ABSTRACT #72

Introduction: Guanidinoacetate methyltransferase (GAMT) deficiency is one of three inborn errors of cerebral creatine deficiency that causes a combination of autistic behavior, seizures, speech delay that is generally severe, hypotonia, and, in some cases, movement disorders. The other inborn errors of cerebral creatine deficiency, arginine: glycine amidotransferase (AGAT) deficiency and creatine transporter defect (CRTR), present similarly (figure 1). GAMT and AGAT deficiencies are inherited as autosomal recessive traits, while CRTR is an X-linked trait. Despite that GAMT deficiency was first reported over 15 years ago, there have only been around 50 published cases. We present our experience with three additional patients. Although they were diagnosed at different ages, all three had manifestations that included developmental delay, especially in the area of speech and language development. Two of the three patients also had seizures at the time of diagnosis, while one of them developed seizures about nine months after diagnosis.

Patients and Methods: A retrospective chart and neuroradiology review was conducted for patients identified at our center over five years. Data are presented in table 1.

Patient 1 was diagnosed at 65 months of age with a history of pervasive developmental delay after developing seizures at 54 months. Seizures occurred up to 30 times per day. She did not respond to antiepileptic medications. She had delayed speech (10-20 words) and macrocephaly (head circumference > 98th percentile). After 13 months of therapy, seizures reduced in frequency and intensity and the patient has a rich vocabulary with short but understandable sentences.

Patient 2 was diagnosed at 15 months of age after presenting with seizures that onset at 6 months. Seizures occurred about 15 times per day. He also had global developmental delays (was unable to speak or stand). After 39 months of therapy, the patient was learning new words, could speak in sentences, used sign language, and had normal gross and fine motor ability. Seizures stopped about one month after starting therapy.

Patient 3 was diagnosed at 11 months of age after presenting with clenched fists (5-6 months of age) and fluctuating tone abnormalities. At that time, developmental testing indicated an approximate six month delay in motor and language function. She had a history of hypothyroidism which had been treated since she was 11 days of age. At the time of diagnosis, she was extremely hypotonic. She was treated with creatine supplements alone until 3 years of age, during which time she had slow progress in motor milestones and also her first seizure (at 20 months of age). She then was started on mild protein restriction and ornithine supplements in addition to the creatine. The family was only intermittently compliant with therapy and moved to a different state. At 54 months of age, she spoke a few words, had a wide-based, ataxic gait, but continued to gain new skills.

Results: All patients had decreased creatine peaks in the brain MR spectroscopy (figure 2). Additionally, patient 1 had a decrease in the myoinositol peak. Patients 2 and 3 had abnormal signals in the globi pallidi. Plasma creatine levels were reduced in all patients with marked elevation of guanidinoacetate.

DNA testing in all patients confirmed the diagnosis and identified previously reported or novel mutations (table 1). Creatine (500-1000 mg/kg per day) and ornithine (500-850 mg/kg per day) supplements alone until 3 years of age, during which time she had slow progress in motor milestones and also her first seizure (at 20 months of age). She then was started on mild protein restriction and ornithine supplements in addition to the creatine. The family was only intermittently compliant with therapy and moved to a different state. At 54 months of age, she spoke a few words, had a wide-based, ataxic gait, but continued to gain new skills.

Conclusions: GAMT deficiency can cause mental retardation/developmental delay, seizures, hypotonia, and autistic behavior. MR spectroscopy identifies reduced or absent creatine peaks while brain MRI may identify abnormalities of the globi pallidi. Patients have wide variability in their diagnostic creatine and guanidinoacetate levels that are, however, all well outside the normal range. Despite the presence of significant delays at time of diagnosis, patients can have improvement of neurological symptoms and possibly progression of their development with adherence to the recommended therapies. Early diagnosis could prevent brain damage and possibly lead to normal development; thus, consideration has been given to adding GAMT deficiency to newborn screening panels.

REFERENCES

Table 1: Patients with GAMT deficiency followed in the Metabolic Clinic at the University of Utah

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at diagnosis (months)</th>
<th>Clinical features at diagnosis</th>
<th>MRI/MRS findings</th>
<th>Diagnostic plasma creatine (µmol/L)</th>
<th>Diagnostic plasma GAA (µmol/L)</th>
<th>GAMT gene sequencing</th>
<th>Current age / duration of therapy</th>
<th>Creatine mg/kg/day</th>
<th>Ornithine mg/kg/day</th>
<th>Protein g/kg/day</th>
<th>Plasma creatine on therapy (µmol/L)</th>
<th>Plasma GAA on therapy (µmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>seizures, macrocephaly, limited speech, autism spectrum disorder (PDD-NOS)</td>
<td>normal MRI: diminished creatine and ornithine peaks on MRS</td>
<td>4.7</td>
<td>9.6</td>
<td>c.299G&gt;c.311A/p.Glu103Lys</td>
<td>6 yr 8 mo / 13 mo</td>
<td>690</td>
<td>690</td>
<td>1.2</td>
<td>989</td>
<td>6.9</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>seizures, developmental delay, clumsiness</td>
<td>abnormal intensity of glob pallid on MRI: diminished creatine peak on MRS</td>
<td>2.1</td>
<td>21.3</td>
<td>c.522G&gt;T/p.Arg174Cys; c.327G&gt;A/p.K109fsX26 (splice mutation)</td>
<td>4 yr 7 mo / 40 mo</td>
<td>508</td>
<td>508</td>
<td>0.6</td>
<td>900</td>
<td>9.8</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>hypotonia: clenched fists; developmental delay; seizures occurred 9 mos after diagnosis</td>
<td>abnormal intensity of glob pallidi and pons on MRI: absence of creatine peak on MRS</td>
<td>2</td>
<td>13.8</td>
<td>c.403G&gt;T/p.D135N; c.327G&gt;A/p.K109fsX26 (splice mutation)</td>
<td>8 yr 7 mo / 7 yr family relocated</td>
<td>994</td>
<td>829</td>
<td>1.3</td>
<td>ND</td>
<td>ND</td>
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