Triheptanoin dramatically reduces the frequency of paroxysmal movement disorders in GLUT1 deficiency

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Background

Glucose transporter type 1 deficiency syndrome (GLUT1-DS) is caused by impaired glucose transport across the blood-brain barrier and into astrocytes, leading to cerebral energy deficiency.

Based on our previous work with triheptanoin, a compound that provides key substrates to the Krebs cycle in the brain, we wished to assess its therapeutic benefit in patients with glucose transporter type 1 deficiency syndrome.

Methodology

GLUT1-DS patients with non-epileptic paroxysmal manifestations (n = 8, age range = 7 – 47 yrs)

Study assessment

- Clinical: clinical global impression scale, comprehensive patient diary to record all motor and non-motor events.
- Biological: Blood sampling after overnight fast for standard analyses, plasma C3-carnitine and C5-ketone bodies.
- MRS: Phosphorus-functional Magnetic Resonance Spectroscopy (13P MRS) with AMARES method allowed the quantification of high energy phosphates from which we calculated the Pi/PCr ratio, defined as the metabolic marker.

13P MRS showed an abnormal brain energy profile in GLUT1-DS patients with no change in Pi/PCr ratio during visual stimulation. After 2 months of treatment with triheptanoin, the profile was corrected and we observed an increase in Pi/PCr ratio during visual stimulation followed by a decrease during recovery (p = 0.021). Increased Pi/PCr ratio during brain activation reflected a proportional elevation of ADP, allowing increased mitochondrial ATP production with triheptanoin.

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Results

Total paroxysmal manifestations in GLUT1-DS patients

A significant reduction of non-epileptic paroxysmal manifestations was observed when patients were treated with triheptanoin for 2 months (* p = 0.05). Of note, the total number of events was comparable between the baseline and withdrawal phases. In addition, on the clinical global impression-improvement scale (CGI-I) patients reported a clear improvement when treated and a clear worsening after drug withdrawal.

Conclusion

- Triheptanoin dramatically reduced the number of paroxysmal manifestations in GLUT1-DS patients.
- This was associated with a significant production of C5-ketone bodies and the normalization of the MRS bioenergetics profile during brain activation.
- The confirmation of our data in a larger controlled study would hold promise for an alternative therapeutic approach to ketogenic diet in GLUT1-DS.