Case Report

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Novel guanidinoacetate methyltransferase (GAMT) mutation associated with cerebral creatine deficiency syndrome in a Syrian child: a case report

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Introduction: Guanidinoacetate methyltransferase (GAMT) deficiency, also known as cerebral creatine deficiency syndrome type 2 (CCDS2), is an uncommon disease caused by an innate genetic defect in the metabolic pathway of creatine inherited in an autosomal recessive manner. It is a rare cause of neurological regression and epilepsy. In this report, we present the first GAMT deficiency case in Syria related to a novel variant.

Case Presentation: A 2.5-year-old boy presented to the paediatric neurology clinic with evidence of neurodevelopmental delays and intellectual disabilities. Recurrent eye blinking, generalized non-motor (absence) seizures, hyperactivity, and poor eye contact were revealed in the neurological examination. Some athetoid and dystonic movements were noticed. His electroencephalography (EEG) was very disturbed because of generalized spike-wave and slow-wave discharges. Based on these findings antiepileptic drugs were administered. His seizures slightly improved, but then relapsed with myoclonic and drop attacks. After 6 years of unbeneficial treatment, a genetic test was required. Whole-exome sequencing was conducted and identified a novel homozygous GAMT variant (NM_138924.2:c.391 + 5G > C). Treatment with oral creatine supplementation, ornithine, and sodium benzoate was administered. After 1.7 years of follow-up, the child was almost seizure-free with a remarkable reduction of epileptic activity on EEG. He demonstrated good—but not complete—behavioural and motor improvement due to delayed diagnosis and treatment.

Conclusion: GAMT deficiency should be considered in differential diagnoses in children with neurodevelopmental regression along with drug-refractory epilepsy. A special concern is needed in Syria for such genetic disorders; regarding the high prevalence of consanguinity. Whole-exome sequencing and genetic analysis can be used to diagnose this disorder. We reported a novel GAMT variant to extend its mutation spectrum and provide an additional molecular marker for the definitive diagnosis of GAMT deficiency patients and prenatal diagnosis in the affected families.

Keywords: case report, CCDS, cerebral creatine deficiency syndromes, epilepsy, GAMT deficiency, intellectual disability, novel variant

Introduction

Cerebral creatine deficiency syndromes (CCDS) are a group of innate genetic defects in the metabolic pathway of creatine including three of these: Arginine: glycine amidino transferase (AGAT), guanidinoacetate methyltransferase (GAMT), which are both autosomal recessively inherited, and X-linked creatine transporter deficiency (SLC6A8). Intellectual developmental disorders and lack of brain creatine are the defining characteristics of CCDS[1,2].

GAMT deficiency, also known as cerebral creatine deficiency syndrome type 2 (CCDS2) (OMIM: 612736), is an uncommon

HIGHLIGHTS

- Cerebral creatine deficiency syndrome type 2 (CCDS2) is a rare and treatable cause of neurological regression and epilepsy.
- CCDS2 is a genetic defect inherited in an autosomal recessive manner.
- Drug-refractory epilepsy along with family history should raise the suspicion of a genetic cause.
- The definitive diagnosis of CCDS2 can be made through genetic analysis.
- A novel variant can provide an additional molecular marker for the definitive diagnosis and early detection of the disease.
- Treatment of CCDS2 should begin at a very young age to prevent the illustration of neurologic outcomes and irreversible brain damage.

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disease and was the first CCDS to be described[3,4]. Mutations in the GAMT gene cause deficiency of the GAMT enzyme leading to an error in the methylation of guanidinoacetate (GAA) that converts it into creatine in the creatine synthesis pathway[1,5]. Lack of GAMT activity causes the accumulation of GAA and missing out on synthesizing creatine. Some studies have shown that long-term high levels of GAA are neurotoxic and may cause epileptogenic effects. This probably occurs due to its activation of $GABA_A$ receptors and its inhibition of the complex between Na + /K + -ATPase and Creatine Kinase; thus, disturbing brain energy[1,5,6]. GAMT deficiency features the most severe clinical manifestations, including some or all of the following: intellectual disabilities, behavioural disturbances, such as autism and aggression/hyperactivity, speech delay, a wide range of seizure types, such as absence, tonic-clonic, myoclonic, focal, or generalized seizures, Electroencephalography (EEG) abnormality, and basal ganglia changes[1].

Hence, as GAMT deficiency is a rare cause of neurological regression and epilepsy, in this report, we present a case of a child diagnosed with GAMT deficiency which is, to our knowledge, the first case in Syria and related to a novel variant in the GAMT gene. This case report has been reported in line with the SCARE criteria[7].

Case presentation

A 2.5-year-old boy presented to the paediatric neurology clinic with evidence of neurodevelopmental delay. He was the first child of healthy consanguineous parents born through a caesarean section without any complications. His motor development was normal but he walked at 1.8 years. As he grew up, he started to show developmental delays and intellectual disabilities. He manifested speech delay, abnormal social interactions even with his parents, hyperactivity, impaired toileting ability, eye blinking at an early age, and learning disabilities. His family history reveals a similar case in his sister who had an intellectual disability and epileptic encephalopathy with disturbed EEGs. She was dead of unexplained causes during her treatment.

On physical and neurological examination, his weight was 12 kg and his head circumference was 50 cm, which were both within the normal range. He had no morphological malformation. Recurrent eye blinking and generalized non-motor (absence) seizures were revealed. He was hyperactive and had attention deficit and poor eye contact. Some athetoid and dystonic movements were noticed. The rest of the neurological evaluation was normal.

His EEG was very disturbed because of generalized paroxysmal spike-wave and slow-wave discharges with slowing in background activity in addition to generalized delta activity **Figure 1**. His brain MRI scan was normal, including the appearance and intensity of brain parenchyma, ventricular system, posterior fossa, Sella turcica, orbits, and paranasal sinuses.

In light of these findings, antiepileptic drugs were decided to be administered. Gradually increasing doses of Depakene (Valproic acid) were used and then Clonazepam was added to the treatment. His seizures initially showed a minor improvement, but then relapsed with myoclonic and drop attacks, and eye blinking continued. Six years of unbeneficial treatment of refractory epilepsy along with the existence of a family history of an affected sister raised the suspicion of a genetic reason. Thus, a genetic test was required.

At the age of 9, a large panel of genes related to neurological diseases (CentoNeuro) was analyzed and was negative, including: AAAS, AARS1-2, ABAT, ADAT3, ATP6AP2, B3GLCT, BAG3, CA8, CA5A, CACNB2, CCDC78, DGUOK, DHODH, DHX30, EDNRB, EFHC1, EEF1A2, EPM2A, FBXL4, FGF12, FOXP1, FRMPD4, FRRSIL, …… etc. Supplemental Digital Content 1, http://links.lww.com/MS9/A55. Thereafter, whole-exome sequencing (WES) was conducted including next-generation sequencing (NGS)-based copy number variants (CNV) analysis. The genetic study revealed an unreported homozygous GAMT variant (NM_138924.2:c.391 + 5G > C). This novel variant has not been reported in any available databases including (gnomAD, ESP, 1000G, and CentoMD) and it was classified as a Variant of Uncertain Significance VUS (class 3) based on American College of Medical Genetics ACMG recommendations. The effect of the GAMT variant c.391 + 5G > C is unknown; however, it is predicted to disturb the highly conserved donor splice site. To provide more comprehensive and relevant genetic information, more variants in genes associated with severe and early-onset diseases were studied and no relevant pathogenic or likely pathogenic variant was identified.

Regarding clinical and genetic findings, we found that our patient had many typical clinical phenotypes of CCDS2 with a family history of these presentations. In addition, no other mutation was identified to be related to his disease. Thus, we predicted that the novel GAMT variant c.391 + 5G > C should be responsible for CCDS2.

For further evaluation, magnetic resonance spectroscopy (MRS) was required but the mother refused to perform this procedure on her child because his sister suffered from complications after undergoing it.

Treatment consisting of three components was administered four times a day: oral creatine supplementation at a dose of 2600 mg (400 mg/kg/day), ornithine at a dose of 650 mg (100 mg/kg/day), and sodium benzoate at a dose of 650 mg (100 mg/kg/day). The patient was under observation during the treatment to modify the doses. Improvement in clinical picture and EEG findings was noticed after treatment. The patient showed better eye contact, concentration, and social communication. Eye blinking almost disappeared. In addition, He was quieter with improving in course of his hyperactivity. Improvement in EEG findings was also noticed. The antiepileptic drugs were subsequently reduced gradually in doses.

After 1.7 years of follow-up, the child showed almost complete disappearance of seizures. EEG was much better with a significant reduction of epileptic activity and no clear spike discharge was recorded **Figure 2**. He demonstrated good—but not complete—behavioural and motor improvement. Higher cognitive and intellectual functions could not be reached due to delayed diagnosis and treatment. The mother was pregnant so chorionic villus sampling was taken to extract DNA to evaluate the foetus and a blood sample from the mother was also taken. The same GAMT variant c.391 + 5G > C was identified in a heterozygous state in both the foetus and the mother. When the new sibling will be born, he/she will be under careful observation for any manifestation of CCDS2 and neurological regression to start treatment as early as possible.

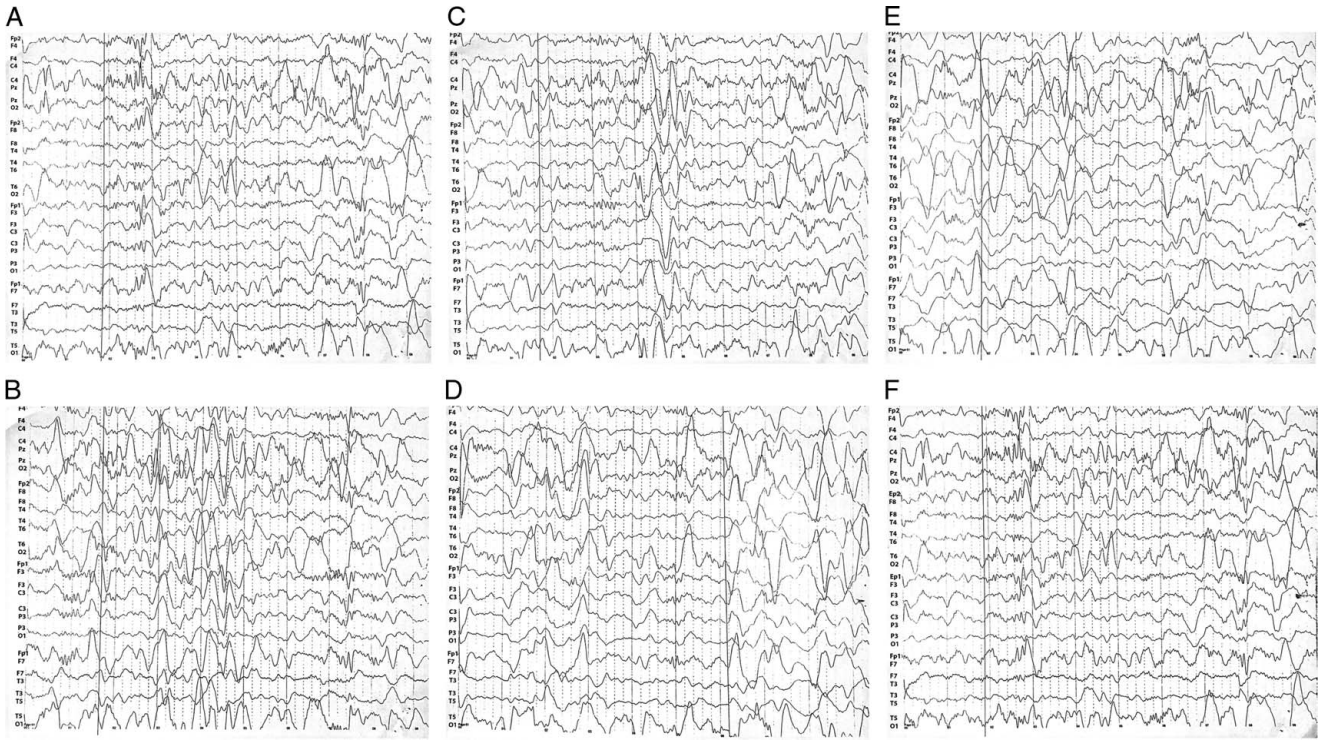

Figure 1. Electroencephalography (EEG) of the patient at the time of diagnosis. It was very disturbed showing generalized spike-wave and slow-wave discharge, and slowing in background activity. Generalized delta activity could also be noticed.

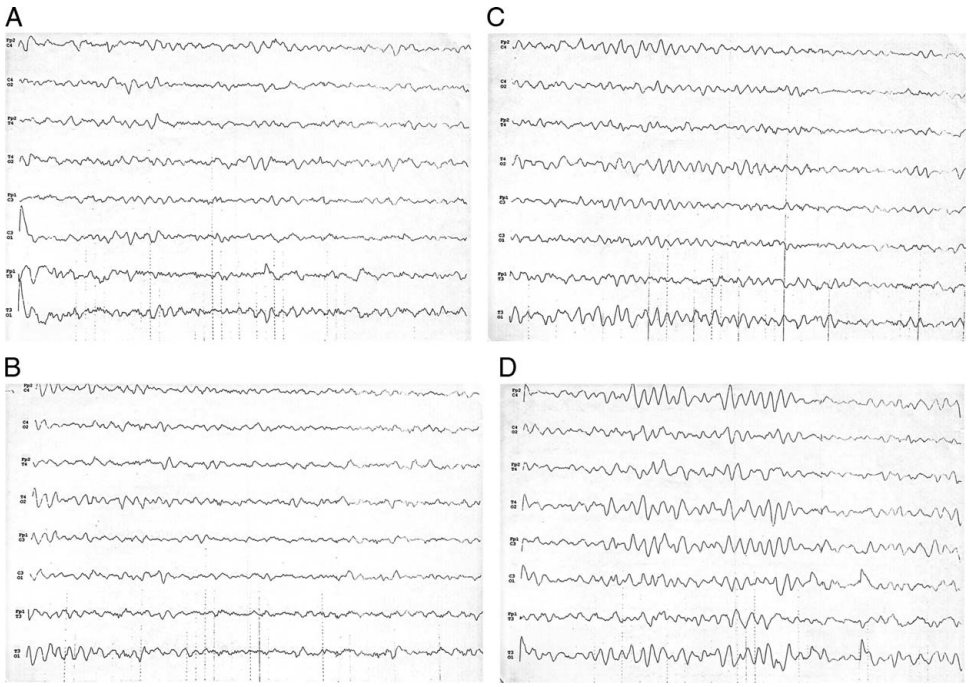

Figure 2. Electroencephalography (EEG) of the patient after treatment with creatine and ornithine. It showed a significant reduction of epileptic activity and no clear spike discharge was recorded.

Discussion

GAMT deficiency is an uncommon disease first described in 1994[4]. Approximately 130 subsequent cases were reported worldwide with an incidence rate of 1:550,000–1:2,640,000[8,9]. However, this is the first case of GAMT deficiency reported in Syria. We suspect its underdiagnosis in Syria for several reasons: low knowledge of paediatric neurologists and professionals about CCDS, as well as, rare use of MR spectroscopy and laboratory investigations of creatine and GAA in clinical practice. On the other hand, consanguinity is a deep-rooted tradition in Syria which increase the risk of recessive genetic disorders[10].

GAMT deficiency is a disease with wide clinical manifestations. Intellectual disability is the most frequent one and presents in almost all cases, which makes it a clinical hallmark of the disease. Epilepsy is the second consistent manifestation. It may be partially/completely refractory to the treatment with no specific seizure type and probably more than one type in the same patient at different ages. Other manifestations may include movement disorders, like extrapyramidal mainly dystonic hyperkinetic disorders, language and learning difficulties, behavioural disturbances such as autism, hyperactivity, and poor eye contact or social interaction[1,8,11]. Our patient manifested intellectual disability with neurodevelopmental delay, many types of seizures including absence seizures initially and myoclonus and drop attacks later in older age, as well as some behavioural and movement disorders.

EEG is a crucial tool in diagnosing epilepsy and determining which epilepsy syndrome is present in most cases. Idiopathic generalized epilepsy, which is also known as genetic generalized epilepsy (GGE), is a subtype of generalized epilepsy and classifies in an age-related manner. Childhood absence epilepsy syndrome is characterized by recurrent brief absences associated with eyelid myoclonia and generalized spike-wave discharge on EEG with frontocentral dominant or maximal expression in the occipital region in some patients. Background activity may be normal or with some degree of slowing[12,13]. This syndrome is the type that initially presents in our patient. As a major biomarker for epilepsy, EEG can be used as a phenotyping tool in genetic studies[12], it was used in our case to help in diagnosis and in observation after determining the genetic cause.

Neuroimaging can help in diagnosing GAMT deficiency. Brain MRI can reveal relevant, but nonspecific findings ranging from nearly normal to mildly delayed myelination, hyperintensities, thin corpus callosum, mildly enlarged ventricles/extracerebral spaces, and cerebral/cerebellar atrophy[14]. Nevertheless, using MRI scanners, proton MRS can be performed to measure brain neural metabolites. The hallmark of all three CCDS in MRS is the profound decrease in combined creatine and phosphocreatine peak. In addition, MRS can illustrate an increase in GAA in some cases of GAMT deficiency. Although MRS is highly specific and sensitive for CCDS, it is typically used to get spectra for only a single region in the brain. It also needs anaesthesia and it is not available in all MRI systems[5]. As for our case, MRI was normal whereas MRS is not usually available in most medical centres in Syria and it is not usually performed. In addition, patients may consider it unsafe and refuse to undergo it.

The confirmatory diagnosis of CCDS requires DNA sequence analysis or enzymatic/uptake measurement in vitro. Enzymatic studies are not usually commercially available, so they may not be performed in most cases[5], including ours. DNA sequencing includes all coding and non-coding regions to study the gene (AGAT, GAMT, or SLC6A8) responsible for the disease. More than 50 different pathogenic GAMT variants have been reported including nonsense and missense variants, insertions, deletions, frameshifts, and splice errors. Furthermore, DNA analysis can be helpful in carrier identification as well as prenatal and preimplantation testing[5].

As for our patient whole-exome sequencing was performed and showed a novel variant (c.391 + 5G > C) in the GAMT gene. The effect of this variant is still not definitive, but it almost affects the donor splice site. Therefore, further studies should be done to determine its specific effect and genotype-phenotype correlation, and include it in pathogenic variants.

Treatment strategies have two basic purposes. The first one is creatine supplementation to compensate for the lack of creatine in the brain[1]. Administering a high dose of creatine can noticeably increase its concentration in the brain even with the restriction of the blood–brain barrier which prevents the transfer of creatine into the central nervous system[15]. Creatine recommended dosage is 400–800 mg/kg/day and it can be given orally or enterally as creatine-monohydrate[1]. The second purpose is to reduce the guanidinoacetate levels. This can be achieved through supplementation of ornithine (100–800 mg/kg/day) and/or sodium benzoate (100 mg/kg/day)[1,5]. Furthermore, arginine or dietary protein restriction can be helpful in reducing serum levels of GAA[5].

Clinical manifestations of GAMT deficiency vary in course of responsiveness to the treatment. Epilepsy was found to be the most improved symptom. The frequency of epileptic seizures decreases significantly and the disorder can become seizure-free. Movement disorders may show perceptible improvement. Neuromotor development and behavioural disturbances are less responsive. Intellectual functions are much less influenced by the treatment, especially in case of late diagnosis with far better outcomes in early diagnosis and treatment[10]. Our patient showed improvement in seizures, movement, and behavioural disorders. However, normal neurodevelopment could not be reached because of delayed diagnosis.

Prenatal testing for the younger sibling was performed since previous literature showed its importance in early detection of the disease which allows starting treatment early in life to prevent illustration of neurologic outcomes and irreversible brain damage[16].

Conclusion

GAMT deficiency is a rare but treatable cause of neurologic disorders. It should be considered in differential diagnoses in children with intellectual disability and neurodevelopmental regression along with drug-refractory epilepsy, especially when presenting with a family history. A special concern is needed to raise awareness of such genetic disorders in Syria; regarding that, it is a country with a high prevalence of consanguinity. Whole-exome sequencing and genetic analysis can be used to diagnose this disorder. We reported a novel GAMT variant to extend its mutation spectrum and provide an additional molecular marker for the definitive diagnosis of GAMT deficiency patients and prenatal diagnosis in the affected families. Future further studies are needed to establish the genotype-phenotype correlation of this variant.

Ethical approval

No ethical approval was needed.

Consent

Written informed consent for publication was obtained from the patient's parents for publication of this case report and accompanying images. No identifiable information was revealed in this report. Only medical data were reported for scientific purposes. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article and have given their approval for this version to be published. D.A., D.A., and R.S. reviewed the literature, collected relevant clinical information, wrote the initial draft of the manuscript and revised it, added the figures, and made grammar and spelling language editing. S.B. provided medical management and participated in therapeutic decisions. D.A. provided medical treatment and therapeutic decisions, supervised the scientific and academic aspects of the manuscript, and critically revised it. All authors read and approved the final manuscript.

Conflicts of interest disclosure

Authors declare no conflict of interest.

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