Correlation between Brain Metabolites and Very Long Chain Fatty Acid Levels in Asymptomatic Boys with X-linked Adrenoleukodystrophy

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Introduction

Elevation of very long chain fatty acids (VLCFA) is believed to play an important role in the pathogenesis of cerebral demyelination in boys with X-linked adrenoleukodystropy (ALD). Prophylactic reduction of systemic VLCFA levels using dietary therapy (known as "Lorenzo's oil" (LO)) has recently been shown to be effective in reducing the risk of developing brain lesions on MRI (1). However, the mechanism of this protective effect is largely unknown. This study was therefore undertaken to examine the relationship between brain metabolite and VLCFA levels in asymptomatic ALD boys with normal brain MRI enrolled in a trial of LO.

Material and Methods

Conventional brain MRI and water- and lipid-suppressed multi-slice proton MR spectroscopic imaging (MRSI; TR/TE 1700/280 ms, 3 slices, voxel size 0.8 cm^3) were performed on 34 asymptomatic ALD boys (age 4.9 ± 3.1 years) using a transmit-receive head coil at 1.5 Tesla (2). All boys were on LO, although they had variable compliance or response, resulting in a range of VLCFA levels from normal to elevated. 10 of the 34 boys also returned one year later for a repeat MRI/MRSI exam. Peripheral VLCFA levels (in particular, hexacosanoic acid, C26) were measured within 24 hours of the MRSI examination.

MRSI data were analyzed as described previously (3), and ratios of NAA/Cho, NAA/Cr and Cho/Cr were calculated bilaterally for 12 different brain regions in both white and gray matter. Statistical analysis, using the SPSS software package, consisted of uni- and multi-variate linear regression models. The level of statistical significance was set at $P < 0.05$.

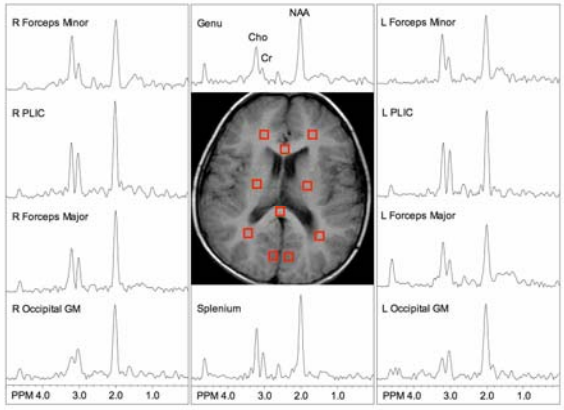

Figure 1. Representative MRSI data from one slice

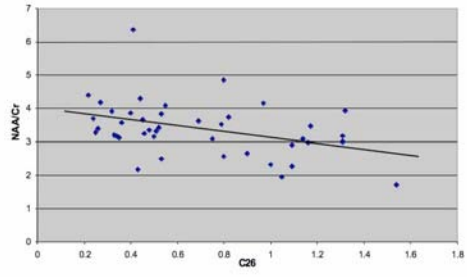

Figure 2. NAA/Cr in the splenium of the corpus callosum versus C26 levels

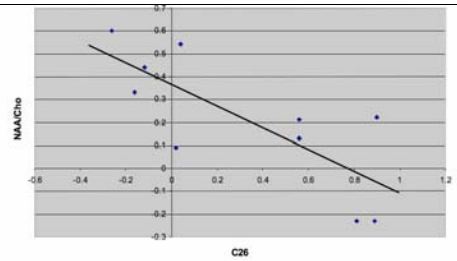

Figure 3. 1-year differences in optic radiation NAA/Cho versus change in VLCFA.

Results

Representative MRSI data in a 6 year old boy with ALD are shown in figure 1. Initial covariate selection showed that the only covariates that might explain changes in C26 were the following: splenium of the corpus callosum NAA/Cr, optic radiation NAA/Cr, and posterior white matter NAA/Cho. In each region, lower metabolite ratios (suggesting lower NAA levels) corresponded to increased C26 levels. Each model shows a p-value less than 0.05. No other metabolite ratio in any gray or other white matter region showed any relationship to C26. A regression plot of splenium NAA/Cr versus C26 is shown in Figure 2.

Figure 3 shows the difference in optic radiation NAA/Cho plotted versus changes in C26 levels one year apart. It can be seen that NAA/Cho increased with age in patients whose C26 levels were stable over time, but was lower (or decreased) in patients whose C26 levels increased with time. In the posterior white matter, Cho/Cr levels also increased in patients whose C26 levels increased over the one-year time period ($p < 0.05$).

Discussion

This study is the first that we are aware of that demonstrates a relationship between brain metabolite ratios and plasma VLCFA levels in asymptomatic boys with ALD. These results indicate that failure to control VLCFA levels leads to reduced levels of NAA (suggesting neuroaxonal damage or dysfunction) in the key brain regions commonly involved in ALD – the splenium of the corpus callosum, and posterior white matter regions. In addition, whereas low C26 levels were associated with normal, age-related increases in NAA/Cho, patients with increasing C26 levels over a 1-year period showed smaller increases or (in two cases) decreases of NAA/Cho in the optic radiations. These data suggest that white matter metabolite levels (in particular, NAA) in key brain regions appear to be adversely affected by elevated VLCFA levels in asymptomatic boys with ALD, and that boys with normal levels of C26 (i.e. those successfully lowered by LO) have more normal metabolism and development. Therefore, it appears that LO has an ongoing, positive effect on brain metabolism in asymptomatic ALD boys when it successfully lowers VLCFA levels. Proton MRSI may have a role in monitoring therapeutic response to LO in boys with ALD.

Acknowledgement

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References

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