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Original scientific article

A NOVEL VARIATION OF GAMT IN CEREBRAL CREATINE DEFICIENCY SYNDROME, FIRST COMPLETE HOMOZYGOUS DELETION OF GAMT

Habibe Koc UCAR[1,*], Fatma Derya BULUT[2], Berrak Bilginer GURBUZ[2], Okan DİLEK[3], Ilker GUNEY[4]

[1]Department of Pediatric Neurology, Ministry of Health, Adana City Training and Research Hospital, Adana, Turkey
[2]Depatment of Metabolism and Nutrition, Ministry of Health, Adana City Training and Research Hospital, Adana, Turkey
[3]Depatment of Radiology, Ministry of Health, Adana City Training and Research Hospital, Adana, Turkey
[4] Department of Genetics, Ministry of Health, Adana City Training and Research Hospital, Adana, Turkey

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Cerebral Creatine Deficiency Syndromes (CCDS) are congenital metabolic disorders in the creatine metabolism pathway. In this study, we evaluated the clinical, phenotypic, radiological and genetic features of patients with CCDS. We tried to identify early diagnosis clues in patients. Especially, we reviewed the causes of delay in patients with late diagnosis.

Corresponding author: Habibe Koc Ucar, MD.,Adana City Training and Research Hospital, Department of Pediatric Neurology,01220, Yüreğir, Adana/Turkey,Phone: +90 506 5146605,E-mail: hkocselanik@gmail.com ; drfizyoloji@gmail.com

In line with these findings, the diagnosis is confirmed by enzyme tests and next generation sequencing based whole genome sequencing. In this study, 6 patients whose diagnosis was genetically confirmed were presented (5 GAMT mutations (someone is complete homozygous deletion in GAMT gene), 1 SLC6A8 mutation). 5 of these patients were from the same family, and 4 patients were patients with a late diagnosis. Two of the 4 patients who were diagnosed late were moderate and two had severe phenotype. The neurological findings consisted of patients with different clinical findings such as speech disorder, cognitive retardation, autism and epilepsy. Patients received appropriate treatment for the type of cerebral creatine deficiency.

While response to treatment was good in early diagnosed cases, a partial clinical improvement was detected in cases diagnosed late. The patient, who was started treatment before neurological symptoms appeared, was neurodevelopmentally normal. It was observed that there was a strong relationship between age at diagnosis and phenotype and prognosis.

We compared the clinical findings, phenotype and genotype characteristics of patients with CCDS. We reviewed the causes of delay in patients with late diagnosis. Thus, we wanted to raise awareness about early diagnosis and treatment of CCDS, one of the rare metabolic diseases.

Keywords: autism, cerebral creatine deficiency; epilepsy, guanidinoacetate methyltransferase, *SLC6A*, cognitive impairment

INTRODUCTION

Cerebral Creatine Deficiency Syndromes (CCDS) are inherited metabolic disorders affecting creatine synthesis or transport. Creatine is synthesized in a two-step enzymatic reaction and delivered to brain via a Na^+/Cl^--dependent creatine transporter. Failures in these processes result in clinical phenotypes linked to *GATM, GAMT* and *SLC6A8* gene mutations (LEUZZI 2002, STOCKLER, SCHUTZ *et al.* 2007).

1. *AGAT (MIM #612718) deficiency; L-arginine: glycine amidino transferase [AGAT] enzyme breaks down dietary arginine and produces guanidinoacetate [GAA]. It is the rarest cause of CCDS. It is caused by biallelic mutations in the GAMT gene*.

2. *GAMT (MIM #612736) deficiency; The guanidinoacetate methyltransferase [GAMT] enzyme uses GAA to synthesize creatine. It is the second most common defect that causes CCDS and is inherited autosomal recessively.*

3. *CRTR (MIM #300036) deficiency; Creatine transporter [CRTR] transports creatine to brain cells and muscles for use. Circulating creatine occurs due to sodium-dependent creatine transporter defects, so while creatine is in the bloodstream, it cannot be transported to the brain and muscles. CRTR deficiency is an X-linked disease due to SLC6A8 gene mutations, thus it is the most common cause of CCDS.*

As creatine plays a role in normal brain development and function, the most common phenotype of CCDS is mild to severe intellectual disability.

In addition, it may present with a wide range of symptoms such as developmental delay (delayed speech and motor developmental delay), behavioral problems (attention deficit hyperactivity disorder [ADHD], Shyness, aggression, self-injury), autism, epilepsy, and movement disorders (dystonia, dyskinesia) (LEUZZI 2002, SCHULZE 2003, STOCKLER, SCHUTZ *et al*. 2007, SCHAEFER, MONTUFAR-SOLIS *et al*. 2013). Clinical symptoms can be observed between the ages of three months and three years. A significant decrease in creatine signal in brain proton magnetic resonance spectroscopy (^{1}H-MRS) is a strong indicator of creatine biosynthesis and transport disorders. In some patients, serum creatinine levels are low. Determination of urine GAA and urine creatine-creatinine ratio is essential for the diagnosis and exclusion of other disorders. Diagnosis is confirmed by molecular genetic testing and identification of biallelic pathogenic or likely pathogenic variants (LEUZZI 2002, STOCKLER, SCHUTZ *et al.* 2007, MERCIMEK-MAHMUTOGLU, MUEHL *et al.* 2009). Timely treatment provides significant biochemical and clinical improvement or stabilization in patients with AGAT and GAMT deficiencies. Early diagnosis and treatment of these two disorders can result in normal development. Treatment for CRTR deficiency has been less successful.

In this study, we evaluated the clinical, radiological and genetic features of six patients with CCDS. Especially, we reviewed the causes of delay in patients with late diagnosis. Thus, identification early diagnostic clues and raising awareness about early diagnosis and treatment of CCDS in these patients were aimed.

MATERIAL AND METHODS

Patients

Six patients, 2 males and 4 females, from 5 families who were diagnosed between January 2020 and December 2020 at a tertiary care hospital were included. Six patients with confirmed CCDS (all patients from the same center, 5 patients with *GAMT* and 1 patient with *SLC6A8* mutations) were diagnosed based on clinical and brain ^{1}H-MRS findings. Demographic data, clinical findings (global developmental delay/intellectual disability, seizures, movement and behavioral disorders) of all patients included in the study, biochemical and molecular investigations, brain magnetic resonance imaging (MRI) and ^{1}H-MRS, and duration of treatment, treatment response, and follow-up clinical, laboratory and ^{1}H-MRS findings were described. Arginine restricted diet, creatine monohydrate (400-800 mg/kg/day) and L-ornithine (400-800 mg/kg/day) were given to patients with GAMT deficiency as specific treatment. The only patient with *SLC6A8* mutation was supplemented with creatine monohydrate (400 mg/ kg/day) and L-arginine (400 mg/kg/day) and L-glycine (150 mg/kg/day).

Clinical Investigations

Patients' neurological examination and clinical severity score (CSS) at the beginning of treatment and on follow-up, and treatment responses were recorded. Individuals' scores were crosschecked by the care-providing physician (HKU). Clinic severity score (BRUUN, SIDKY *et al*. 2018) and detailed age-appropriate developmental tests (Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III) or Wechsler Intelligence Scale for Children Fourth

Edition (WISC-IV Full-Scale IQ) were applied. In addition, the parents were questioned about the patients' behavioral and clinical responses. Four patients were lately diagnosed, and the reasons for the delay in patients with late diagnosis were reviewed. The genotypic, phenotypic and clinical features of the patients were compared in terms of early diagnosis clues in patients with late diagnosis.

Neuroimaging, Biochemical and Molecular Genetic Investigations

Laboratory and ^{1}H-MRS records were also reviewed of all patients before treatment and at least 3 months after the beginning of treatment. Brain ^{1}H-MRS scans were performed with 1.5 Tesla MR (Philips Ingenia 1.5T, Philips Medical System) at the level of the basal ganglia multi-voxel spectroscopy (Supplemental data-1). DNAs were collected and examined for the whole genome sequencing in the blood samples of five patients (RefSeq accession number NM), whereas the SLC6A8 variant analysis in the blood samples of was performed for the other one patients (RefSeq accession number NM). The variant nomenclature used follows that defined at http://www.hgvs.org./mutnomen/. All of the variants were investigated using ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/) whether they are novel or previously reported.

This retrospective cohort study was approved by the Research Ethics Review Board of Institute of The Ministry of Health University, Adana City Training & Research Hospital (Approval #1252).

RESULTS

Six patients from five parental consanguinity were included in this retrospective cohort study (2 males and 4 females two of siblings) (Table 1). The current age of the patients was between 9 months and 14 years 6 months. The age of diagnosis was between 6 months and 14 years 3 months, and the age of starting treatment was between 7 months and 14 years 5 months. The age of onset of neurological symptoms was between 18-24 months. The onset of language retardation and motor retardation was between 12-18 months. Nutritional problems were often between 12-18 months (Table 2). Age of diagnosis, age of treatment, results of treatment with clinical features, urine creatine to creatinine ratio, urine GAA, 1H-MRS, and molecular genetic results of the patients are summarized in Table 1.The early diagnostic indicators based on the clinical history of the patients are summarized in Table 2.

Patients

All patients (except one detected during family screening) had applied with one or more of cognitive retardation, developmental delay (verbal and motor), behavioral problems (attention deficit hyperactivity disorder / ADHD, shyness, aggression, self-injury), autism and resistant epilepsy. There were no risk factors before and during parturition. There was consanguinity, except for one patient with CTR. There was a history of developmental delay in their family history and autism in two patients. The auditory brainstem-evoked response was normal in the etiology investigations. Basal metabolic tests such as liver function tests, creatine phosphokinase (CK), Gas chromatography-mass spectrometry (GC-MS), blood lactate, ammonia and urine

organic acid analysis were normal. CCDS was suspected with clinical, laboratory and imaging findings. After it was genetically confirmed, treatment was initiated.

Table 1. Clinical, radiological findings and genotypes of the patients

Patient/ sex	*Age diagnosed*	*Age treatment started*	*Clinical score pre-treatment /on treatment*	*Remark*	^{1}H-MRS[a] *pre-treatment /on treatment*	*Urine GAA*[b]*/ serum creatine*[c]	Gene Mutation[d,e]
1//F	9yrs, 4mo	9yrs, 6mo	S/S	Improvements in behavior and social interactions and seizures-free	Peak absent/ Mi peak	0,16[c]/ 0,05[c]	c.244_327+64del[d]
2/F	6 mo	7 mo	Mi/Mi	NC	Peak absent/ Peak	0,05[c]	c.244_327+64del[d]
3/F	7yrs, 7mo	7yrs, 9mo	Mo/Mo	Improvements in behavior and social interactions	Peak absent/ Peak absent	1765.59[b] / 0,18[c]	c.327G>A (p.Lys109=)[d]
4/M	3yrs, 3mo	3yrs, 6mo	Mi/Mi	More cooperative, better receptive language	(-)//Peak	1181.27[b] / 0,03[c]	Complete homozygous deletion[d]
5/F	11yrs ,2mo	11yrs, 4mo	Mo/Mo	Improvements in behavior and social interactions and seizures-free	Peak absent/N	0,07[c]	NM_000156.6 c.327G>A (p.Lys109=)[d]
6/M	14yrs, 3mo	14yrs, 5mo	S/S	Improvements in behavior and social interactions	Peak absent/N	0,28	NM_005629.4 c.945_949delTTCTT(p. F315Lfs*148) (Phe315LeufsTer148)[e]

Abbreviations (listed alphabetically): F = female, GAA = guanidinoacetate, M= male, Mi = mild, Mo = moderate, mo = months, N: no, NC = no change, S = severe, yrs. = years
[a]: 1H-MRS creatine peak absent, [b]: urine GAA: umol/mmol, [c]: serum creatine: mg/dl
[d]: GAMT gene, [e]: SLC6A8 gene

Clinical, biochemical and molecular genetic investigations

Serum creatine levels were low in five patients (4 different families), two of whom were siblings. Two patients (Patient3 / Patient4) who could undergo urine creatine metabolic screening had urinary creatine / creatinine ratio and high urine GAA. Patient 4 had homozygous novel complete GAMT gene deletion was detected by next generation sequencing based whole genome sequencing. Genetically, mutation variants were detected in two siblings (Patient-1,2) c.244_327 + 64del, and NM_000156.6 c.327G> A (p.Lys109 =) in the other two patients (Patient 3/5). Unlike other patients, Patient-6 had no consanguinity, had a history of cognitive, motor retardation and autism, and serum creatine was 0.28 mg / dl. It was observed that behavioral problems (aggression, self-injury), autism and severe cognitive retardation were in the foreground. Since the blood creatine level was moderately low, NM_005629.4 homozygous mutation c.945_949delTTCTT (p.F315Lfs*148) (Phe315LeufsTer148) was detected by firstly

using SLC6A8 gene analysis with next generation sequencing based whole genome sequencing. This mutation was a variant presented as pathogenic with a high probability according to the Clinvar database and ACGM criterias (Table 1).

Neuroimaging and Biochemical Investigations on Treatment Outcome

Brains MRI of all patients were normal. No creatine peak was observed at 3.03 ppm in proton-MRS TE of 2000 ms. With the treatment, serum creatinine levels returned to normal in the first month. Creatine peak was observed in patients who received treatment early among the patients whose ^{1}H-MRS control could be taken at 3 months (Figures 1a-1b). While minimal creatine peak was observed in one of the patients who received treatment late, the peak was not observed in the other (Figures 2a-2b) (Table 1).

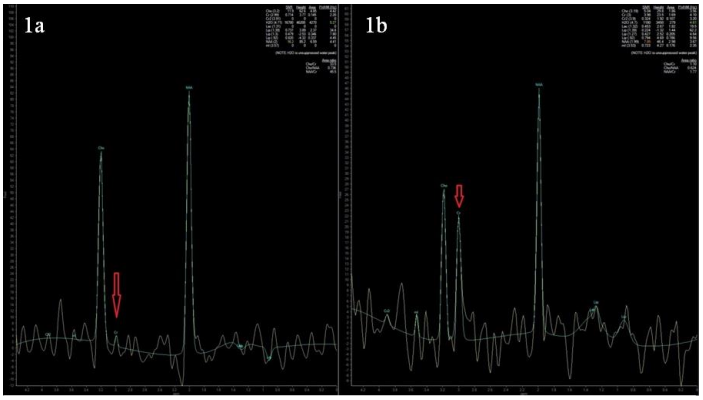

Fig. 1. Increment in creatine peak was observed in Patient 2 who received treatment early between pretreatment (1a) and 3 months post-treatment (1b) ^{1}H-MRS images.

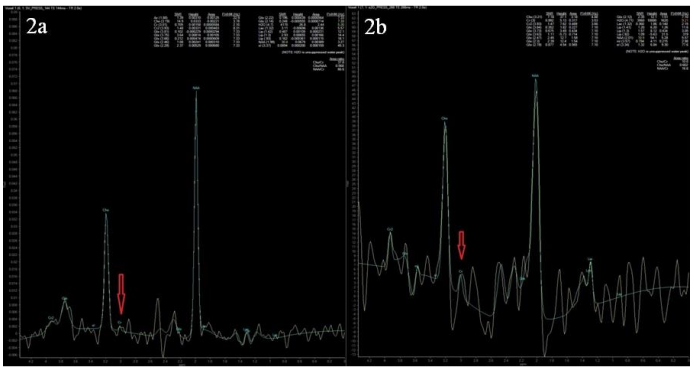

Fig. 2. Increment in creatine peak was not observed in Patient 3 who received treatment early between pretreatment (2a) and 3 months post-treatment (2b) ^{1}H-MRS images.

Clinical Score Pre-treatment /on Treatment and Remark

Before and after treatment, according to CSS, 2 patients had mild, 2 patients had moderate, and 2 patients had severe phenotype. Three patients had seizures (2 antiepileptic drug [AED] resistant, 1 AED-responsive). Five patients had behavioral disorders. The most common behavioral disorder was aggressive behavior. Aggression was observed in 4 patients. Autism spectrum disorder and intellectual disability were reported in 2 patients. While early-diagnosed cases showed normal or nearly normal development, subjective clinical improvement was detected in late-diagnosed cases. However, this clinical improvement was not documented in clinical severity score (CSS). Two patients became seizure free with increased perception, showed improvement in behavioral disturbances, decrease in aggression and increase in social adaptation (Table 1).

Early diagnostic indicators based on the clinical history of the patients

The most common findings were verbal and motor delay. With the exception of one patient diagnosed before the age of one year, all patients were unable to reach the developmental milestones appropriate for their peers with feeding problems and delayed motor and verbal skills between 12-18 months (Table 2). Only one patient was diagnosed under one year of age which was via family screening. Unfortunately, five patients were diagnosed 2 to 14 years later after their first symptoms were observed between age at diagnosis and phenotype and prognosis.

Table 2. Early Diagnostic Indicators in Clinical Findings of the Patients

Patient/ Sex	Parental consanguinity	Family history	Age at first neurologic symptom	Age at Verbal involvement	Age at Motor involvement	Age at Feeding problems	Age at Behavioral involvement	Age at First Seizure	Clinical Features
1/F	(+)	(+)	(2 yrs)	(1 yrs)	(1 yrs)	(1 yrs)	(2,5 yrs)	(4,5 yrs)	Shyness, Agg, DRE, ID
2/F	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
3/F	(+)	(+)	(1,5 yrs)	(1,5 yrs)	(1,5 yrs)	(1,5 yrs)	(3,5 yrs)	(-)	S&L Disorders, Shyness, Agg, BD
4/M	(+)	(-)	(2 yrs)	(1 yrs)	(-)	(-)	(3 yrs)	(-)	Shyness, BD, S&L Delay, BD
5/F	(+)	(+)	(2 yrs)	(1 yrs)	(1 yrs)	(1,5 yrs)	(3 yrs)	(5 yrs)	Shyness, Agg, BD, Epilepsy
6/M	(-)	(+)	(2 yrs)	(1 yrs)	(1 yrs)	(1 yrs)	(2 yrs)	(1,5 yrs)	DRE, Shyness, Agg, Self-İnjury, Autism

Agg=Aggression, DRE= Drug-resistant Epilepsy, ID=Intellectual disability, BD=Behavioral Disorders, S&L Delay=Speech and Language Delay/Disorder

DISCUSSION

In this study, we aimed to shed light on the causes of delay in diagnosis of these patients, four of whom had neurological involvement, and to raise awareness about early diagnosis. Urine screening and / or ^{1}H-MRS were used as first-line selective screening of CCDS

for the patients with compatible phenotype before genetic confirmation. It was observed that there was no creatine peak in MRS in five patients who had ^{1}H-MRS before treatment. Increased guanidinoacetate levels in the urine was detected of a patient of whom proton ^{1}H-MRS could not be performed before the treatment. Four patients were over 6 years old; one patient was 3 years old, and the other patient was diagnosed at 7 months of age during family screening.

MILLER JS *et al.*, in their study in 2019, as early indicators of CRTR deficiency, they identified motor developmental retardation and feeding problems before the age of one year (MILLER, THOMAS *et al.* 2019). Similarly, neurological symptoms were first observed in the first 2 years of age in our patients who could not reach their developmental milestones. Before one year of age, the most important problems were difficulties in feeding, hypotonia and motor retardation. Sociocultural levels of these patients' families prevented early recognition of developmental delay of these children. For this reason, we think that this points the importance of educating family physicians and pediatricians and raising awareness about the early indicators of this rare disease to enable early diagnosis and treatment for these patients.

GAMT mutations were found in 5 patients, and *SLC6A8* mutation was found in one. This was an interesting finding contrary to literature. The underlying reason may be high parental consanguinity rate in our region, thus autosomal recessive inherited diseases are more common. At least 50 different pathogenic *GAMT* variants have been reported, and the most common are c.327G>A (p.K109K) and c.59G>C (p.W20S) (STOCKLER, HANEFELD *et al.* 1996, STOCKLER-IPSIROGLU, VAN KARNEBEEK *et al.* 2014). Homozygous c.327G> A (p.K109K) variants in *GAMT* gene which is reported to be most common were also identified in Patient 3 and 5 who were unrelated (SHARER, BODAMER *et al.* 2017). These two patients have different clinical outcomes. Patient 1 and 2 were siblings who had the same novel, homozygous c.244_327+64del mutation but were diagnosed at different ages and for this reason clinical phenotypes were strikingly different. This situation suggests that early diagnosis is a far better predictor of clinical phenotype than genotypic features.

Complete gene deletions are rare, complete deletion in the *GAMT* gene was detected in one patient who was not previously reported in databases to the best of our knowledge. The goal of treatment in GAMT-deficient patients is to reduce the production of GAA and to normalize creatinine levels in brain and blood. Typically, patients are given oral creatine monohydrate and L-ornithine supplements. In addition, dietary protein restriction is another approach to further reduce GAA accumulation. It was reported that considering the results of treatment with creatine monohydrate in symptomatic individuals with GAMT deficiency, it was found reported only 21% of the patients improved in developmental delay and intellectual disability. Despite treatment, none of the patients could have normal development and cognitive functions.

It has been reported that 50% of the patients have a decrease in the frequency of seizures and 18% became seizure free (STOCKLER-IPSIROGLU, VAN KARNEBEEK *et al.* 2014, MERCIMEK-MAHMUTOGLU, POP *et al.* 2016). Viau *et al.* also reported clinical improvement and better seizure control with treatment.(VIAU, ERNST *et al.* 2013) In line with the literature, subjective clinical findings improved in our patients with the use of creatine monohydrate and L-ornithine. Interestingly, 2 patients with drug-resistant seizures became seizure free despite being diagnosed after the age of 6. However, as reported in the literature, none of our patients who

started treatment after the onset of neurological symptoms could not achieve normal development or cognitive functions.

The most important factor in the prognosis of the disease is early diagnosis. Neurological development was found to be normal in individuals with asymptomatic GAMT deficiency who were diagnosed and treated in the neonatal period and had a positive sibling family history with GAMT deficiency (SCHULZE, HOFFMANN ET AL. 2006, EL-GHARBAWY, GOLDSTEIN *et al*. 2013, VIAU, ERNST *et al.* 2013). On the other hand, Dhar et al. reported in their study an interesting patient with developmental delay and hypotonia at the age of 11 months despite the fact that the patient received treatment since the age of eight days. The authors suggested that the reason for this situation may be in adherence to treatment (DHAR, SCAGLIA *et al.* 2009). Similar to the literature, the neurodevelopmental outcome was normal in only one patient, who was asymptomatic when she was diagnosed less than 1 year of age and received early treatment. It should not be forgotten is the fact that delays in diagnosis and treatment cause severe sequelae.

GAMT deficiency can be detected by increased GAA levels and therefore, it is a candidate disorder for newborn screening (SCHULZE, HOFFMANN *et al*. 2006, EL-GHARBAWY, GOLDSTEIN *et al*. 2013, VIAU, ERNSt *et al.* 2013). In addition, considering that these patients are subjected to exhausting etiological evaluations, including repeated metabolic tests, whereas urine creatine metabolite screening will be a much more accessible and feasible study. X-linked CRTR deficiency is the second most common cause of mental retardation after Fragil-X syndrome. Its prevalence in patients with cognitive retardation is estimated as 1,4%. The treatment responses of individuals with CRTR deficiency are generally not satisfactory (VAN DE KAMP, MANCINI *et al*. 2014). However, with combined creatine, arginine and glycine treatment; increased muscle mass, improved gross motor skills and amelioration in locomotor and personal social IQ subscales were obtained in some patients (MERCIMEK-MAHMUTOGLU, CONNOLLY *et al*. 2010, VALAYANNOPOULOS, BODDAERT *et al*. 2012, VAN DE KAMP, POUWELS *et al.* 2012).

BRUUN *et al.* used pre- and post-treatment CSS to evaluate CRTR-deficient patients' clinical response to treatment in their study (BRUUN, SIDKY *et al.* 2018). Although CSS improved with treatment in some of the patients and CSS did not improve in some of them, despite subjective clinical improvement in their behavior has been reported. The authors observed that treatment did not prevent disease progression in males with *SLC6A8* mutations but some improvement was seen in female phenotypes. Our patient with *SLC6A8* mutation, who had autism, behavioral problems, motor, mental retardation and self-mutilation at the forefront, was the oldest diagnosed patient, due to the low sociocultural level and lack of social support, he could not adequately comply with the treatment. Nonetheless, shortly after starting treatment his behavioral disturbances improved, especially his aggressive behaviors were diminished. After the treatment, we found varying rates of improvement and subjective clinical improvement in CSS in our GAMT-deficient patients. The most important improvement was a decrease in aggression and an increase in social adaptation.

Due to the rarity of the disease, the small number of patients and retrospective findings are the limitations of our study. It is promising that even the short-term treatment provided clinical improvement, even in patients with late diagnosis, albeit subjective. We suggest that with creatine monohydrate, L-ornithine and dietary protein restriction, even in late diagnosed

patients with GAMT deficiency, at least the progression of the patients can be stopped. The common characteristics of all patients are that they have growth failure with nutritional problems in the first 1-2 years accompanied by delayed motor and verbal skills. Therefore, family physicians, pediatricians and pediatric psychiatrists should be aware, as it may be the leading sign of CCDS.

Clinicians' awareness allows early referrals of these patients. We observed in late-diagnosed patients that families seek medical care when they first recognized delay in their children's developmental milestones and physical growth. Once the patients were diagnosed simply as having intellectual disability and families did not continue follow-up for further investigations. We think that this situation is due to social isolation caused by having a child with disability whose care is increasingly difficult. Therefore, we believe that patients with CCDS are certainly underdiagnosed and the true prevalence is expected to be higher.

In conclusion, cerebral creatine deficiency is one of the rare treatable inborn errors of metabolism. GAMT deficiency is a candidate disorder for newborn screening because early interventions for metabolic disturbances will provide a better prognosis. Delay in diagnosis and treatment leads to severe neurological sequelae. CCDS should be excluded in patients with feeding problems, verbal and motor developmental delay, hypotonia, seizures and movement disorders in early childhood; cognitive retardation, epilepsy, movement disorders and behavioral problems and autism in late childhood. Low serum creatinine levels are an alerting laboratory finding but it is not obligatory. We believe that awareness should be raised among family physicians, pediatricians and pediatric psychiatrists, especially on the early symptoms of CCDS. In addition, we think that a simple metabolite screening for blood-urine creatinine, creatine and GAA or ^{1}H-MRS increases the diagnostic sensitivity for this disease, which can be treated with early diagnosis, and it is vital for early diagnosis and prognosis.

Ethics Approval

This study was approved by the Research Ethics Review Board of Institute of The Ministry of Health University, Adana City Training & Research Hospital (Approval #1252-13/01/2021).

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NOVA VARIJACIJA GAMT-A U SINDROMU CEREBRALNOG NEDOSTATKA KREATINA, PRVA POTPUNA HOMOZIGOTNA DELECIJA GAMT-A

Habibe Koc UCAR[1,*], Fatma Derya BULUT[2], Berrak Bilginer GURBUZ[2], Okan DİLEK[3], Ilker GUNEY[4]

[1] Odelenje za dečiju neurologiju, Ministarstvo zdravlja, Gradska bolnica za obuku i istraživanje grada Adana, Adana, Turska
[2] Odelenje za metabolizam i ishranu, Ministarstvo zdravlja, Gradska bolnica za obuku i istraživanje, Adana, Turska
[3] Odeljenje radiologije, Ministarstvo zdravlja, Gradska bolnica za obuku i istraživanje grada Adana, Adana, Turska
[4] Odjeljenje za genetiku, Ministarstvo zdravlja, Gradska bolnica za obuku i istraživanje grada Adana, Adana, Turska

Izvod

Sindromi cerebralnog nedostatka kreatina (CCDS) su urođeni metabolički poremećaji u putu metabolizma kreatina. U ovoj studiji procenili smo kliničke, fenotipske, radiološke i genetske karakteristike pacijenata sa CCDS-om. Pokušali smo da identifikujemo tragove rane dijagnoze kod pacijenata. Posebno smo razmotrili uzroke kašnjenja kod pacijenata sa kasnom dijagnozom.
U skladu s ovim nalazima, dijagnoza je potvrđena enzimskim testovima i sekvencioniranjem sledeće generacije zasnovano na sekvenciranju celog genoma. U ovoj studiji predstavljeno je 6 pacijenata čija je dijagnoza genetski potvrđena (5 GAMT mutacija (neko je potpuna homozigotna delecija u GAMT genu), 1 mutacija SLC6A8). Od ovih pacijenata 5 su bili iz iste porodice, a 4 pacijenta su bili pacijenti sa kasnom dijagnozom. Dva od 4 pacijenta kojima je kasno dijagnosticirano bila su umerena, a dva su imala teški fenotip. Neurološki nalazi su se sastojali od pacijenata sa različitim kliničkim nalazima kao što su poremećaj govora, kognitivna retardacija, autizam i epilepsija. Pacijenti su primili odgovarajući tretman za tip cerebralnog nedostatka kreatina. Dok je odgovor na lečenje bio dobar u rano dijagnosticiranim slučajevima, delomično kliničko poboljšanje otkriveno je u kasno dijagnosticiranim slučajevima. Pacijent, koji je započeo lečenje prije nego što su se pojavili neurološki simptomi, bio je neurorazvojno normalan. Uočeno je da postoji jaka veza između dobi u trenutku postavljanja dijagnoze i fenotipa i prognoze. Uporedili smo kliničke nalaze, karakteristike fenotipa i genotipa pacijenata sa CCDS-om. Pregledali smo uzroke kašnjenja kod pacijenata sa kasnom dijagnozom. Stoga smo želeli podići svest o ranoj dijagnostici i lečenju CCDS-a, jedne od retkih metaboličkih bolesti.

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