Quantitative Tract Analyses in Adrenomyeloneuropathy: In Vivo Evidence Of Distal Axonopathy

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Background: Adrenomyeloneuropathy (AMN) is a progressive neurodegenerative disorder primarily affecting long tracts of the spinal cord. Post-mortem studies show that the ascending dorsal column is most severely affected in cervical region and descending corticospinal tracts in the thoraco lumbar region. This pattern is consistent with dying back axonopathy unlike Wallerian degeneration in which the axon segment distal lesion dies off [1]. These reports have not been investigated during the course of the disease due to lack of sensitivity of conventional MR techniques to non-inflammatory pathologies of the spinal cord. We employed Diffusion Tensor Imaging (DTI), which enables three dimensional visualization of white matter tracts of the spinal cord, such as corticospinal tracts, and medial lemniscus-dorsal column system. We measured tract specific diffusion parameters to quantitatively assess axonal integrity along trajectory of fibers and sought to detect dying back axonopathy during disease course. **Methods**: Total study population was 44 with 22 patients [11 males and 11 women compared with 22 age and gender matched volunteers]. Conventional MR imaging [axial transverse T2- (3,000/30–100) weighted] and DTI [Single shot-EPI; TR/TE of 7622/80 ms; max b value=700 s/mm2; 30 different gradient directions; 2.5 mm resolution; 3 repetitions] was performed at 1.5 Tesla scanner combined with SENSE technique - sense factor (R) of 2.5. For DTI processing, six independent variables in the DT were calculated from the DT images. Four tracts were reconstructed 3 dimensionally using previously published fiber tracking protocol [2]. Corticospinal tracts (CST) and Medial Lemniscus (trans-synaptic for spinal cord dorsal column) were chosen because they are known to be involved in post-mortem studies. Corpus Callosum fibers (genu and Splenium) were chosen to evaluate if the disease specifically involves long tracts. Multiple parameters were measured along the selected tracts; these included the number of pixels in the tract, average number of fibers/voxel, fractional anisotropy (FA), and mean apparent diffusion coefficient (mADC). Student's t-test was used for statistical evaluation. **Results:** Conventional MRI (T1 and T2 Weighted) was normal in all but 1 patient (mild T2 abnormalities in brain-stem and Internal Capsule). DTI color coded images demonstrate bilateral corticospinal tract atrophy, more severe in distal segments, compared to segments proximal to motor cortex *(Fig 2 and Fig 3b)*. The mean FA was significantly reduced bilaterally in corticospinal tracts in patients compared to controls [***Male Patient vs. Male Controls: Rt. CST: 0.52±0.03 vs. 0.57±0.02, p value=0.004, Lt. CST: 0.52±0.026 vs. 0.57±0.02. p=0.0008] [Female Patients vs. Female Controls: Rt. CST: 0.52±0.03 vs. 0.55±0.02, p=0.03, Lt. CST: 0.52±0.03 vs. 0.52±0.02, p=0.02].*** The mADC was significantly elevated in left CST *(p=0.008)* but not in right CST *(p=0.6)* in patients compared to controls. The number of pixels, and the number of fibers per voxel was significantly reduced in the *Rt. CST, (p=0.0002, and p=0.001 resp.)*. On the left CST the number of pixels were significantly reduced *(p=0.04)*. No significant abnormalities were detected in Medial Lemniscus, Genu or Splenium of the corpus Callosum *(p>0.05)*. **Conclusion:** Results provide *in vivo* evidence of prominent distal axonopathy specific to corticospinal tract in AMN patients. The trans-synaptic part of dorsal column (medial lemniscus) was normal and distal portions of tract were more severely affected. These findings are consistent with dying back pattern[1]. Greater deficits in FA compared to mADC or T2 suggest a prominent non-inflammatory axonal involvement. The lack of prominent involvement of genu or splenium demonstrates relative selectivity towards long tracts. This study suggests lack of sensitivity of conventional MRI in non-inflammatory axonal pathologies. DTI provides additional and tract specific quantitative information, enabling *in vivo* detection of dying back axonopathy extending up to the cerebral hemispheres in AMN patients, who had normal conventional MRI.

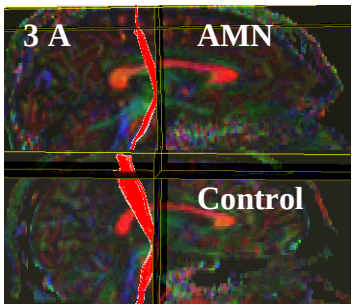

Figure 1: Grossly visible Atrophic Right. CST in 32 year old AMN patient compared to age match control male. Patient had severe spastic paraparesis. Conventional MRI was normal.

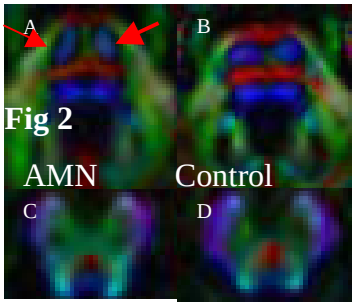

Figure 2: Demonstrating Right sided Corticospinal Tract atrophy in a 32 year old Male AMN patient (A) compared to age and gender matched healthy control (B)) volunteer. Atrophy is also apparent in slice at the level of Cerebral Peduncles (C vs. D).

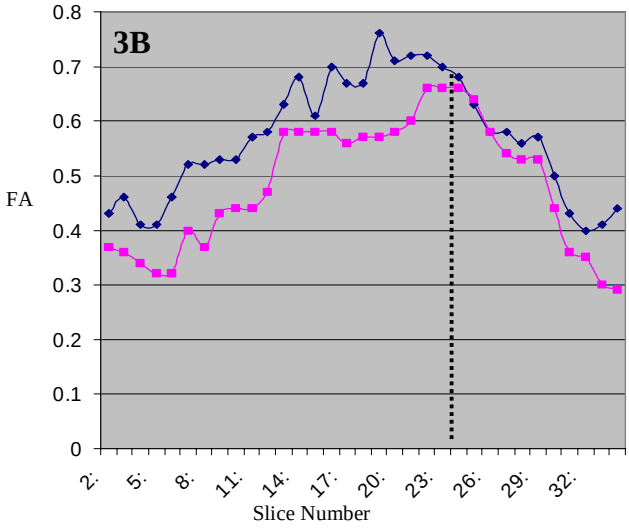

Figure 3B. FA values along the CST of a control (blue) and a patient (pink) show abnormality in lower slices from 2 (Medulla) to 25 (Posterior Limb Internal Capsule).

Dotted line showing the slice level below which the abnormality is more severe

References:

1. Powers JM, et al. Adrenomyeloneuropathy: a neuropathologic review featuring its noninflammatory myelopathy. J Neuropathol Exp Neurol. 2000;59:89-102.
2. Stieltjes B et al. Diffusion tensor imaging and axonal tracking in the human