Cerebral motor cortex in amyotrophic lateral sclerosis at 7T: morphologic features and clinical correlations

Poster No.: C-2073
Congress: ECR 2015
Type: Scientific Exhibit
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Keywords: Imaging sequences, MR, Neuroradiology brain, Motility
DOI: 10.1594/ecr2015/C-2073

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Aims and objectives

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by upper and lower motor neuron impairment. Phenotypic presentations of the disease are heterogeneous depending on various elements including the body region of symptoms onset, the predominant upper or lower motor neuron involvement and the rate of disease progression [1].

While conventional MRI examination is performed to exclude other pathologies whose symptoms can mimic ALS, recent studies at high magnetic field have reported differences in thickness and signal intensity of primary motor cortex (M1) in patients compared to healthy controls. The thickness of M1 was evaluated using full-thickness measures and its thinning in patients [2-5] seemed to reflect the neuronal loss within the cortex [6, 7]. M1 signal intensity was recently investigated using T2\(^{w}\) Gradient Recalled Echo (GRE) acquisition sequence and was found to be lower in ALS patients than in controls. Ex vivo ultra high field MR acquisition revealed that signal hypointensity was in the deeper cortical layers and seemed to reflect the iron accumulation by microglial cells [7]; this feature was reported as a promising MRI biomarker of ALS thanks to its high sensitivity and specificity [8].

The present study uses high resolution 7T-MRI sequences to investigate in vivo the morphology of deeper layers of M1 in ALS and its correlation with clinical scores.
Methods and materials

Data collection and processing

Thirteen patients with definite ALS according to the El Escorial revised criteria [9] and 13 age-matched healthy subjects (HS) underwent a 7T-MR examination of the brain after giving their informed consent to the enrollment; epidemiological features of patients and HS are shown in Table 1. We used a 7T GE 950 MR system (GE Healthcare Medical Systems, Milwaukee, WI, USA) equipped with a 2ch-tx/32ch-rx head coil (Nova Medical, Wilmington, MA USA). A high-resolution T2*w multi echo GRE sequence targeted on M1 was performed on axial plane in all subjects (parameters were: echo time = 10 ms and 20 ms, repetition time = 500 ms, flip angle = 30 degrees, number of excitations = 2, slice thickness = 2mm, field of view = 112 mm and in-plane resolution = 250 µm).

Deeper layers of M1 were identified as the hypointense layer immediately subjacent to the superficial hyperintense layer. For each cerebral hemisphere thickness and signal intensity of the deeper layers of M1 were measured in four anatomical regions corresponding to Penfield’s area of foot, leg, hand and face (Fig. 1). Signal intensities were normalized with respect to that of the superficial cerebral cortex of left precuneus. Measures of cortical thickness and signal intensities were then averaged to obtain mean values from both cerebral hemispheres.

The same day of MRI exam, patients underwent a neurological examination and three clinical scores were calculated: a score of disease severity according to the ALS Functional Rating Scale-Revised (ALS-FRSr) [10] and a score of upper motor neuron burden (UMN-score) (Table 2); the disease progression rate (DPR) was calculated as (48 - ALS-FRSr)/disease duration (in months) [5].

Statistical analysis

An expert neuroradiologist blinded to clinical status of subjects visually evaluated images on the basis of morphologic criteria. When deeper layers of M1 were pronouncedly thin and hypointense (Fig. 1) images were referred to ALS patients. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy in distinguishing between patients and HS were calculated. Differences in UMN-score between correctly diagnosed and misdiagnosed patients were investigated applying a heteroscedastic t-test.

Quantitative data of cortical thickness and signal intensity of M1 were compared between patients and HS using a paired t-test. In the group of patients, correlations of morphometric parameters (cortical thickness and signal intensity) with clinical scores (ALS-FRSr, UMN-score and DPR) were investigated using Pearson correlation coefficient.
Using the median of DPR as cut-off, patients were divided into two groups: "faster" and "slower" progression rate. A heteroscedastic t-test was applied to investigate differences in morphometric parameters between the two groups.
Table 1: Epidemiological features of patients and HS.

<table>
<thead>
<tr>
<th></th>
<th>ALS patients</th>
<th>Healthy Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>number</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>males; females</td>
<td>10; 3</td>
<td>5; 8</td>
</tr>
<tr>
<td>age range</td>
<td>42–84</td>
<td>40–80</td>
</tr>
<tr>
<td>mean value ± st. dev.</td>
<td>61±12</td>
<td>57±13</td>
</tr>
</tbody>
</table>

Fig. 1: Seven Tesla high resolution GRE images of M1 of one healthy subject (A) and one ALS patient (B). Deeper layers of M1 appear significantly thinner and more hypointense in patient than in HS. In the right columns are reported examples of ROIs and ruler placement for signal and thickness measurement.

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## Table 2: Scale for clinical evaluation of upper motor neuron impairment.

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Results

In patients the average ALS-FRSr was 38 (st.dev.=6) and the average UMN-score was 10 (st.dev.=6).

The reader revealed a signal hypointensity and thinning of the deeper layers of M1 in 9 out of 13 ALS patients and in 3 out of 13 HS.

At subjective visual evaluation the sensitivity, specificity, PPV, NPV and diagnostic accuracy in distinguishing between patients and HS on the basis of morphologic criteria were low (69%, 77%, 75%, 71% and 73% respectively).

The UMN-score was significantly higher in correctly diagnosed patients than in misdiagnosed ones (p=0.002) (Table 3, Fig. 2).

Cortical thickness was significantly lower in patients than in HS (p=0.011) and showed a moderate-strong correlation with UMN-score (R=-0.63) (Table 4, Fig. 3). Cortical thickness had a weaker correlation with DPR (R=-0.30) and ALS-FRSr (R=0.42) (Fig. 3).

Signal intensity did not differ between ALS patients and HS (Table 4).

Signal intensity showed moderate-strong correlations with UMN-score (R=-0.65), DPR (R=-0.71) and ALS-FRSr (R=0.62) (Fig. 3).

Signal intensity in the subgroup of patients with faster DPR was significantly lower than in the slower DPR subgroup (p=0.004), while no significant difference in cortical thickness was found between subgroups (Table 5).
Table 3: UMN-score of patients correctly and wrongly diagnosed after a visual subjective evaluation.

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<table>
<thead>
<tr>
<th>UMN-score (maximum score =33)</th>
<th>patients correctly diagnosed</th>
<th>patients misdiagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean value ± st. dev.</td>
<td>14 ± 9.1</td>
<td>1 ± 1.2</td>
</tr>
<tr>
<td>p-value among groups</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2: High resolution GRE images of misdiagnosed patients resulted false negative. In these ALS patients the deeper layers of M1 (red arrows) were not considered thinned neither significantly hypointense.

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Table 4: Distribution of thickness and signal intensity of deeper layers of M1 among patients and HS.

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<table>
<thead>
<tr>
<th></th>
<th>ALS patients</th>
<th>Healthy Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cortical thickness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean value ± st. dev. (mm)</td>
<td>1.5 ± 0.3</td>
<td>2.0 ± 0.4</td>
</tr>
<tr>
<td>p-value among groups (paired t-test)</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td><strong>Signal intensity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean value ± st. dev.</td>
<td>63.0 ± 11.5</td>
<td>66.7 ± 6.2</td>
</tr>
<tr>
<td>p-value among groups (paired t-test)</td>
<td>0.331</td>
<td></td>
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</table>

Fig. 3: Summary table (A) and scatterplot (B) of correlations of morphological parameters with clinical scores.
Table 5: Distribution of morphological parameters among subgroups of patients with slower and faster DPR.

<table>
<thead>
<tr>
<th></th>
<th>Patients with slower DPR</th>
<th>Patients with faster DPR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cortical thickness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean value ± st. dev. (mm)</td>
<td>1.5 ± 0.3</td>
<td>1.5 ± 0.4</td>
</tr>
<tr>
<td>p-value among groups</td>
<td>0.852</td>
<td></td>
</tr>
<tr>
<td><strong>Signal intensity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean value ± st. dev.</td>
<td>71.9 ± 8.8</td>
<td>55.3 ± 7.1</td>
</tr>
<tr>
<td>p-value among groups</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

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Conclusion

High resolution MRI at 7T demonstrated in vivo that 69% of ALS patients had signal hypointensity of the deeper layers of M1 resembling the ferritin distribution within the activated microglia demonstrated in the cerebral cortex of ALS patients [7].

Subjective diagnosis at visual inspection of high resolution GRE images of M1 was unsatisfactory for the low diagnostic accuracy. Since we revealed a correlation between the M1 hypointensity and the UMN impairment, the capability of the reader to correctly diagnose ALS depends by the grade of UMN impairment in the sample of patients. The low sensitivity of visual inspection is related to the relative spearing of UMN in ALS patients that we misdiagnosed as HS. Summarizing the morphologic appearance of M1 depended not only on the presence of the disease but primarily by the degree of UMN impairment: to a greater UMN involvement seemed to correspond a more hypointense deep motor cortex and quantitative analysis confirmed this hypothesis.

Thickness of deeper layers of M1 was significantly different between patients and HS while signal intensity was not, suggesting that cortical thickness was the more reliable morphologic parameter in the diagnosis of ALS. On the other hand, signal intensity correlated with all clinical scores suggesting that it could be the most suitable morphologic parameter to represent the overall clinical status of patients. Moreover the correlation of signal intensity with DPR and the most pronounced hypointensity in patients with faster disease progression indicated the cortical signal as a promising prognostic marker of disease. Further longitudinal studies are necessary to confirm these preliminary data.

In conclusion, high resolution imaging at 7T allows studying the fine structure of the cerebral motor cortex and could have a role in revealing ALS patients with prevalent upper motor neuron impairment. Further investigation are necessary to assess the role of UHF-MR imaging in monitoring progression rate.
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