Diffusion Parameters Correlate with Reduced N-Acetylaspartate in Adrenomyeloneuropathy: Evidence of Structural Axonal Damage.

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Introduction: Reduction of N-acetylaspartate (NAA) in Magnetic Resonance Spectroscopic Imaging (MRSI) may reflect a structural abnormality (such as reduced axonal density or reduced viability of neurons), or it may reflect abnormal function of structurally normal neurons. Diffusion tensor imaging (DTI) on the other hand is reflective of structural integrity of axonal tract measured by *in vivo* water diffusivity quantification. The degree to which myelin and axons affect water anisotropy in brain remains a matter of debate. Therefore a combination of DTI and MRSI offers an opportunity to investigate the pathologic process in neurodegenerative disorders We applied this multimodal imaging approach to Adrenomyeloneuropathy (AMN), a chronic neurodegenerative disorder affecting the CNS which on histopathology shows some evidence of distal axonal neuropathy in the brain [1]. Our objective was to investigate the cerebral neurodegenerative process in this disease.

Methods: Multi-slice Proton Magnetic Resonance Spectroscopic Imaging **(**MRSI) was performed on 12 AMN males (Age (yrs) 34.6±7.5) who had normal conventional brain MRI and compared with 19 age matched controls. For proton MR spectroscopic imaging, three oblique-transverse sections were selected [nominal thickness, 15 mm; intersectional gap, 2.5 mm, TR/TE: 2,500/280; field of view, 24 cm; matrix size, 28 x 28; nominal voxel size=1.1 cm, one signal acquired]. DT imaging (2) (Single shot-EPI; TR/TE of 7622/80 ms; max b value=700 s/mm^2; 30 different gradient directions; 2.5 mm resolution; 50 axial slices; 5min 24s scan time per sequence; 3 repetitions] was performed at 1.5 Tesla scanner combined with SENSE (3) technique - sense factor (R) of 2.5, in 8 AMN patients and compared with 8 controls. Data processing for Spectroscopy was done using Peak areas estimation in the frequency domain, with assumption of Gaussian line shapes made by using a simplex routine (4). For DT imaging analysis, four ROIs, namely in internal capsule, corona radiata, parietal and frontal white matter, were selected. Using color-coded orientation map as anatomical guidance, four anatomical locations were identified and ROIs were manually delineated. Mean apparent diffusion coefficient (ADC) and fractional anisotropy (FA) parameters were obtained from four ROIs. Spectroscopy voxels were localized in corresponding regions and metabolite ratios obtained. Logarithmic transformation was performed to fulfill normality assumptions. Pearson's correlation, Student's ttest were performed under parametric assumptions.

Results and Discussion: MRSI: There was a significant reduction of NAA/Cho (1.43±0.19 vs. 1.78±0.55,p=0.04) and NAA/Cr in the parietal white matter (2.3±0.31 vs. 2.8±0.71, p=0.04) with no significant changes in the Cho/Cr ratio. The internal capsule also demonstrated NAA/Cho reduction in AMN vs. Controls (1.31±0.20 vs. 1.67±0.37, p=0.004) and a trend towards NAA/Cr reduction (1.9±0.5 vs. 2.3±0.53,p=0.08). **DTI:** These patients also had significantly lowered FA and no change in mADC in the same regions when compared to age matched controls [5]. **MRSI+DTI**: The parietal white matter demonstrated a logarithmic trend between FA and NAA/Cr (r=0.64, p=0.09) a similar logarithmic trend was between ADC elevation and NAA/Cr reduction (r=-0.66,p=0.07) as well as ADC elevation and NAA/Cho reduction (r=-0.67, p=0.06). In the internal capsule, an inverse logarithmic relationship was seen between ADC and NAA/Cho (r=-0.72, p=0.04). In conclusion, Reductions in NAA provide evidence of axonal impairment in brain of AMN patients despite normal conventional MRI. These findings confer the pathologic reports showing axonal loss with minimal demyelination [1]. This may suggest a neuroaxonal basis of a disease that is currently believed to manifest as an adult onset demyelination in about 20% patients. The most frequently involved parietal white matter demonstrated reduced NAA along with reduced FA that correlated with each other, suggesting that these patients might have axonal damage in this region and also that lowered NAA is not a pure functional deficit in a structurally intact neuron. These findings are in agreement with prior reports that indicate axonal membrane as the prime determinant of anisotropy (6). Serial multi-modal brain-imaging studies may enable greater understanding of evolution of disease process in neurodegenerative disorders such as AMN.

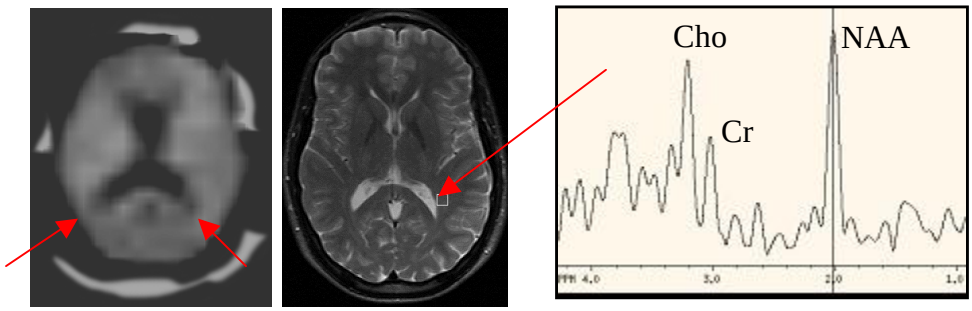

Fig1: Metabolite Map (a) showing periventricular parietal white matter NAA reduction (arrows) in a 37- year old AMN male, with no visible abnormality on T2-weighted MRI (b), spectra from the peri-ventricular white matter of the same patient shows lowered NAA peak relative to choline and creatine peaks. The bright signal around the metabolite map is due to peri-cranial lipid.

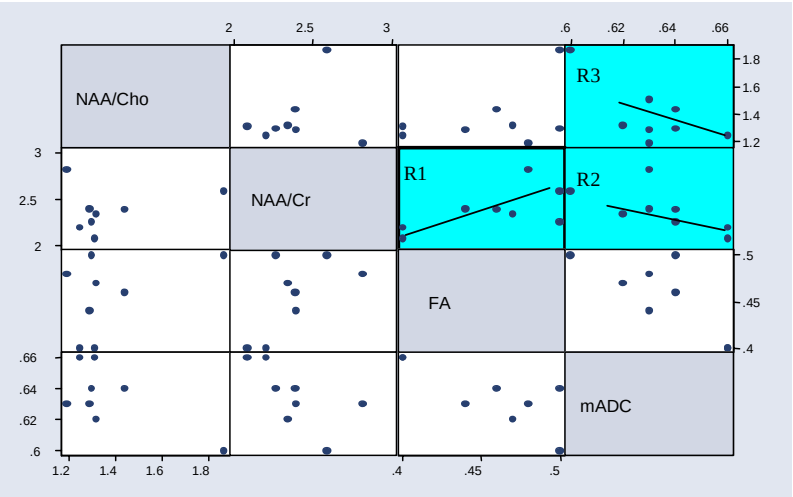

Fig. 2: Scatter plot matrix displaying correlation data points for FA, mADC, NAA/Cho, NAA/Cr, Cho/Cr ratios in parietal white matter. R1 (NAA/Cr and FA), R2 (NAA/Cr and mADC) and R3 (NAA/Cho and mADC) demonstrate the line of best fit.

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