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GAMT Deficiency Among Pediatric Population: Clinical and Molecular Characteristics and Management

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Abstract

Objective: Analyze the treatment modalities used in real practice by synthesizing available literature. **Methods:** We reviewed and evaluated 52 cases of GAMT deficiency including 4 novel cases from Saudi Arabia diagnosed using whole-exome sequencing. All data utilized graphical presentation in the form of line charts and illustrated graphs. **Results:** The mean current age of was 117 months (±29.03) (range 12-372 months). The mean age of disease onset was 28.32 months (±13.68) (range 8 days – 252 months). The most prevalent symptom was developmental delays, mainly speech and motor, seizures, and intellectual disability. The male-to-female ratio was 3:1. Multiple treatments were used, with 54 pharmacological interventions, valproic acid being the most common. Creatinine monohydrate was the prevalent dietary intervention, with 25 patients reporting an improvement. **Conclusion:** The study suggests that efficient treatment with appropriate dietary intervention can improve patients' health, stressing that personalized treatment programs are essential in managing this disorder.

Keywords

GAMT, guanidinoacetate methyltransferase deficiency, creatine, cerebral creatine deficiency, epilepsy, newborn screening

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Introduction

Guanidinoacetate methyltransferase (GAMT) deficiency is a rare inherited disorder defined as one of the creatine deficiency syndromes (CDS) which was recently discovered and includes three inborn errors of creatine synthesis and transporter,[1] with the first case to be reported by Stockler et al. in 1994.[2] The biosynthesis of creatine in the liver and the pancreas requires the presence of two essential enzymes, arginine: glycine amino-transferase (AGAT), guanidinoacetate methyltransferase (GAMT), and creatine transporter (CRTR).[3] With GAMT deficiency, there will be decrease or even diminished of creatine level[4] and patients presenting with elevated concentrations of guanidino-acetate (GAA).[5] A reduction in GAA is important as its accumulation can lead to brain toxicity.[6] This has been found in molecular interactions between GAA and GABAA (γ-aminobutyric acid type A) receptors in murine brain studies which has been also proposed as the potential mechanism explaining the neurological phenotypes in GAMT deficiency.[7] Such reduction is important by utilizing a strategy of arginine restriction that is a substrate for GAA synthesis. GAMT deficiency is attributed to various forms of mutations in the gene encoding chromosome 19p13.3.[3] Consanguineous marriages play a major role as a risk factor that has been found in

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many reported cases.[8–10] A higher prevalence of this disorder is predicated among communities of higher consanguinity rates including a country like Saudi Arabia.[11] Furthermore, the clinical presentation is variable from mild to severe intellectual disability,[3,9] with non-specific findings including the presence of speech delay, hypotonia, seizure, autistic behavior, and extrapyramidal features are also reported.[4,9,12] One of the latest studies in 2023 reviewed 4 novel case reports in Saudi Arabia and over 50 published case reports all over the world, showing that intellectual disability followed by seizures are the most frequently reported presentation.[9] Moreover, the diagnosis of this disorder is made by correlating clinical and biochemical findings. Molecular gene testing is then done to confirm the diagnosis of GAMT deficiency.[1] However, although the literature on diagnosing GAMT deficiency is slowly increasing, we still lack validated data on the management of this disorder, and until today; there are no published guidelines for the management of CDDs.[1] Treatment of GAMT deficiency aims to replenish creatinine levels of the brain using creatinine monohydrate.[13,14] In addition, an arginine-restricted diet and sodium benzoate reduce GAA levels, and high doses of L-ornithine supplementation competitively inhibit AGAT activity.[15] Biochemical, imaging, and clinical monitoring with treatment should be done to monitor the efficacy of treatment. However, a study determined that the initiation of treatment early on has been highly beneficial in reducing cognitive and intellectual disabilities and other clinical symptoms that will affect the development of the child.[3] They were followed up and showed normal development. This prompts the importance of newborn screening among patients to help avoid long-term complications relating to under and misdiagnosed patients.[15,16] As there is no published consensus for the management of GAMT deficiency, our study aims to collect and analyze treatment methods and outcomes of patients diagnosed with GAMT deficiency in Saudi Arabia compared to others previously reported in the literature.

Materials and Methods

Ethical Approval

The study's aim, protocol, and procedure were approved on May 2, 2023, by the Unit of Biomedical Ethics Research Committee at the Faculty of Medicine at King Abdulaziz University (number 245-23). The study was conducted under the guiding principles of the World Medical Association Declaration of Helsinki. Patients personal data were masked and consent was obtained prior to the enrollment of the local cases. All information was kept private and anonymous.

Sample Collection

Following appropriate ethical and logistical measures, we obtained the genetic sample of the patients from King Abdulaziz University Hospital. Whole exome sequencing (WES) was carried out on the four patients to detect the pathogenic variants. Sequencing was performed on Double-stranded DNA capture baits against approximately 36.5 Mb of the human coding exome (targeting >98% of the coding RefSeq from the human genome build GRCh37/hg19) were used to enrich target regions from fragmented genomic DNA with the Twist Human Core Exome Plus kit. The generated library was sequenced on an Illumina platform to obtain at least 20-fold coverage depth for >98% of the targeted bases. An in-house bioinformatics pipeline, including read alignment to GRCh37/hg19 genome assembly, variant calling (single nucleotide and small deletion/insertion variants), annotation, and comprehensive variant filtering were applied. Primary data analysis was performed using Illumina bcl2fastq converter v2.19. Secondary analysis is performed using Illumina DRAGEN Bio-IT Platform v.3.4.12. Tertiary data analysis is performed using SnpEff v5.0 and PerkinElmer's internal ODIN v.1.01 software. CNV and absence of heterozygosity are assessed using BioDiscovery's NxClinical v5.1 software.

Study Design and Setting

Following the Narrative Review Checklist developed,[17] we conducted an analytical exploratory study in which we reviewed published case reports on January 2023 for cases with GAMT deficiency. A total of 52 studies were retrieved from the literature. The literature search included the following study designs: A) case reports B) case series C) review articles. The time period was set from 1996 to January 2023. The following terms were used to identify literature: GAMT, Guanidinoacetate Methyltransferase, and Deficiency. The exploited databases include MEDLINE/PubMed. The following data were obtained: age, gender, genetic mutation, age of disease onset, reporting country, family history, clinical profile, management plans, and diagnostic and laboratory workup. No restrictions on ages were made and patients of all ages were included in the study. After synthesizing the obtained cases, only 45 studies were either in accordance with the scope of the study or obtained clinical significance. The findings of these cases were compared to four novel cases for patients from our clinic.

Statistical Analysis

Microsoft Excel 2014 (Microsoft Corp., Redmond, WA, USA) served as a spreadsheet tool to conduct the data assembly and entry. Statistical analysis was made using the Statistical Package for the Social Science (SPSS) version 26 (IBM Corp., Armonk, NY) and SmartPLS. Variables were exclusively qualitative in nature. Qualitative variables were described in frequency tables with percentages. All data utilized graphical presentation in the form of line charts and illustrated graphs. Clinical symptoms were stratified according to gender (male, and female), age groups (0-1 years: infants; 2-4 years: toddlers; 5-12 years: children), and reporting region (Europe, Asia, or North America).

Table 1. Pharmacological and Electrographical Characteristics of the Four Reported Cases. the Dose Range Indicated the Starting Dose and Maximumly Reached Dose.

Case No.	Antiepileptic medications	Dietary	Clinical outcome	EEG	MRI
Case 1	• Valproic acid, 250 mg twice per day (30 mg/kg/day)	• Daily dosage of creatinine and ornithine is 400–800 mg/kg/day	• 50% seizure reduction	• Slow background for age and a slow spike and waves	• Normal MRI
Case 2	• Clobazam	• Daily dosage of creatinine and ornithine is 350–450 mg/kg/day	• 100% seizure reduction	• Slow spikes and waves and generalized paroxysmal fast activities	• Normal MRI
Case 3	• Valproic acid • Clobazam	• Creatinine 400–800 mg/kg/day and 12 ornithine capsules (0.5 g each)	• 50% seizure reduction	• Sharp and slow wave activity	• Normal MRI
Case 4	• Valproic acid • Clobazam, • Levetiracetam	• Creatinine (350–450 mg/kg/day)	• 50% seizure reduction	• Abnormally low background activity with multifocal spikes	• Normal MRI

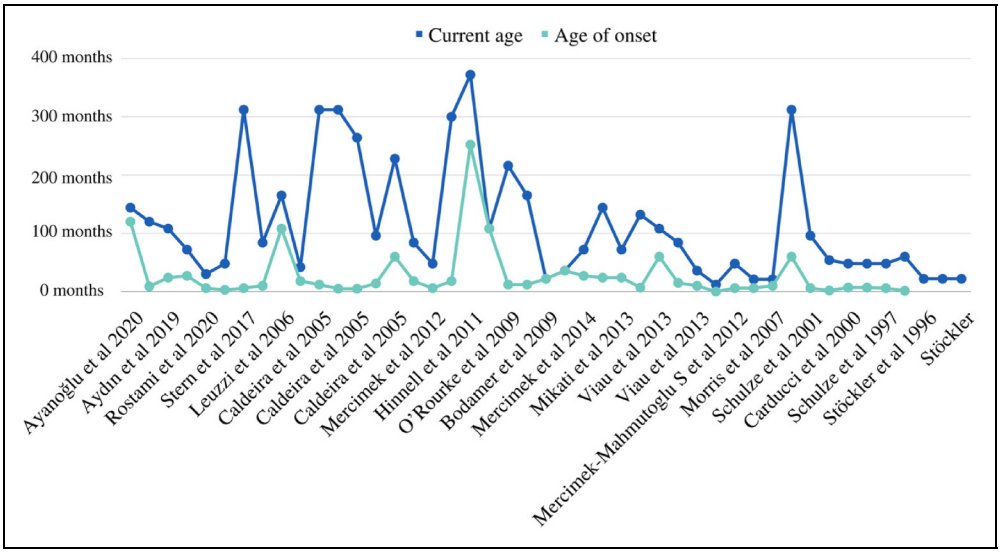

Figure 1. Line chart comparing the current age of patients and the age of disease onset. The Y-axis represents ages in months. The X-axis represents articles in a chronological order.

Results

In this study, we reviewed the pharmacological, dietary, and electrophysiological information and clinical outcomes of 44 literature cases of patients with confirmed pathogenic variants in the GAMT gene. Additionally, we presented 4 cases that have been previously described in the literature by the same authors (Table 1).[9] However, in the previous description only the clinical data were presented and now the novel therapeutic details are presented. The pathogenic variant in the novel cases was detected using WES. In total, this study included 48 patients).[14,16–42] The mean current age of patients was 117 months (±29.03) (range 12-372 months). The mean age of disease onset was 28.32 months (±13.68) (range 8 days – 252 months). A summary of the current age and age of disease onset was illustrated in Figure 1 in accordance with the report of each published case. The gender distribution showed a slight male predominance of 27 male patients to 21 female patients. The most prevalent clinical symptoms were developmental delay, which was predominately in speech and motor, seizures of various forms, and intellectual disability. The prevalence of these symptoms was 28%, 22%, and 13.6%, respectively. Other symptoms and their respective percentages are summarized in Figure 2. Patients were grouped according to their age groups. It included infants (0-1 year), toddlers (2-4 years), children (5-12 years), and others (>12 years). Their age distribution was summarized according to their gender in Figure 3. Turkey and the United States had the most reported cases (n = 6 each). Followed by Germany and Italy (n = 5 each). Other countries included Saudi Arabia, Austria, Ireland, the United Kingdom, Bulgari, Portugal, The Netherlands, China, Iran, Lebanon, Iraq, and Canada.

In our case presentation, the male-to-female ratio was 3:1. Although various treatment modalities were used among the

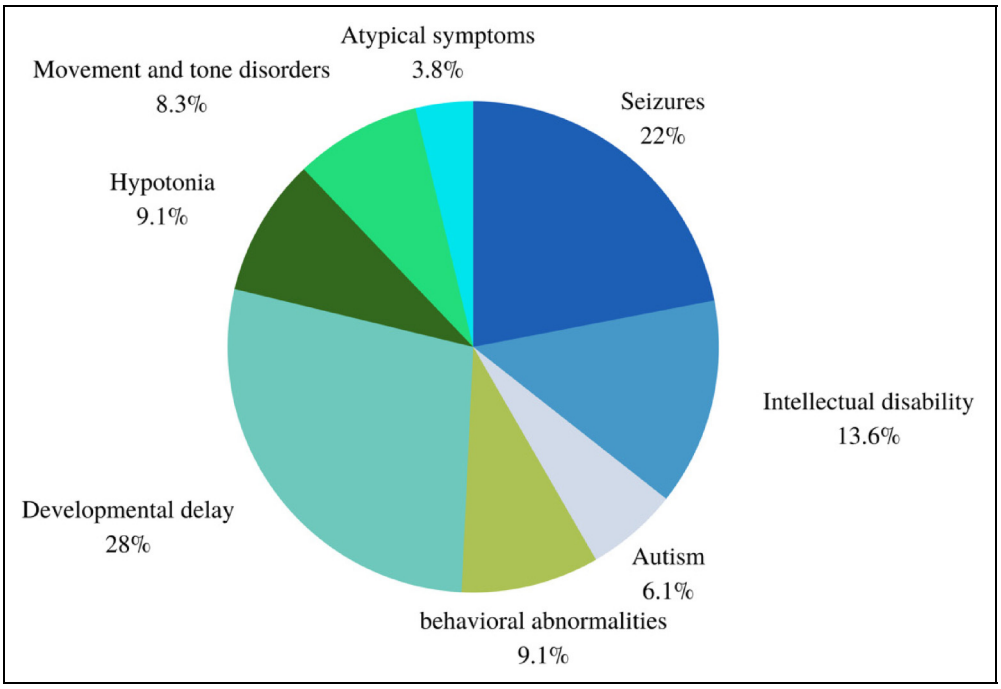

Figure 2. Pie chart of the most common clinical manifestations of the reported cases.

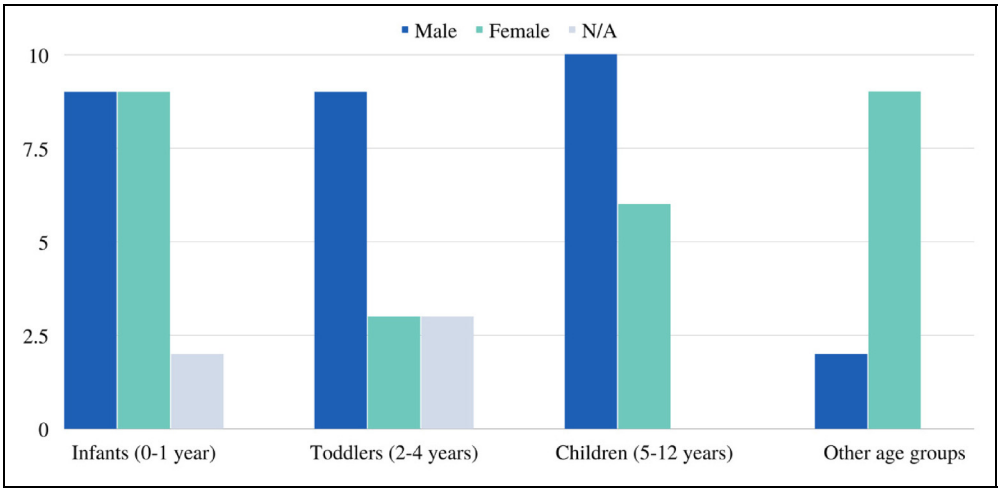

Figure 3. Bar chart of patients' current ages according to each pediatric age group with their gender characteristics. X-axis represents the number of patients. The Y-axis represents each age group.

patients, in total, we detected 54 different pharmacological interventions reported within the cases. Sodium valproate/valproic acid was the most frequently reported medication in 12 patients. Other medications included risperidone, aripiprazole, baclofen, phenobarbital, levetiracetam, lamotrigine, primidone, and others. A single report combined the management plan with ACTH for two patients. The clinical data for dietary intervention was available among 32 cases in the literature. The most commonly used dietary intervention was creatinine monohydrate at multiple doses that ranged from 200–400 mg/kg/day followed by l-ornithine supplementation, a low-protein diet, sodium phenylbutyrate, arginine hydrochloride, and, essential amino acid supplements. Meanwhile, 12 literature cases did not mention any dietary intervention. Nine cases reported mono-therapy, the majority of these mono-therapy were creatinine supplements. Six cases reported dual therapy that included a combination of creatinine supplement and arginine hydrochloride, creatinine monohydrate and restricted protein diet, creatinine monohydrate, and l-Ornithine. There were 16 reported cases that included treatment modalities of more than 3 different types of treatment. This includes a combination of creatinine monohydrate, protein-restricted diet, and l-ornithine

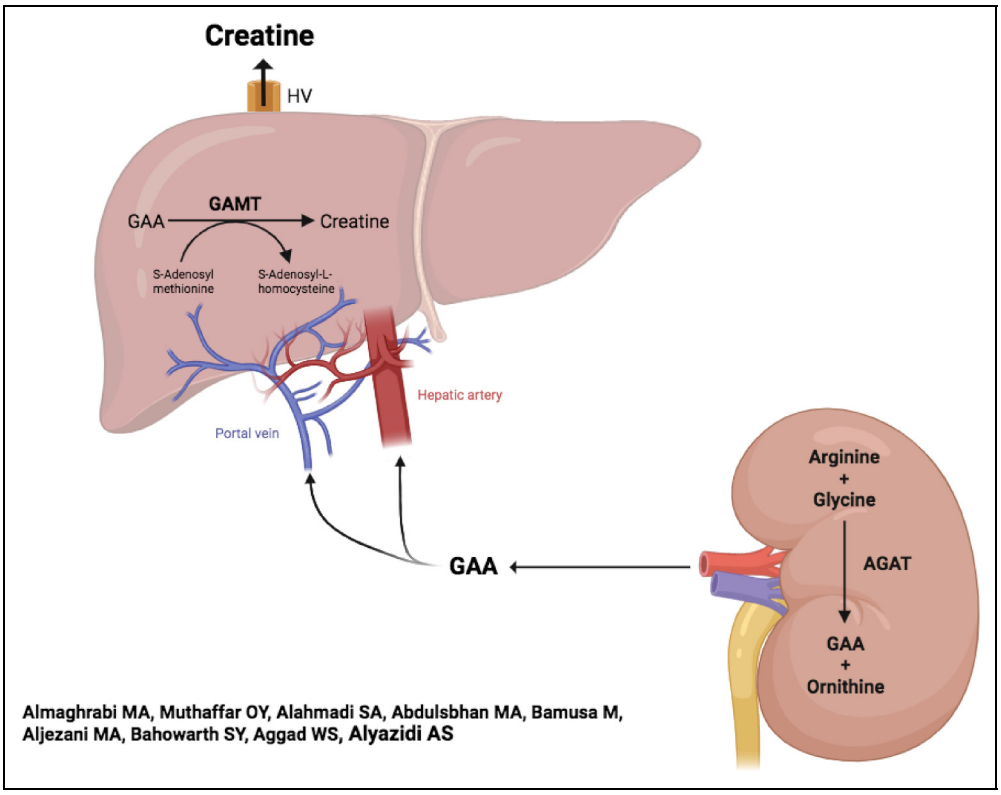

Figure 4. Metabolic pathway showing the biosynthesis of creatinine in the kidney and liver from the amino acids arginine and glycine.

supplement. In some cases, the same triple therapy was used with the substitution of arginine arginine-restricted diet for the protein-restrictive diet. Other combinations and doses were highlighted in Table 2 according to the availability of such information by the original authors.

Overall, 25 patients reported to have some form of clinical or neuroradiological improvement. Of those, 12 patients were reported to be seizure-free or controlled after the treatment. Five patients were reported to demonstrate improved motor functions. Two patients had specific speech improvement and enhanced verbal abilities. However, in some patients (case 38), hypotonia and rigidity progressed and worsened. Lack of speech improvement was reported in 5 patients. These worsening clinical symptoms were a combination of lack of seizure control, lack of cognitive improvement, the continuation of developmental delay, and persistent worrying signs on magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and electroencephalogram (EEG) in some cases as summarized in Table 2.

Twenty-six patients performed EEG. The majority had abnormal findings. This includes multifocal spike and slow-wave discharges mostly in the frontal region, dysrhythmic background, and rare periods of generalized suppression in some patients. Normal EEG was reported among 2 patients. Twenty-one patients had abnormal MRIs compared to 15 patients with normal MRIs. Reduced creatinine peak was noted among 20 patients that ranged from complete absence to moderately reduced creatinine flow. This reduction was repeatedly reported mostly in the basal ganglia and peritrigonal white matter. Atrophy was also reported in the cerebellar and supratentorial regions. Toxicometabolic changes were also reported in the globus pallidi, pons, central tegmental tract with reticular formation. T2 hyperintense signal abnormalities were seen in 8 patients.

Case Studies

Case 1. The proband is an 8-year-old boy with a homozygous missense pathogenic variant in the GAMT gene (NM_138924.2: c.160G>C p.[Ala54Pro]) diagnosed using WES. He first presented with disease onset at the age of 2 years. As for the child's clinical presentation, he had an initially normal gain of milestone, However later in life, he presented with speech delay, intellectual disability, learning disability, and seizures. Upon assessing the patient physically, he had an unsteady gait, normal power, tone, and reflexes in the four limbs. Laboratory investigation included a fragile-x gene test and MRI of the brain. Both tests were normal. Regarding the child's seizure semiology, it was polymorphic, tonic spasms, generalized tonic-clonic seizures, and myoclonic seizures. His seizure remained interactable in which five ASMs failed but started to be controlled especially after undergoing vagal nerve stimulation (50% seizure reduction). Currently, the patient is on valproic acid, 250 mg twice per day (30 mg/kg/day) with slow

Table 2. Pharmacological and Electrographical Characteristics of the Literature Cases. the Dose Range Indicated the Starting Dose and Maximumly Reached Dose.

Authors	Case No.	Antiepileptic medications	Dietary	Clinical outcome	EEG	MRI/MRS
Ayanoğlu et al 2020 [28]	5	• Risperidone (0.25 and 0.50 mg, twice daily) • Aripiprazole (10 mg/day) • Valproic acid (300 mg, twice daily) • Baclofen (0.5 mg/kg/day)	• Protein restricted diet • L-ornithine supplement • Creatinine monohydrate (400 mg/kg/day)	• Controlled seizure • Improve attention and anxiety • No improvement in speech disturbance	• Compatible with the encephalopathy pattern • No extreme delta-brush	• Mild cerebral atrophy • Sharply reduced creatinine peak in the white matter and basal ganglia
Rostami et al 2020 [37]	6	• Levetiracetam • Lamotrigine • Primidone	• Creatinine supplement (25 mg/kg/day) • Arginine hydrochloride (400 mg/kg/day)	• Controlled seizure	• Burst attenuation multifocal sharp activity	• Supratentorial atrophy • Mild cerebellar atrophy
Rostami et al 2020 [37]	7	NM	• Low protein diet (1 g/kg/day) • Creatinine monohydrate (200 mg/kg/day)	• Improve speech disturbance • Improve motor function	• Scattered sharp activity	• Normal MRI
Aydın et al 2019 [38]	8	• Unspecified antiepileptic medications	• Protein restricted diet • Creatinine monohydrate (400 mg/kg/day) • L-ornithine (400 mg/kg/day)	NM	• Rare periods of generalized suppression	• Sharply reduced creatinine peak in the white matter and basal ganglia
Aydın et al 2019 [38]	9	• Phenobarbital	NM	NM	NM	• Toxico-metabolic changes in the globus pallidi, pons, central tegmental tract and reticular formation
Sun et al 2017 [39]	10	• Unspecified antiepileptic medications	• Arginine restricted diet (< 20–25 g/day) • Creatinine supplement (25 mg/kg/day) • Cyclinex-2 and Pro-Phree, mixed with Orange Fanta (BID) or Special therapeutic nutrition • L- Ornithine (10 g/TID)	• Improve speech disturbance • Verbal ability remarkably enhanced	NM	• Sharply reduced creatinine peak in the white matter and basal ganglia and peritrigonal white matter
Stern et al 2017 [40]	11	• Sodium valproate • Phenytoin • Lamotrigine • Levetiracetam • Carbamazepine	• Creatinine supplement (24 g/day)	• Controlled seizure • Improve attention and anxiety • Reported side effects included increased appetite, initial weight gain (now stable) and	• Slow interictal EEG background dominated by moderate amplitude theta and more irregular delta • No definite posterior dominant rhythm • High-amplitude 1–2 Hz	NM

(continued)

Table 2. Continued.

Authors	Case No.	Antiepileptic medications	Dietary	Clinical outcome	EEG	MRI/MRS
				increased urinary frequency.	sharp-slow wave complexes • Sharp transients over the right centrotemporal region	
Iliyana et al 2016 [41]	12	NM	• Creatinine monohydrate	• Controlled seizure • Improve motor function • No improvement in speech disturbance	• Epochs of disorganized, high amplitude slow wave 1–2 Hz activity with rare multifocal spikes or sharp waves among delta and theta background activity	• Normal MRI • Sharply reduced creatinine peak in the white matter and basal ganglia
Mercimek et al 2014 [42]	13	• NM	• Arginine-restricted diet (13.2 mg/kg/day) • Creatinine supplement (540 mg/kg/day) • L-Ornithine (416 mg/kg/day) • Essential amino acid supplement (0.8 g/kg/day) • Sodium benzoate (250 mg/kg/day)	• Disease progression stabilized • Mild to moderate intellectual disability and accumulation of GAA in CNS could not be normalized	NM	• Increased signal intensity on axial T2 images adjacent to the trigone bilaterally • Sharply reduced creatinine peak in the white matter and basal ganglia
Mikati et al 2013 [43]	14	• Valproic acid • Phenytoin • ACTH (0.5 mg every other day)	• Creatinine supplement (250 mg/kg/day)	• Seizure-free	• Bursts of irregularly formed generalized 1–2-Hz sharp and slow wave activity, superimposed on a slow background in wakefulness, and almost continuous high-voltage semi-rhythmic delta activity in sleep	• Normal MRI • Sharply reduced Creatinine peak in the white matter and basal ganglia
Mikati et al 2013 [43]	15	• Valproate • Pyridoxine • ACTH	• Creatinine supplement (300 mg/kg/day)	• Seizure-free	• Diffuse, high-voltage, poorly organized background with multifocal sharp wave activity	• Normal MRI • Sharply reduced creatinine peak in the white matter and basal ganglia
Viau et al 2013 [16]	16	NM	• Creatinine restricted diet • Ornithine restricted diet • Protein restricted diet	• Lack of improvement	NM	• Focal T2 hyperintense signal abnormalities in the basal ganglia and dorsal pons • Sharply reduced creatinine peak in the white matter and basal ganglia
Viau et al 2013[16]	17	• Unspecified	• Creatinine restricted diet	• Controlled seizure	NM	• Normal MRI • Sharply reduced creatinine

(continued)

Table 2. Continued.

Authors	Case No.	Antiepileptic medications	Dietary	Clinical outcome	EEG	MRI/MRS
		antiepileptic medications	• Ornithine restricted diet • Protein restricted diet			peak in the white matter and basal ganglia
Viau et al 2013[16]	18	NM	• Creatinine restricted diet • Ornithine restricted diet • Protein restricted diet	• Improved motor function • less concern for autistic behavior	NM	• Hyperintense T2 signal in globus pallidus • Sharply reduced creatinine peak in the white matter and basal ganglia
Viau et al 2013[16]	19	NM	• Creatinine supplementary diet • Ornithine supplementary diet • Protein restricted diet • Sodium benzoate restricted diet	• Development improved dramatically after starting treatment	• Normal EEG	• Hyperintense T2 signal in globus pallidus • Sharply reduced creatinine peak in the white matter and basal ganglia
Viau et al 2013[16]	20	NM	• Creatinine supplementary diet • Ornithine supplementary diet • Protein restricted diet • Sodium benzoate restricted diet	• Normal development	• Not done	• MRI not done
Mercimek-Mahmutoglet et al 2012[18]	21	NM	NM	NM	NM	• Sharply reduced creatinine peak in the white matter and basal ganglia
Mercimek-Mahmutoglet al. 2012[18]	22	NM	NM	NM	NM	• Sharply reduced creatinine peak in the white matter and basal ganglia
Mercimek-Mahmutoglet et al 2012[18]	23	NM	• Arginine restricted diet (14 mg/kg/day) • Creatinine supplement (400 mg/kg/day) • L-Ornithine (400 mg/kg/day) • Essential amino acid supplement (Vitaflow EAA) (15 g Protein/day)	• Slow progress in development • MRI showed improvement	• Dysrhythmic background and rare independent spikes in the left frontal and parietal regions in sleep	• Mild prominence of the lateral and third ventricles and of the extra-axial subarachnoid spaces • Symmetrical hyperintensity in the lentiform nuclei and posterior pontine region in T2 • Sharply reduced creatinine peak in the white matter and basal ganglia
Hinnell et al 2011[19]	24	• Unspecified antiepileptic medications	NM	NM	NM	NM
Hinnell et al 2011[19]	25	NM	NM	NM	NM	NM
Tassini et al 2010[20]	26	NM	NM	NM	• Clear multifocal pattern	• High putative guanidinoacetic acid peak

(continued)

Table 2. Continued.

Authors	Case No.	Antiepileptic medications	Dietary	Clinical outcome	EEG	MRI/MRS
O'Rourke et al 2009[21]	27	• Sodium valproate • Vigabatrin • Risperidone • Other unspecified failed antiepileptic medications	• Arginine-restricted diet • Creatinine monohydrate (2g/ kg /day) • Ornithine supplement • Low-protein diet (0.9g/kg /day) • arginine-free amino acid mixture (0.7g/ kg /day)	• Controlled seizure	• Generalized spike and slow wave (3 Hz) activity	• Hyperintense T2 signal in globus pallidus • Sharply reduced creatinine peak in the white matter and basal ganglia
O'Rourke et al 2009[21]	28	• Sodium valproate • Vigabatrin	• Arginine-restricted diet • Ornithine supplement • Creatinine monohydrate (2g/ kg /day) • Low-protein diet (0.9g/kg /day) • arginine-free amino acid mixture (0.7g/ kg /day)	• Appearance of the Creatinine peak	• Generalized spike and slow wave activity	• Normal MRI • Sharply reduced creatinine peak in the white matter and basal ganglia
Bodamer et al 2009[22]	29	NM	• Creatinine monohydrate (800 mg/kg) • L-Ornithine (300 mg/kg)	NM	NM	• Normal MRI • Sharply reduced creatinine peak in the white matter and basal ganglia
Verbruggen et al 2007[23]	30	NM	• Creatinine monohydrate (375 mg/kg/day) • L-Ornithine (800 mg/ kg/day)	• Clinical and developmental improvement	NM	• NM
Morris et al 2007[24]	31	NM	• Arginine restricted diet • Creatinine supplements • Ornithine supplements	• Controlled seizure • Improve motor function • No improvement in cognitive impairment • No expressive language	NM	• Hyperintense T2 signal in globus pallidus
Leuzzi et al 2006[44]	32	NM	• NM	NM	• Sharp waves and spikes in frontal regions and poor organization of background activity • Short seizure was associated with a 6 s spike-wave discharge in the left temporal region	• Normal MRI • Sharply reduced Creatinine peak in the white matter and basal ganglia
Sijens et al 2005[26]	33	NM	• Creatinine supplements • Ornithine supplements	NM	NM	• No structural abnormalities • Slightly increased excretion of mucopolysacharides

(continued)

Table 2. Continued.

Authors	Case No.	Antiepileptic medications	Dietary	Clinical outcome	EEG	MRI/MRS
Caldeira et al 2005[27]	34	• Sodium valproate • Carbomazepine • Clonazepam	NM	• No improvement for seizures	• Multifocal spike wave changes	• Normal MRI
Caldeira et al 2005[27]	35	• Sodium valproate • Carbomazepine • Clonazepam	NM	• No improvement for seizures	• Multifocal spike wave changes	• Normal MRI
Caldeira et al 2005[27]	36	• Sodium valproate • Carbomazepine • Clonazepam	NM	• Died at age 22	• Multifocal spike wave changes	• Normal MRI
Caldeira et al 2005[27]	37	• NM	NM	NM	• Normal	• Normal MRI
Caldeira et al 2005[27]	38	• Sodium valproate	NM	• Generalized hypertonia and rigidity have worsened with age	• Multifocal spike wave changes	• Normal MRI
Ensenauer et al 2004[29]	39	• Valproic acid	• Low-protein diet • Arginine restriction (15 mg/kg) • Intermittent high-dose Creatinine (750 mg/kg/day) • L-Ornithine(100 mg/kg/day) • Essential amino acids • Sodium phenylbutyrate (100 mg/kg/day)	• Positive behavioral changes were observed • Improve motor function • No improvement in speech disturbance	• Abnormal EEG	• Normal MRI
Schulze 2003[45]	40	• Unspecified antiepileptic medications	• Creatinine monohydrate (400 mg/kg/day) • L-Ornithine (800 mg/kg/day) • Arginine restriction (15 mg/kg/day) • L-Ornithine (50 mg/kg/day) • Sodium benzoate (100 mg/kg/day)	• Seizure free • The patient was no longer wheelchair bound • His behavior and his capability to follow simple instructions improved • Gaining developmental skills • But has not shown any active speech development so far	• Frontal sharp and spike waves	• Normal MRI • Disappearance of guanidinoacetate and an increase of Creatinine to an intensity (peak area)
Schulze et al 2001[6]	41	• Phenytoin • Clobazam • Primidone	• Ornithine hydrochloride restricted diet • Arginine restricted diet • Creatinine substitution combined with a	• Marked clinical improvement • Controlled seizure • Improve attention	• Severe slowing and unspecific abnormal activity	NM

(continued)

Table 2. Continued.

Authors	Case No.	Antiepileptic medications	Dietary	Clinical outcome	EEG	MRI/MRS
			guanidinoacetate-lowering diet • Ornithine enriched diet			
Mudd et al 2001[30]	42	NM	• Methionine low diet	NM	NM	NM
Carducci et al 2000[31]	43	NM	• Creatinine supplements	NM	NM	NM
Leuzzi et al 2000[25]	44	• Unspecified antiepileptic medications	• Creatinine monohydrate (350 mg/kg/day)	• Seizure-free • Improvement in development	• Bilateral frontal spike and slow-wave discharges	• Pallidal and periaqueductal alterations • Brain Creatinine depletion
Schulze et al 1997[33]	45	• Phenobarbital • Valproate • Ethosuximide • Vigabatrin • Carbamazepine • Lamotrigine • Corticoids	• Creatinine monohydrate (500 mg/kg/day)	• Striking clinical improvement within the first 2 months of treatment • No further progress during the following 18 months of treatment	• Bilaterally synchronous and diffuse slow spike waves	• Bilateral myelination delay of white matter • Large cisterna magna • Multiple tiermolds
Ganesan et al 1997[34]	46	• Antibiotic prophylaxis • Unspecified antiepileptic medications	• Exclusion diet • Creatinine supplement (2 g/kg/day)	• Clinical improvement	NM	• Hyperintense T2 signal in globus pallidus • Sharply reduced Creatinine peak in the white matter and basal ganglia
Stöckler et al 1996[35]	47	NM	• Creatinine-monohydrate (350 mg/kg/day)	• Extrapyramidal signs had resolved • Began to make substantial developmental progress • EEG and MRI were normalized	• Very slow background activity and multifocal spikes	• Hyperintense T2 signal in globus pallidus • Sharply reduced Creatinine peak in the white matter and basal ganglia
Stöckler S, Isbrandt D et al 1996[36]	48	NM	• Creatinine-monohydrate • Ornithine supplements	NM	• Abnormally low background activity with multifocal spikes	• Accumulation of guanidinoactetate

weaning schedule. His last EEG showed a slow background for age and a slow spike and waves suggestive of Lennox-Gastaut syndrome. As for replacement therapy, he was on creatinine monohydrate capsules. Six capsules twice a day of 7.5g was administered. He was also on 12 ornithine capsules (0.5 g each). His daily dosage of creatinine and ornithine started on 400 mg/kg/day and reached a maximum of 800 mg/kg/day with no remarkable changes were observed in his seizure activity after administrating and augmenting the diet. The patient's parents are consanguineous and the other two siblings are healthy. No similar family history was reported. He continues to follow up with the pediatric neurology team.

Case 2. The proband is a 6-year-old boy with a homozygous pathogenic variant in the GAMT gene (NM_000156.6:c.160G > C [p.Ala54Pro]) found on WES. Speech delay was the first symptom he presented by the age of 2 years, with restriction in language development. Also, the family noticed regression on his skill along with symptoms of hyperactivity attention deficit hyperactivity disorder (ADHD), and intellectual disability. There was positive consanguinity with a positive family history of seizures. The patient had intractable seizures in different forms including tonic seizures and head drops, his seizure was labeled as Lennox-Gastuat syndrome, not responding to multiple ASMs including valproic acid, clobazam, levetiracetam, topiramate, rufinamide, and perampanel. With time, his ability to walk was affected by his seizures. His neurological examination was normal, and no dysmorphic features were apparent on inspection. The patient underwent an MRI which came back normal, however, his EEGs showed slow spikes and waves and generalized paroxysmal fast activities. After diagnosis was reached by genetic testing, he started on creatinine (maximum dose reached is 450 mg) and ornithine he dramatically responded to it in the form of improving his language restriction and interaction, with time he became seizure-free and weaned off his antiepileptic medication.

Case 3. The third proband is a 10-year-old girl with a homozygous pathogenic variant in the GAMT gene (exon6:x.577c > T: pQ193X) found on WES. Our patient was suffering from speech delay started to be noticed by the age of 2 years, with global development delay and cognitive impairment. Her seizures started by the age of 4 years with myoclonic and tonic seizures and abnormal EEG findings. MRI, however, was not significant for any abnormality. She started her therapy with 3 ASMs, which was able to wean to only one medication after reaching the diagnosis, and started on creatinine 400 mg/kg/day and reached 800 mg/kg/day. She was also on 12 ornithine capsules (0.5 g each) and showed no remarkable changes in his seizure pattern after starting this diet.

Case 4. The fourth proband was presented at the age of 4 years old and now he is 14 years old. At the time of presentation, he was noticed to have speech delay, with symptoms of hyperactivity, and intractable seizure in the form of tonic seizures that was not responding to 3 ASMs. Genetic testing was performed and he was found to have a homozygous GAMT gene for a sequence variant designated c.406C > T which is predicted to result in an amino acid substitution (p.Thr136Met). Improvement was achieved after he was started on creatinine (started on 350 mg/kg/day and reached a maximum of 450 mg/kg/day) which made a difference in his seizure frequency from once a week to once in month.

Discussion

In this study, we investigated the management efficacy and outcome of cases diagnosed with GAMT deficiency among forty-eight patients in different age groups worldwide. GAMT deficiency is a rare disorder first described in 1994[2] and it is part of the cerebral creatinine deficiency syndromes. The mutation in the gene leads to an error in the methylation of guanidinoacetate that converts it into creatinine in the creatinine synthesis pathway Figure 4.[46,47] In our review we found that developmental delay represents the highest percentage (28%) of all clinical presentations, therefore the importance of early detection of the disease and early management play essential roles in the development and cognitive function of the child. In the study by Viau et al.,[48] the authors presented a patient who was early detected and diagnosed at the age of 8 days with a positive family history of GAMT deficiency and initiated early intervention resulting in normal development function without loss or delay in millstones. The patient treated at birth remains developmentally normal.[48] In fact, the majority of patients carrying such mutation manifest with severe phenotype of early onset with a symptom-free prodrome in infancy in which early detection is essential to prevent future impairment in development.[21] In such scenarios or in limited resources sittings, biochemical findings including absent or significantly decreased creatinine peak in the brain is highly associated with GAMT deficiency.[49,50] This can be observed in multiple reported patients (Table 2). Such findings are echoed by another reported case of a sibling with the affected disease diagnosed prenatally with mutation analysis resulting in initiating the treatment antenatally by providing creatinine supplement to the mother up to 28 weeks of gestational age, continuously providing care and treatment to the neonate from after birth resulted in normal development in cognitive functions, motor functions, and speech abilities.[51] Moreover, various treatment modalities were used among our patients (n = 48) including pharmacological and dietary. However, a quarter of them did not report the type of treatment administered to their patients. The majority of remaining cases (n = 32) received dietary supplements with different modalities either monotherapy (creatinine supplement), dual therapy (creatinine and arginine hydrochloride or creatinine monohydrate and protein-restricted diet or creatinine monohydrate and 1-ornithine) or triple therapy (creatinine monohydrate, 1-ornithine, and protein-restricted diet\arginine restricted diet. Meanwhile, valproic acid was a common medication that showed variable efficacy in nearly half of patients. Others, however, received different medications including phenobarbital, levetiracetam, lamotrigine, primidone, baclofen, risperidone, aripiprazole, and

ACTH. Overall, 69% of patients showed clinical improvement. Furthermore, the majority of cases become seizure-free or controlled after the treatment, 20% showed better motor function, 8% had speech improvement and enhanced verbal abilities, and 4% showed clinical worsening and regression (hypotonia, progressing in rigidity, lack of seizure control, lack of cognitive improvement and continuation of developmental regression), and in 20% did not show any speech improvement.

Conclusion

This study concluded several promising treatment modalities and combinations for patients with GAMT deficiency. The systematic analysis of reported cases revealed the importance of adequate and well-mannered pharmacological and dietary intervention towards such patients. Presymptomatic detection has shown a synergetic effect on the health of patients when combined with proper treatment modalities. Such modalities had high variation and showed that personalized management plans can potentially lead to a successful disease course. However, many cases remain refractory to treatments due to the complexity of the clinical background and comorbidities. For that, it is important to further understand the condition and emphasize the need for early detection, screening, and intervention.

Limitations of This Study

The study was limited by the un-systematic approach adopted by each author and subjectively reporting the clinical outcomes. Specifically there were no standardized symptom reporting or standardized treatment in the reported cases. Additionally there was not a standardized age at which various diagnostic testing was done. Future studies should investigate using standardized terms and parameters and includes a large cohort similarly to this study which included every reported case.

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References

1. Mercimek-Andrews S, Salomons GS. Creatinine deficiency disorders - PubMed. Published 2009. Accessed August 24, 2023. https://pubmed.ncbi.nlm.nih.gov/20301745/
2. Stöckler S, Holzbach U, Hanefeld F, et al. Creatinine deficiency in the brain: A new, treatable inborn error of metabolism. *Pediatr Res*. 1994;36(3):409-413. doi:10.1203/00006450-199409000-00023
3. Stöckler S. Salomons 16.1 clinical presentation-241 16.2 metabolic derangement-242 16.3 genetics-243 16.4 diagnostic tests-243 16.5 treatment and prognosis-244 references-245. doi:10.1007/978-3-642-15720-2_16
4. Dhar SU, Scaglia F, Li FY, et al. Expanded clinical and molecular spectrum of guanidinoacetate methyltransferase (GAMT) deficiency. *Mol Genet Metab*. 2009;96(1):38-43. doi:10.1016/J.YMGME.2008.10.008
5. Verhoeven NM, Guérand WS, Struys EA, Bouman AA, Van Der Knaap MS, Jakobs C. Plasma creatinine assessment in creatinine deficiency: A diagnostic pitfall. *J Inherit Metab Dis*. 2000;23(8):835-840. doi:10.1023/A:1026764703486
6. Schulze A, Ebinger F, Rating D, Mayatepek E. Improving treatment of guanidinoacetate methyltransferase deficiency: Reduction of guanidinoacetic acid in body fluids by arginine restriction and ornithine supplementation. *Mol Genet Metab*. 2001;74(4):413-419. doi:10.1006/MGME.2001.3257
7. Neu A, Neuhoff H, Trube G, et al. Activation of GABAA receptors by guanidinoacetate: A novel pathophysiological mechanism. *Neurobiol Dis*. 2002;11(2):298-307. doi:10.1006/NBDI.2002.0547
8. Schulze A. Creatine deficiency syndromes. *Handb Clin Neurol*. 2013;113:1837-1843. doi:10.1016/B978-0-444-59565-2.00053-8
9. Alyazidi A, Muthaffar O, Shawli M, et al. Phenotypic and molecular spectrum of guanidinoacetate N-Methyltransferase deficiency: An analytical study of a case series and a scoping review of 53 cases of guanidinoacetate N-Methyltransferase. *J Microsc Ultrastruct*. 2023;10(4):147–218. doi:10.4103/JMAU.JMAU_16_22
10. Bamaga AK, Alyazidi AS, Arabi TZ, et al. Clinical and demographic characteristics of families attending the epilepsy, neuromuscular, and child wellbeing clinics. *Cureus*. 2023;15(8):e43651. doi:10.7759/CUREUS.43651
11. Al-Abdulkareem AA, Ballal SG. Consanguineous marriage in an urban area of Saudi Arabia: Rates and adverse health effects on the offspring. *J Community Health*. 1998;23(1):75-83. doi:10.1023/A:1018727005707
12. Stöckler S, Holzbach U, Hanefeld F, et al. Creatinine deficiency in the brain: A new, treatable inborn error of metabolism. *Pediatr Res*. 1994;36(3):409-413. doi:10.1203/00006450-199409000-00023
13. Silvia CL, Chandramohan A, Palanisamy S. Guanidinoacetate methyltransferase deficiency: A treatable cause of developmental delay diagnosed by magnetic resonance spectroscopy. *Ann Indian Acad Neurol*. 2022;25(6):1196-1198. doi:10.4103/AIAN.AIAN_597_22
14. Muthaffar OY. Treating epilepsy with options other than antiepileptic medications. *Neurosciences*. 2020;25(4):253. doi:10.17712/NSJ.2020.4.20200010
15. Stockler-Ipsiroglu S, van Karnebeek C, Longo N, et al. Guanidinoacetate methyltransferase (GAMT) deficiency: Outcomes in 48 individuals and recommendations for diagnosis, treatment and monitoring. *Mol Genet Metab*. 2014;111(1):16-25. doi:10.1016/J.YMGME.2013.10.018
16. Viau KS, Ernst SL, Pasquali M, Botto LD, Hedlund G, Longo N. Evidence-based treatment of guanidinoacetate methyltransferase

(GAMT) deficiency. *Mol Genet Metab*. 2013;110(3):255-262. doi:10.1016/J.YMGME.2013.08.020
17. Green BN, Johnson CD, Adams A. Writing narrative literature reviews for peer-reviewed journals: Secrets of the trade. *J Chiropr Med*. 2006;5(3):101. doi:10.1016/S0899-3467(07)60142-6
18. Mercimek-Mahmutoglu S, Al-Thihli K, Roland E. Is low serum creatinine kinase a nonspecific screening marker for creatinine deficiency syndromes? *Mol Genet Metab*. 2012;106(2):251-252. doi:10.1016/J.YMGME.2012.04.007
19. Hinnell C, Samuel M, Alkufri F, et al. Creatinine deficiency syndromes: Diagnostic pearls and pitfalls. *Can J Neurol Sci*. 2011; 38(5):765-767. doi:10.1017/S0317167100054160
20. Tassini M, Zannolli R, Buoni S, et al. [(1)H] magnetic resonance spectroscopy of urine: Diagnosis of a guanidinoacetate methyl transferase deficiency case. *J Child Neurol*. 2010;25(1):98-101. doi:10.1177/0883073809336120
21. O'Rourke DJ, Ryan S, Salomons G, Jakobs C, Monavari A, King MD. Guanidinoacetate methyltransferase (GAMT) deficiency: Late onset of movement disorder and preserved expressive language. *Dev Med Child Neurol*. 2009;51(5):404-407. doi:10.1111/J.1469-8749.2008.03227.X
22. Bodamer OA, Iqbal F, Mühl A, et al. Low creatinine: The diagnostic clue for a treatable neurologic disorder. *Neurology*. 2009;72(9): 854-855. doi:10.1212/01.WNL.0000343955.66292.07
23. Verbruggen KT, Sijens PE, Schulze A, et al. Successful treatment of a guanidinoacetate methyltransferase deficient patient: Findings with relevance to treatment strategy and pathophysiology. *Mol Genet Metab*. 2007;91(3):294-296. doi:10.1016/J.YMGME.2007.03.006
24. Morris AA, Appleton RE, Power B, et al. Guanidinoacetate methyltransferase deficiency masquerading as a mitochondrial encephalopathy. *J Inherit Metab Dis*. 2007;30(1):100. doi:10.1007/S10545-006-0478-2
25. Leuzzi V, Bianchi MC, Tosetti M, et al. Brain creatinine depletion: Guanidinoacetate methyltransferase deficiency (improving with creatinine supplementation). *Neurology*. 2000;55(9):1407-1409. doi:10.1212/WNL.55.9.1407
26. Sijens PE, Verbruggen KT, Meiners LC, Soorani-Lunsing RJ, Rake JP, Oudkerk M. 1H Chemical shift imaging of the brain in guanidino methyltransferase deficiency, a creatinine deficiency syndrome; guanidinoacetate accumulation in the gray matter. *Eur Radiol*. 2005;15(9):1923-1926. doi:10.1007/S00330-005-2670-8
27. Caldeira Araújo H, Smit W, Verhoeven NM, et al. Guanidinoacetate methyltransferase deficiency identified in adults and a child with mental retardation. *Am J Med Genet*. 2005;133A(2):122-127. doi:10.1002/AJMG.A.30226
28. Ayanoğlu M, Korgali E, Sezer T, Aydin HI, Sönmez FM. Coexistence of guanidinoacetate methyltransferase (GAMT) deficiency and neuroleptic malignant syndrome without creatinine kinase elevation. *Brain Dev*. 2020;42(5):418-420. doi:10.1016/J.BRAINDEV.2020.02.001
29. Ensenauer R, Thiel T, Schwab KO, et al. Guanidinoacetate methyltransferase deficiency: Differences of creatinine uptake in human brain and muscle. *Mol Genet Metab*. 2004;82(3):208-213. doi:10.1016/j.ymgme.2004.04.005
30. Mudd SH, Cerone R, Schiaffino MC, et al. Glycine N-methyltransferase deficiency: A novel inborn error causing persistent isolated hypermethioninaemia. *J Inherit Metab Dis*. 2001;24(4):448-464. doi:10.1023/A:1010577512912
31. Carducci C, Leuzzi V, Carducci C, Prudente S, Mercuri L, Antonozzi I. Two new severe mutations causing guanidinoacetate methyltransferase deficiency. *Mol Genet Metab*. 2000;71(4): 633-638. doi:10.1006/MGME.2000.3108
32. Leuzzi V, Mastrangelo M, Battini R, Cioni G. Inborn errors of creatinine metabolism and epilepsy. *Epilepsia*. 2013;54(2):217-227. doi:10.1111/epi.12020
33. Schulze A, Hess T, Wevers R, et al. Creatinine deficiency syndrome caused by guanidinoacetate methyltransferase deficiency: Diagnostic tools for a new inborn error of metabolism. *J Pediatr*. 1997;131(4):626-631. doi:10.1016/S0022-3476(97)70075-1
34. Ganesan V, Johnson A, Connelly A, Eckhardt S, Surtees RAH. Guanidinoacetate methyltransferase deficiency: New clinical features. *Pediatr Neurol*. 1997;17(2):155-157. doi:10.1016/S0887-8994(97)00083-0
35. Stöckler S, Hanefeld F, Frahm J. Creatinine replacement therapy in guanidinoacetate methyltransferase deficiency, a novel inborn error of metabolism. *Lancet*. 1996;348(9030):789-790. doi:10.1016/S0140-6736(96)04116-5
36. Stöckler S, Isbrandt D, Hanefeld F, Schmidt B, Von Figura K. Guanidinoacetate methyltransferase deficiency: The first inborn error of creatinine metabolism in man. *Am J Hum Genet*. 1996; 58(5):914. Accessed August 24, 2023. /pmc/articles/PMC1914613/?report = abstract
37. Rostami P, Hosseinpour S, Ashrafi MR, Alizadeh H, Garshasbi M, Tavasoli AR. Primary creatinine deficiency syndrome as a potential missed diagnosis in children with psychomotor delay and seizure: Case presentation with two novel variants and literature review. *Acta Neurol Belg*. 2020;120(3):511-516. doi:10.1007/S13760-019-01168-6
38. Aydın Hİ, Sönmez FM. A novel mutation in two cousins with guanidinoacetate methyltransferase (GAMT) deficiency presented with autism. *Turk J Pediatr*. 2019;61(1):92-96. doi:10.24953/TURKJPED.2019.01.014
39. Sun W, Wang Y, Zu Z, et al. First reported Chinese case of guanidinoacetate methyltransferase deficiency in a 4-year-old child. *Clin Chim Acta*. 2017;470:42-45. doi:10.1016/J.CCA.2017.04.013
40. Stern WM, Winston JS, Murphy E, Cross JH, Sander JW. Guanidinoacetate methyltransferase (GAMT) deficiency: A rare but treatable epilepsy. *Pract Neurol*. 2017;17(3):207-211. doi:10.1136/PRACTNEUROL-2016-001475
41. Pacheva I, Ivanov I, Penkov M, Kancheva D, Jordanova A, Ivanova M. Creatinine deficiency syndrome could be missed easily: a case report of guanidinoacetate methyltransferase deficiency presented with neurodevelopmental delay, seizures, and behavioral changes, but normal structural MRI - PubMed. Accessed August 24, 2023. https://pubmed.ncbi.nlm.nih.gov/27650626/
42. Mercimek-Mahmutoglu S, Salomons GS, Chan A. Case study for the evaluation of current treatment recommendations of guanidinoacetate methyltransferase deficiency: Ineffectiveness of sodium benzoate. *Pediatr Neurol*. 2014;51(1):133-137. doi:10.1016/J.PEDIATRNEUROL.2014.02.011
43. Mikati AG, Abu Gheida I, Shamseddine A, Mikati MA, Karam PE. Epileptic and electroencephalographic manifestations of guanidinoacetate-methyltransferase deficiency. *Epileptic Disord*. 2013;15(4):407-416. doi:10.1684/EPD.2013.0609
44. Leuzzi V, Carducci C, Carducci C, et al. A mutation on exon 6 of guanidinoacetate methyltransferase (GAMT) gene supports a different function for isoform a and b of GAMT enzyme. *Mol Genet Metab*. 2006;87(1):88-90. doi:10.1016/J.YMGME.2005.09.017
45. Schulze A, Bachert P, Schlemmer H, et al. Lack of creatinine in muscle and brain in an adult with GAMT deficiency. *Ann Neurol*. 2003;53(2):248-251. doi:10.1002/ANA.10455

46. Stockler-Ipsiroglu S, Van Karnebeek CDM. Cerebral creatinine deficiencies: A group of treatable intellectual developmental disorders. *Semin Neurol*. 2014;34(3):350-356. doi:10.1055/S-0034-1386772
47. Clark JF, Cecil KM. Diagnostic methods and recommendations for the cerebral creatinine deficiency syndromes. *Pediatr Res*. 2015;77(3):398-405. doi:10.1038/PR.2014.203
48. Viau-Guay A, Bellemare M, Feillou I, Trudel L, Desrosiers J, Robitaille MJ. Person-centered care training in long-term care settings: Usefulness and facility of transfer into practice. *Can J Aging*. 2013;32(1):57-72. doi:10.1017/S0714980812000426
49. Van De Kamp JM, Mancini GMS, Pouwels PJW, et al. Clinical features and X-inactivation in females heterozygous for creatinine transporter defect. *Clin Genet*. 2011;79(3):264-272. doi:10.1111/J.1399-0004.2010.01460.X
50. van de Kamp JM, Mancini GM, Salomons GS. X-linked creatinine transporter deficiency: Clinical aspects and pathophysiology. *J Inherit Metab Dis*. 2014;37(5):715-733. doi:10.1007/S10545-014-9713-8
51. El-Gharbawy AH, Goldstein JL, Millington DS, et al. Elevation of guanidinoacetate in newborn dried blood spots and impact of early treatment in GAMT deficiency. *Mol Genet Metab*. 2013;109(2):215-217. doi:10.1016/J.YMGME.2013.03.003