Background

Pyridoxine-dependent epilepsy (PDE) is an autosomal recessive epileptic encephalopathy characterized by a therapeutic response to pharmacological dosages of pyridoxine and resistance to conventional antiepileptic treatment. It is caused by alpha-aminoadipic semialdehyde dehydrogenase deficiency (ALDH7A1), an enzyme facilitating lysine catabolism, resulting in chemical inactivation of pyridoxal phosphate and accumulation of the potentially neurotoxic metabolites AAASA, P6C and pиперидол acid (Fig.1).

Despite adequate seizure control with pyridoxine in most cases, neurodevelopmental outcome is poor with 75-80% suffering developmental delay/intellectual disability. We hypothesized that dietary lysine restriction -similar to therapy for Glutaric Aciduria type I- can reduce neurotoxic compounds with potential benefit to clinical outcomes.

Objective

To evaluate the safety & efficacy of dietary lysine restriction as an adjunct to pyridoxine therapy on biochemical parameters, seizure control, and developmental/cognitive outcomes in children with ATQ deficiency.

Methods

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Observational</th>
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</thead>
<tbody>
<tr>
<td>Centers</td>
<td>3 sites (Canada, USA, Germany)</td>
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<tr>
<td>Subjects</td>
<td>7 (6 girls &amp; 1 boy)</td>
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<tr>
<td>Treatment</td>
<td>Lysine restriction based on the Ross guidelines for Glutaric Aciduria type I.</td>
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<tr>
<td>Outcomes</td>
<td>Biochemical outcomes (pipercolic acid and AAASA levels in body fluids)</td>
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<td></td>
<td>Seizures (EEG &amp; Clinical evaluation)</td>
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<tr>
<td></td>
<td>Developmental/cognitive outcomes (Age-appropriate tests and parental observations)</td>
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<tr>
<td>Duration</td>
<td>Approximately 4 yrs (2008-2012)</td>
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</tbody>
</table>

Results

Lysine restriction- well tolerated, good compliance & no adverse events

Biomarker reduction in all patients: Plasma pipercolic acid (20-67%), Urinary AAASA (13-72%), In Patient #2: CSF pipercolic acid (87.2%) and CSF AAASA (81.7%). (Fig.2)

Improvement in age-appropriate skills was observed in 4 out of 5 patients with pre-diet developmental delays, and seizure control was maintained or improved in 6 out 7 children

Illustrative Case

This boy (c.7500G>A (V250V) / c.1195G>C (E399Q)) presented at age 2 months with focal clonic seizures treated with a loading dose of pyridoxine and maintenance pyridoxine, folic acid and phenobarbital (latter stopped at age 1.5 years). Triggered by fever or missed medication, seizures worsened and he showed developmental and behavioral improvement with age-appropriate functional skills and a behavioral deterioration.

Conclusions

This is first study reporting the effect of dietary lysine restriction adjunct to pyridoxine treatment in PDE due to ATQ deficiency (manuscript accepted for publication).

We conclude that this therapy (evidence level 4):

- is well tolerated
- leads to significant decrease of AAASA and pipercolic acid in different body compartments
- has the potential to maintain/improve seizure control and/or developmental

Future Directions

To generate a stronger level of evidence before this potentially burdensome dietary therapy becomes the mainstay treatment, we have:

- established an international PDE consortium (www.pdeonline.org);
- developed a protocol to conduct future diet studies with an all inclusive integrated study design (funding pending);
- a website containing up-to-date information on PDE;
- a methodological toolbox;
- and an online registry to facilitate the participation of interested physicians, scientists and families in PDE research.

References