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Brief Communication

Evaluation of two year treatment outcome and limited impact of arginine restriction in a patient with GAMT deficiency

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ABSTRACT

A 4-year-old female with history of developmental regression and autistic features was diagnosed with guanidinoacetate methyltransferase deficiency at age 21 months. Upon treatment, she showed improvements in her developmental milestones, sensorial-neural hearing loss and brain atrophy on cranial-MRI. The creatine/choline ratio increased 82% in basal ganglia and 88% in white matter on cranial MR-spectroscopy. The CSF guanidinoacetate decreased 80% after six months of ornithine and creatine supplementation and an additional 8% after 18 months of additional arginine restricted diet. We report the most favorable clinical and biochemical outcome on treatment in our patient.

1. Introduction

Guanidinoacetate methyltransferase deficiency (GAMT-D) (MIM #612736) is an autosomal recessively inherited disorder of creatine biosynthesis [1]. Creatine has a buffering and transport functions of high-energy phosphates in brain and muscle and is essential for growth cone migration, dendritic and axonal elongation, neurotransmitter release, and co-transmission on GABA postsynaptic receptors in the central nervous system [2–4].

Creatine deficiency in cranial magnetic resonance spectroscopy (MRS), and elevated guanidinoacetate (GAA) levels are the biochemical hallmarks of GAMT-D [1,2]. Clinical features are developmental delay and intractable epilepsy in infants and intellectual disability, movement disorder and behavioral problems in children. We report a new patient with GAMT-D and her two year successful clinical and biochemical outcome upon treatment.

2. Patient and results

This 4-year-old girl was born after an uneventful pregnancy at term to non-consanguineous Caucasian parents. Her developmental milestones were age-appropriate until 6 months of age (head control at 2 months, rolling over at 5 months). She had first a plateau followed by regression in her developmental milestones after 9 months of age (crawling and babbling at 12 months; walking independently at 20 months; pincer grasp at 21 months). Mild to moderate hearing loss was identified at age 17 months.

Abbreviations: GAMT-D, Guanidinoacetate methyltransferase deficiency; MRS, Magnetic resonance spectroscopy; MRI, Magnetic resonance imaging; GAA, Guanidinoacetate; BG, Basal ganglia; WM, White matter; NAA, N-acetylaspartic acid; CDS, Creatine deficiency syndromes; BSID-III, Bayley Scales of Infant and Toddler Development 3rd Edition; CSF, Cerebrospinal fluid; PDMS-2, Peabody Developmental Motor Scales 2nd edition; EAA, Essential amino acid supplement; Cr/Cho, Creatine to choline ratio; NAA/Cho, NAA to choline ratio; ADOS, Autism Diagnostic Observation Schedule Module 1; ADI-R, Autism Diagnostic Interview-Revised; DSM-IV-TR, Diagnostic and Statistical Manual-Fourth Edition-Text Revision.

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She was referred to our hospital for developmental delay at age 18 months. Physical examination revealed her head circumference at 98th, height at 90th and weight at 80th percentiles. She had poor eye contact with multiple stereotypies and frequent head banging movements. The cranial nerves were intact. She had decreased muscle bulk and decreased axial and peripheral tone. Deep tendon reflexes were 2+ and symmetrical. She had an ataxic wide based gait.

Her EEG showed a dysrhythmic background and rare independent spikes in the left frontal and parietal regions in sleep. Her cranial magnetic resonance imaging (MRI) revealed mild prominence of the lateral and third ventricles and of the extra-axial subarachnoid spaces, and symmetrical hyperintensity in the lentiform nuclei and posterior pontine region in T2-weighted images. Her cranial MRS (single voxel PRESS localization; TE 35–144 ms, TR 2 s) showed markedly reduced peaks of creatine in the basal ganglia (BG) and peritrigonal white matter (WM) with normal peaks of N-acetylaspartic acid (NAA) and choline-containing compounds (Cho) at age 20 months. This result was consistent with a creatine deficiency syndrome (CDS). Her urinary GAA measured using a previously reported method [5] was moderately elevated suggestive of GAMT-D (Table 1a) The diagnosis was confirmed by the most common disease causing splice site mutation (c.327 G>A) in the *GAMT* gene. Both parents were heterozygous for this mutation confirming homozygosity in the patient. GAMT enzyme activity in the cultured skin fibroblasts was undetectable [6].

We monitored urinary and serum GAA levels every 1–3 months (data not shown) and cerebral creatine and cerebrospinal fluid (CSF) GAA levels at 6th and 24th months of therapy (Table 1a). Her development was assessed by The Bayley Scales of Infant and Toddler Development 3rd Edition (BSID-III), Gessell or Peabody Developmental Motor Scales — 2nd edition (PDMS-2) every 6–12 months (Tables 1b and 1c). Hearing was assessed every 6–12 months.

Creatine supplementation was started at a dose of 400 mg/kg/day (four doses) at diagnosis. Ornithine was started at 400 mg/kg/day (three doses) after one month. An arginine restricted diet was initiated after 6 months with a daily arginine intake of 20 mg/kg/day (260 mg/day) which was decreased gradually to 14 mg/kg/day (250 mg/day) within 14 months according to serum GAA levels. Essential amino acid supplement (Vitaflow EAA) (15 g Protein/day) was given to meet age appropriate protein requirements.

After two years of therapy (45 months of age) she was making constant, but slow progress in her development. She was hyperactive, but able to interact with objects and respond to instructions. She was making eye contact and guiding her family to communicate her interests nonverbally. She was using 8–10 words sign language and had only one spoken word. Physical examination revealed head circumference at 98th, height at 90th and weight at 95th percentiles. She had normal axial tone with mildly decreased peripheral tone, normal gait and normal muscle strength.

Her cranial MRI showed improvement of the mild prominence of the lateral and third ventricles and of the extra-axial subarachnoid spaces at 6th and 24th months of the therapy. In WM, the intensity ratio of Cr/Cho increased from 0.07 at baseline to 0.59 at 6 months of therapy and further to 0.69 at 24 months of therapy (normal institutional values 0.78 ± 0.07). In the BG, a similar increase from 0.12 to 0.68 was observed which remained stable also after 24 months of therapy (normal institutional values 0.96 ± 0.13). Intensity ratios NAA/Cho were within normal range at all examinations.

She had mild hearing loss at 3000–4000 Hz in pure-tones at 6 months of therapy which improved at 4000–6000 Hz in pure tones by visual reinforcement audiometry at 1.5 years of therapy. She had normal range hearing threshold in sound fields at 2 years of therapy.

An autism assessment was performed at age 34 months (1 year of therapy) using clinical application of the Autism Diagnostic Observation Schedule Module 1 (ADOS; 2001), Autism Diagnostic Interview-Revised (ADI-R; 2003), and Diagnostic and Statistical Manual-Fourth Edition-Text Revision (DSM-IV-TR; 2000). The total ADOS score was above the threshold for autism. The ADI-R demonstrated limited facial expressions and no reciprocal smile in non-verbal behaviors to regulate social interaction. Her communication was characterized by limited use of intuitive gestures thus she met the clinical criteria for autism.

Standardized developmental assessments were not able to be completed due to inability to sustain focused attention and follow instructions. Developmental ages in Tables 1b and 1c were given as clinical estimates based on observation of how the patient interacted with standardized test items. Sensory processing behaviors such as walking constantly round the room from object to object, head-banging, feet-stomping, slapping her hand on surfaces and tactile defensive posturing of her hands at the diagnosis have been improved at two years of therapy.

3. Discussion

Less than 60 patients with GAMT-D have been reported so far [1,7–18]. Clinical phenotype includes three subgroups: severe, moderate and mild. Forty-eight percent of the patients had severe clinical phenotype in a retrospective review of 27 patients [11]. Intellectual disability, epilepsy and movement disorder were consistent clinical features in all patients with severe phenotype, whereas only 21% had movement disorder and only 7% had intractable epilepsy with moderate to mild clinical phenotype [11]. The treatment is based on two principals: replenishment of cerebral creatine deficiency by oral creatine supplementation [19] and aiming to normalize GAA levels by ornithine supplementation, dietary restriction of arginine and removal of glycine by sodium benzoate supplementation (arginine and glycine are the substrates of creatine biosynthesis) [20]. High dose creatine and ornithine supplementation reduce GAA synthesis by competitive inhibition of arginine:glycine amidinotransferase (AGAT) enzyme which is the first enzyme of creatine biosynthesis and synthesizes GAA from arginine and glycine. High dose ornithine might also reduce GAA in two different mechanisms: by counteracting arginine-maintaining mechanism and by competitive inhibition of tubuler arginine reabsorption. Arginine and ornithine use same dibasic amino acid transporter, thus high dose ornithine supplementation might reduce tubuler reabsorption of arginine by competitive inhibition [20]. Increase of ornithine dose up to 800 mg/kg/day might have an additional effect to decrease GAA levels.

In a retrospective review of 27 patients with GAMT-D, nine patients showed improvements in epilepsy and/or movement disorder;

Table 1a
Urinary, serum and CSF GAA levels at baseline and on treatment.

Treatment	Urinary GAA Reference range 16–228 mmol/mol creatinine	Serum GAA Reference range 0.35–1.8 μmol/L	CSF GAA Reference range 0.036–0.224 μmol/L
Baseline	611	20.1	11.6
1 month of creatine therapy	597	9.8	Not performed
6 months of ornithine and creatine therapy	336	5.5	2.3
2 years of creatine, ornithine and arginine restricted diet therapy	195	3.3	1.4