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Diffusion tensor imaging in early amyotrophic lateral sclerosis using 3T magnetic resonance imaging

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Abstract

Objective: Amyotrophic lateral sclerosis (ALS) is a multisystem condition which impairs white matter, corticospinal tract and frontotemporal functions including cognition and behavior. This study aimed to perform diffusion tensor imaging (DTI) to detect white matter microstructural abnormalities, and also understanding the pathophysiology in ALS using 3T magnetic resonance imaging.

Methods: The study examined 12 patients (7 males, 5 females) with sporadic ALS and 10 subjects in the control group (7 males, 3 females) by voxel-based analysis of DTI with 3T MRI. We compared fractional anisotropy (FA) and apparent diffusion coefficient (ADC) parameters in the corticospinal tracts among patients who had ALS and those in the healthy control by DTI region of interest (ROI) and tractography techniques.

Results: The FA and ADC measurements of the patient group were respectively 0.638±0.041 and 0.350±0.01 ($p<0.001$). The results of the healthy control group were respectively 0.701±0.054 and 0.288±0.027 ($p<0.05$). DTI showed decreased fractional anisotropy in bilateral corticospinal tracts and internal capsule posterior crus. There was a correlation between the FA reductions in this region and the severity of the disease in the patients with ALS.

Conclusion: Consequently, with this longitudinal DTI study, the progress of upper motor fiber degeneration in ALS was demonstrated. It may be useful to utilize DTI to monitor the progress and effectiveness of treatment interventions, as well as understanding the pathophysiology of ALS.

Keywords: Amyotrophic lateral sclerosis, diffusion tensor imaging, magnetic resonance imaging

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative condition described by motor neuron loss and axonal degeneration, demyelination, and reactive gliosis in the primary motor cortex, brain stem, and spinal cord anterior horn (1-6). Oxidative damage, mitochondrial dysfunction, defects of axonal transport, aberrant RNA metabolism, and glutamate excitotoxicity are the putative mechanisms of neuronal damage (7, 8). The highest occurrence of the disorder happens in the age range of 50-75 years. The average survival is about 3 years (8).

It is not possible to demonstrate the characteristic or pathognomonic changes showing loss of upper motor neurons in ALS by conventional magnetic resonance imaging (MRI) (1). Advanced MRI methods such as diffusion tensor imaging (DTI), were demonstrated to be more effective in showing early degenerative changes in ALS (1-6, 9-12).

Diffusion tensor imaging allows measurement of the random diffusional movements of molecules of water and provides the determination of the structural and orientation features of white and gray matter (8, 12-15). Fractional anisotropy (FA) is a quantity of water diffusion directionality. The microstructure alterations associated with ALS may change

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water diffusion characteristics, which can be detected with FA measurements. Regions in the brain are connected to each other as a network, affecting each other significantly (8, 12, 13, 15). As an advanced MRI technique, DTI allows us to demonstrate the network and connections of the brain. Also, recent studies have elucidated the brain as a complicated structure that consists of regions that interact with each other (8, 12, 13, 15-18). Local upper motor degeneration may have prevalent effects on the network in the brain. Recently, studies on DTI showed decreased FA values along the corticospinal tract (CST), and non-motor gray and white matter areas and temporal regions in the corpus callosum of patients with ALS (7, 9, 11, 14, 16, 18).

Fractional anisotropy reduction in the CST may be a special biomarker of ALS. This study aimed using 3T MRI to perform DTI for detection of early white matter microstructural abnormalities in ALS.

METHODS

Twelve patients (7 males and 5 females; mean age: 53.5 years, age range: 34-71 years, mean duration of disease: 18.9 months, disease duration range: 6-24 months) who had definite, sporadic ALS defined as a score of ≥20 on the revised ALS Functional Rating Scale (r-ALSFRS) and the El Escorial criteria, were included in the study. Ten healthy individuals (7 males, 3 females) without any history of neurologic or psychiatric disorders were selected as controls. Before MRI imaging, the r-ALSFRS questionnaire was administered by neurologists with 5 years' experience of evaluating patients with ALS. Involvement of lower motor neurons (LMN) and upper motor neurons (UMN) was assessed by totaling the number of pathologic signs. Bulbar onset was seen in seven patients and spinal (lumbar or cervical) onset was seen in five patients (Table 1).

The study was permitted by the Local Board of Institutional Review, and informed consent was signed by all subjects before the MRI examination.

MRI acquisition: Conventional sequences and voxel-based analysis of DTIs were obtained using a 3T system (3T Intera Achieva, Philips Medical Systems, Best, the Netherlands) with 30 mT/m as the maximum gradient amplitude, a slew rate of 150 T/m/s, and an 8-channel SENSE head coil. Axial images of fluid-attenuated inversion recovery (FLAIR) were acquired using the following values: TR: 11000 ms, TE: 125 ms, TI: 2800 ms, Turbo factor: 27, EPI factor: 1, NSA: 1, FOV: 240 mm, slice thickness: 4 mm, slice gap: 1.0 mm, ACQ: 0.65/0.92/5.00, REC: 0.45/0.45/5.00, number of sections: 28, RFOV: 80%, matrix size: 264/512.

DTI images were obtained with following parameters: flip angle; 90 slab thickness; 2.5 mm, 60 axial slice, diffusion encoding gradients applied in 32 noncollinear directions (b: 0 and b: 800 s/mm^2) TR: 10000 ms, TE: 53 ms, EPI factor; 67, NSA: 1, FOV: 240 mm, slice thickness: 2.5 mm, slice gap; 0.0, ACQ: 1.88/1.90/2.50, REC: 0.94/0.94/2.50, number of slice; 60, RFOV; 100%, matrix size: 128/256, total slice number: 2040.

Post-processing and quantitative DTI analysis: We assigned the DTI data to a workstation and used a manufacturer-supplied

Table 1. Patients' demographic and clinical features, and UMN and LMN scores summarized

Patient Number	Sex	Age	Disease Duration (Months)	El Escorial Score	r-ALSFRS	First Symptom score Level	LMN score	UMN
1	F	57	18	3	38	spinal	5	1
2	F	42	9	3	41	spinal	3	0
3	M	49	6	5	44	bulbar	1	0
4	M	55	24	2	34	bulbar	5	1
5	M	54	10	5	31	spinal	4	1
6	F	45	20	3	42	spinal	2	0
7	M	71	24	1	34	bulbar	5	1
8	M	34	18	1	25	bulbar	5	1
9	M	65	24	1	33	bulbar	5	1
10	F	61	24	2	37	bulbar	3	0
11	F	68	24	1	34	spinal	6	1
12	M	41	24	2	44	bulbar	3	1

EEC: El Escorial Criteria; r-ALSFRS: revised ALS Functional Rating Scale; LMN: Lower motor neuron; UMN: Upper motor neuron; LMN score: Lower motor neuron score; from 7 (normal speech and swallowing) to 0 (maximal bulbar dysfunction)
UMN signs: 0 absent, 1 present

Figure 1. a-c. Images obtained from reference healthy/normal subject, normal DTI map and FA, ADC measurements of the internal capsule posterior limb b=0 (a), Fractional anisotropy and directions (b), Fractional anisotropy maps (c).

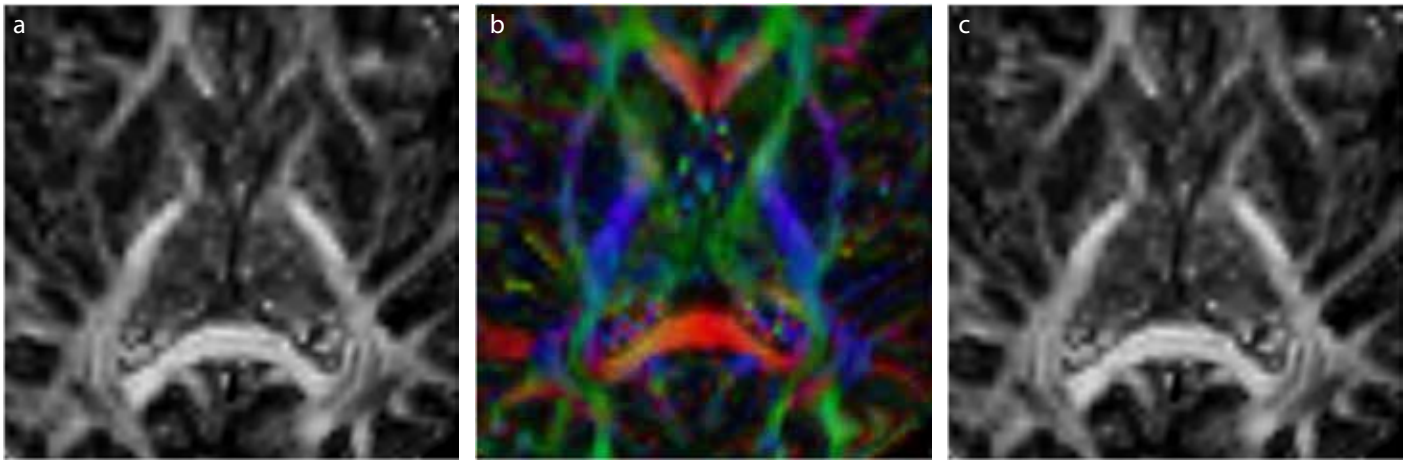
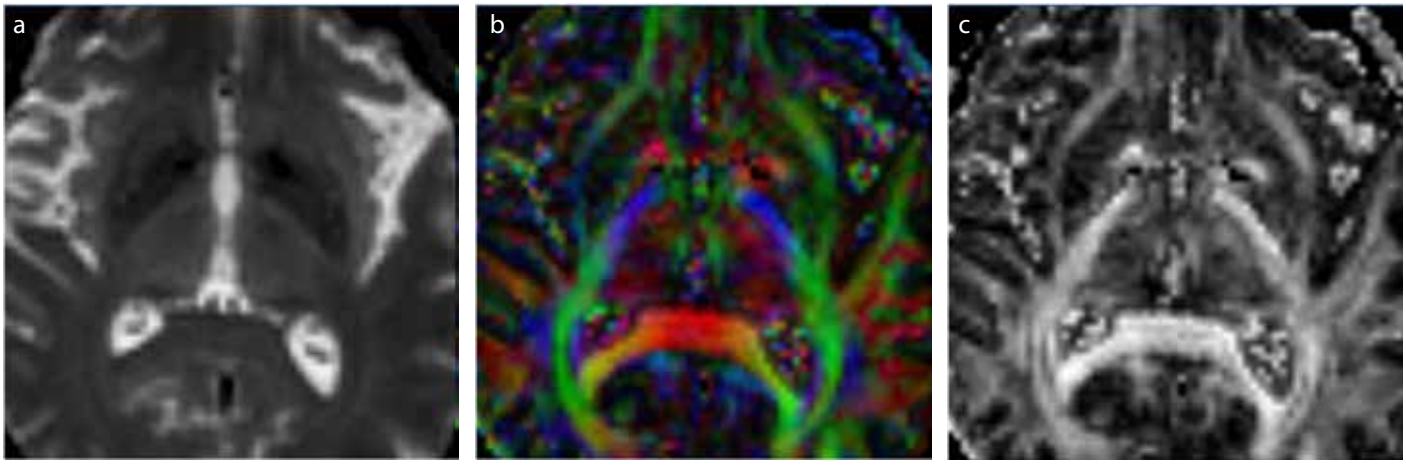


Figure 2. a-c. A right-handed 42-year-old woman was admitted with excessive fatigue, weight loss, and weakness of the hands and arms, which she had had for the last 1 year b=0 (a), Fractional anisotropy and directions (b), Fractional anisotropy maps of the bulbar-onset patient with ALS (c). This patient had rapidly progressive symptoms. There was a significant decrease in fractional anisotropy of the posterior limb of internal capsule (2b) compared with healthy control group (1b)



software (PRIDE, Philips Medical Systems, Best, The Netherlands) for measurements. We compared the FA and apparent diffusion coefficient (ADC) values of the corticospinal tracts (from internal capsule posterior crus, pons, pyramid, and spinal cord levels) between ALS patients and healthy subjects.

Tractography was performed by a radiologist and a radiology technologist with 5 years of DTI post-processing experience. We obtained color-coded maps in the axial plane. We then placed circular regions of interest (ROIs) in the CST based on the information in the axial color-coded maps.

The Statistical Package for the Social Sciences, version 13.0 (SPSS Inc.; Chicago, IL, USA) was used for statistical analyses. The patients' DTI, FA, and ADC values were compared between the ALS and healthy control groups. The FA and ADC values of the CST were compared using student's t-test. The groups were compared based on age and the duration of symptoms using Pearson's correlation test, and functional scales (El Escorial criteria and r-ALSFRS scale), UMN, and LMN findings. The level of significance was accepted as $p<0.05$ for all tests.

RESULTS

Hyperintensities were detected bilaterally along the CST in the FLAIR and T2-weighted images of 4/12 (33%) patients with ALS. There was no signal abnormality or significant alteration of the control group's FA and ADC values. Figure 1a, 1b and 1c show normal FA and ADC values and color map.

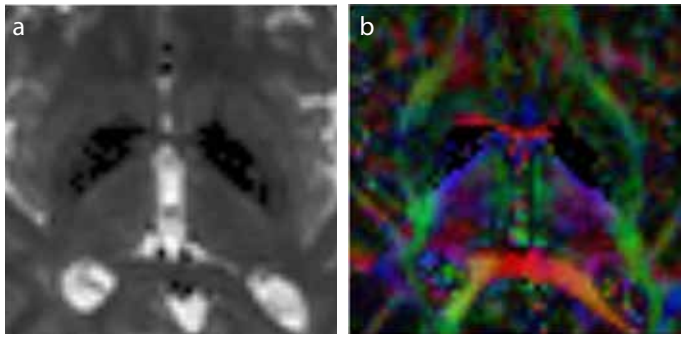
Within the patient group, there was a significant correlation with symptoms/disease duration and upper and lower motor neuron scores ($p<0.05$). Statistical analysis indicated a strong correlation with El Escorial criteria, r-ALSFRS, and disease duration ($p<0.001$). Bulbar onset was the most exhibited level (Table 1-2 summarize clinical findings, severity of disease, and FA and ADC values of the internal capsule posterior crus for each patient).

Table 2. Right, left side, and average FA and ADC values of the internal capsule posterior crus

	Right				Left				Average	
Patient Number	Mean FA	SD FA	Mean ADC	SD ADC	Mean FA	SD FA	Mean ADC	SD ADC	FA	ADC
1	0.643	0.106163	0.341904	0.032715	0.719685	0.116348	0.342791	0.047578	0.681164	0.342348
2	0.629	0.138725	0.342701	0.082672	0.576915	0.225956	0.348051	0.11179	0.602758	0.345376
3	0.627	0.116117	0.363319	0.02583	0.699232	0.118315	0.353946	0.034851	0.662995	0.358633
4	0.628	0.08772	0.347195	0.026133	0.587568	0.112927	0.39895	0.034851	0.607765	0.373073
5	0.674	0.053598	0.368957	0.021541	0.694575	0.19114	0.2992	0.069142	0.684237	0.334079
6	0.566	0.140047	0.355325	0.032834	0.61865	0.111609	0.338326	0.018534	0.592321	0.346826
7	0.749	0.068998	0.357347	0.029479	0.680632	0.075799	0.356997	0.034866	0.714587	0.357172
8	0.705	0.110704	0.337346	0.052784	0.615121	0.119811	0.349826	0.065197	0.659935	0.343586
9	0.622	0.130207	0.336999	0.031395	0.653565	0.09208	0.335969	0.024905	0.637968	0.336484
10	0.556	0.139107	0.35259	0.02327	0.657898	0.089412	0.357343	0.018633	0.60716	0.354967
11	0.606	0.104692	0.352431	0.032213	0.626267	0.111793	0.346359	0.022976	0.616021	0.349395
12	0.584	0.110143	0.362564	0.022677	0.59682	0.123969	0.362985	0.034347	0.590421	0.362775

FA: fractional anisotropy, ADC: apparent diffusion coefficient SD: standard deviation

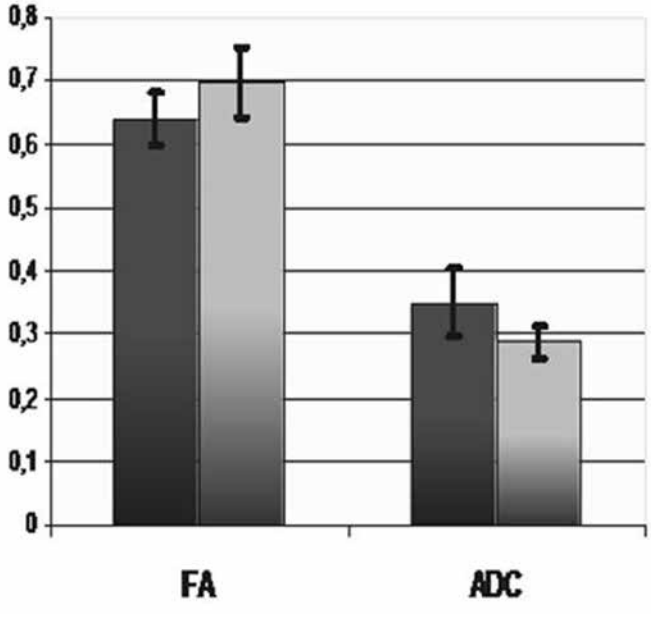
Figure 3. a, b. A 53-year-old male patient with ALS had increasing weakness in his right hand and arm for 3 years. 1a: b=0 and 2b: Color map shows significant decrease of the fractional anisotropy at the internal capsule posterior limb level.



The results of FA and ADC measurements from the posterior limb of the internal capsule in the patient group were respectively 0.638±0.041 and 0.350±0.01 ($p<0.001$), and the results of the healthy group were 0.701±0.054 and 0.288±0.027, respectively ($p<0.05$) (Table 3). Along the corticospinal tract, the most pronounced reductions were seen at the posterior limb of the internal capsule. Figure 2, 3 show prominent alterations in the internal capsule. Tables 1, 3 and Figure 4 report clinical findings and the DTI metrics from the internal capsule's posterior limb, and the average metric of the patients with ALS and healthy group's results.

In comparison of the FA skeletons of the ALS and control groups using either ROI-based approaches or tractography,

Figure 4. Graphic shows the FA (fractional anisotropy) and ADC (apparent diffusion coefficient) values of the ALS (gray bar) and control (white bar) group.



we observed reduced FA values in the bilateral corticospinal tracts (Figure 2, 3). Also, the reduction of the FA values of the CST significantly correlated with the clinical scores, disease progression, and disease severity. All of the patient group were right handed. The decreased right posterior limb internal capsule FA values were more prominent, which might be

Table 3. The difference between FA and ADC values of the internal capsule posterior crus

	FA	ADC
ALS	0.638±0.041	0.350±0.01
NORMAL	0.701±0.054	0.288±0.027

FA: fractional anisotropy; ADC: apparent diffusion coefficient

related with the dominant cerebral hemisphere (Figure 3). Measurements from the pons and bulbar level showed a significant decrease in FA values, and decreased FA values were correlated with UMN and LMN (cervical and thoracic spinal cord) findings, El Escorial scale, and r-ALSFRS scores. However, thoracic and cervical spinal cord images showed prominent geometric distortion.

DISCUSSION

In this study, a prominent reduction of FA along the CST at the internal capsule posterior limb was found in the DTI data of the patients with ALS with respect to the subjects in the control group, which agreed with the results of previous studies. Also, in patients with ALS, a correlation between FA reduction and clinical impairment and r-ALSFRS scores was identified. We found that DTI detected microstructural brain abnormalities in early stages of ALS. It is helpful to use color-coded anisotropy maps to identify the CST, there is a likelihood for manually drawn ROIs to have issues about the non-affected white matter structures. Along a tract, the average FA has been reported to provide more sensitive results when there is a relatively local impairment of the tract. Based on previous DTI studies, the white matter tracts that were the most extensively affected were the corticospinal and colossal tracts in ALS (1-6, 9-15). Furthermore, our results indicate that DTI is a sensitive and specific method for evaluating CST damage in patients with ALS.

More than 40% of patients with ALS undergo inappropriate medical treatment, including surgery. Electromyography can help confirm the diagnosis of lower motor neuron involvement (16). However, in early stages of the disease, it is more difficult to prove involvement of the upper motor neuron. Pooled DTI data showed that the low FA values were remarkable for the early diagnosis of ALS. Therefore, the lower FA values in patients with ALS proves the upper motor neuron pathology (17).

As known, diffusion anisotropy describes differences in the diffusion of the water molecules in different directions (1-6). Anisotropy is most commonly quantified with measurement of FA. It was demonstrated that decreased FA values are related to degeneration of axonal fibers and breakdown of myelin. Thus, the degree and directionality of water diffusion may be used to estimate CST degeneration (1-3, 5, 6). Nevertheless, FA measurements are affected by a number of factors such as models of instruments, gradients, magnetic inhomogeneity, cut-off values, and operators (18-20). However, many recent studies detected that there was a correlation between ALS disease severity and CST DTI findings and FA values (18-20). Also, ALS-related changes in functional and structural connectivity within the cerebral network, and ASL-specific degeneration of the corpus callosum have been described with DTI (19). The results of studies showed that the lowest FA values were particularly remarkable in corpus callosum genu and splenium, centrum semiovale, and deep the parietal lobe's white matter. Even so, all studies showed that at diagnosis of suspected ALS, the cerebral peduncle, the internal capsule's posterior limb, and corona radiata can be used as the first set of ROIs (16). In addition, some studies showed efficiency decreases in a widespread network of motor connectivity. The results of these studies suggest that ALS also affects primary motor regions' capacity of connection and communication with supplemental motor regions (21-24).

Several studies have shown FA value reductions in the CST of patients with ALS. Primary motor cortex and axonal degeneration of the CST with pyramidal motor neuron loss, glial cell proliferation, expansion of the extracellular matrix, and intra-neuron abnormalities may explain the CST's changes in DTI (4, 8, 11, 12). Studies have reported FA values to decrease along the CST from the corona radiata through the internal capsule and into the brain stem with voxel-based approaches and DTI studies (3-6, 9, 11-13, 15, 25, 26). Also, studies have shown gray and white matter changes in other brain regions. Based on the findings, ALS does not only affect primary motor connections (17, 21-24, 26). However, it is needed to conduct MRI studies that are structural and functional in order to confirm the hypothesis of disease progression along the motor network's functional and structural connections from primary motor regions towards secondary ones.

Extra-motor degenerative outcomes were reported in ALS in a number of voxel-based morphometry (VBM) studies on gray and white matter as well as DTI studies (21, 23, 24). One limitation of our study may potentially be the disproportionate between the numbers of control subjects and patients. Further, we did not perform DTI or FA measurements from gray matter and cortico-cortical connections.

Although DTI has been established as a method to examine white matter changes, there is still much to understand about it. FA is used prevalently to assess white matter integrity, but it is affected by several factors such as crossing fibers, fiber re-organization, elevated membrane permeability, intracellular compartment destruction and glial alterations.

In addition to the factors described above related with DTI, there were some further limitations of our study. One short-

coming was the small patient group. However, the pons, corticobulbar tract, and cervical spinal cord were not included. Magnetic field inhomogeneity, motion artefacts arising from patient instability, and susceptibility artefacts between the skull and pons limited the brainstem and cervical spine images.

In conclusion, upper motor fiber degeneration in cases of ALS can be captured by longitudinal DTI. It may be useful to utilize DTI to follow progression of ALS and for treatment intervention effectiveness.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Marmara University School of Medicine Research Ethics Committee (B.30.2 MAR 0 01.00 02/AEK-424).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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