Highfield proton MRSI in adult patients with X-linked adrenoleukodystrophy

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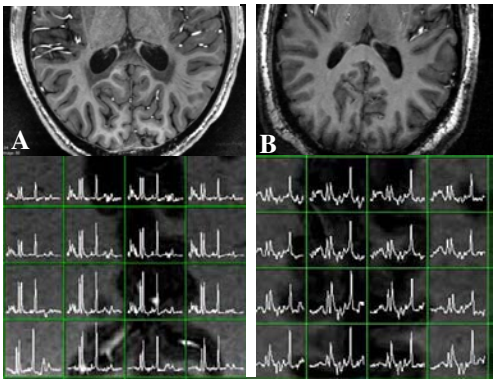
Introduction: In childhood, X-linked adrenoleukodystrophy (X-ALD) may manifest as rapidly progressive inflammatory demyelination. Although it is not possible to predict phenotype by mutation analysis or biochemical assays, multislice proton MRS imaging (MRSI) is able to identify impending or beginning degeneration in white matter that still appears normal on conventional MRI[1]. Single voxel MRS at high field has revealed extensive neurochemical changes in childhood ALD [2]. In adulthood, the disease manifests as adrenomyeloneuropathy (AMN), a spastic paraparesis that is due to a chronic axonopathy of the spinal cord. Most commonly adult patients with X-ALD show symmetric corticospinal tract (CST) lesions that are thought to follow a benign course and lack progression [3]. Nevertheless, approximately 20% of adult patients with AMN develop inflammatory cerebral demyelination in addition [4]. We set out to examine adult patients with X-ALD by proton MRSI and determine whether, beyond the white matter changes, there were metabolic abnormalities in the cortex as well.

Methods: Seven adult patients (5 male hemizygotes, 2 female heterozygotes; mean age: 36±9) with the biochemical defect for ALD and four healthy control subjects (3 male, 1 female, mean age: 34±8) were enrolled in this study. MR imaging and spectroscopy experiments were performed on a 7.0 T MRI scanner (Siemens AG, Erlangen, Germany) using an 8 channel surface coil. The imaging exam included sagittal T2 weighted images and an MPRAGE [resolution 0.6x0.6x1mm^3, TE/TR/TI=3.6/2500/1100, 120 slices] of which the VOI for MRSI was prescribed. 2D proton MRSI spectra were acquired at the levels of the white matter semiovale as well as the cingulate cortex. The VOI was selectively excited using PRESS (TE=35 and/or 50, TR=2000) with CHESS water suppression. The FOV was partitioned into 16 x 16 phase encoding steps. Spectra were processed off-line using the LCModel analysis program to determine quantities of the brain metabolites including N-acetylaspartate (NAA), creatine (Cr), choline (Chod), glutamine and glutamate (Glx), and myo-inositol (MI). [5] Average metabolite ratios of male hemizygotes, female heterozygotes and controls were compared using ANOVA and Holm's t-tests. The analysis was repeated separately for voxels attributed to gray and white matter for noncerebral ALD (NCALD) and cerebral ALD (CALD) as well as controls.

Results: *Gray Matter:* In 4/5 male X-ALD patients we found decreased NAA/Cr in the cortical gray matter compared to controls (p=0.005) and lower values compared to female heterozygotes (p=0.05). No lesions were seen in the cortex of X-ALD patients. Cho/Cr ratios in gray matter of X-ALD patients showed no significant difference compared to controls. *White Matter:* Three patients had lesions within the splenium of the corpus callosum (see Figure 1) and one had a lesion in the CST. We confirm prior reports of decreased NAA/Cr (p=0.01) and increased Cho/Cr (p=0.1) in normal appearing white matter (NAWM) of X-ALD patients [1,6]. Glx was significantly decreased in both gray matter (p<0.0001) and white matter (p=0.028) of X-ALD patients. MI was increased in the NAWM of one CALD patient.



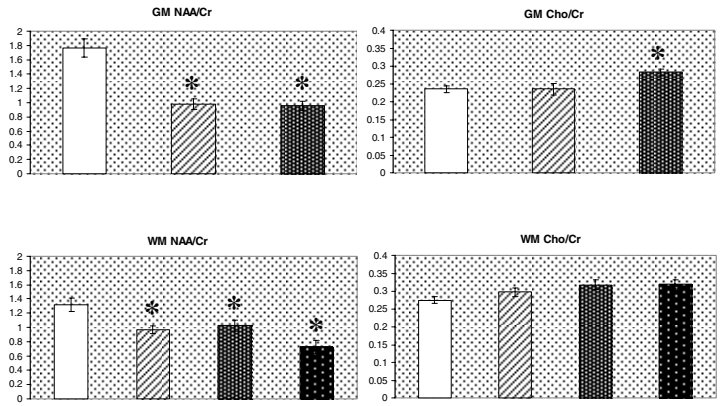


Figure 1 (above). MPRAGE of an adult ALD patient (A) and a normal control (B). A lesion within the splenium is visible in the patient. Proton MRSI shows a decrease in NAA/Cr in cortex and white matter compared to controls. **Figure 2** (left). Differences of metabolite ratios are shown in gray and white matter (GM, WM) in normal controls (white), NCALD (striped) and CALD (dotted). The lesion in CALD is plotted separately (dark with dots).

Conclusions: Our findings of metabolic abnormalities in the cortex may reflect the chronic axonopathy of the CST that is invariably seen in adult X-ALD patients. It may also be a secondary result of longstanding stable lesions within the white matter underlying cortical regions.

Dementia, depression and emotional disturbances are common in male AMN patients as well as female heterozygotes and may be explained by a metabolic derangement in the cortex of X-ALD patients. Highfield MRSI allows for localized biochemical analysis employing short echo time MRS and correlation with high resolution structural imaging.

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