Multi-Parametric Spinal Cord MRI as Potential Progression Marker in Amyotrophic Lateral Sclerosis

Mohamed-Mounir El Mendili1,2,3, Julien Cohen-Adad4, Melanie Pelegrini-Issac1,2,3, Serge Rossignol5, Regine Morizot-Koutlidis6, Veronique Marchand-Pauvert1,2,3, Caroline Iglesias1,2,3, Sina Sangari1,2,3, Rose Katz1,2,3, Stephane Lehericy7,8, Habib Benali1,2,3, Pierre-Francois Pradat1,2,3,9*

1 Sorbonne Universites, UPMC Univ Paris 06, UMR CR 2, Laboratoire d'Imagerie Biomédicale, Paris, Ile-de-France, France, 2 CNRS, UMR 7371, Laboratoire d'Imagerie Biomédicale, Paris, Ile-de-France, France, 3 INSERM, U 1146, Laboratoire d'Imagerie Biomédicale, Paris, Ile-de-France, France, 4 Ecole Polytechnique de Montreal, Departement de genie electrique, Montreal, Quebec, Canada, 5 Université de Montreal, GRSMN, Faculty of Medicine, Montreal, Quebec, Canada, 6 AP-HP, Groupe Hospitalier Pitie-Salpetriere, Departement d'Explorations Fonctionnelles Neurologiques, Paris, Ile-de-France, France, 7 Inserm U975, UPMC Univ Paris 6, UMR 5975, CNRS UMR7225, Centre de recherche de l'Institut du Cerveau et de la Moelle epiniere – CRICM, Centre de Neuroimagerie de Recherche – CENIR, Paris, Ile-de-France, France, 8 APHP, Groupe Hospitalier Pitié-Salpêtrière, Service de Neuroradiologie, Paris, Ile-de-France, France, 9 APHP, Groupe Hospitalier Pitié-Salpêtrière, Département des Maladies du système Nerveux, Paris, Ile-de-France, France

Abstract

Objective: To evaluate multimodal MRI of the spinal cord in predicting disease progression and one-year clinical status in amyotrophic lateral sclerosis (ALS) patients.

Materials and Methods: After a first MRI (MRI1), 29 ALS patients were clinically followed during 12 months; 14/29 patients underwent a second MRI (MRI2) at 11±3 months. Cross-sectional area (CSA) that has been shown to be a marker of lower motor neuron degeneration was measured in cervical and upper thoracic spinal cord from T2-weighted images. Fractional anisotropy (FA), axial/radial/mean diffusivities (λ1, λ2, MD) and magnetization transfer ratio (MTR) were measured within the lateral corticospinal tract in the cervical region. Imaging metrics were compared with clinical scales: Revised ALS Functional Rating Scale (ALSFRS-R) and manual muscle testing (MMT) score.

Results: At MRI1, CSA correlated significantly (P<0.05) with MMT and arm ALSFRS-R scores. FA correlated significantly with leg ALSFRS-R scores. One year after MRI1, CSA predicted (P<0.01) arm ALSFRS-R subscore and FA predicted (P<0.01) leg ALSFRS-R subscore. From MRI1 to MRI2, significant changes (P<0.01) were detected for CSA and MTR. CSA rate of change (i.e. atrophy) highly correlated (P<0.01) with arm ALSFRS-R and arm MMT subscores rate of change.

Conclusion: Atrophy and DTI metrics predicted ALS disease progression. Cord atrophy was a better biomarker of disease progression than diffusion and MTR. Our study suggests that multimodal MRI could provide surrogate markers of ALS that may help monitoring the effect of disease-modifying drugs.

Introduction

Amyotrophic Lateral Sclerosis (ALS) is the most frequent motor neuron disease characterized by degeneration of both upper and lower motor neurons. Disease progression is characterized by worsening of weakness and physical disability with a median survival ranging from 2.5 to 3 years [1,2]. There is no curative treatment and the only available neuroprotective drug is riluzole that showed only a modest effect on survival but no evidence of effect on the progression of disability [3]. There is an unmet need for biomarkers in amyotrophic lateral sclerosis, not only for better diagnosis but also to assess disease progression and the effect of disease-modifying drugs in clinical trials (surrogate markers) [4,5,6]. There is an increasing body of knowledge suggesting that new neuroimaging approaches, including diffusion tensor imaging (DTI) and magnetization transfer imaging, may provide promising biomarkers in ALS [7–10].

MRI studies in ALS mostly investigated neurodegenerative changes in the brain and thus only investigated upper motor neuron involvement [11–15]. Spinal cord MRI has the advantage of investigating the two motor system components that are involved in ALS, i.e the lower motor neuron (via gray matter atrophy) and upper motor neuron (via degeneration of corticospinal tract). However, spinal cord imaging has technical limitations due to the small diameter of the spinal cord, physiological motions (respiratory and cardiac movements) and susceptibility artifacts [16,17,18]. Recently, progress in neuroimaging protocols using...
multi-parametric MRI approaches (DTI, MT and atrophy measurement) allowed to detect abnormalities in the cervical cord of ALS patients [10,19–22]. Some metrics being correlated with upper or lower motor neuron involvement as assessed by transcranial magnetic stimulation (TMS) results [10]. Two transversal MRI studies showed a correlation between CSA and clinical disability [10,22]. For MRI metrics to be used as surrogate markers of neurodegeneration, longitudinal studies are mandatory to determine whether these metrics are sensitive to changes over time and correlate with clinical progression. To address this issue we performed a spinal cord MRI longitudinal study in a series of ALS patients.

Materials and Methods

Subjects

Twenty-nine patients with probable or definite ALS were enrolled in the study and underwent a baseline spinal MRI examination (MRI1). A follow-up MRI (MRI2) was performed in 14 of these patients after a mean delay of 11.1 months (±2.7 months). Follow-up MRI was not feasible in other patients due to transportation and MRI examination impossible (n = 1), loss of orthopnea (n = 9), worsening of the general condition rendering follow-up (n = 2), death (n = 2) and refusal (n = 1). The local Ethics Committee of our institution approved all experimental procedures (Paris-Ile de France Ethical Committee under the 2009-A00291–56 registration number), and written informed consent was obtained from each participant. All clinical investigations have been conducted according to the principles expressed in the Declaration of Helsinki.

Revised ALS Functional Rating Scale [23] data were obtained at MRI1, one year after MRI1 in all 29 ALS patients and at MRI 2 for the 14 ALS patients. We calculated an arm ALSFRS-R subscore pertaining to functions such as handwriting, cutting food and handling utensils, and a leg ALSFRS-R subscore (walking, climbing stairs). The patients were also scored on manual muscle testing (MMT) using the Medical Research Council score [24]. MMT was performed at baseline in all ALS patients and at one year in the subgroup of patients who had a second MRI. Seven muscles in each limb were assessed. Information about patients’ demographics and clinical disability are given in Table 1. It includes disease duration, which was defined as the delay between the onset of weakness and MRI examination. Patients were scored on the day of each MRI.

MRI Acquisition

Acquisitions were performed using a 3T MRI system (TIM Trio, Siemens Healthcare, Erlangen, Germany), with a body coil for signal excitation and a neck/spine coil for signal reception. Anatomical imaging was performed at the cervical and upper thoracic levels. DTI and magnetization transfer imaging were performed from vertebral C2 to T2 using the following protocol:

Anatomical data. A sagittal T2-weighted three-dimensional (3D) turbo spin echo (TSE) image with slab selective excitation was acquired. Imaging parameters were: isotropic voxel size 0.9 mm3; FOV = 280×280 mm2; 52 sagittal slices; TR = 1500 ms; TE = 120 ms; acceleration factor = 3; acquisition time ~ 6 min.

Diffusion weighted-imaging. DTI data were acquired using a single shot EPI sequence with monopolar diffusion-weighting scheme. The acquisition was cardiac-gated. Eight axial slices covering C2 to T2 vertebral levels were acquired. Imaging parameters were: voxel size = 1×1×3 mm3; FOV = 128×128 mm2; TR = 700 ms; TE = 96 ms; acceleration factor = 2; b-value = 1000 s/mm2; 64 diffusion encoding directions; 4 averages; acquisition time ~ 15 min.

Magnetization transfer. 3D gradient echo images with slab-selective excitation were acquired with and without magnetization transfer (MT) saturation pulse (Gaussian envelope, duration

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**Table 1.** Patients demographics and clinical features in the whole population and in the subgroup of patients who had a second MRI (mean ± SD).

| Characteristics | At baseline | At follow up |
|-----------------|-------------|--------------|
| **Gender**      | Whole population | Sub-group | Sub-group | Delta | Rate of change |
| Gender          | 9 Females/20 Males | 4 Females/10 Males | – | – | – |
| **Age**         | 53.1 ± 9.8 years | 52.6 ± 11 years | 53.5 ± 11 years | – | – |
| Recruitment period | Feb 2010– Feb 2011 | Feb 2010– Feb 2011 | Jun 2011– Jul 2012 | – | – |
| Disease duration | 26.8 ± 26.9 months | 28.7 ± 27.6 months | 39.8 ± 28.8 months | 11.1 ± 2.7 months | – |
| Site of onset   | 16 Upper; 11 Lower; 6 Upper; 8 Lower | 2 Upper+Lower | – | – | – |
| **ALSFRS**      |              |              |              |              |              |
| Arm (/8)        | 5.00 ± 2.25 | 5.71 ± 2.30 | 2.93 ± 2.89 | −48.75% | −0.25 units/month |
| Leg (/8)        | 4.72 ± 2.47 | 4.93 ± 2.23 | 3.50 ± 2.71 | −28.99% | −0.12 units/month |
| Total (/48)     | 37.14 ± 6.35 | 39.93 ± 6.18 | 30.57 ± 9.40 | −21.47% | −0.76 units/month |
| **MMT**         |              |              |              |              |              |
| Arm (/70)       | 52.90 ± 11.90 | 56.79 ± 11.11 | 45 ± 16.44 | −22.14% | −1.06 units/month |
| Leg (/70)       | 59.72 ± 17.85 | 61.14 ± 16.94 | 53.79 ± 17.13 | −12.03% | −0.58 units/month |
| Total (/140)    | 112.62 ± 23.80 | 117.93 ± 18.29 | 98.00 ± 24.95 | −16.90% | −1.64 units/month |
| **TMS**         |              |              |              |              |              |
| Threshold (ms)  | 68.01 ± 20.82 | 63.65 ± 18.46 | – | – | – |
| Amplitude (mV)  | 1.92 ± 1.38 | 1.63 ± 0.97 | – | – | – |

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9984 µs, frequency offset 1200 Hz). Imaging parameters were: voxel size = 0.9 x 0.9 x 2 mm³; FOV = 230 x 230 mm²; axial orientation with 52 slices (covering the same C2-T2 region as the DTI scans), TR = 28 ms; TE = 3.2 ms; acquisition time ~3 min per volume.

For an exhaustive description of the MRI acquisition parameters, the reader is referred to [25].

TMS Examination

TMS was performed within two weeks of the MRI using a MAGSTIM 200 device, delivering monophasic stimulation through a round coil (9 cm diameter). Responses of hand muscle (adductor digiti minimi) were recorded with surface electrodes using a KNnet 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 [26]. The motor evoked potential amplitude was measured to assess lower motor neurons impairment. The motor evoked potential threshold was measured to assess CST degeneration [27] (Table 1).

Cord atrophy. Cord cross-sectional area (CSA) was measured by an experienced operator on the segmentation technic (i.e. four years experience) on the T2-TSE images in the middle of vertebral levels from C2 to T6 using the semi-automatic method that has been shown to be accurate and with a low inter-observer variability [28,29,30]. The plane perpendicular to the spinal cord was resampled to minimize partial volume between spinal cord and cerebrospinal fluid [31]. To increase reproducibility and accuracy of the used segmentation method, images were segmented by an experienced operator on the technic.

DTI. Data were corrected for motion slice-by-slice using FSL FLIRT [32] with three degrees of freedom (Tx, Ty, Rz). Diffusion metrics were estimated voxel-wise using FSL DTIFIT: fractional anisotropy (FA), radial diffusivity ($\lambda_r$), axial diffusivity ($\lambda_a$) and mean diffusivity (MD).

Magnetization transfer. Gradient echo volumes with and without magnetization transfer pulse were coregistered using FSL FNIRT non-linear algorithm. Magnetization transfer ratio (MTR) was computed voxel-wise following the equation 100 x ($S_0 - S_{MTR}$)/$S_0$, where $S_0$ and $S_{MTR}$ represent the signal without and with the magnetization transfer pulse, respectively.

### Table 2. Results of stepwise linear regressions.

| Predictors          | ALSFRS-R | MMT     |
|---------------------|----------|---------|
|                     | Arm      | Leg     | Total | Arm   | Leg   | Total |
| FA                  | 0.7198   | 0.0003(*)| 0.0393(*)| 0.7766 | 0.1280 | 0.1975 |
| $\lambda_a$         | 0.6664   | 0.4428 | 0.7222 | 0.5399 | 0.1439 | 0.5993 |
| Cord area           | 0.0493(*) | 0.1492 | 0.04142| 0.0193(*)| 0.0434(*)| 0.08317|

Dependent variables were the ALSFRS-R (arm, leg and total scores) and the MMT (arm, leg and total scores) at MRI. Predictors were gender, age, disease duration, site of onset, DTI metrics (FA, $\lambda_a$, $\lambda_r$, and MD), MTR, CSA, TMS measurements (MEP threshold and amplitude). Significant values are marked with (*). Only significant predictors are represented here.

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Figure 1. Regions of interest definition. (A) T2-weighted MRI mid-sagittal slice for an ALS patient. (B,C) T1-weighted data for MTR (B) and mean diffusion-weighted data for DTI (C). (D,E) Defined anatomical ROIs. ROIs were selected in the dorso-lateral (red) aspect of the spinal cord to include most of the CST. (F,G) T2-weighted data before (F) and after (G) cord outlining. A, anterior; I, inferior; L, left; R, right; P, posterior; S, Superior. doi:10.1371/journal.pone.0095516.g001

Table 2. Results of stepwise linear regressions.
Table 3. Results of stepwise linear regressions.

| Predictors | ALSFRS-R |
|------------|-----------|
|            | Arm       | Leg       | Total     |
| FA         | 0.5342    | 0.0022(*) | 0.0002(*) |
| $\lambda_1$ | 0.6667    | 0.1377    | 0.0093(*) |
| Cord area  | 0.0129(*) | 0.7775    | 0.0140(*) |

Dependent variables were the ALSFRS-R (arm, leg and total scores) one year after MRI1. Predictors were gender, age, disease duration, site of onset, DTI metrics (FA, $\lambda_1$, $\lambda_{l1}$, and MD), MTR, CSA, TMS measurements (MEP threshold and amplitude). Significant values are marked with (*). Only significant predictors are represented here. doi:10.1371/journal.pone.0095516.t003

ROI-based analysis. The lateral portion of the cord was delineated manually and using geometry-based information by an experienced operator on segmentation. To minimize bias, these regions of interest (ROIs) were defined on the mean diffusion-weighted images (for DTI analysis) and on the 3D gradient-echo T1-weighted image (for MT analysis) (Figure 1). This method has been shown to be sensitive enough to discriminate changes between sensory (posterior) and motor (lateral) tracks in the context of ALS [10] and spinal cord injury [25]. For an exhaustive description of ROIs definition, the reader is referred to [25].

Statistics

Statistical analysis was performed using Matlab (The Mathworks Inc, MA, USA).

Correlations of MRI metrics with clinical disability at baseline. Stepwise linear regression was used to find the best predictor of clinical disability at MRI1 in all 29 patients. Dependent variables were: ALSFRS-R (total, arm subscore and leg subscore) and MMT. Predictors were: gender, age, site onset, disease duration, FA, $\lambda_1$, $\lambda_{l1}$, MD, MTR, cross-sectional area, MEP threshold and amplitude. 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.

Prediction of clinical disability after one-year follow-up. Stepwise linear regression was used to find the best predictor of clinical disability in all 29 ALS patients one year after MRI1. Dependent variable was: ALSFRS-R (arm, leg and total scores) one year after MRI1. Predictors were gender, age, site onset, disease duration, FA, $\lambda_1$, $\lambda_{l1}$, MD, MTR, cross-sectional area, MEP threshold and amplitude measured at baseline. 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.

Longitudinal MRI Study

Comparisons between baseline and follow-up MRI. Wilcoxon signed rank test was performed to evaluate changes in MRI metrics from MRI1 to MRI2. Correlation between changes in MRI metrics over time and progression of clinical disability. Spearman’s rank correlation coefficient was used to investigate correlations between MRI metrics and rate of change of clinical disability scores, defined as the change of a variable between MRI1 and MR2 scans, divided by the time interval between the two scans.

Results

Correlations of MRI Metrics with Clinical Disability at Baseline

Cord CSA was the only significant predictor associated with the arm subscore of ALSFRS-R ($P = 0.049$) and MMT ($P = 0.019$ for arm and 0.04 for leg scales). FA measure in the lateral segment of the spinal cord was the only predictor of leg subscore ($P = 3 \times 10^{-5}$) and total score ($P = 0.039$) of the ALSFRS-R. Results of stepwise linear regression analysis are summarized in Table 2 (Bonferroni non corrected, significance level $\alpha_{Bonf} = 0.0056$).

Prediction of Clinical Disability after One-Year Follow-up

Results of the stepwise linear regression analysis revealed that the mean spinal cord CSA at MRI1 was the only predictor of the arm ALSFRS-R subscore ($P = 0.015$, Table 3). FA measured at MRI1 was the only predictor of the leg ALSFRS-R subscore ($P = 0.002$). FA, $\lambda_1$ and CSA measurements predicted the total ALSFRS-R score ($P = 3.10^{-3}$, $P_{\lambda_1} = 0.009$, $R_{CSA} = 0.014$). There was no predictor of the decline of the arm or leg ALSFRS-R subscores ($P > 0.05$) (Bonferroni non corrected, significance level $\alpha_{Bonf} = 0.0056$).

Table 4. MRI metrics at baseline and follow-up in ALS patients (mean ± SD).

| MRI metrics          | Baseline | Follow-up | $P$-value | Delta | Rate of change |
|----------------------|----------|-----------|-----------|-------|----------------|
| FA                   | 0.523±0.054 | 0.512±0.048 | 0.168      | –     | –              |
| $\lambda_1$ (×10^{-3} mm²/s) | 0.740±0.128 | 0.782±1.113 | 0.127      | –     | –              |
| $\lambda_{l1}$ (×10^{-3} mm²/s) | 1.740±0.117 | 1.679±0.102 | 0.052      | –     | –              |
| MD (×10^{-3} mm²/s)  | 1.051±0.115 | 1.087±0.098 | 0.068      | –     | –              |
| MTR                  | 33.22±2.51  | 30.00±3.15  | 0.0029(*)  | −9.68%| −0.33 units/month |
| Cord area (mm²)      | 59.7±6.7    | 58.1±6.9    | 0.00085(*) | −2.73%| −0.14 mm²/month |

Significant differences are marked with (*). doi:10.1371/journal.pone.0095516.t004
Comparisons between Baseline and Follow-up MRI

MRI metrics for MRI1 and MRI2 in ALS patients are indicated in Table 4.

The cord CSA decreased in all patients, except in one case, by a mean of 0.14 mm$^2$/month ($P=9.10^{-4}$). Only one patient did not show a decrease in spinal cord area (minor increase of 0.04 mm$^2$/month), within the range of sensitivity of the segmentation method [30]. Furthermore, this patient had a very long disease duration (9 years) and was clinically stable between the two MRI. MTR decreased by 0.33 units/month ($P=0.003$). Figure 2 shows plots of CSA and MTR at baseline and follow-up.

No significant change was detected either for FA ($P=0.168$), $\lambda_{perp}$ ($P=0.127$), $\lambda_{par}$ ($P=0.052$) or for MD ($P=0.068$) (Bonferroni corrected, significance level $\alpha=0.008$).

Figure 2. Comparisons between ALS patients at baseline and follow-up for individual cross-sectional area and MTR in the dorso-lateral aspect of the spinal cord that includes mostly the corticospinal tract. Group differences were assessed using Wilcoxon signed rank test. Levels of significance are indicated as: *$P<0.01$, **$P<0.001$. doi:10.1371/journal.pone.0095516.g002

Figure 3. Correlations between cord area rate of change and the ALSFRS-R arm subscore rate of change and MMT arm subscore rate of change. Correlation coefficients and $P$-values are derived from Spearman's correlation. doi:10.1371/journal.pone.0095516.g003
Correlation between Changes in MRI Metrics Over Time and Progression of Clinical Disability

Results of correlations are shown in Figure 3. The atrophy rate of the spinal cord area (i.e., CSA rate of change) was highly correlated with worsening in clinical functional status, the correlations being higher when considering the arm subscore of the ALSFRS-R ($R = 0.702, P = 0.005$) and the arm subscore of the MMT ($R = 0.717, P = 0.004$). No correlations were detected between the atrophy rate of change and rates of changes in the leg subscore of the ALSFRS-R ($R = 0.376, P = 0.185$), the total ALSFRS-R ($R = 0.481, P = 0.084$), and the leg subscores of the MMT ($R = 0.153, P = 0.601$).

No correlations were detected between the rate of change in MTR and the rates of changes in the arm ALSFRS-R ($R = 0.037, P = 0.914$), leg ALSFRS-R ($R = -0.432, P = 0.184$), arm MMT ($R = -0.059, P = 0.863$) and leg MMT ($R = 0.009, P = 0.979$) subscores (Bonferroni corrected, significance level $\alpha = 0.025$).

Discussion

Results show that spinal cord atrophy and MTR are sensitive markers of the tissue neurodegenerative process in the spinal cord in ALS patients. The cord area at baseline was predictive of the functional ability of the arms after a one-year follow-up duration. Between MRI, and MRL, MTR decreased significantly in the lateral segments of the spinal cord by 0.33 units/month and the cross sectional area decreased significantly by 0.14 mm²/month. Furthermore, the atrophy rate of change was strongly correlated with the rates of change in the arm ALSFRS-R and MMT subscores.

Significant decrease in cord area in ALS patients followed longitudinally was previously reported [20], although no correlation with the ALSFRS score was found. Several factors may explain this lack of correlation in the study of Agosta et al. First, the lower field strength (1.5T versus 3T) might have been associated with lower resolution and/or lower signal-to-noise ratio, yielding less precision in delineating the spinal cord. Second, the present study includes a larger rostro-caudal portion of the spinal cord, which may have increased the sensitivity to detect motor neuron degeneration affecting the ALSFRS score. Third, the follow-up period was shorter (9 versus 11 months in the present study) and patients showed a slower ALSFRS decline (0.5 versus 0.8 in the present study). Finally, variability in the population studied, given the small sample sizes, may also account for the differences. Among our cohort of 29 patients, a follow-up MRI was only feasible in 14 patients. This relatively high level of dropout rate (52%) is common in longitudinal studies in ALS (from 27% to 75%, depending on the duration of the follow-up) [20,33–39]. The development of respiratory insufficiency is a frequent cause of death in ALS patients. Inclusion of respiratory insufficiency rates is a valid surrogate marker of disease progression in ALS. In conclusion, we demonstrated a significant relationship between atrophy rate and disease progression in our cohort of ALS patients. In addition, our results suggest that spinal cord cross-sectional area and MTR are more reliable markers of longitudinal neurodegeneration in the spinal cord compared to DTI metrics such as FA or radial diffusivity. However, neither significant difference nor trends were observed in the diffusion metrics submitted to the same processing (spatial resolution was almost the same for DTI and MTR). Although previous studies introduced atrophy as a confound for isolating the effect of a dependent variable [41], it is often a delicate process due to the high correlation between atrophy and other MRI metrics (not due to partial volume effects, but due to degenerative processes).

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Author Contributions

Conceived and designed the experiments: PFP. Performed the experiments: MMEM PFP. Analyzed the data: MMEM HB PFP. Contributed reagents/materials/analysis tools: MMEM HB. Wrote the paper: MMEM JCA MPI SR RMK VMP CI SS RK SL. PFP. MRI platform availability: SL.

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