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Differential involvement of corticospinal tract (CST) fibers in UMN-predominant ALS patients with or without CST hyperintensity: A diffusion tensor tractography study

Venkateswaran Rajagopalan[a,b], Erik P. Pioro[c,d,*]

[a] Department of Electrical and Electronics Engineering, Birla Institute of Technology and Science Pilani, Hyderabad Campus, Hyderabad, 500078, India
[b] Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195, United States
[c] Neuromuscular Center, Department of Neurology, Neurological Institute, Cleveland Clinic, Cleveland, OH 44195, United States
[d] Department of Neurosciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195, United States

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ABSTRACT

Diagnosis of amyotrophic lateral sclerosis (ALS) depends on clinical evidence of combined upper motor neuron (UMN) and lower motor neuron (LMN) degeneration, although ALS patients can present with features predominantly of one or the other. Some UMN-predominant patients show hyperintense signal along the intracranial corticospinal tract (CST) on T2- and proton density (PD)-weighted images (ALS-CST+), and appear to have faster disease progression when compared to those without CST hyperintensity (ALS-CST−). The reason for this is unknown. We hypothesized that diffusion tensor tractography (DTT) would reveal differences in DTI abnormalities along the intracranial CST between these two patient subgroups. Clinical DTI scans were obtained at 1.5T in 14 neurologic controls and 45 ALS patients categorized into two UMN phenotypes based on clinical measures and MRI. DTT was used to quantitatively assess the CST in control and ALS groups.

DTT revealed subcortical loss ('truncation') of virtual motor CST fibers (presumably) projecting from the precentral gyrus (PrG) in ALS patients but not in controls; in contrast, virtual fibers (presumably) projecting to the adjacent postcentral gyrus (PoG) were spared. No significant differences in virtual CST fiber length were observed between controls and ALS patients. However, the frequency of CST truncation was significantly higher in the ALS-CST+ subgroup (9 of 21) than in the ALS-CST− subgroup (4 of 24; $p = 0.049$), suggesting this finding could differentiate these ALS subgroups. Also, because virtual CST truncation occurred only in the ALS patient group and not in the control group ($p = 0.018$), this DTT finding could prove to be a diagnostic biomarker of ALS. Significantly shorter disease duration and faster disease progression rate were observed in ALS patients with CST fiber truncation than in those without ($p < 0.05$). DTI metrics of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) were also determined in four regions of interest (ROIs) along the CST, namely: cerebral peduncle (CP), posterior limb of internal capsule (PLIC), centrum semiovale at top of lateral ventricle (CSoLV) and subcortical to primary motor cortex (subPMC). Of note, FA values along the left hemisphere virtual CST tract were significantly different between controls and ALS-CST+ patients ($p < 0.05$) only at the PLIC level, but not at the CSoLV or subPMC level. Also, no significant differences in FA values were observed between ALS subgroups or between control and ALS-CST− groups ($p > 0.05$) in any of the ROIs. In addition, comparing FA values between ALS patients with CST truncation and those without in the aforementioned four ROIs, revealed no significant differences in either hemisphere. However, visual evaluation of DTT was able to identify UMN degeneration in patients with ALS, particularly in those with a more aggressive clinical disease course and possibly different pathologic processes.

Abbreviations: ALS, Amyotrophic lateral sclerosis; cMRI, Conventional MRI; CNS, Central nervous system; CP, Cerebral peduncle; CSoLV, Centrum semiovale at top of lateral ventricle; CST, Corticospinal tract; DTI, Diffusion tensor imaging; DTT, Diffusion tensor tractography; DW, Diffusion weighted; EMG, Electromyography; EPI, Echo planar imaging; FA, Fractional anisotropy; FLAIR, Fluid attenuated inversion recovery; FSE, Fast spin echo; LMN, Lower motor neuron; MD, Mean diffusivity; MR, Magnetic resonance; MRI, Magnetic resonance imaging; PD, Proton density; PLIC, Posterior limb of the internal capsule; PMC, Primary motor cortex; PoG, Postcentral gyrus; PrG, Precentral gyrus; PSC, Primary sensory cortex; ROI, Region of interest; SNR, Signal-to-noise ratio; SS-EPI, Single shot echo planar imaging; SubPMC, Subcortical to primary motor cortex; TE, Echo time; TR, Repetition time; UMN, Upper motor neuron.

* Corresponding author at: Neuromuscular Center, S90, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, United States.
E-mail address: PIOROE@ccf.org (E.P. Pioro).

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disorder with no known cure. Current delay to diagnosis is approximately 12 months from onset of symptoms and only 60% of cases are diagnosed correctly on their initial evaluation (Mitusmoto et al., 1998). Current ALS diagnosis is based on clinical signs and symptoms and by excluding conditions that mimic ALS (Mitusmoto et al., 1998). According to the revised El Escorial criteria (Brooks et al., 2000), ALS diagnosis is based on the presence of both upper motor neuron (UMN) and lower motor neuron (LMN) signs which cannot be explained by other causes. One of the main pathologic hallmarks of ALS is the UMN degeneration of corticospinal tract (CST) from precentral gyrus (PrG) passing through internal capsule to spinal cord (da Rocha et al., 2004). Electromyography (EMG) is an objective test for LMN degeneration, but no easily accessible equivalent test exists to objectively identify UMN dysfunction (Mitusmoto et al., 1998). This can contribute to delays in clinical diagnosis of ALS (Kaufmann et al., 2004). Therefore, there is interest in identifying biomarkers of UMN degeneration in ALS to allow early diagnosis, recognize disease subtypes (which exist phenotypically), monitor disease progression and assess the efficacy of therapeutic interventions.

Even though ALS patients have clinical evidence of both UMN and LMN dysfunction, a proportion of patients begin with UMN abnormalities before developing identifiable LMN signs. Earlier studies have observed that between 17% and 67% (median 40%) of ALS patients with predominant UMN signs have bilateral CST hyperintensity visible on conventional T2-, proton density (PD)-, and fluid attenuated inversion recovery (FLAIR)-weighted images (Mitusmoto et al., 1998). While we too have found a proportion of UMN-predominant ALS patients to have CST hyperintensity, other patients with similar clinical features do not. Of note, UMN-predominant ALS patients with CST hyperintensity are significantly younger (Mitusmoto et al., 1998; Matte and Pioro, 2010), have faster disease progression rate (Matte and Pioro, 2010) and shorter survival period (Matte and Pioro, 2010) compared to those without CST hyperintensity. The reason for this discrepancy is unclear and the underlying pathologic substrate causing these changes is unknown.

Most previous MRI brain studies in ALS have identified such CST hyperintensity qualitatively (i.e. relying on visual evaluation) using conventional MRI (cMRI) such as T2-, PD-, and FLAIR-weighted images (Mitusmoto et al., 1998; da Rocha et al., 2004; Ngai et al., 2007), which is prone to error and does not provide quantitative evidence of underlying neuronal changes causing the signal change. Diffusion tensor imaging (DTI) quantifies the directional movement of water molecules at the microscopic level, which is not feasible with cMRI. Therefore, DTI has been used to non-invasively evaluate pathophysiological changes in the CNS of patients with various neurodegenerative diseases, including ALS (Ellis et al., 1999). An elegant feature of DTI is its ability to reconstruct virtual neural fiber tracts ("tractography"), which is not possible with cMRI techniques.

We objectively identified virtual CST fibers with diffusion tensor tractography (DTT) to determine non-invasively and visually if ALS patients could be distinguished from neurologic controls as well as from each other, depending on the presence or absence of CST hyperintensity identified by cMRI. We hypothesized that the qualitative presence or absence of CST hyperintensity on cMRI would be objectively identified by DTT in the form of truncated virtual motor fibers. Truncation of virtual hyperintense but not non-hyperintense CST fibers would support the presence of different underlying pathological substrates in such UMN-predominant ALS patients and potentially represent differing disease mechanisms.

2. Method

2.1. Patient demographics

2.1.1. Data acquisition

DTI data obtained as part of clinical neuroimaging evaluation were approved by the Institutional Review Board at Cleveland Clinic to be stored and analyzed as de-identified images after patients provided verbal consent. DTI data were obtained in 14 neurological controls (with non ALS-mimic diagnoses indicated in Supplementary Table 1) and in 45 ALS patients with the following clinical phenotypes: UMN-predominant with CST hyperintensity (ALS-CST+) ($n = 21$, 14 male, 7 female, aged 52.3 ± 11.4, mean ± SD), and UMN-predominant without CST hyperintensity (ALS-CST−) ($n = 24$, 13 male, 11 female, aged 58.3 ± 11.4). UMN-predominant ALS patients were those in whom LMN signs were either undetectable, or restricted to only one neuraxial level (bulbar, cervical, or lumbosacral) at the time of MRI. UMN patients with CST hyperintensity were those in whom hyperintense signal was observed along the CST in both T2- and PD-weighted images. Clinical features of ALS patients are given in Table 1.

2.2. Imaging protocol

2.2.1. Diffusion tensor imaging protocol

DTI data were acquired on a 1.5T magnet (Siemens Symphony, Erlangen, Germany) using single shot-echo planar imaging (SS-EPI) sequence along 12 diffusion weighted ($b = 1000$ s/mm^2) directions and one $b = 0$ s/mm^2. Imaging parameters were: 30 slices, 4-mm thick, with 1.9 × 1.9 mm in-plane resolution; pulse sequence parameters were: repetition time TR = 6000 ms, echo time TE = 121 ms, EPI factor = 128, and scan time = 7.54 min.

2.2.2. Field map imaging protocol

Gradient-echo field maps were acquired to correct for geometrical distortion caused by susceptibility artifacts. Field map imaging parameters were: number of slices = 30, slice thickness = 4 mm, slice gap = 4 mm, TR = 500 ms, TEs = 6.11 ms and 10.87 ms.

2.2.3. T2- and PD-weighted imaging protocol

CST hyperintensity was assessed using T2- and PD-weighted images obtained using dual-echo fast spin echo (FSE) sequence whose imaging parameters were: 40 contiguous slices, slice thickness = 4 mm, in-plane resolution = 0.9 × 0.9 mm; TR = 3900 ms, TEs = 26 ms and 104 ms, total scan time = 3.5 min.

2.3. Data processing

DTI images were first corrected for susceptibility artifacts using FSL's FUGUE (Jenkinson, 2003; Jenkinson, 2004; Smith et al., 2004) and then for eddy current distortion effects. The b-matrix was rotated in order to preserve correct orientation information (Leemans and Jones, 2009; Sage et al., 2009). These images were then processed using DTI Studio open software (https://www.nitrc.org/projects/mri_studio/) and DTT of CST was performed in the following manner (Jiang et al., 2006). Virtual neural fibers were reconstructed using the fiber assignment by

Table 1
Clinical parameters of ALS patients.

Clinical measure/ALS subgroups	ALS-CST+ mean ± SD	ALS-CST− mean ± SD	*p*
n	21	24	NS
Age (years)	52.3 ± 11.4	59.5 ± 12.1	<0.05
Symptom duration prior to MRI (months)	9.6 ± 5.5	36.4 ± 44.2	<0.001
ALSFRS-R score	34.6 ± 7.8	34.1 ± 8.1	NS
Disease progression rate	1.38 ± 1.64	0.46 ± 0.43	0.001

Key:
SD - Standard deviation.
ALS-CST+ - ALS patients with predominant upper motor neuron (UMN) signs and hyperintense signal along the corticospinal tract (CST) on conventional proton density (PD) and T2-weighted images and no clinical dementia.
ALS-CST− - ALS patients with predominant UMN signs without CST hyperintensity and no clinical dementia (ALS-CST−).
ALSFRS-R - ALS functional rating score-revised.
NS - Not significant.