Involvement of spinal sensory pathway in ALS and specificity of cord atrophy to lower motor neuron degeneration

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Abstract
Our objective was to demonstrate that ALS patients have sensory pathway involvement and that local cord atrophy reflects segmental lower motor neuron involvement. Twenty-nine ALS patients with spinal onset and twenty-one healthy controls were recruited. Diffusion tensor imaging (DTI), magnetization transfer and atrophy index were measured in the spinal cord, complemented with transcranial magnetic stimulations. Metrics were quantified within the lateral corticospinal and the dorsal segments of the cervical cord. Significant differences were detected between patients and controls for DTI and magnetization transfer metrics in the lateral and dorsal segments of the spinal cord. Fractional anisotropy correlated with ALSFRS-R (p = 0.04) and motor threshold (p = 0.02). Stepwise linear regression detected local spinal cord atrophy associated with weakness in the corresponding muscle territory, i.e. C4 level for deltoid and C7 level for hand muscles. In conclusion, impairment of spinal sensory pathways was detected at an early stage of the disease. Our data also demonstrate an association between muscle deficits and local spinal cord atrophy, suggesting that atrophy is a sensitive biomarker for lower motor neurons degeneration.

Key words: ALS, spinal cord, diffusion tensor imaging, magnetization transfer, atrophy

Introduction
Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by combined effects on upper motor neurons and lower motor neurons. In conjunction with the progressive damage of the corticospinal tract (CST), autopsy cases and animal studies showed involvement of sensory pathways (1,2), which was further confirmed by morphometric measures in the somatosensory cortex (3) as well as functional imaging (4) and structural imaging in the white matter (5). Moreover, electrophysiological measurements in ALS patients showed sensory symptoms and lower amplitude of compound action potential amplitudes of the sural nerve (2,6). Assessing in vivo the damage of the spinal sensory pathway would bring additional insights for understanding the physiopathology of the disease and its various phenotypes.

Magnetic resonance diffusion tensor imaging (DTI) characterizes water diffusion in the white matter and can probe CST degeneration in the brain (5,7–12) and spinal cord (13,14). Notably, Nair et al. found larger DTI abnormalities in more caudal parts of the spinal cord, suggesting that degeneration...
of the CST follows a retrograde pattern (‘dying-back’). Magnetization transfer imaging is sensitive to water bound to macromolecules and correlates with myelin content (15,16), as shown in ALS patients (17,18). While the specificity of DTI and magnetization transfer to white matter pathology is still under debate (19,20), their combination can potentially improve spinal cord assessment (21,22).

In addition to CST impairment, the degeneration of lower motor neurons occurs at various spinal levels, and gives rise to signs and symptoms such as weakness, atrophy, cramps and fasciculations. Detecting local spinal atrophy in metameres corresponding to specific altered muscle might have a significant impact for the future non-invasive detection and objective quantification of lower motor neuron degeneration.

This study combines DTI, magnetization transfer, atrophy measurements in the spinal cord of 29 ALS patients, along with clinical evaluation and electrophysiological measurements. We hypothesized that: 1) patients have sensory pathway involvement that could be detected with MRI; and that 2) local cord atrophy reflects segmental lower motor neuron involvement.

### Material and methods

#### Subjects

Patients with ALS (n = 29, seven females, mean age 53 ± 10 years, median disease duration 1.4 years) and age-matched control subjects (n = 21, 11 females, mean age 52 ± 13 years) were recruited from the Paris ALS Centre and were diagnosed with probable, laboratory-probable or definite ALS according to El Escorial criteria (23). None of the patients had sensory signs or symptoms. Patients had sporadic ALS except for one female and one male with SOD1-linked familial ALS. All patients had spinal onset (upper limb, 16; lower limb, 11; upper limb + lower limb, 2). Exclusion criteria were significant acute and chronic medical condition, significant psychiatric or neurological history (other than ALS for patients) – and standard contraindications to MRI. The local ethics committee of our institution approved all experimental procedures of the study, and written informed consent was obtained from each participant.

Patients were clinically assessed on the day of MRI and scored on muscle testing using the Medical Research Council (MRC) score (see Table I). MRC scores were 8/3 for the deltoid and 6/3 for the pectoralis brevis (median/interquartile). The revised ALS Functional Rating Scale (ALSFRS-R) (24) was also evaluated on the same day. The ALSFRS-R was 38/11.5 (median/interquartile).

#### TMS measurements

TMS was performed on 25 subjects within two weeks of the MRI. One patient died before TMS examination and three patients could not come back for the TMS examination. TMS was performed using a MAGSTIM 200 device, delivering monophasic stimulation through a round coil (9 cm diameter). Subjects had no contraindications to TMS. Responses of hand muscle (adductor digiti minimi) were recorded with surface electrodes using a KPnet system (Natus/ Dantec, Denmark). The stimulation was first applied at the cervical level (C7-D1) to excite the root near its exit from the spinal cord (25). The peripheral conduction time, and the motor evoked potential (MEP) amplitude were measured to assess lower motor neurons impairment. Higher Facilitation Motor Threshold (FMT) has been associated with the degeneration of CST (26). We defined the FMT as the minimal stimulus intensity that evoked a response of at least twice the mean activity amplitude. Intensity was decremented − then incremented − in a 10%-steps paradigm, starting at 100%. The minimal FMT amplitude was selected out of four trials. The FMT was 60/43.12% (median/interquartile).

The latency of the response obtained at FMT enabled measurement of the total conduction time. The central conduction time was calculated by subtracting the total conduction time and the peripheral conduction time. Peripheral conduction time was 13.33/1.59 ms and the central conduction time was 11.91/5.71 ms (median/interquartile).

#### MRI acquisition

Acquisitions were conducted using a 3T MRI system (TIM Trio, Siemens Healthcare, Erlangen, Germany) and a neck/spine coil. For an exhaustive description of the MRI acquisition parameters, the reader is referred to (22).

#### Anatomical

Cord atrophy was assessed using a sagittal T2-weighted 3D turbo spin echo (TSE) with slab selective excitation: 52 slices, field of view (FOV) = 280 mm, TR/TE = 1500/120 ms, voxel size = 0.9 × 0.9 × 0.9 mm³, R = 3 acceleration factor, acquisition time ~6 min.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>5</td>
<td>Muscle contracts normally against full resistance.</td>
</tr>
<tr>
<td>4</td>
<td>Muscle strength is reduced but muscle contraction can still move joint against resistance.</td>
</tr>
<tr>
<td>3</td>
<td>Muscle strength is further reduced such that the joint can be moved only against gravity with the examiner’s resistance completely removed. As an example, the elbow can be moved from full extension to full flexion starting with the arm hanging down at the side.</td>
</tr>
<tr>
<td>2</td>
<td>Muscle can move only if the resistance of gravity is removed. As an example, the elbow can be fully flexed only if the arm is maintained in a horizontal plane.</td>
</tr>
<tr>
<td>1</td>
<td>Only a trace or flicker of movement is seen or felt in the muscle or fasciculations are observed in the muscle.</td>
</tr>
<tr>
<td>0</td>
<td>No movement is observed</td>
</tr>
</tbody>
</table>

### Table I. Medical Research Council (MRC) scale for muscle strength.
DTI. Cardiac-gated DTI data were acquired using a single-shot EPI sequence with monopolar scheme and eight axial slices covering C2 to T2 vertebral levels. Parameters were: FOV = 128 mm, TR/TE = 700/96 ms, voxel size = 1 x 1 x 5 mm³, R = 2, b-value = 1000 s/mm², 64 directions, four repetitions.

Magnetization transfer. 3D gradient echo images with slab-selective excitation were acquired with and without magnetization transfer saturation pulse (Gaussian envelop, duration = 9984 µs, frequency offset = 1200 Hz). Parameters were: axial orientation, 52 slices (covering the same C2-T2 region as for the DTI scans), FOV = 230 mm, TR/TE = 28/3.2 ms, voxel size = 0.9 x 0.9 x 2 mm³, acquisition time ∼5 min for each volume.

Data processing

Atrophy measurement. Cord area was measured on the anatomical T2-TSE images in the middle of vertebral levels C4, C5, C6 and C7 using the semi-automatic method described in (27). The plane perpendicular to the spinal cord was resampled to maximize the accuracy of area measurements (28).

DTI. Motion correction was applied slice-by-slice using FSL FLIRT (29) with three degrees of freedom (Tx, Ty, Rz). Diffusion tensor and its related metrics were estimated voxel-wise: fractional anisotropy (FA), axial (λx) and radial (λr) diffusivities and mean diffusivity.

Magnetization transfer. Gradient echo data with and without magnetization transfer pulse were coregistered using the non-linear algorithm available in FSL (FNIRT). Magnetization transfer transfer ratio was computed voxel-wise following the equation [(S0 − SM) / S0] x 100, where S0 and SM represent the signal without and with the magnetization transfer pulse, respectively.

ROI-based analysis. Regions of interest (ROI) were manually defined on each slice and using geometry-based information (22). To avoid any user bias, ROIs were defined on the T2-weighted b = 0 EPI (for DTI analysis) and on the 3D gradient-echo T1-weighted image (for magnetization transfer analysis). The lateral portion of the cord (including CST) and the dorsal columns were circumscribed from C2 to T2 (Figure 1).

Statistical analysis

Statistical analysis was conducted with Matlab (The Mathworks, MA, USA).

Differences between controls and patients. Gaussian distribution of cord area measurements, DTI and magnetization transfer metrics were assessed within patients and controls using a χ² goodness of fit (p < 0.05). A two-way ANOVA was performed to assess cord atrophy in patients versus controls and to evaluate the effect of vertebral level (C4 to C7). Post hoc analyses used one-tailed t-test, given that ALS patients would exhibit decrease of spinal cord area. Difference in DTI and magnetization transfer metrics between patients and controls was assessed using a linear regression. Metrics tested were: FA, λx, λy, λz, mean diffusivity and magnetization transfer ratio in the lateral and dorsal ROIs. Given that cord atrophy could lead to greater partial volume effect in patients, cord area was added as a regressor.

To investigate whether posterior pathways were also hampered at an early stage of the disease, we selected a subset of 12 patients with early onset (mean age 52 ± 9 years, median/maximum disease duration 9/12.6 months) and 12 age-matched controls (mean age 53 ± 11 years) and re-ran linear regressions in these two sub-populations.

Correlations with clinical disability scores and TMS. Multiple regression analyses (forward-stepwise algorithm) were performed to find the best predictor of...
clinical disability and CST impairment. Dependent variables were: ALSFRS-R, FMT, central conduction time and peripheral conduction time. Predictors were: age, FA, λ₁, λ₂, mean diffusivity, magnetization transfer ratio and cord area. The probability for a predictor to enter the stepwise model was based on a Fisher’s test, with a \( p \)-value set to 0.05.

**Relationship between atrophy level and muscle deficits.** The specificity of atrophy at a given vertebral level in relation to the muscle MRC score and TMS was tested using a stepwise linear regression model. The hypothesis was that deficit of the deltoid muscle (C5 spinal level, equivalent C4 vertebral level) is associated with atrophy at C4 vertebral level and that deficit of the abductor pollicis brevis or adductor digiti minimi (C8 spinal level, equivalent C7 vertebral level) is associated with atrophy at C7 vertebral level. Dependent variables were muscle scores (deltoid and abductor pollicis brevis) and the MEP amplitude (adductor digiti minimi) and predictors were cord area at levels C4, C5, C6 and C7.

**Dying-back versus dying-forward hypothesis.** FA and magnetization transfer ratio were calculated from C2 to T2, in the lateral ROI (14). A relationship between MRI metrics and the vertebral level was tested using Spearman’s correlation. For magnetization transfer ratio, since we disposed of 52 slices – as opposed to eight slices for DTI – we computed the nominal vertebral level by interpolating the C3-T1 region into 52 samples.

**Results**

**Comparison patients/controls**

Table II lists mean cord area for controls and patients from C4 to C7. Two-way ANOVA demonstrated a significant difference between patients and age-matched controls (reduction of cord area in patients, \( F = 27.82, p < 10^{-6} \)) and between vertebral levels (\( F = 40.67, p < 10^{-6} \)). The interaction between population and vertebral level was not significant (\( F = 0.23, p = 0.8 \)). Two-sample one-tailed \( t \)-tests of level-wise analysis revealed significant difference of cord area at C4, C5 and C6 levels (Bonferroni-corrected).

**Figure 2A** shows plots of MRI metrics in the lateral segments. Linear regression between the two populations demonstrated decrease in FA (beta = 0.53, \( p = 2 \times 10^{-6} \)), increase in \( \lambda_1 \) (beta = 7.7 \( \times 10^{-4} \), \( p = 0.005 \)) and decrease in magnetization transfer ratio (beta = 30.4, \( p = 0.008 \)) in patients. No significant difference was detected for \( \lambda_2 \) (beta = 1.9 \( \times 10^{-3}, p = 0.1 \)) and mean diffusivity (beta = 1.1 \( \times 10^{-3}, p = 0.13 \)).

**Figure 2B** shows MRI metrics measured in the dorsal segment (ascending fibres). Linear regression demonstrated significant differences in the dorsal column with a decrease in FA (beta = 0.56, \( p = 0.002 \)) and increase in \( \lambda_1 \) (beta = 7.8 \( \times 10^{-4}, p = 0.02 \)) in patients. The two patients with modified SOD1 mutation-linked familial ALS are circled in red in Figure 2. These two patients exhibited particularly low FA compared to the other ALS patients.

**Correlations with clinical disability and TMS**

Results of stepwise linear regression revealed that FA measured in the lateral segments was the best predictor of the ALSFRS-R (beta = 45.54, StdErr = 20.59, \( p = 0.036 \)) and FMT (beta = -194.09, StdErr = 70.49, \( p = 0.012 \)). No predictor was found for the peripheral conduction time and central conduction time. Figure 3 shows plots and linear line slope of FA versus ALSFRS-R (R = 0.38, \( p = 0.04 \)) and FMT (R = -0.47, \( p = 0.02 \)).

**Cord atrophy and muscle deficits**

Table III shows the results of the stepwise regression analysis that tested the specificity of local spinal cord atrophy to muscle score (deltoid and hand muscle). Spinal cord area at C4 vertebral level was associated with the deltoid MRC score (beta = 0.15, StdErr = 0.06, \( p = 0.017 \)). Spinal cord area at C7 vertebral level (equivalent C8 spinal level) was associated with abductor pollicis brevis MRC score (beta = 0.19, StdErr = 0.06, \( p = 0.005 \)) and adductor digiti minimi MEP amplitude (beta = 0.08, StdErr = 0.04, \( p = 0.048 \)).

**Dying-back versus dying-forward hypotheses**

Figure 4 shows the FA and magnetization transfer ratio (controls/patients) plotted against the nominal vertebral level. Spearman’s correlation demonstrated significant relationship for FA (\( \rho = -0.83, p = 0.015 \)) and magnetization transfer (\( \rho = -0.51, p = 0.008 \)). The negative correlation indicates a decrease of these metrics towards the more caudal segments.

**Discussion**

Multi-parametric MRI of the spinal cord in ALS patients demonstrated: 1) DTI and magnetization...
Spinal sensory impairment and atrophy in ALS

Figure 2. Regression analysis between ALS patients and controls. A. Individual MRI metrics averaged in the lateral (CST) segments of the spinal cord in controls and patients. MTR stands for Magnetization Transfer Ratio. B. Individual plots of MRI metrics averaged in the dorsal columns. The mean is represented as a thick black line and the standard deviation as a light grey rectangle. Group differences were assessed using linear regression (normal distribution). Levels of significance are indicated as: * \( p < 0.05 \), ** \( p < 0.005 \), *** \( p < 0.0005 \). Patients with SOD1 gene are circled in red.

Figure 3. Correlations. A. Plots of ALSFRS-R versus FA. B. Plots of FMT versus FA. Correlation coefficients and \( p \)-values are derived from Pearson’s correlation.

Spinal cord biomarkers in ALS

In ALS, most neuroimaging studies were conducted in the brain (30) and provided non-invasive markers characterizing the involvement of the motor structures classically involved (the CST) as well as non-motor structures (sensory systems). In this study, spinal cord imaging provided additional information on the involvement of the lower motor neurons and central sensory pathways. Using multi-parametric MRI, we quantified the degree of local spinal cord atrophy, which probably reflects the degeneration of lower motor neurons (but not only, as discussed later), and the degree of white matter lesions using DTI and magnetization transfer, which reflect spinal pathways abnormalities. Our results confirm previous DTI studies (13,14) and add further evidence from magnetization transfer measurements. FA was decreased and radial diffusivity was...
Table III. Relationship between muscle deficits and local cord atrophy. p-values (truncated at 2 digits) resulting from multiple regression analyses (stepwise model). Significant values are marked with (*). The best predictor of deltoid deficit is spinal cord atrophy at C4 vertebral level. The best predictor of abductor pollicis brevis deficit and adductor digiti minimi MEP amplitude (from TMS measurement) is spinal cord atrophy at C7 vertebral level.

<table>
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<tr>
<th>Dependent variable</th>
<th>Predictors: Atrophy index</th>
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<tr>
<td></td>
<td>C4</td>
</tr>
<tr>
<td>Deltoid (MRC)</td>
<td>0.01(*)</td>
</tr>
<tr>
<td>Abductor pollicis brevis (MRC)</td>
<td>0.86</td>
</tr>
<tr>
<td>Adductor digiti minimi (TMS)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Increased, suggesting secondary demyelination (31). Relative preservation of axonal architecture might then explain the lack of MD and axial diffusivity changes.

Multiple regression analysis showed significant correlations between FA measured in the lateral segments and both ALSFRS-R and FMT. Correlations were positive for ALSFRS-R and negative for FMT, i.e. lower FA was associated with lower ALSFRS-R (i.e. larger functional deficits) and higher electrical threshold to evoke muscular response with TMS. These results are in line with previous studies reporting that FA in the CST correlates with disease severity (9,12,30). However, correlations with magnetization transfer and with DTI metrics other than FA were non-significant, which may be related to the somewhat lower sensitivity of these metrics compared to FA. This lack of correlation may have also been due to the use of the total ALSFRS-R score, which includes bulbar scores and may therefore be less specific to spinal involvement. However, we performed the same analyses using the ALSFRS-R score without including the bulbar score and have not found any significant MRI predictor. We explain these negative results by the somewhat low specificity of the ALSFRS score and the relatively small population used here.

Despite the relatively high in-plane spatial resolution used here (1×1 mm²), partial volume effect was inevitably present in the lateral and dorsal ROI. The lateral ROI, which aimed at including most of the descending CST, probably included ascending spinothalamic and spino cerebellar tracts. It is possible that the degeneration of the spino cerebellar tract (see next section) partially contributed to MRI differences within the lateral ROI.

Abnormalities in the spinal sensory pathway

Previous studies have shown that neurodegeneration in ALS is not restricted to the primary motor system but also extends to sensory cortical areas (2–5) and to the spino cerebellar system (1,32). At the spinal level, convincing evidence for impairment of central sensory pathways came from autopsy studies (1,2). In patients with ALS, electrophysiological and pathological findings also indicate a pattern of sensory peripheral axonal loss that predominantly affects the large-calibre myelinated fibres (2,6). Our study shows impairment in the dorsal columns, in patients within a year of onset of symptoms. However, none of our patients showed any clinical evidence of proprioceptive, or any other sensory, deficit. The discrepancy between the clinical evaluation and the radiological findings might arise from the fact that MRI is sensitive to abnormalities of a sub-type of fibres related to the amyotrophy, i.e. type Ia fibres originating from muscle spindles. Hence, it is possible that only these fibres degenerated and produced MRI abnormalities, whereas most large fibres remained intact, explaining the absence of sensory symptoms in this cohort. An impairment of the sensory pathways, with a degeneration of the dorsal funiculus, has been detected in an animal model of SOD1-linked ALS (33), and can occur early in the course of the disease (34). Two recent studies in a

Figure 4. ‘Dying-back’ hypothesis. A. FA ratio (control/patient) plotted versus the nominal vertebral level. The ratio increases toward the caudal direction, suggesting larger degeneration toward caudal segments. B. Magnetization transfer ratio (MTR, control/patient) versus the nominal vertebral level. Spearman’s correlation assessed relationship between the two variables. The reason there are more samples in panel B compared to panel A is that MTR measurements are derived from the T1-weighted scans (with and without MT pulse). As opposed to the DTI scans that only have one slice per vertebra, the T1 scans have about 2–3 times more slices per vertebra.
mouse model of another motor neuron degenerative disease, spinal muscular atrophy, demonstrated an early impairment of proprioceptive inputs originating from muscle spindles to motor neurons (35,36). Abnormal somatosensory evoked potentials have also been found in humans (37–41). All these findings support the involvement of sensory neurons and their axonal projections in the central and peripheral nervous pathology of ALS, extending the established concept of a multi-system degenerative process.

In the present study, the two patients having a mutation of the SOD1 gene had a lower FA and magnetization transfer ratio in the dorsal columns compared to the other patients. Those two patients had a classical ALS phenotype and had a combination of upper and lower motor neuron signs, without sensory signs or symptoms. Another DTI study showed different CST involvement in a group of disability-matched SOD1 patients (42). These observations support that atypical sensory signs and symptoms are more frequent in SOD1-linked ALS (43,44). Further studies must be conducted to confirm/deny this possibility.

**Dying-back versus dying-forward hypotheses**

Previous studies investigated whether axonal degeneration in ALS progresses anterogradely (‘dying-forward’) (45–48) or from the extremity to the cell bodies (‘dying-back’ hypothesis) (14,49–51). Here we investigated the pattern of CST degeneration along the cervical spinal cord and confirmed the observation from Nair et al. (14), i.e. FA appeared to be lower at more caudal levels of the spinal cord, with additional evidence from magnetization transfer measurements. Our results are also consistent with the study of Iwata et al. (52), in which the greatest reduction in FA occurred in the distal portions of the intracranial corticospinal tract of ALS patients.

Greater degeneration in more caudal segments of the cord could be explained by 1) neurotoxic events close to the lower motor neuron that invade terminals of the CST and induce a dying back reaction; or 2) a process affecting the cell body in the cortex that might lead to a degeneration of more distal terminals first (53).

**Cord atrophy and muscle deficit**

Atrophy at C5 spinal level was associated with deltoid deficits and atrophy at C8 spinal level was associated with deficits in hand muscles. Although atrophy may partly be explained by degeneration of white matter pathways (via degeneration of upper motor neurons), the specific association between C8 atrophy and MEP amplitude of the adductor digiti minimi provides a strong evidence for grey matter atrophy, given that MEP amplitude obtained after stimulation at the level of C8 nerve root reflects impairment of lower motor neurons, not CST. Our findings suggest that regional spinal cord atrophy as measured using MRI is potentially a sensitive biomarker of anterior horn cell degeneration in ALS. Specificity for grey matter degeneration may come with higher spatial resolution.

**Acknowledgements**

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