MRS in the diagnosis and monitoring of Maple Syrup urine Disease

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INTRODUCTION

Maple syrup urine disease (MSUD) is an autosomal recessive disorder, caused by defects in the decarboxylation of branch chain amino acids (BCAA). This leads to excessive accumulation of BCAA and their derivatives the 2-oxoacids (BCOA) and hydroxy-acids (BCHA). These compounds – in particular leucine and 2-oxoisocaproic acid are neurotoxic resulting in brain damage and coma. Untreated, patients die in metabolic crisis, however eraly diagnosis and dietary treatment limits neurological damage. Quantitative MR spectroscopy can directly detect elevated cerebral BCAA levels and may have a role in determining the efficacy of dietary treatment.

This abstract details serial proton MR spectroscopy demonstrating fluctuating concentrations of BCAA within the brain over a 21 month period in a child diagnosed with MSUD at two weeks of age.

METHOD

MR imaging and spectroscopy examinations were performed approximately every six months. The results were compared with results from physical and neurologic examinations and plasma levels of branch chain amino acids measured every 4-8 weeks. MR exams were performed at 1.5T (Magneton SP4000, Siemens Medical Systems) using a circularly polarized 26cm head coil. Localized proton MR spectra was acquired using a short echo time STEAM sequence (2000/20 with a 30 msec Tm). 256 averages were collected in a 6cm x 6cm x 2cm (72cc) voxel which was positioned posteriorly within the centrum semiovale straddling the midline to include both hemispheres and containing predominantly white matter. Quantification of the BCAA and derivatives was determined by calculating peak ratios (comparing areas under the curves with respect to creatine). The concentration of creatine was assumed to be constant in MSUD (as it is not a disease involving primary failure of energy metabolism). Absolute quantification of cerebral BCAA was estimated from the product of the metabolite ratios (with respect to creatine) and age corrected absolute creatine concentration.

RESULTS

Results are summarized in Table 1.

Initial Presentation: age 18 days. The blood plasma level of leucine was 2.2mM which was grossly elevated (26 times the upper range of normal), and leucine constituted 93% of the abnormal BCAA in the plasma (2.4mM). The MR spectroscopy appearance of the metabolites, N-acetylaspartate (NAA) and myoinisitol (MI), was unremarkable, and in particular the NAA/creatine (Cr), and the MI/Cr ratios were normal for age. The choline/creatine (Cho/Cr) ratio was elevated at 1.6 – believed to relate the demyelination and gliosis in MSUD. There were a series of abnormal doublets centered at 0.96 ppm and 1.33ppm. The range of these doublets included the resonances of the BCAA, BCOA and BCHA and also of lactate at 1.33 ppm. As many of these compounds resonate at adjacent frequencies there is some overlapping of the peaks, making spectroscopic quantification of some of the compounds difficult, although leucine was clearly distinguishable on this spectrum at 0.96ppm. The brain concentration of the compounds in the 0.6–1.1ppm range (limited to exclude lactate) was 5.7mM. (Fig.1).

Second exam at 7–1/2 months: Despite dietary protein restriction under clinical supervision, the plasma BCAA levels remained persistently elevated, though the constituent proportions had changed. Between the first two MRS studies the total plasma BCAA had dropped, largly due to a reduction in leucine, however the amounts of the other BCAA had increased by between 6 and 22 fold. On the second MRS exam the concentration of compounds in the range 0.6ppm to 1.1ppm was 6.9mM. The leucine peak which had dominated the first spectrum was greatly reduced, and there was proportionately more of the other BCAA and metabolites. The Cho/Cr ratio remained elevated at 1.05 (normal 0.93). The rest of the spectrum remained normal for age. The changes in the MRS were mirrored in the blood levels.

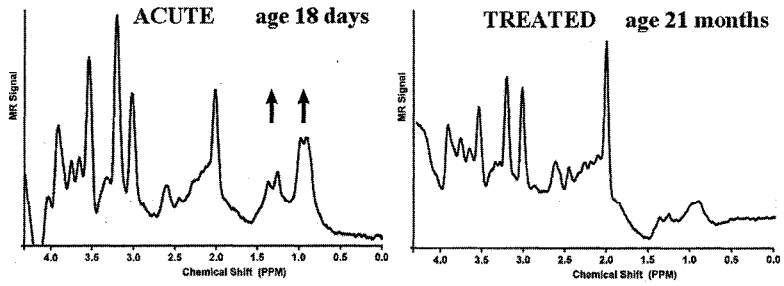
Third exam at 14 months: Total plasma BCAA was 1.4mM. The MR spectrum was similar to the second study. Cerebral concentrations of BCAA and metabolites in the same range was 5.0mM.

Forth exam at 21 months: Total plasma BCAA was a little reduced at 1.2mM. The MR spectrum was similar to the previous study though cerebral concentrations of BCAA and metabolites in the same range were also down at 3.4mM.

DISCUSSION

MSUD is a difficult disease to manage. Dietary restriction of protein attempts to keep the BCAA at levels low enough to limit cerebral damage, but not too low such as to limit growth and result in a chronic catabolic state which may elevate BCAA levels from catabolized protein. There is a discrepancy in the measured plasma and brain levels of BCAA and their metabolites with plasma/brain ratios ranging from 1:2.4 to 1:3.4. This may be accounted for by the limited plasma BCAA assay. The plasma assay measures only the four BCAA (leucine, isoleucine, valine and alloisoleucine), whereas the cerebral MR spectroscopy measures these as well as all BCOA and BCHA compounds. We know from the literature that BCOA accumulate in the plasma in direct proportion to the BCAA levels. The cerebral levels of the BCAA and metabolites between 0.6-1.1 ppm maintained a fairly constant relationship with the total plasma BCAA levels even though the blood leucine levels ranged from .0024 to 2.2mM.

Accurate *in vivo* monitoring is essential. MR spectroscopy of the brain can clearly detect elevated cerebral levels of BCAA and its metabolites. This proved useful in confirming the diagnosis in the early stages. It also allowed for ongoing monitoring of BCAA and metabolite levels.



Age	$[leucine]_{blood}$	$[BCAA]_{blood}$	$[metabolite]_{MRS}$
18d	2.2 mM	2.4 mM	5.7 mM
6.5m	0.002 mM	1.6 mM	6.9 mM*
14m	1.07 mM	1.4 mM	5.0 mM
21m	0.58 mM	1.2 mM	3.4 mM

Table 1