

# MR Imaging and MR Spectroscopy in a Patient with Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

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## ABSTRACT

*Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) have been investigated in a single neurodegenerative disease manifesting as either amyotrophic lateral sclerosis (ALS) or frontotemporal dementia (FTD) alone, but have not been examined in combined disorders such as ALS with FTD (ALS-FTD). To our knowledge, this study is the first attempt to demonstrate relationship between MRI abnormalities and MR spectroscopic metabolite changes of the motor cortex, frontal white matter and corticospinal tract in a patient with the diagnosis of ALS with probable upper motor neuron signs (ALS-PUMNS) and FTD. Patient presented underwent MRI of the brain and MRS. The ratio of N-acetylaspartate (NAA) to creatine (Cr), choline to Cr, myo-inositol (mI) to Cr and glutamate-glutamine (Glx) to Cr were derived from peak area measurement. Spectra from the right motor cortex, frontal white matter and corticospinal tract were obtained. MR images were evaluated for sulcus centralis enlargement, corticospinal tract hyperintensity and frontal lobes atrophy. Spectra showed reduced NAA/Cr and Glx/Cr ratio, yet the ratio of Cho/Cr exhibited significant elevation. MR images revealed sulcus centralis enlargement, high signal intensity of corticospinal tract and atrophy of both frontal lobes. Proton spectroscopic metabolic changes in a current patient fully correlate with previously reported MRS metabolic changes in ALS alone. Surprisingly, normal mI (glial marker) values have been found in almost all measured voxels of interest except in the frontal white matter. These findings differ from the previous findings in ALS or FTD alone. In conclusion, these findings support the concept that ALS, FTD and ALS-FTD may represent different manifestations of a single pathological continuum.*

**Key words:** magnetic resonance imaging, magnetic resonance spectroscopy, amyotrophic lateral sclerosis, frontotemporal dementia.

## Introduction

Recent literature provided neuroradiologic<sup>1,2</sup> neurocognitive<sup>3,4</sup> neuropathologic<sup>5</sup> and genetic<sup>6</sup> evidence of possible association between amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). These reports suggest that ALS and FTD represent two points of a single pathological continuum and affect the same neuroanatomic substrate<sup>7,8,9</sup>. Currently, the antemortem diagnosis of ALS is based on a spectrum of clinical, electrophysiological, and sometimes, muscle biopsy findings<sup>10</sup>. The diagnosis of FTD is established by using international clinical criteria<sup>11,12</sup> and supported by electrophysiological findings and brain imaging. There is no definitive diagnostic test for ALS-FTD condition, and the

interest in the diagnostic value of the magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) of the brain in these patients has aroused. Brain imaging and proton spectroscopy have been investigated in a single neurodegenerative disease manifesting as either amyotrophic lateral sclerosis<sup>2</sup> (ALS) or frontotemporal dementia (FTD) alone<sup>13,14</sup>, but no evidence has been reported to demonstrate MRS metabolic changes of the brain in relation with MR signal changes in patient with both ALS and FTD.

In vivo proton spectroscopy studies of the precentral gyrus (motor cortex) regions in ALS patients have shown:

a decrease in the peak area ratio of *N*-acetyl aspartate to total creatine (NAA/Cr)<sup>15</sup>, in the ratio of NAA to Cr plus choline (Cho)<sup>16</sup>, in the ratio of glutamate and glutamine (Glx) to Cr (Glx/Cr), or elevation in the peak area ratio of Cho to Cr ratio and in the ratio of *myo*-inositol to Cr (mI/Cr) in precentral gyrus<sup>17</sup>, motor cortex and cuneus gyrus<sup>2</sup>. So far, no attempt has been made to relate imaging findings and in vivo MR spectroscopic metabolic changes of precentral gyrus, frontal white matter and corticospinal tracts in a patient with both ALS-FTD condition.

## Clinical evaluation

A 54-year-old woman with a negative family history was initially seen for evaluation of upper limb weakness and dysarthria that has developed for a past two years. She completed in teacher degree, married and worked successfully until her early-50s, when she retired. At age 52, she exhibited behaviour changes, apathy, agitation, memory disturbances, disorientation associated with changes in social and personal conduct that has becoming progressively worse. She noticed slurred speech and difficulty with swallowing. Her Mini-Mental State Examination score was 25 of 30. On neurological examination she exhibited euphoria and disinhibition. Cranial nerves examination has shown brisk jaw jerks, slurred speech and tongue fasciculation. Arms were 3/5 and legs 4/5 in strength, more pronounced for the left side. She had triceps muscles fasciculation. Reflexes were normal throughout. Except diminished fine motor coordination, any of other upper motor neuron (UMN) signs have been observed including Hoffmann sign, Babinski sign, clonus or snout reflex. The diagnosis of ALS with probable upper motor neuron signs (ALS-PUMNS) was highly likely. In addition, no clinical signs of sensory loss, sphincter problems, visual disturbances or autonomic dysfunction have been detected. Electromyography revealed acute and chronic denervation. Disease severity was 12 according to the Jablecki et al score<sup>18</sup>. We found significant deficits on the Recognition Memory Test, Wisconsin Card Sorting Test, Consonant Trigrams Test and Block Design Test, Frontal behavioural scale<sup>19</sup>, BEHAVE-AD<sup>20</sup>, Neuropsychiatric Inventory<sup>21</sup>, Frontal Behavioral Inventory<sup>22</sup>. In the absence of neuropathologic findings, neurologist has established the diagnosis of ALS and FTD primarily based on a spectrum of clinical features<sup>10,11</sup> and supported by additional investigations including, neuropsychology, electrophysiology, MR imaging and MR spectroscopy.

## Brain Imaging Studies

All MR investigations were conducted with a 2.0-T MR imager (GE Medical Systems) at the Croatian Institute for Brain Research, School of Medicine, University of Zagreb, Diagnostic Center »Neuron«. A brain MRI protocol included the following: a) T1-weighted spin-echo (SE) sagittal imaging (650/12/1, field of view, 23 cm; imaging matrix, 256 × 256, section thickness, 5 mm); b)

T2-weighted fast spin-echo (FSE) coronal imaging (5600/90; field of view, 23 × 23 cm; imaging matrix, 250 × 296; section thickness, 5 mm); c) T2-weighted FSE axial imaging (8500/2200/126; field of view, 23 × 26 cm; imaging matrix, 252 × 296; section thickness, 5 mm); and d) EPI-SE diffusion weighted imaging (DWI) axial imaging (3000/108; field of view, 37.3 × 23.1 cm imaging matrix, 128 × 128; section thickness, 5 mm). The brain MRI evaluation was followed by the brain MRS study. MRI and MRS were evaluated blind to the conditions of the patient.

MR images were interpreted by one neuroradiologist (G.P) for the following signs:

a) enlargement of the central sulcus on sagittal T1-SE, b) atrophy of frontal and temporal lobes on coronal T2-FSE, c) increased signal intensity within the corticospinal tracts in the posterior limb of the internal capsule at the level of the anterior commissure and hypointensity of precentral gyrus (motor cortex) on axial FSE and DWI.

MR images features in the sagittal T1-SE (Figure 1) sequences show atrophy of the frontal lobes and enlargement of the central sulcus; in the coronal T2-FSE (Figure 2) demonstrate dilated subarachnoid space over frontal lobes signifying atrophy; in the axial T2-FSE (Figure 3) at the level of anterior commissure, increased signal intensity (arrows) was depicted within the right and left corticospinal tracts (within the posterior limbs of both internal capsules); in the axial EPI-SE DWI (Figure 4) show increased signal (lower diffusivity); in the corticospinal tracts at the level of anterior commissure in the axial EPI-SE-DWI (Figure 5) show a curvilinear hypointensity (arrows) in the region of the motor cortex of the precentral gyri.

MRI evaluation that consisted of T2-FSE axial imaging have been followed by the single-voxel proton MRS.



Fig.1. Sagittal T1-weighted spin-echo (SE) image (650/12 with one signal acquired) in a 54-year-old woman with ALS – FTD shows enlargement of the central sulcus (arrow) and atrophy of the frontal lobe. ALS – amyotrophic lateral sclerosis, FTD – frontotemporal dementia.

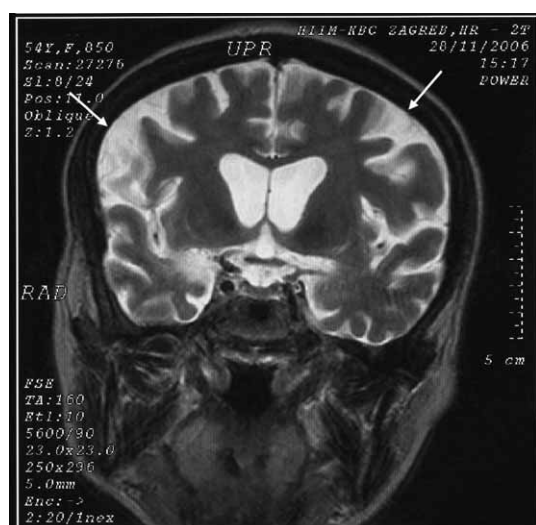


Fig. 2. Coronal T2-weighted fast spin-echo (FSE) images (5600/190) shows frontal lobes atrophy (arrows) more prominent on the right side.



Fig. 3. Axial T2-weighted fast spin-echo (FSE) images (8500/2200/126) shows symmetrical high signal intensity of the corticospinal tracts (within the posterior limbs of both internal capsules) at the level of anterior commissure (arrows).

The single-voxel proton MR spectroscopic studies were performed with a point-resolved spectroscopic sequence, supplied by the manufacturer (1500754). Preimaging required about 4 minutes, and imaging required 8 minutes to obtain each MRS spectrum. Spectra were obtained and analyzed by one observer (G.P.). We used metabolite ratios found in published literature<sup>23,24</sup> and compared with our results of metabolite ratios. This approach seems to be very useful because metabolite ratios are the same measured in any group of controls with any scanner and anywhere, and differ in various diseases. The metabolite ratios were obtained because of the time consuming and technical limitations of the clinical application of quantitative proton spectroscopy<sup>25</sup>.



Fig. 4. Axial diffusion-weighted images (DWI) (3000/108) shows hyperintense corticospinal tracts of the corticospinal tracts (within the posterior limbs of both internal capsules) at the level of anterior commissure (arrows).

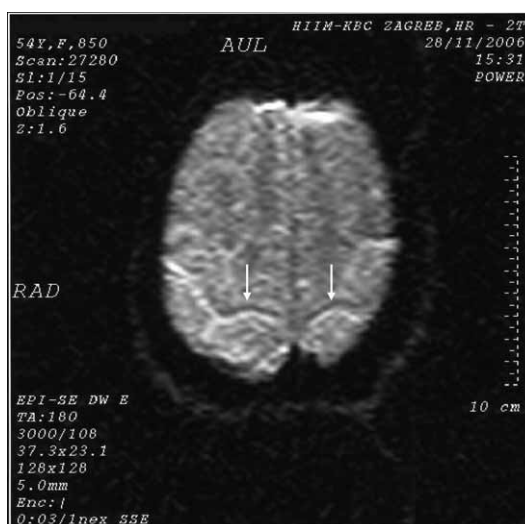


Fig. 5. Axial diffusion-weighted image (DWI) (3000/108) shows a curvilinear hypointensity (arrows) in the region of the motor cortex of the precentral gyri.

Peak area ratios of NAA/Cr, NAA/Cho, Cho/Cr, Glx/Cr and mI/Cr in the right precentral gyrus (motor cortex), right frontal white matter and right corticospinal tract were calculated. Because of limited availability of the MR imager, other voxels of interest (VOI) were omitted, as was the MR imaging study of the cervical spine.

Axial T2-FSE images (8500/2200/126) were obtained, followed by placement of a single 8-cm<sup>3</sup> voxel (2 × 2 × 2 cm) over right motor cortex, right frontal white matter and corticospinal tracts at the level of anterior commissure and cerebral peduncle. MR spectroscopy demonstrated peaks of NAA at 2.02 ppm, Cr at 3.0 ppm, Cho at 3.2 ppm, Glx at 2.1 to 2.5 ppm and mI at 3.5 ppm.

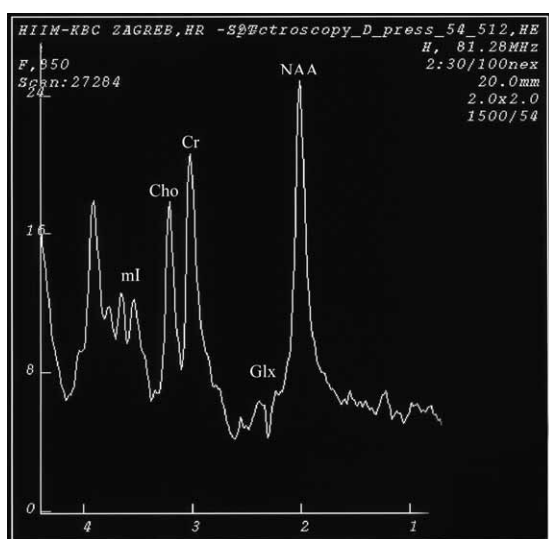


Fig. 6. Magnetic resonance spectroscopy (MRS) of the right precentral gyrus (motor cortex) region. Axial T2-weighted FSE (8500/2200/126) was obtained. MRS demonstrates peaks of NAA at 2.02 ppm, Cr at 3.0 ppm, Cho at 3.2 ppm, glutamate and glutamine at 2.1 to 2.5 ppm and mI at 3.5 ppm. Spectra shows decreased NAA/Cr (10%), Glx/Cr (10%), increased Cho/Cr ratio (32%) and mI/Cr ratios. NAA – N-acetylaspartate, Cr – creatine, Cho – choline, Glx – glutamate and glutamine, mI – myo-inositol.

The first spectrum was acquired from the right precentral gyrus and the peak ratios are printed on the screen, as they appeared in (Figure 6): NAA/Cr = 1.20 (decreased for 10% compared to normal gray matter); Cho/Cr = 0.87 (increased about 32%); Glx/Cr = 0.17 (decreased, 10%); mI/Cr 0.55 (normal). An additional spectrum was acquired from the right frontal white matter and the area peak ratios were (Figure 7): NAA/Cr 0.94 (reduced for 33%); Cho/Cr = 0.95 (increased for 13%);

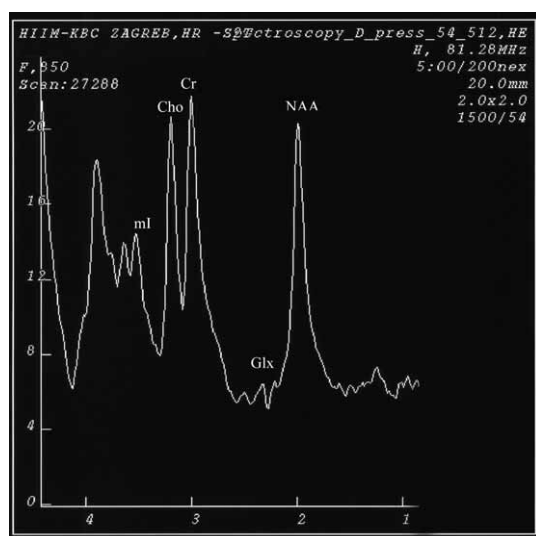


Fig. 7. MRS of the right frontal white matter region shows reduction in NAA/Cr (33%), Glx/Cr ratios (14%), mI/Cr (10%) and increased Cho/Cr (13%) ratio.

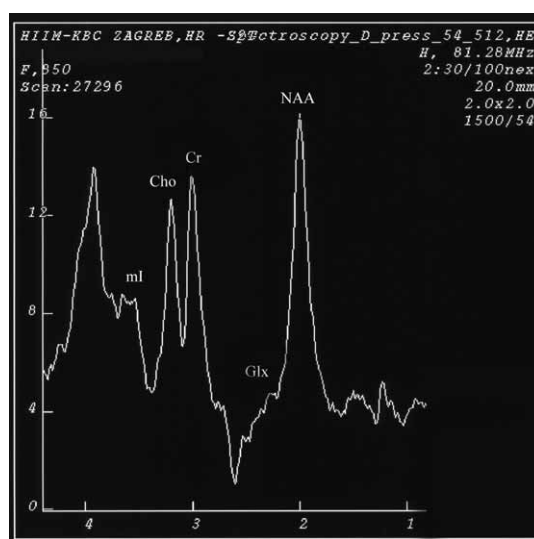


Fig. 8. MRS of the right corticospinal tract region at the level of cerebral peduncle shows reduced NAA/Cr (14%), Glx/Cr ratio (16%), increased Cho/Cr ratio (10%), lower reduction and normal mI/Cr ratio.

Glx/Cr = 0.3 (decreased 14%); mI/Cr = 0.68 (decreased 10%). The area peak ratios from the right corticospinal tract at the level of cerebral peduncle (Figure 8) were: NAA/Cr = 1.18 (decreased for 14%), Cho/Cr (increased for 10%), Glx/Cr (decreased 16%) and mI/Cr = 0.68 (within the normal range). The metabolite ratio of the right corticospinal tract at the level of internal capsule was: NAA/Cr = 1.2 (decreased for 14%); Cho/Cr = 0.9 (decreased for 12%); Glx/Cr = 0.29 (decreased for 10%); mI/Cr = 0.63 (normal).

## Discussion

To our knowledge, this study is the first attempt to demonstrate findings of MRI and MRS of the precentral gyrus, frontal white matter and corticospinal tract at the level of anterior commissure and cerebral peduncle in the patient with ALS-FTD and to determine relationship among results of current techniques.

Brain images were generally consistent with previous findings in ALS<sup>23,24,25</sup>. Conventional MRI excluded brain-stem lesion in the presence of bulbar signs and revealed disproportionate frontotemporal atrophy, enlargement of the central sulcus, hypointensity in the motor cortex (thought to be due to iron deposition) and hyperintense corticospinal tracts (within the posterior limbs of both internal capsules) at the level of anterior commissure and cerebral peduncle. However, absence of unequivocal UMN signs has not correlated with noticeably MRI finding that suggested UMN affection. In contrast to this finding, clinical pattern of FTD reflected the topographic pattern of frontal lobes atrophy visible on MR images.

Slightly reduced NAA/Cr ratio (10%) was detected in the motor cortex location, in the corticospinal tract at the level of cerebral peduncle and anterior commissure (14%) and very much decreased in the frontal white mat-

ter (33%). Because NAA is considered a neuronal marker, our results of decreased NAA/Cr ratio in frontal white matter suggested frontal lobes neuronal degeneration. Because no significant reduction in NAA values has been observed in the motor cortex, these results may be interpreted as evidence of non-significant UMN degeneration and fully correspond with absent clinical signs of UMN affection. Previous studies have shown higher NAA values in the white than in the grey matter in healthy controls<sup>26</sup>. An additional MR spectroscopic abnormality was excess of Cho/Cr ratio, more pronounced in the precentral gyrus (32%) than in the frontal white matter (13%) and corticospinal tracts (10%) at the levels of cerebral peduncle and anterior commissure. Raised Cho in the precentral gyrus of the current patient differs from the results of Gredal and colleagues<sup>27</sup> who found no increase in Cho level, but our results partially correspond with 10% increase in Cho/Cr ratio reported by Block et al<sup>17</sup>. Axonal degeneration, demyelination<sup>29</sup> of subcortical white matter may contribute in higher Cho of precentral gyrus. We found normal level of the mI (glial marker). Normal mI values have been found in almost all measured VOI except in the frontal white matter region where mI/Cr ratio was slightly decreased (10%). These findings differ from the previous findings in ALS or FTD alone. Block et al detected 16% increase in the mI/Cr ratio in the precentral gyrus of ALS patients. Ratio of mI/Cr was not sufficiently raised to bring these results into the range of FTD.

The patient presented in our study is an example of a more difficult case because an additional metabolite abnormality was detected. An astrocyte marker (Glx) was significantly reduced, corresponding with results from previous studies. Perry and colleagues<sup>30</sup> reported that Glx is decreased up to 45%, selectively in the motor cortex of ALS patients. In contrast to this, we found reduced Glx/Cr ratio in the corticospinal tract at the level of internal capsule for 10%; in the corticospinal tract at the level of cerebral peduncle 16%, in the frontal white matter for 14%, and in precentral gyrus (motor cortex) for 10%.

Although cognitive impairment have already been documented in ALS<sup>18,19</sup> and cognitive functioning has been explored in patients with ALS by using a multimodal approach including MRS<sup>9</sup>, no studies examining in vivo the use of MRS for the detection and quantification of neurodegenerative changes in both ALS-FTD has not been performed. Despite of lacking pathologic confirmation, clinical diagnosis of ALS and FTD was firmly established using institutional criteria for ALS and international clinical criteria for FTD, including additional investigations such as neuropsychology, electromyography, electroencephalography and brain imaging (structural and functional). Neuropsychological investigations showed significant impairment of frontal lobes in the absence of severe amnesia and aphasia. These findings strongly support the diagnosis of FTD and fully correspond with findings reported in the literature<sup>12,13,15,20,21</sup>. Although neuropsychological and psychiatric examination is highly specific in determining the cognitive and

behavioral disturbances in FTD, these methods do not provide explanation of mechanisms by which brain is affected in ALS plus FTD.

Because FTD arises when gradual personality change are associated with frontotemporal abnormalities visible on MRI<sup>26,27,28,29</sup> extensive neuroimaging has been performed. On MRI, there was great anterior atrophy of both frontal lobes, more pronounced on the right side.

The MRS study resulted in spectra entirely consistent with the spectral pattern of ALS patients<sup>7,8,9</sup>, but not in FTD. Previous studies showed that spectra obtained from precentral gyrus (motor cortex) are characterized by lower NAA/Cr and Glx/Cr ratios, and increased Cho/mI ratio. In our case, the spectra showed reduced NAA/Cho ratio, prominently in the frontal white matter, decreased Glx/Cr ratio in all VOI, but more pronounced in the corticospinal tract at the level of cerebral peduncle, increased Cho/Cr (32%) especially in the precentral gyrus, and normal level of myo-inositol (mI) in all VOI. Therefore, reduced NAA/Cho ratios suggested significant neuronal loss in the regions examined, decreased Glx/Cr ratio indicated neuronal and astrocyte loss and increased Cho/mI and Cho/Cr ratios suggested diffuse axonal injury. Spectra obtained, deviated the most in NAA/Cr ratio in the frontal white matter, Glx/cr in all measured voxels and Cho/Cr ratio especially in precentral gyrus. In parallel to these findings, there were no similar abnormalities from striatum and hippocampus. Reduced glutamate from motoric and somatosensory cortex and normal level from striatum and hippocampus is finding consistent to ALS, not to dementia disorder<sup>30</sup>. In the presence of normal mI, only decreased NAA/Cr ratio brought this case into range of dementia of non AD type, whereas the FTD was more likely.

One of the drawbacks of this study is that neuropathologic confirmation was lacking and a very small sample (only one patient), limited detection of statistically significant changes between patients. Nevertheless, the clinical diagnosis was firmly established using established international clinical criteria.

## Conclusion

Conventional, MRI and MR spectroscopy represent powerful diagnostic techniques for assessing neurodegeneration in ALS-FTD condition by monitoring the biochemistry of the brain. Proton spectroscopy may represent more specific methods for detecting UMN or LMN (lower motor neuron) degeneration in ALS than MR imaging, taking into account presence and severity of clinical UMN and LMN signs. By comparing the MR spectra of the present patient, we confirmed the findings of the previous reports investigating exclusively ALS patients. We provided new observations regarding MR spectroscopic metabolic changes in both ALS and FTD that was fully consistent with MR spectroscopic pattern in ALS alone. In addition to the previous studies, we found decreased Glx in precentral gyrus, as well as in the frontal white matter and corticospinal tract. We presumed that

it may be demonstrated in a large sample, that ALS-FTD patients can be separated from controls with a high sureness using combined MRI and MR spectroscopic techniques. However, much additional work is needed to identify relationship among the results of MR imaging and MR spectroscopy taking into account severity of clinical UMN and LMN signs. An alternative imaging techniques, such as diffusion tensor imaging (DTI) and magnetic transfer ratio (MTR) may help to overcome the

drawbacks of the combined MRI and MRS results. To detect statistically significant changes between ALS-FTD patients and among ALS subgroups, a larger sample size of patients need to be used. A more comprehensive model in a diagnosing ALS-FTD condition is needed by involving combined MRI and MRS. Additional research using MRI, fMRI and MRS is underway in our Centre to support antemortem diagnosis of ALS-FTD patients.

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## MAGNETSKA REZONANCIJA I SPEKTROSKOPIJA MAGNETSKOM REZONANCIJOM U PACIJENTICE S AMIOTROFIČNOM LATERALNOM SKLEROZOM I FRONTOTEMPORALNOM DEMENCIJOM

### SAŽETAK

Brojne su studije istraživale upotrebu magnetske rezonancije (MRI) i spektroskopije magnetskom rezonancijom (MRS) u dijagnostici pojedinačnih neurodegenerativnih bolesti, kao što su amiotrofična lateralna skleroza (ALS) ili frontotemporalna demencija (FTD) pojedinačno, ali ne i u kombiniranim stanjima kao što je amiotrofična lateralna skleroza udružena s frontotemporalnom demencijom (ALS-FTD). Prema našim spoznajama, ova studija je prvi pokušaj usporedbe strukturalnih abnormalnosti motoričkog korteksa, bijele tvari čeonog režnja i kortikospinalnog trakta pomoću konvencionalnog MRI-a i metaboličkih promjena istih struktura mozga pomoću MRS u pacijentice kod koje je dijagnosticirana ALS s vjerojatnom degeneracijom gornjeg motoričkog neurona udružene s FTD. Kod pacijentice je učinjen MRI mozga i naknadno MRS. Dobiveni su spektri iz područja motoričkog korteksa, bijele tvari čeonog režnja i kortikospinalnog trakta, a potom izračunati omjeri N-acetil aspartata (NAA) i kreatinina (Cr); kolina (Cho) i Cr; myo-inositola (mI) i Cr te glutamata i glutamine (Glx). Analizirane su MRI snimke prvenstveno na prošireni centralni sulcus, povišen signal u području kortikospinalnog trakta i atrofiju čeonih režnjeva. Spektar je pokazao snižene omjere NAA/Cr i Glx/Cr, dok je omjer Cho/Cr bio povišen. MRI je otkrio proširen centralni sulcus, povišen signal u području kortikospinalnog trakta i atrofiju čeonih režnjeva. MRS u prikazane pacijentice korelira s rezultatima prethodnih studija ALS, ali ne i FTD. Naši rezultati podupiru koncept da ALS, FTD i ALS-FTD predstavljaju različite manifestacije jedinstvenog patološkog kontinuuma.