

White Matter NAA levels and Very Long Chain Fatty Acid Levels in Asymptomatic Boys with X-linked Adrenoleukodystrophy undergoing Lorenzo's oil therapy

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Introduction

Childhood X-linked adrenoleukodystrophy (ALD) is an inherited disorder in boys that is associated with elevated peripheral levels very long chain fatty acids (VLCFA, in particular particularly hexacosanoate, C26), adrenal gland dysfunction, and (in some cases) acute cerebral demyelination (1). The dietary therapy known as 'Lorenzo's oil' (LO) competitively inhibits VLCFA synthesis, resulting in lower levels VLCFA levels in plasma which is believed to provide a degree of neuroprotection in asymptomatic ALD boys (2). Until recently, however, evidence of any direct effect of LO on the brain was lacking (3). This abstract presents updated results from an ongoing clinical trial of LO, and reports significant associations between VLCFA levels and NAA/Cho and NAA/Cr ratios in key white matter regions in ALD.

Material and Methods

Multi-slice proton MR spectroscopic imaging (MRSI; TR/TE 1700/280 ms, 3 slices, voxel size 0.8 cm³) was performed on 58 asymptomatic ALD boys under 10 years of age, using a transmit-receive head coil at 1.5 Tesla (4). All boys were on LO and are being followed with yearly scans; 27 patients have had two scans to date, 12 have had three scans, and 1 has four scans. 12 patients were considered non-compliant with the LO dietary therapy. Peripheral VLCFA levels (in particular, hexacosanoic acid, C26) were measured within 24 hours of the MRSI examination.

MRSI data were analyzed as described previously (5), 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 consisted of uni- and multi-variate linear regression models. The level of statistical significance was set at P < 0.05.

Results

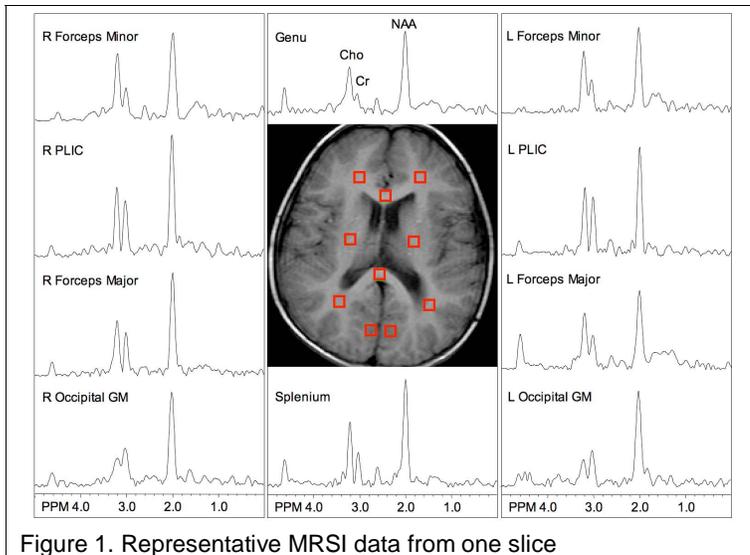


Figure 1. Representative MRSI data from one slice

Figure 1 shows regions of interest used for analysis and representative spectra from the central MRSI slice of one subject. At visit one, VLCFA (C26) levels were 0.785±0.390 (N=58, 46 compliant (0.833±0.411) 12 non-compliant (0.843±0.413)), at visit two, C26 in compliant patients was 0.339±0.101 (N=15) and 0.565±0.140 in non-compliant (N=12), and at visit 3 C26 in compliant patients was 0.347±0.071 (N=8) and 0.813±0.322 in non-compliant (N=4).

Correlation analysis revealed significant negative correlations between C26 and NAA/Cr in posterior white matter (R=-0.293, P=0.025) and splenium of the corpus callosum (R=-0.345, P=0.009). NAA/Cho was also negatively correlated with C26 in posterior white matter (R=-0.379, P=0.003). NAA/Cr showed a trend to negatively correlate with C26 in centrum semiovale (R=-0.244, P=0.065) and visual cortex gray matter (R=-0.191, P=0.063). No other metabolite ratios or brain regions showed any significant correlations with C26.

Discussion

This study confirms earlier results (in a smaller number of subjects (3)) that found significant negative correlations between NAA/Cr ratios and C26, in posterior white matter regions and splenium of the corpus callosum only. This result is intriguing in that these are the regions of the brain that show lesion formation in approximately 80% of cases who develop cerebral demyelination under 10 years of age (6). It appears that these regions may be susceptible to axonal damage/dysfunction associated with elevated VLCFA levels, which can be alleviated by LO. The significance of this finding in terms of predicting lesion formation and clinical outcome remains to be determined.

References

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