Original article

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Epileptic and electroencephalographic manifestations of guanidinoacetate-methyltransferase deficiency

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ABSTRACT – *Aim*. Describe the seizure-related manifestations of guanidinoacetate methyltransferase (GAMT) deficiency in two new cases and compare these to the related literature. *Methods*. We reviewed the clinical and electroencephalographic manifestations of two siblings with GAMT deficiency. We also performed a thorough literature review of all cases of GAMT deficiency, using the PubMed database, and compared our findings to those previously reported. *Results*. One sibling presented with Lennox-Gastaut syndrome while the second had manifestations of late-onset West syndrome. Based on a literature search, we found that the clinical picture of GAMT deficiency has been described in a total of 58 cases, including our two patients, 45 of whom had at least some description of EEG and/or seizure manifestation. Epilepsy was present in 81%, with age at onset usually between 10 months and 3 years. Drug resistance was observed in approximately 45%. Initial seizures were febrile, tonic, or tonic-clonic. Drop attacks and generalised seizures were the most frequent seizure type. Absence and febrile seizures also occurred. Less frequently, focal seizures and late-onset infantile spasms (one prior case) were observed. Multifocal spikes and generalised <3-Hz-spike slow waves were common while only one prior single case report of hypsarrhythmia was described. Lennox-Gastaut syndrome was common, while progressive myoclonic epilepsy was also, less frequently, reported. *Conclusions*. To our knowledge, this is the second report of the occurrence of West syndrome in GAMT deficiency. The majority of patients with GAMT deficiency have seizures and approximately half are drug-resistant. Late-onset of hypsarrhythmia and/or epileptic spasms could potentially prove to be a distinctive, albeit infrequent, feature of this treatable metabolic disorder.

Key words: creatine deficiency syndrome, GAMT, guanidinoacetate methyltransferase deficiency, Lennox-Gastaut, West syndrome, hypsarrhythmia

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Creatine and its metabolite phosphocreatine play an important role in the brain by allowing the transport of ATP from the mitochondria to the cytoplasm (Longo *et al.*, 2011). Creatine is synthesized from arginine, lysine, and S-adenosylmethionine by the enzymes L-arginine:glycine amidinotransferase (AGAT) and guanidinoacetate methyltransferase (GAMT). Mutations in these two genes, as well a mutation in the creatine transporter gene on the X chromosome, lead to creatine deficiency syndromes which share many clinical characteristics. GAMT deficiency is a relatively newly recognised metabolic disorder (Stockler *et al.*, 1994). Mutations in the *GAMT* gene, located on chromosome 19 (19p13.3), are autosomal recessive. Biochemically, GAMT deficiency manifests with an increase in plasma and urine guanidinoacetic acid, as well as decreased or sometimes normal plasma creatine, in addition to a decreased or absent creatine peak on brain magnetic resonance spectroscopy (MRS). The clinical features of GAMT deficiency include developmental delay, muscular hypotonia, weakness, progressive extrapyramidal signs (mainly chorea and athetosis), ataxia, epilepsy, and autism, and/or self-aggressive behaviour (Mercimek-Mahmutoglu *et al.*, 2006). This syndrome is typically treated, with good response, by creatine supplementation, ornithine, and dietary protein restriction (Schulze, 2003).

The epilepsy syndromes, seizure semiology, and electroencephalographic (EEG) features of GAMT deficiency still remain to be fully characterised (Mercimek-Mahmutoglu *et al.*, 2006; Dhar *et al.*, 2009; Longo *et al.*, 2011). Descriptions of these features based on the published case series of this disorder are limited and do not illustrate or detail the EEG manifestations or characterise the full epilepsy syndrome profiles. In this article, our aim was to report a family with two siblings in whom one sibling presented with features of Lennox-Gastaut syndrome and the other with features of late-onset West syndrome, and compare these findings to those of previously reported cases, as ascertained through a comprehensive review of the literature. This is only the second report, to our knowledge, of the occurrence of West syndrome in GAMT deficiency and the first in which one sibling had West syndrome and the second had the related, but distinct, Lennox-Gastaut syndrome.

Methods

Case studies

We conducted a retrospective review of the medical records and EEGs of our two GAMT-deficient siblings. Our review included clinical presentation, age at onset, type of seizure, EEG manifestations, and evolution of clinical findings with age, as well as response to antiepileptic drug treatments and creatine replacement therapy.

Comparison with the literature

We performed a literature search on PubMed using the search terms: GAMT, guanidinoacetate methyltransferase deficiency, epilepsy, seizure, EEG, West syndrome, and infantile spasms, alone and in different combinations with no limits added. We reviewed the GAMT-deficient cases and specifically looked for those with descriptions of seizure manifestation and accompanying EEG findings. A comparison of epileptic and EEG manifestations between the previously reported cases and our patients was then performed.

Results

Case studies

Patient 1

A male was born to consanguineous parents by Caesarean section due to failure of progress of labour, with no history of prenatal, perinatal or postnatal complications. He started walking at the age of 1 year and 1 month, but his speech was delayed. At the age of 2 years and 6 months, he was still communicating using single words and knew only about 20 words. At the age of 2 years and 3 months, he started to have multiple drop attacks per day consisting of sudden diffuse tonic stiffening, lasting a few seconds. This was usually associated with eye deviation to the left and, at times, with a few right-arm jerks. At 2 years and 5 months of age, he had, in the same day, two episodes of generalised tonic-clonic seizure activity, lasting about one minute each. Brain computerised tomography (CT), brain magnetic resonance imaging (MRI), otoacoustic emissions, and urine organic acids and serum amino acids were normal. EEG showed a slow background in wakefulness, excessive delta activity in sleep, and frequent generalised bursts of 1-2-Hz spike and polyspike slow wave discharges. He was, thus, diagnosed with Lennox-Gastaut syndrome. Therapy with valproic acid and phenytoin was not successful in controlling his seizures. Consequently, he was started, one month later, on a course of ACTH (0.5 mg every other day for eight weeks, followed by an additional two-week taper). He responded with complete resolution of his seizures and remained seizure-free for the next five years. At the age of 4 years and 6 months, he was able to combine two words and at the age of 6 years, he was still using two-word sentences and was able to give his full name. At the age of 7 years and 6 months, he again started to have drop attacks which were first noticed after an acute illness. His EEG showed bursts of

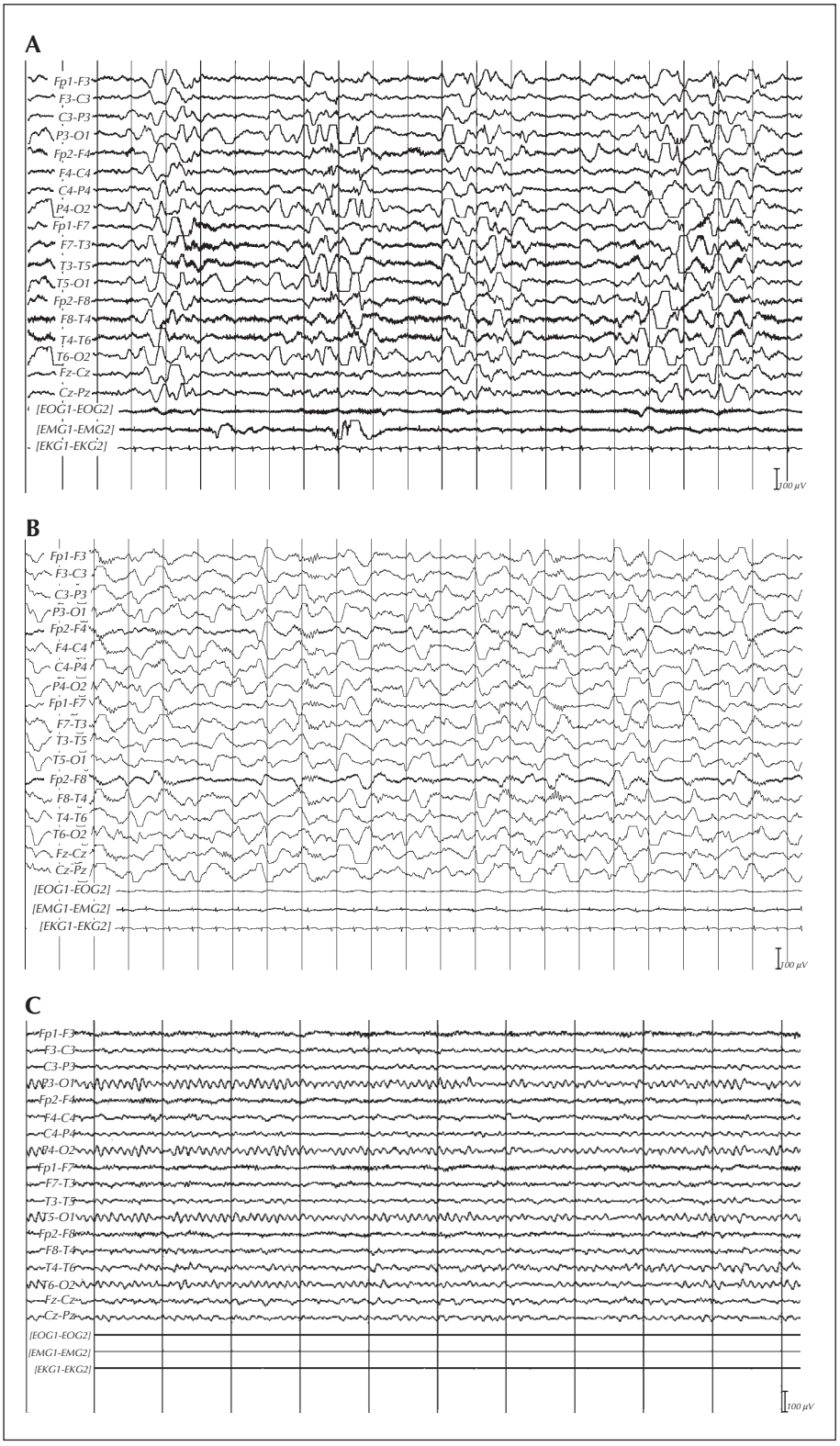

Figure 1. A) EEG of Patient 1, during wakefulness, at the age 7 years and 6 months, showing bursts of irregularly formed generalised 1-2-Hz sharp and slow wave acitivty, superimposed on a slow background. B) EEG of Patient 1, at the same age, during sleep, showing almost continuous high-voltage semirhythmic delta activity. C) EEG of Patient 1 during wakefulness, at age 12 years, showing normal background for wakefulness, with 9-Hz posterior alpha activity. There were no abnormal discharges on this 38-minute EEG in which the patient underwent hyperventilation, photic stimulation, and sleep.

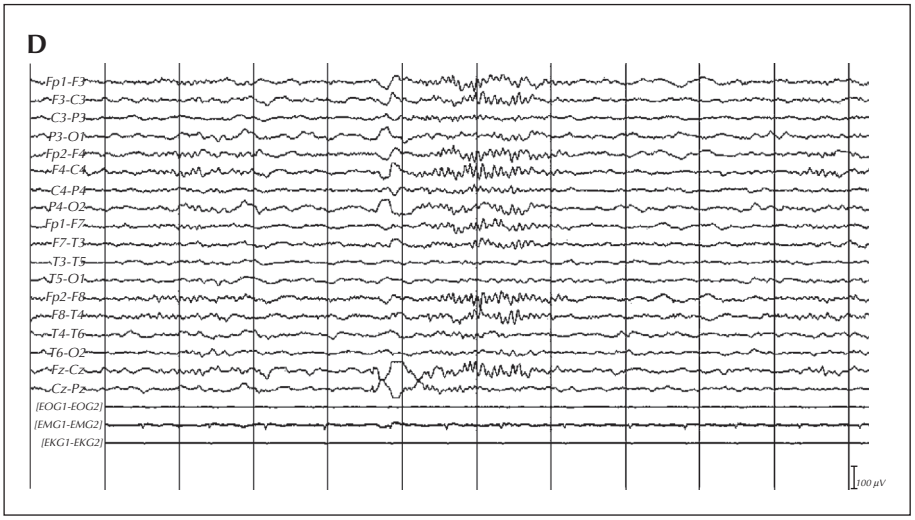

Figure 1. D) EEG during sleep taken during the same study as (C), showing vertex wave and sleep spindle activity (for all figures, low and high pass filters were 70 Hz and 1 Hz, notch filter on).

irregularly formed generalised 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 (*figure 1*). He was thus treated with a second course of ACTH using the same treatment protocol as before. He did not respond and over the following year, he continued to have two to three generalised myoclonic seizures per week, despite valproate monotherapy. Follow-up, at the age of 8 years and 6 months, showed no progress in his development. At the age of 10 years, when we diagnosed his younger sister with GAMT deficiency (testing of this disorder was not available in the country at the time of his initial presentation and subsequent follow-up), we investigated him for this disorder. Plasma creatine was found to be low at 15 µmol/L (normal range: 34-130 µM/L), urine guanidinoacetic acid was elevated at 733.8 mmol/mol creatinine (normal range: 28-180 mmol/mol creatinine), and brain MRS showed no creatine peak. We thus initiated creatine replacement therapy that resulted in cessation of all clinical seizure activity and improvement in all areas of his development and general well-being, including improvement in his appetite (*table 2*). Follow-up EEG at the age of 12 years was normal (*figure 1*). He was maintained on creatine replacement at a dosage of 250 mg/kg/day, divided in three doses. Ornithine could not be given, as it was not available in the country. Valproic acid was tapered and discontinued without recurrence of seizures.

Patient 2

Patient 2 was the younger female sibling of the above patient. She was born at term, by Caesarean section due to failure of progress of labour. There were no prenatal, perinatal or postnatal complications. During her first two years of life, she was noted to have significant psychomotor delays. She sat unsupported at the age of 1 year and began walking with an abnormal wide-based gait at the age of 1 year and 11 months. At that age, she was able to say only two or three words, and at 2 years of age, she was able to only use seven to eight words. Over the following few months, her verbal skills regressed, such that, five months later, she was no longer speaking. In addition, her gait became even more unsteady. Brain MRI revealed no abnormality and otoacoustic emissions were normal. At the age of 2 years and 5 months, she presented to our centre with a history of seven seizures occurring over the preceding two consecutive days. These were episodes of sudden massive neck, limb, and trunk extension. Each lasted about one second and resulted in the patient falling over if she was standing or sitting. She experienced several such episodes during her admission and did not have any other seizure type. Physical examination revealed her developmental delay and a wide-based gait. Blood chemistry panel, plasma amino acid chromatography, very long chain fatty acids, urine organic acids, and repeat otoacoustic emissions were all normal. EEG showed diffuse, high-voltage, poorly organised background with multifocal sharp wave activity, consistent with hypsarrhythmia (*figure 2*). She was diagnosed with late-onset West syndrome. Her spasms were treated with valproate, pyridoxine, and with a course of ACTH, using the same ACTH treatment protocol used for her brother. Although she was lost during follow-up over the next few months, subsequent encounters at the age of 3 years indicated that her spasms had resolved after

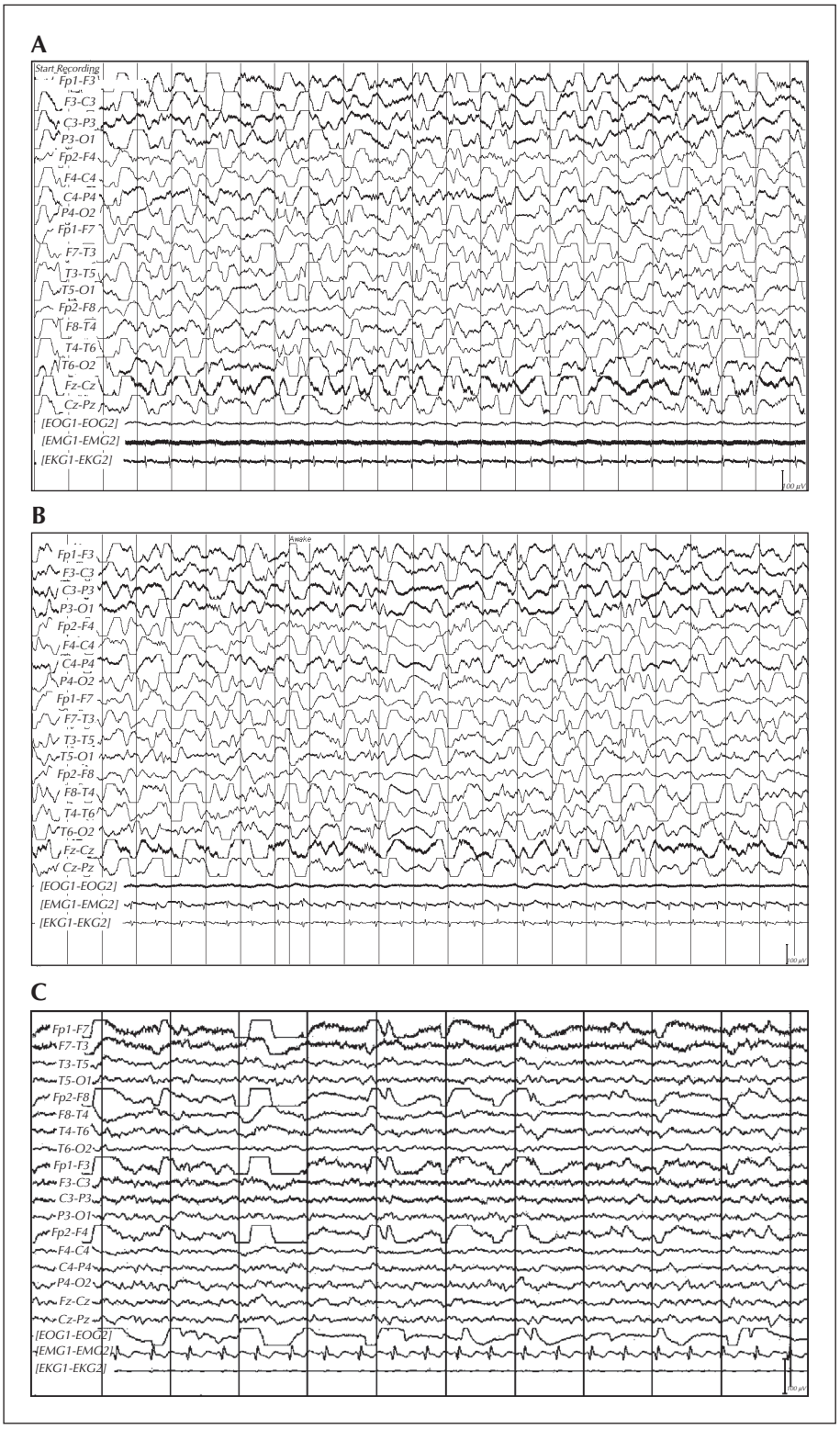

Figure 2. A) EEG of Patient 2, at the age of 2 years and 5 months during sleep, showing a hypsarrhythmic patten of high-voltage, disorganised, predominantly delta background with intermingled sharp wave activity. B) EEG of Patient 2, during wakefulnes, at the same age, showing similar, but slightly lower, amplitude. C) EEG during wakefulness of Patient 2, at the age of 6 years and 2 months, showing a background of intermingled alpha and theta activity. There were no discharges noted during either wakefulness or sleep.

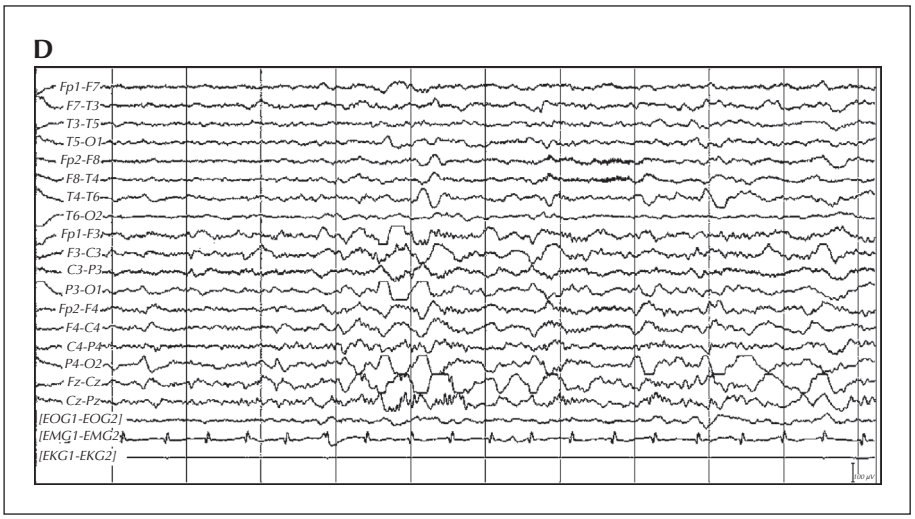

Figure 2. D) EEG during sleep taken during the same study as (C), showing vertex wave and sleep spindle activity (for all figures, low and high pass filters were 70 Hz and 1 Hz, notch filter on).

ACTH therapy. Metabolic work-up revealed that urine guanidinoacetic acid was elevated at 553.3 mmol/mol creatinine (normal range: 28-180 mmol/mol creatinine), serum creatine was decreased at 0.23 mg/dL (normal range: 0.5-1.1 mg/dL), and there was absence of the creatine peak on brain MRS. Thus, she was started on creatine replacement therapy at a dose of 215 mg/kg/day, divided in three doses (equivalent to 1 g of creatine three times daily). One month later, she was able to walk up and down stairs and had better coordination and decreased ataxia in her gait. Three months later, she could understand simple commands and had started to use several single words again. At that point, creatine was increased to 300 mg/kg/day, divided into three doses. Ornithine could not be given to the patient, as it was not available in Lebanon. She continued to improve and during follow-up, at the age of 4 years, she was seizure-free while on subtherapeutic serum levels of valproate. At the age of 6 years and 3 months, she was only mildly delayed and was still seizure-free on valproate and creatine replacement therapy (*table 2*). Her EEG at the age of 6 years and 2 months was normal (*figure 2*).

Review of the literature

We reviewed the publications on 56 cases of GAMT deficiency previously described in the literature. We were able to identify 45 GAMT-deficient patients in whom some description of seizure or EEG manifestation was mentioned, albeit usually very briefly. For these cases, as well the two cases presented here, we analysed seizure type, EEG findings, and response to antiepileptic drug treatment. In the literature, there was a single previous case report of epileptic spasms at the age of 2 years and 5 months (Schulze *et al*., 2003) and another of hypsarrhythmia based on EEG at the age of 4 years, without a description of seizure type (Ensenauer *et al*., 2004). Patient 1 is thus only the second, or perhaps third, case of infantile spasms in the literature. In addition, we found no reports that were similar to those of our two siblings, both of whom presented at the same age, one with Lennox-Gastaut and the other with late-onset West syndrome. We found that 81% cases of GAMT deficiency had seizures, and that approximately 45% of these did not respond to antiepileptics (*table 1*). This is consistent with findings of drug resistance in 8 of 27 cases reviewed by Mercimek-Mahmutoglu *et al*. in 2006 (*table 1*). Not all patients are drug-resistant as some patients respond to antiepileptic drugs, as reported by Schulze *et al*. (2003), and/or creatine supplementation, as reported by O'Rourke *et al*. (2009) (*table 1*). Of note, there is currently increasing interest in neonatal screening for GAMT deficiency (El-Gharbawy, 2013) which hopefully will reduce the risks of epilepsy and drug resistance due to the anticipated early initiation of creatine and related dietary therapy.

Discussion

In this article, one of our main findings is that a patient with GAMT deficiency presented with the clinical picture of late-onset West syndrome. West syndrome typically presents during infancy, however, late-onset after the age of 1 year and as late as 4 (Pellock *et al*., 2010; Ensenauer *et al*., 2004) and even 5 years of age (Dhar *et al*., 2009) has been reported in a few cases.

Table 1. Type of seizure, EEG manifestation, and AED response in patients with GAMT deficiency.

Reference	N	Seizure type	EEG	AED Response
Stockler *et al.*, 1994	1	NR	Slow background (1.5-3 Hz), multifocal slow-spike wave	Yes
Schulze *et al.*, 1997	1	GM seizures + drop attacks + absences.	Synchronous diffuse slow-spike waves	No
Ganesan *et al.*, 1997	1	Tonic	NR	No
van der Knaap *et al.*, 2000	2	Subtle myoclonus NR	Multifocal epileptic activity NR	NR Yes
Leuzzi *et al.*, 2000	1	NR	Bilateral frontal slow-spike wave discharges (2-2.5 Hz)	No
Leuzzi, 2002	5	Febrile seizures later GM + drop attacks + absences	Bilateral synchronous, diffuse slow-spike waves	No
		Tonic	NR	No
		Febrile convulsions later staring and subtle myoclonus	Multifocal epileptic activity	NR
		Febrile seizures	Normal	Yes
		Partial TC seizures then GTC	Bilateral frontal slow-spike waves	NR
Schulze *et al.*, 2003	1	Infantile spasms, GTC, drop attacks, atypical absence	Frontal sharp and slow-spike waves	No
Ensenauer *et al.*, 2004	1	NR	Hypsarrhythmia	Yes
Vilarinho *et al.*, 2004	3	NR	NR	Yes
	1	NR	NR	No
Araujo *et al.*, 2005	4	Febrile seizures + TC, head drops	Multifocal slow-spike waves	Yes
		TC + head drops	Multifocal slow-spike waves	Yes
		TC + head drops	Multifocal slow-spike waves	Yes
		Head drops	Multifocal slow-spike waves	Yes
Leuzzi *et al.*, 2006	1	Irregular polymorphic seizures; akinesis, motor partial fits with secondary generalisation	Frontal sharp waves and spikes + poor organisation of background activity	Yes
Mercimek-Mahmutoglu *et al.*, 2006	3	NR	NR	No
	5	NR	NR	Yes
Morris *et al.*, 2007	1	NR	NR	NR
Vodopiutz *et al.*, 2007	1	Generalised seizures	Slow baseline activity, multifocal and generalised spikes	NR
Engelke *et al.*, 2009	7	NR	NR	No
Dhar *et al.*, 2009	4	Myoclonic epilepsy	"Diffuse epileptic encephalopathy"	No
		NR	NR	NR
		NR	Generalised epileptiform activity	NR
		NR	Slow dysrhythmia	NR
O'Rourke *et al.*, 2009	1	Myoclonic and staring episodes	Generalised spike and slow waves	No*
Mercimek-Mahmutoglu *et al.*, 2012	1	No documented seizures	Dysrhythmic background Rare independent spikes in left frontal and parietal regions	NR
Kakisaka *et al.*, 2012	1	NR	Generalised spikes, intermittent slowing	No
Current report	2	Drop attacks, GTC, generalised myoclonic	Slow background in wakefulness, excessive delta activity in sleep + frequent generalised bursts of 1-2-Hz spike + slow-polyspike wave discharges.	No
		Infantile spasms	Hypsarrhythmia	Yes

N: number of patients; NR: not reported; GM: grand mal; GTC: generalised tonic-clonic; TC: tonic-clonic; AED: antiepileptic drug.
*Initially resistant, then controlled by antiepileptics at 5 years of age.

Table 2. Clinical presentation and evolution of GAMT deficiency in the two siblings.

		Age	Seizures	Treatment (responsiveness)	Language development	Motor development	Other findings
Patient 1	**onset**	2.2 y	Drop attacks, tonic, GTC	Valproate (no) Phenytoin (no)	20 m	27 m	-
	evolution	2.5 y	Drop attacks, tonic, GTC	ACTH (yes)	20 m	30 m	-
		7.5 y	Drop attacks, myoclonic	ACTH (no) Valproate (no)	48 m	Normal	-
		10 y	Drop attacks, myoclonic	Creatine start	48 m	Normal	-
		13 y	None	Creatine	5 y	Normal	-
Patient 2	**onset**	1 y	No	-	8 m	8 m	-
	evolution	2 y	No	-	20 m	14 m	-
		2.4 y	Spasms	Valproate (no) ACTH (yes)	8 m	14 m	Ataxia
		3 y	No	Creatine start	8 m	14 m	Ataxia
		3.1 y	No	Creatine	12 m	22 m	Less ataxia
		4 y	No	Creatine	20 m	36 m	No ataxia
		6.2 y	No	Creatine	5 y	5 y	No ataxia

*Based on Denver's scale for development.
m: months; y: years.

Our two patients developed epilepsy after the age of 2 years, which is a relatively late age of onset of seizures for GAMT deficiency (usual onset is at 10 months to 3 years). Recognition of the range of presentation of a treatable metabolic disorder is key to raising the index of suspicion in patients who may prove to have such a disorder.

Our other main finding is that the other sibling had milder developmental delay with related Lennox-Gastaut syndrome at around the same age. This too is a novel finding. Although the two syndromes are thought to often reflect similar underlying processes, the differences between our two siblings raise the possibility of epigenetic factors or modifier gene effects.

For GAMT deficiency, it has been reported that the initial seizures are most often febrile, tonic, or tonic-clonic. Drop attacks and generalised seizures are the most frequently observed seizures throughout the course of the disorder. Absence seizures also occur and focal seizures and late-onset infantile spasms (one prior case) have less frequently been reported (*table 1*). Based on a number of different studies, the most common seizure types were head drop, myoclonic, or atonic seizures (Schulze *et al*., 1997; Leuzzi, 2002; Schulze *et al*., 2003; Araujo *et al*., 2005), generalised tonic or tonic-clonic seizures (Leuzzi *et al*., 2006; Vodopiutz *et al*., 2007), febrile seizures (Leuzzi, 2002; Araujo *et al*., 2005), and absence seizures (Leuzzi, 2002; Schulze *et al*., 2003). Subtle myoclonias were also described (van der Knaap *et al*., 2000; Leuzzi, 2002) as well as the myoclonic seizures associated with staring episodes in one patient (O'Rourke *et al*., 2009).

The most common EEG manifestations included slow background, multifocal spikes, and generalized <3-Hz-spike slow waves, while only a single prior case report of hypsarrhythmia, other than our case, has been described. Slow background, multifocal spikes, and generalised or bilateral frontal 2-2.5-Hz-spike slow wave discharges were reported in a relatively large series of 11 patients (Leuzzi, 2002; Araujo *et al*., 2005). In another report of a single patient, EEG showed generalised discharges as well frontal and unilateral focal

temporal spikes (Schulze *et al*., 2003). Furthermore, other GAMT-deficient patients who had slow EEG background with multifocal and generalised spikes have also been described (Vodopiutz *et al*., 2007; Dhar *et al*., 2009; O'Rourke *et al*., 2009). Finally, an EEG showing "dysrhythmic" background and rare independent spikes in the left frontal and parietal regions with no reported seizures was documented in one GAMT-deficient patient (Mercimek-Mahmutoglu *et al*., 2012) and generalised spikes with intermittent slowing were reported in another (Kakisaka *et al*., 2012).

Lennox-Gastaut syndrome was the most common epilepsy syndrome, while progressive myoclonic epilepsy was also, albeit less frequently, reported. Lennox-Gastaut syndrome has been reported in GAMT deficiency either at presentation or later in the evolution of epilepsy in four patients (Leuzzi, 2002; Araujo *et al*., 2005). Schulze *et al*. (2003) reported a GAMT-deficient patient who developed epileptic spasms at the age of 2 years and 5 months. This was followed by generalised tonic-clonic seizures and drop attacks at the age of 4 years, and then frequent head drops and atypical absences by the age of 26 years. The above clinical picture was considered to be consistent with evolution from late-onset epileptic spasms to Lennox-Gastaut syndrome. This would make our above-reported case the second case of infantile spasms due to GAMT deficiency in the literature. Although there is a previous report of two siblings with GAMT deficiency with generalised absence and myoclonic epilepsy, neither one of these two siblings had West syndrome or epileptic spasms (O'Rourke *et al*., 2009). In another report of a patient who developed epilepsy and hypsarrhythmia, after the age of 4, the type of seizure, whether spasms or not, was not specified (Ensenauer *et al*., 2004). We suspect that, with increasing experience of epileptic manifestations of GAMT deficiency, late-onset of hypsarrhythmia and/or epileptic spasms could potentially prove to be a distinctive, albeit infrequent, feature of this metabolic disorder.

Conclusions

We conclude that epilepsy occurs in most children with GAMT deficiency (81%) and is drug resistant in approximately half of these (45%). The initial seizures can often be febrile, myoclonic, tonic, or tonic-clonic. Later, atypical absence and myoclonic seizures commonly occur. Focal seizures are less common. Slow background, multifocal spikes, and generalised, often <3-Hz-spike, slow wave discharges are common, making Lennox-Gastaut syndrome a frequent manifestation. The picture of progressive myoclonic epilepsy and late-onset epileptic spasms can also occur. Awareness of the above manifestations should raise the index of suspicion of this treatable neuro-metabolic condition. Also, with more experience, late-onset West syndrome could potentially prove to be a distinctive, albeit infrequent, feature of GAMT deficiency. □

Disclosures.
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