

Cerebellar tract alterations in PLS and ALS

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Abstract

The cerebellum shows neuropathological change in a number of neurodegenerative conditions where clinical involvement is not the primary feature, including amyotrophic lateral sclerosis (ALS). Whether these changes are associated with disruption to the direct cerebellar tract pathways to the motor cortex and spinal cord in ALS is uncertain. Diffusion tensor imaging was used to examine the integrity of two primary cerebellar pathways, the dentato-rubro-thalamo-cortical (DRTC) and spino-cerebellar (SC) tracts. ALS patients with an upper motor neuron-predominant phenotype (n=9), were matched to a group with the upper motor neuron-only condition primary lateral sclerosis (PLS, n=10) and healthy controls (n=17). Significant alterations across diffusion metrics in the DRTC proximal to the motor cortex were found in both patient groups. PLS patients were found to have an independent diffusion abnormality in the cerebellar region of the DRTC and SC tracts. Disruption to primary cerebellar tracts in PLS is therefore postulated, adding to other markers of its divergent pathogenesis from ALS.

Keywords: amyotrophic lateral sclerosis, primary lateral sclerosis, diffusion tensor imaging, cerebellum

Short Report

MRI has identified progressive cerebellar degeneration in ALS, although typically without overt clinical signs ^{2 3}, perhaps masked by a high burden of corticospinal tract pathology. However, in the rarer upper motor neuron (UMN) only condition of primary lateral sclerosis (PLS), disrupted cerebro-cerebellar connectivity has been specifically identified ⁴.

To investigate the integrity of direct cerebellar pathways to the motor cortex and spinal cord, the dentato-rubro-thalamo-cortical (DRTC) and spino-cerebellar (SC) tracts were examined in a group of PLS and UMN-predominant sporadic ALS patients, alongside healthy controls. UMN burden was used as selection criteria so that differences in observed neural alterations would not simply reflect greater clinical UMN involvement inherent to PLS. A previously validated pathological reflex scale of UMN burden was employed ⁵.

Patients were recruited from the 'BioMOx' cohort (PLS = 10, ALS = 9, healthy controls = 17). All ALS patients fulfilled categories of 'probable' or 'definite' according to revised El Escorial criteria. Groups were matched for: age (mean 60, SD 10.7), years of education (mean 14.9, SD 4), clinical UMN burden [0-15; ALS, mean 13.4 (SD 1.1); PLS, mean 14 (SD 1.6)], and revised ALS functional rating scale score [ALSFRS-R; ALS, mean 33.9 (SD 6.5); PLS, mean 33 (SD 5.7)]. ALS and PLS groups significantly differed in disease duration [ALS, mean years 2.7 (SD 1.9); PLS, mean years 12.2 (SD 8.5)] and disability progression rate [ALS, mean 0.5 (SD 0.2); PLS, mean 0.1 (SD 0.1)]. Whole-brain diffusion images (3T; 60 directions; b-value = 1000 s/mm²; 2 mm³ voxel; 65 slices) were acquired. Scans were preprocessed using FSL and tractography carried out using PROBTRACKX ⁶. The DRTC was reconstructed using masks of the dentate nucleus, and contralateral red nucleus, thalamus, and motor cortex. The SC was

reconstructed using masks placed in the inferior cerebellar peduncle at the upper medulla level of the brain, and in the ipsilateral cerebellar hemisphere at the same axial slice. The DRTC tract was thresholded at 30% and divided into 4 segments based on anatomical landmarks to account for inherent regional variations in diffusivity across the brain. Group differences across diffusion metrics were calculated using ANOVA, followed by planned comparisons of each dependent variable between cohorts using Bonferroni correction.

Diffusivity alterations were detected in the thalamic and motor cortical segments of the DRTC in both patient groups compared with controls (Fig. 1). PLS patients showed independent diffusion abnormality in the caudal cerebellar region of the DRTC and SC (Fig. 2).

----INSERT FIGURE 1----

----INSERT FIGURE 2----

In ALS, structural changes have been detected in the dentate gyrus and cerebellar hemispheres, primarily affecting regions integrated in sensorimotor and executive control brain networks ^{1 3}, becoming more prominent with disease progression ⁷. The changes seen here in the thalamic segments of the DRTC are in keeping with the detection of thalamic pathology mirroring cortical involvement ⁸. Volumetric changes in the cerebellum have not been prominent in PLS studies to date, in contrast to the ‘knife-edge’ pre-central gyrus frequently observed ⁹. White matter abnormalities have however been reported in the middle cerebellar peduncle alongside increased cortical connectivity, primarily with the motor cortices ⁴.

These findings suggest that disruption in afferent and efferent cerebellar pathways is more extensive in PLS than previously recognized, which may have additional value alongside emerging functional connectivity markers of the ALS-divergent pathogenesis of PLS ¹⁰. The

dissociation in white matter integrity along the DRTC and SC in the brain stem region may also reflect more widespread diffusivity alteration as a result of longer disease duration. Clinical cerebellar signs are not a prominent feature of PLS, but a broader spinocerebellar network dysfunction may contribute to the symptom of dysequilibrium in particular. One feature that may be further investigated in relation to cerebellar dysfunction is saccadic abnormality, which is causally regulated by firing of neurons in the dentate nucleus ¹¹. Latency and error rate in saccades during visual search paradigms were significantly elevated in a subset of the current PLS cohort ¹².

The conclusions that can be confidently drawn here are limited by low sample size. The selective comparison using ALS patients with high UMN burden means that the observed dissociation in cerebellar pathways alterations may not be applicable to the broader syndrome of ALS.

Nonetheless, white matter degradation in this sub-group of ALS may be most prominent proximal to the motor cortex along tracts connected to the brainstem in contrast to those with PLS, and supports further investigation of the cerebellum's role in the wider ALS-FTD spectrum

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Authorship

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Figure Legend

Figure 1. Group average representation of the left (blue) and right (red) dentato-rubro-thalamo-cortical (DRTC) tract. The DRTC is split into 4 segments: 1) dentate nucleus – pre-decussation, 2) post-decussation – pre-thalamus, 3) thalamus, 4) post-thalamus – motor cortex. Diffusivity value of the DRTC is shown along each segment in ALS, PLS and control participant cohorts. Significance at $p < 0.05$: *PLS vs control; **ALS vs control; *** PLS vs ALS; *a* PLS vs ALS/Control; *b* ALS vs PLS/control; *c* control vs ALS/PLS.

Figure 2. Group average representation of the left (blue) and right (red) spino-cerebellar (SC) tract. Diffusivity value of the SC is shown along each axial slice in ALS, PLS and control participant cohorts. Significance at $p < 0.05$: *a* PLS vs ALS/Control.