

Citation: Gropman AL, Fricke ST, Seltzer RR, et al. ¹H MRS identifies symptomatic and asymptomatic subjects with partial ornithine transcarbamylase deficiency. *Mol Genet Metab.* 2008;95(1-2):21-30. doi:10.1016/j.ymgme.2008.06.003.

Funding: None.

Purpose: This study utilized magnetic resonance spectroscopy (MRS) to investigate biochemical changes that may underlie neuronal damage in patients with partial ornithine transcarbamylase (OTC) deficiency (n=25; 20 female, 5 male; aged 19 to 59 years) and compared findings with healthy controls (n=22; 12 female, 10 male; aged 18 to 59 years). Data were also compared between patients with late-onset, symptomatic OTC deficiency (n=17; based on presentation of clinical symptoms) and those who had not yet presented symptoms (asymptomatic; n=8).

Key takeaways:

- Brain biochemical differences were seen in medically stable adults with OTC deficiency including individuals who were considered asymptomatic and had no anatomical changes detected by magnetic resonance imaging (MRI).
- In patients with late-onset and asymptomatic OTC deficiency, myoinositol (ml) was decreased and glutamine (gln) increased in multiple brain areas, including the parietal white matter (PWM), frontal white matter (FWM), and posterior cingulate gray matter (PCGM); in addition, ml was decreased in the thalamus and gln increased in the frontal gray matter (FGM).
- Decreased ml was shown to inversely correlate with disease severity score (a measure reflecting the number of hyperammonemic episodes and coma).
- Elevations in gln were seen in several brain regions despite normal plasma ammonia and normal plasma gln in some patients with OTC deficiency.
- Concentrations of ml and gln were inversely related in patients with OTC deficiency, but not controls.

Discussion:

- Previous animal studies have shown that gln in the brain serves to rapidly detoxify and buffer excess ammonia, and increases in brain gln can be associated with hyperammonemia.^{1,2}
- The inverse relationship between ml and gln is presumed to reflect limitations of the astrocyte to continue to provide nitrogen buffering in the face of hyperammonemia. The reduction in ml may be indicative of prior hyperammonemic episodes and represent a marker of vulnerability.
- Biochemical changes, such as altered energy and membrane metabolism and the glutamate-glutamine shuttle, may be seen prior to structural MRI changes in patients with OTC deficiency, suggesting that biochemical changes precede structural changes and provide a window of opportunity to intervene prior to irreversible structural damage.
- The difference in brain biochemistry in patients with late-onset OTC deficiency may explain neurocognitive differences.

Additional references: **1.** Jayakumar, et al. *Neurochem Int.* 2006;48(6-7):623-628. **2.** Cooper, et al. *J Biol Chem.* 1979;254(12):4982-4992.