Guanidinoacetate Methyltransferase (GAMT) deficiency: a rare but treatable epilepsy

Authors: Stern, WM[ab], Winston, JS[cd], Murphy, E[e], Cross, H[f], Sander, JWS[abg]

[a] NIHR University College London Hospitals Biomedical Research Centre, Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, WC1N 3BG, UK; [b] Epilepsy Society, Chalfont St Peter, SL9 0RJ, UK; [c]Wellcome Trust Centre for Neuroimaging, UCL; [d] Department of Neurophysiology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK [e] Charles Dent Metabolic Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London; [f] UCL Institute of Child Health, Great Ormond Street, London; [g] Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, Netherlands

Abstract

Epilepsy commonly presents in childhood as part of a syndrome, and some such children may reach adult services without an underlying syndromic diagnosis. For adult neurologists taking over their care, it is often unclear how hard to search for an underlying diagnosis. The diagnostic yield may be small, and such a diagnosis may not change management. Moreover, young adults with learning difficulties are challenging to investigate, as they may not tolerate standard epilepsy tests.

We present such a case, in which a unifying diagnosis was found using simple and non-invasive tests. With the new diagnosis came a creative new treatment, which had a significant impact on seizures and quality of life.

History:

This 26 year old male was the product of a normal pregnancy and birth. By the age of six months his development was delayed compared to his peers. He never learnt to speak, and sitting and walking were delayed. He showed autistic spectrum behaviour.

Seizures began at the age of seven years, including drop attacks, generalised tonic clonic seizures and milder “head dropping” episodes, and were relentless despite treatment with various anti-epileptic drugs.

He was investigated at a tertiary centre for paediatric epilepsy. Magnetic resonance imaging of the brain was normal. EEG captured several clinical events of a deep sigh followed by head dropping. His childhood EEG is presented in figure 1. The interictal EEG background was slow for the patient's age at the time of the study (13), dominated by moderate amplitude theta and more irregular delta, showing no definite posterior dominant rhythm. 11 seizures were captured during the 15 minute recording. Clinically, the patient would start to breathe heavily for 4-5s before stiffening with an accompanying vocalisation; his head would drop slightly with eyes closed and ventilation slowed

significantly. He made a rapid return to baseline behaviour. Electrographically there was an increase in slow activity after clinical onset before high amplitude 1-2 Hz sharp-slow wave complexes (right more sharp than left) dominated the EEG. A brief period in which sharp transients could be seen over the right centro-temporal region followed clinical offset before the patient's normal background activity returned. The EEG was not felt to be diagnostic of a particular syndrome.

An older sibling also had epilepsy and learning difficulties; in view of this, a genetic cause was suspected. A karyotype and gene testing for Angelman's syndrome were both negative.

At the age of 14 he underwent corpus callosectomy as a palliative treatment for his seizures. He was seizure free for two weeks post-operatively before seizures returned to baseline frequency and severity.

Aged 18, his care was handed over to an adult epilepsy clinic. At the point of transfer to adult epilepsy services, he was independently mobile, but fully dependent on others for care, unable to speak, and doubly incontinent. He was experiencing very frequent mild seizures (sometimes more than 1000 in a day), and around two generalised tonic-clonic seizures per year. Seizures were often triggered by hyperventilation in stressful situations, such as medical appointments. He was taking sodium valproate, and it was noted that the following drugs had also failed to control his epilepsy: phenytoin, lamotrigine, levetiracetam and carbamazepine.

On examination, he was not dysmorphic. He was slim but strong, with normal muscle bulk. He had a relatively normal gait, without any obvious lateralising signs, but some flexed posturing of the hands. He was able to walk and run unassisted. He was able to track and interact with objects and recognise carers and relatives. There was frequent hand clasping and he was restless and hyperactive. He was reluctant to stay in the consultation room for more than a few minutes, and did not cooperate with a formal neurological examination. He had no speech.

He was further investigated with an array comparative genomic hybridization (array-CGH) to search for microdeletions or duplications; there were no significant findings. He was thought unlikely to tolerate further imaging or EEG, and these was not pursued.

During a routine follow-up appointment several years later, bloods were sent for full blood count, renal function and liver function. His creatinine was noted to be 20µmol/L (normal range 66-112µmol/L). This raised the suspicion of a creatine biosynthesis disorder as a cause for his syndrome. Further biochemical investigations were arranged, with results shown in table 1.

Table 1: Plasma and urine levels of guanidinoacetate, creatine and creatinine

	Plasma Result (µmol/L)	Plasma Normal Range	Urine Result	Urine Normal Range
Guanidinoacetate	47.0	0.8-3.1	849 µmol/mmol creatinine	10-100
Creatine	12	10-100	3.9 µmol/mmol creatinine	5-510
Creatinine	23	58-102	4.3 mmol/L	N/A

Genetic testing of the *CCDS* gene confirmed the diagnosis of guanidinoacetate methyltransferase (GAMT) deficiency, with a homozygous c.327G>A mutation, the most commonly described pathogenic mutation. His older sibling was subsequently found to have the same homozygous mutation.

Guanidinoacetate methyltransferase (GAMT) deficiency

GAMT deficiency was first described in 1994[1]; a review in 2014 identified 48 people in whom diagnosis and outcomes were reported[2]. The incidence of the condition is unknown, but a recent pilot study using genetic screening in 500 new-borns estimated incidence at 1:250,000[3]. Lack of awareness and relatively non-specific features mean that diagnosis is often made late or missed, even in specialist centres. The condition is inherited in an autosomal recessive fashion; siblings with the condition, such as we report here, are not uncommon, and provide a clue that a genetic condition is responsible.

The typical clinical features include developmental delay from infancy, learning difficulties, epilepsy, autism and behavioural problems. Movement disorder and self-mutilating behaviour are also described, although not present in our case. Speech may be more affected than other cognitive domains, with relative sparing of motor function [2].

GAMT is responsible for converting guanidinoacetate into creatine (see figure 2a). GAMT deficiency causes raised plasma and urine guanidinoacetate and low creatine and creatinine (figure 2b). Low plasma creatinine is a non-specific finding, and needs to be viewed in the context of overall muscle mass, but in the correct clinical setting it suggests the need for more specialised tests.

Biochemical tests in the blood and urine, for guanidinoacetate, creatine and creatinine can be diagnostic, with our patient's results typical. Standard brain MRI may show bilateral hyperintensities in the globus pallidus, but may be normal. Magnetic Resonance Spectroscopy (MRS) shows depleted or absent creatine in the brain, and is instantly diagnostic of the condition, but in our case would have required a general anaesthetic and was not attempted. MRS can be repeated following treatment to demonstrate improvement. Genetic testing from blood or saliva is another way to confirm the diagnosis.

The enzyme deficiency leads to cerebral creatine deficiency and raised guanidinoacetate; both appear to contribute to the clinical syndrome [4]. Creatine and creatine kinase are vital for energy production in all tissues. Humans typically absorb half their creatine through their diet, with synthesis providing the remainder; loss of creatine synthesis appears to affect the brain disproportionately because the blood-brain barrier limits access of dietary creatine to the central nervous system. High levels of guanidinoacetate in the brain are thought to affect GABA-ergic pathways, and also have an epileptogenic affect[4,5].

In the absence of enzyme replacement therapy, the current treatment options include oral creatine supplementation to replace missing endogenously synthesised creatine, and dietary manipulation combining supplementation of ornithine with restriction of arginine, to reduce guanidinoacetate toxicity.

Creatine supplementation is the easier of these two options; high dose creatine is offered in the form of a powder that can be administered with food. Despite the blood-brain barrier restricting creatine transport into the central nervous system, high dose creatine therapy significantly increases brain creatine levels [2]. Dietary arginine restriction (a low protein diet), with ornithine supplementation is more complex, but has been used with some success as a second-line therapy.

If metabolic treatment is offered from birth, it may prevent features of the condition from occurring [6]. There is still limited evidence, as most cases have been diagnosed later in childhood or in adulthood, but there are reports of children with early diagnosis and treatment who have normal

cognition. Once brain damage has occurred, correcting the metabolic imbalance may not improve cognition, but may have a useful impact on seizure frequency, and thus may improve morbidity and even mortality as well as quality of life [5].

Outcome:

The patient was started on oral creatine, which was increased gradually to a dose of 24g daily, in divided doses. A 3 day diet diary indicated that dietary protein intake was not excessive, and due to his learning difficulties and behavioural problems, significant alterations in diet were not felt to be appropriate.

Nine months after starting treatment, he has been seizure free for four months. Previously he had been experiencing multiple daily seizures. He is more alert and affectionate. There has also been some challenging behaviour, possibly as a result of increased alertness. Reported side effects have included an increased appetite, weight gain, and increased urinary frequency.

Blood and urine tests showed a significant improvement, see table 2

Table 2: Plasma and urine levels of guanidinoacetate, creatine and creatinine after six months of treatment

	Plasma Result (µmol/L)	Plasma Normal Range	Urine Result	Urine Normal Range
Guanidinoacetate	8.7	0.8-3.1	464 µmol/mmol creatinine	10-100
Creatine	689	10-100	5066 µmol/mmol creatinine	5-510
Creatinine	31	58-102	5.6 mmol/L	N/A

Conclusion:

GAMT deficiency is a cause of epilepsy and learning difficulties with a unique and effective treatment. The diagnosis can be suspected, as in this case, on the basis of a routine blood test of renal function, and can be confirmed non-invasively using blood and urine samples, genetic testing, or using Magnetic Resonance Spectroscopy. Early treatment appears to affect prognosis; like Wilson's disease, this is a diagnosis not to miss. Treatment as an adult can dramatically reduce seizure frequency, in turn affecting quality of life, morbidity and mortality.

Key Points:

- In a patient with epilepsy and learning difficulties, low creatinine levels can suggest a diagnosis of GAMT deficiency; this can be confirmed using simple and non-invasive tests
- Early treatment affects prognosis; late treatment can dramatically improve seizure control

Figure legends:

Figure 1: EEG from one seizure. A reduced array of electrodes was applied due to the patient's intolerance of the test. Vertical grey dashed lines represent one second, solid grey lines are shown at 10s intervals. Right hemisphere leads are displayed in red, left in blue and midline in black. Note scale bar showing 100µV amplitude. ECG=electrocardiogram; "del"=deltoid surface EMG

Figure 2a: The pathway by which creatine is synthesised, transported and excreted.

Figure 2b: GAMT deficiency causes raised guanidinoacetate and low creatine and creatinine.

Adapted with permission from Stockler-Ipsiroglu et al [7]

Abbrevations: AGAT = L-**Arginine:glycine amidinotransferase, GAMT = Guanidinoacetate Methyltransferase, CK = Creatine Kinase, ATP = Adenosine triphosphate, ADP = Adenosine diphosphate**

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