Ornithine Transcarbamylase Deficiency with Persistent Abnormality in Cerebral Glutamate Metabolism

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Purpose: To determine cerebral glutamate turnover rate in partial ornithine transcarbamylase deficiency (OTCD) patients using carbon 13 MRS.

Background: OTCD, by impairing urea cycle activity results in hyperammonemia and hepatic encephalopathy, a syndrome in which 1H, 31P and 13C MRS have each proven valuable in documenting neurochemical sequelae [2]. The genetic disorder OTCD has many variants and the clinical consequences often remain undiagnosed. By exploring these rare patients with modern MRS techniques we expect to advance diagnosis, prevention and treatments of the often severe neurological consequences [2].

Patient selection and MRS Methods: 10 subjects, 6 patients with OTCD, disease severity scores 0 – 4 and in stable condition, ages 19 – 54 yrs) and 4 healthy controls were examined on a GE 1.5 Tesla clinical MR scanner equipped for 1H MRS and 13C MRS. Because frontal 13C MRS examinations were anticipated, for which non-decoupled observations of the C5 glutamate and glutamine are necessary, studies were performed with either 1-13C or 2-13C glucose as the intravenous precursor.

Results: Uptake and removal of cerebral glucose (1-13C or 2-13C) were comparable in healthy control subjects and subjects with OTCD. Significantly reduced rates of glucose conversion to 13C-glutamate were observed in OTCD (P 0.04), but no difference was noted in 13C glutamine production.

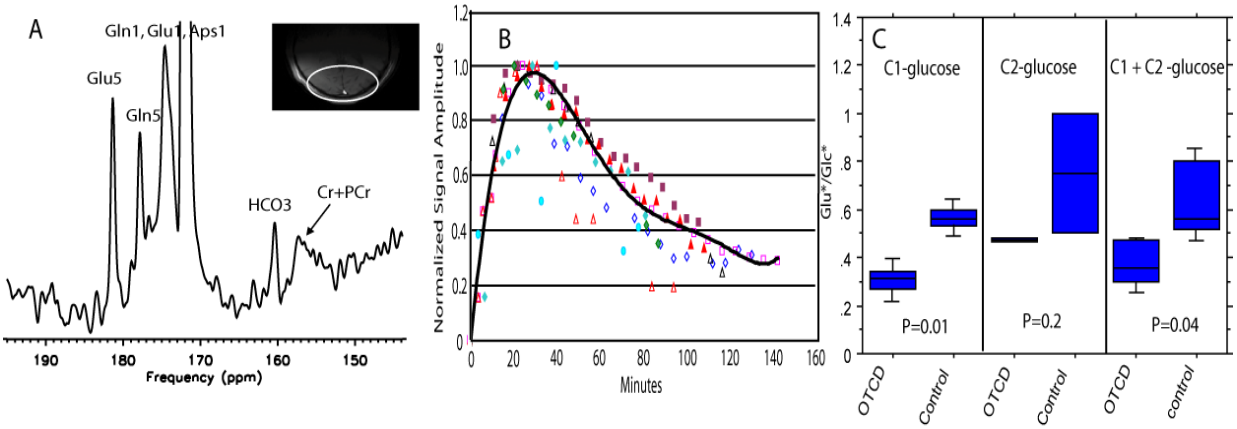

Figure 1A: 13C MR spectra (160-190ppm) of normal brain after enrichment with [2-13C] glucose. Figure 1B:Effect of OTCD on cerebral metabolism of 13C-glucose and glutamate, shows comparative rates of cerebral accumulation and removal of infused [1-13C] and [2-13C] Glucose in OTCD (open symbols) and healthy (solid symbols) subjects. No significant differences between C1 and C2 or between OTCD and healthy subjects were observed. Figure 1C: Box plots of rates of glutamate enrichment from glucose C1, glucose C2 and combination of glucose C1 and C2 in OTCD patients and control subjects.

Discussion and Conclusions: The results described are not dissimilar to those previously presented for 13C studies of adult patients with hepatic encephalopathy [1]. Significant methodological advances described in this report refer to human use of 2-13C glucose as the loading precursor, in place of more usually employed 1-13C glucose, and the consequent ability to examine a brain region more directly concerned with the long-term neuropsychological deficits encountered in the adult survivors of an often fatal inborn error of metabolism. The clinical diagnostic advance is the recognition for the first time, that significant neurochemical abnormalities are present in OTCD even when the clinical picture is normal. Since the long-term outcome for patients with partial urea cycle defects is still questionable, application of readily available MRS methods will contribute to their future management and the reduction in preventable neurological disorders.

References: [1] S. Bluml, et al. Magn Reson Med 45 (2001) 981-93. [2] A.L. Gropman, et al. Mol Genet Metab 94 (2008) 52-60.
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