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Clinical Observations

Case Study for the Evaluation of Current Treatment Recommendations of Guanidinoacetate Methyltransferase Deficiency: Ineffectiveness of Sodium Benzoate

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ABSTRACT

BACKGROUND: Guanidinoacetate methyltransferase deficiency is an autosomal recessively inherited disorder of creatine biosynthesis. We report a new patient with guanidinoacetate methyltransferase deficiency and her >3-year treatment outcome. **PATIENT:** This is a 6-year-old girl who was diagnosed with guanidinoacetate methyltransferase deficiency at the age of 28 months. She presented with moderate global developmental delay, one afebrile seizure, and hypotonia between 6 and 18 months of life. She was treated with creatine and ornithine supplementation and a strict arginine-restricted diet for 42 months. **RESULTS:** Mutation analysis (compound heterozygous mutations, a known c.327G>A and a novel c.58dupT [p.Trp20LeufsX65]) and enzyme studies in primary fibroblasts confirmed the diagnosis. After 33 months of therapy, her cerebrospinal fluid guanidinoacetate level decreased from 47 to 5.3 times the normal level. Brain creatine by proton magnetic resonance spectroscopy increased by >75% but did not normalize in the basal ganglia and white matter after 3 years of therapy. Additional treatment with sodium benzoate for 17 months did not further improve plasma guanidinoacetate levels, which questions the relevance of this therapy. **CONCLUSION:** Treatment did not improve moderate intellectual disability or normalize guanidinoacetate accumulation in the central nervous system.

Keywords: GAMT deficiency, seizure, creatine therapy, global developmental delay, arginine-restricted diet, sodium benzoate
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Introduction

Guanidinoacetate methyltransferase deficiency (MIM [Mendelian Inheritance in Man] #612736) is an autosomal recessively inherited disorder of creatine biosynthesis.[1] Its estimated incidence is 1:114,072 in Utah,[2] and its carrier frequency was 1 per 1475 in a small cohort of newborns in Canada.[3] Creatine has 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 cotransmission on γ-aminobutyric acid postsynaptic receptors in the central nervous system (CNS).[4,5]

Creatine deficiency observed on brain proton magnetic resonance spectroscopy (^{1}H-MRS) and increased guanidinoacetate (GAA) levels in urine, blood, and cerebrospinal fluid (CSF) are the biochemical hallmarks of guanidinoacetate methyltransferase deficiency. Clinical features are global developmental delay (GDD) and seizures in infants and intellectual disability, movement disorder, epilepsy,

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and behavioral problems in children.[6] Hypotonia and gross motor delay together with choreiform movements were recently reported in a 10-month-old patient with guanidinoacetate methyltransferase deficiency as early presenting symptoms.[2] Current treatment recommendations consist of high-dose creatine and ornithine supplementation, arginine-restricted diet, and sodium benzoate therapy to replenish cerebral creatine deficiency and decrease neurotoxic GAA accumulation in the CNS.[7]

We report a new patient with guanidinoacetate methyltransferase deficiency and evaluation of detailed 42-month clinical and biochemical treatment outcome. This patient is an excellent example for very good treatment compliance for an extremely difficult therapy.

Patient

This 6-year-old girl was born after an uneventful pregnancy at term to nonconsanguineous Caucasian parents. She was referred to occupational health services because of concerns of developmental delay at the age of 12 months. She had a nonfebrile generalized tonic-clonic seizure lasting 1 minute at the age of 13 months. She was treated with phenobarbital for 6 months and there were no further seizures. Because of her decreased muscle tone and GDD, she was referred to clinical genetics at the age of 22 months. The investigations revealed mild elevation of orotic acid, which prompted a referral to the metabolic clinic for further investigations at the age of 27 months.

At the age of 27 months, during her initial consultation in our hospital, her early developmental milestones were delayed in all domains. She began crawling at the age of 14 months, walking at the age of 22 months, and had pincer grasp at the age of 20 months. She began babbling at the age of 9 months, but she spoke only six words at the age of 27 months. She had just started pointing for her needs. Simple commands were understood only if they were shown before and if they were part of her daily routine. She fed herself with finger food. She played no creative games. Physical examination revealed normal growth parameters (head circumference at fiftieth, height at sixtieth, and weight at fortieth percentiles). She had plagiocephaly, decreased muscle bulk, decreased axial and peripheral tone, normal deep tendon reflexes, wide-based gait, and toe walking.

Treatment

Creatine dose was between 400 and 540 mg/kg daily (in four doses), and ornithine dose was between 375 and 416 mg/kg daily (in three doses). Arginine intake was 250 mg daily throughout therapy, between 16.8 and 13.2 mg/kg (corresponding natural protein intake 0.26-0.39 g/kg daily). Essential amino acid supplement (0.8 g/kg daily) was added to meet age-appropriate protein requirements. Sodium benzoate dose was between 217 and 250 mg/kg daily.

Biochemical investigations

Plasma and CSF amino acids were measured in routine clinical, biochemical, and genetics laboratories. Urine, plasma, and CSF GAA levels[8] and CSF *S*-adenosylmethionine and *S*-adenosylhomocysteine levels were measured using a previously reported method.[9] Guanidinoacetate methyltransferase enzyme activity in the cultured skin fibroblasts was measured using a previously reported method.[10] Brain creatine levels were measured by ^{1}H-MRS using single-voxel point-resolved spectroscopy localization with echo time 35-144 ms and repetition time 2 seconds.

Urine and serum GAA levels were monitored every 1-3 months, CSF GAA levels at baseline and at the sixth and thirty-third months of therapy, and brain creatine levels by ^{1}H-MRS at baseline and at the sixth and thirty-sixth months of therapy.

Statistical analysis

Two-sample *t* test and confidence interval and Mann-Whitney U test and confidence interval were applied to compare plasma GAA levels with and without sodium benzoate treatment.

Neurodevelopmental assessments

Developmental, language, and neurocognitive functions were assessed using Gesell Developmental Assessments, Peabody Developmental Motor Scales—Second Edition, Receptive-Expressive Emergent Language Test—Third Edition, Wechsler Preschool and Primary Scale of Intelligence—Fourth Edition, Canadian, and Adaptive Behavior Assessment System, Second Edition (teacher and parent assessment).

Results

Diagnostic baseline investigations

Urine GAA level was moderately elevated at the time of the diagnosis (768 μmol/mmol creatinine; reference range 16-228), suggestive of guanidinoacetate methyltransferase deficiency. The diagnosis of guanidinoacetate methyltransferase deficiency was confirmed by compound heterozygous mutations in the *GAMT* gene: a common pathogenic splice-site mutation, c.327G>A (paternally inherited), and a novel one—base pair duplication, c.58dupT (p.Trp20LeufsX65), resulting in frameshift mutation (maternally inherited) and thus is considered a pathogenic mutation as well. Guanidinoacetate methyltransferase enzyme activity was deficient in the cultured skin fibroblasts.

Brain magnetic resonance imaging revealed increased signal intensity on axial T_2 images adjacent to the trigone bilaterally. ^{1}H-MRS (single-voxel point-resolved spectroscopy localization; echo time 35-144 ms and repetition time 2 seconds) showed markedly reduced creatine in the basal ganglia and peritrigonal white matter with normal peaks of *N*-acetylaspartic acid and choline-containing compounds at the age of 28 months.

Treatment

Creatine therapy was initiated at the age of 28 months (baseline of treatment) at 400 mg/kg daily and was gradually increased up to 540 mg/kg daily. Ornithine therapy was initiated 1 month later at 400 mg/kg daily, which was increased to a maximum dose of up to 416 mg/kg daily. Arginine-restricted diet was initiated in the third month of therapy with 250 mg/kg daily arginine intake (16.8 mg/kg daily), which was gradually decreased to 13.2 mg/kg daily. Sodium benzoate therapy was initiated on 14 months of therapy at 250 mg/kg daily dose, which was administered for 17 months. It was discontinued as a result of difficulties in taking it owing to its taste.

Biochemical investigations on treatment

Biochemical investigation results on treatment are provided in Table 1. Plasma GAA results on various treatments are provided in the Figure. There was no arginine deficiency in plasma and in CSF on strict arginine-restricted diet. Plasma ornithine levels were normal on high-dose ornithine supplementation. CSF ornithine level was three times