on the MR spectroscopy findings before and after treatment may also provide evidence for the use of MR spectroscopy for prognosis and treatment effectiveness. With the potential for early detection and intervention, it is essential to increase awareness of GAMT deficiency, promote research efforts, and expand newborn screening programs to enhance the prognosis and well-being of those affected.

Patient consent

Written informed consent was obtained from the patient for the publication of their case.

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