Diffusion tensor imaging of normal-appearing cervical spinal cords in patients with multiple sclerosis: Correlations with clinical evaluation and cerebral diffusion tensor imaging changes. Preliminary experience

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Conflict of interest

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Abstract

Background. Several studies have identified changes in the spinal cord DTI measurements in patients with multiple sclerosis (MS). However, correlations between changes in DTI parameters in normal appearing cervical spine and neurological findings have not been clearly established.

Objectives. To determine whether diffusion tensor imaging (DTI) measurements such as fractional anisotropy (FA) and apparent diffusion coefficient (ADC) are sufficiently sensitive in detecting microstructure alterations in normal-appearing spinal cords in patients with MS and whether they reflect these patients' clinical disability.

Material and methods. Fifteen patients diagnosed with relapsing-remitting MS (RRMS) with normal-appearing cervical spinal cords on plain MRI and 11 asymptomatic volunteers were enrolled in the study. Overall, 75 cervical spinal segments were analyzed. The regions of interest were drawn from the entire spinal cord cross-section and in the normal-appearing white matter tracts: the superior and inferior cerebellar peduncles and the posterior limbs of the internal capsules. Neurological deficit and the level of disability were evaluated using the Expanded Disability Status Scale (EDSS), the timed 25-foot walk test (T25FW) and the 9-hole peg test (9HPT) for manual dexterity.

Results. A significant difference (p < 0.05) in FA values between patients with MS and the control group was found at levels C2 (p = 0.047) and C3 (p = 0.023). No significant changes in ADC values were found. There was correlation between FA and ADC values in selected white matter tracts and at particular spinal cord levels. We also observed significant correlations between diffusion tensor imaging parameters and manual dexterity.

Conclusions. Our preliminary results may suggest that the spinal cord's structural loss is the dominant factor in the inflammatory/demyelinating component in patients with MS. Diffusion tensor imaging changes in the spinal cord correlate with brain DTI changes. Manual functioning seems to be more affected than walking.

Key words: disability, walking, multiple sclerosis, spinal cord, diffusion tensor imaging

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Introduction

Multiple sclerosis (MS) is a chronic disease with a complex background, which is associated with the processes of immune-mediated inflammatory demyelination and axonal loss within the central nervous system (CNS). Multifocal damage to the brain and spinal cord, which develops over time in a relapsing-remitting or less frequently progressive manner, results in a diversity of symptoms and signs of neurological deficit, eventually leading to disability.

Magnetic resonance imaging (MRI) has become the modality of choice for detecting and assessing MS lesions within both the brain and the spinal cord, due to its sensitivity in detecting focal white matter lesions. However, changes observed in plain MRI often do not correlate with patients' clinical presentation, which is called the clinical–radiological paradox or mismatch. On the other hand, MS lesions might not be visible in the spinal cord due to its small volume, despite clinical signs of spinal cord impairment.¹

Diffusion tensor imaging (DTI) is a method which is sensitive to microstructure alterations even within the normal-appearing brain and spinal cord, which enables quantitative assessment of changes almost at the cellular level. The main DTI parameters are fractional anisotropy (FA) and apparent diffusion coefficient (ADC). Fractional anisotropy is a biomarker of white matter integrity, and lower FA values indicate impairment of the white matter fibers' integrity; ADC is a measure of diffusivity which therefore increases over the course of inflammatory/demyelinating processes.²

Several studies have identified changes in the spinal cord DTI measurements in patients with MS.^{3–10} However, correlations between changes in DTI parameters and neurological findings have not been clearly established.^{1,11–14} Some of these studies were not controlled trials. Moreover, relationships between quantitative clinical indices and DTI parameters within normal-appearing spinal cords have not been closely explored.

The aim of this preliminary study was to determine whether quantitative DTI measurements in normal-appearing spinal cords of patients with MS are sensitive in detecting alterations to its microstructure and whether these values are related to the patients' disability indices. Another objective was to assess whether DTI values in normal-appearing spinal cords correlate with the corresponding cerebral ones (within the cortico-spinal and cerebello-spinal tracts).

Material and methods

The study was comprised of 15 patients diagnosed with relapsing-remitting MS (RRMS) according to the current McDonald criteria¹⁵ (14 women and 1 man; age range: 28–48 years, mean age: 35.45 years) and 11 asymptomatic volunteers as control subjects (CS) with no history of neurological disorder (10 women and 1 man; age range:

28–48 years, mean age: 34.2 years). In patients with MS, the duration of illness ranged from 3 to 15 years (mean: 7.06 years). The EDSS results were 1–4 (mean: 2.26). All the patients and controls were right-handed.

The inclusion criterion for the study group was a lack of MS plaques or any other focal lesions in the spinal cord. The exclusion criteria were as follows: acute MS relapse and corticosteroid treatment within 3 months prior to inclusion in the study, the presence of marked cervical spine degenerative disease, previous spinal surgery or any incidental findings seen on plain MRI which would potentially suggest a neurological disorder.

The study was performed in accordance with the guidelines of the local University Ethics Committee for conducting research involving humans. All subjects provided their written informed consent to participate in this study according to the Helsinki Declaration, and the study was approved by the Local Commission of Bioethics.

MRI and **DTI** protocol

The MRI examinations were performed with a 1.5T MRI (SignaHdx; GE Medical Systems, Chicago, USA) with a maximum gradient amplitude of 33 mT/m, a 120 mT/m/s slew rate and a 16-channel HNS coil. The MRI protocol for cervical spinal cord study consisted of sagittal T1-weighted images, sagittal and axial T2-weighted images and sagittal T2-weighted FAT SAT images, followed by axial DTI sequence. Acquisition of DTI was based on single-shot spinecho echo-planar imaging (SE/EPI) with the following settings: TR 10,000 ms; TE 100 ms, 160×160 mm field of view (FOV), 96×96 mm matrix, 1.6×1.6 mm in-plane image resolution, 4 mm axial slices parallel to the intervertebral disk space, no gap and 2 acquisitions. The examination frame was adjusted to cover the length of the spinal cord from vertebrae C1 to C7. Diffusion was measured along 15 non-collinear directions using b values of 0 s/mm² and 1,000 s/mm². The acquisition time of the sequence was about 7 min.

In all patients, a conventional brain MRI was performed according to the standard protocol used in our department 16: sagittal and coronal T2 FRFSE sequences, axial T1 SE, T2 FSE and FLAIR sequences, axial DWI SE/EPI sequence and gadolinium-enhanced 3D-FSPGR sequence. The brain DTI acquisitions were performed using an axial single-shot spin-echo echo-planar imaging sequence (SE/EPI) along 25 different diffusion-encoding directions. For each direction, 2 b values were used: 0 and 1,000 s/mm² (4-mm slice thickness, no gap, TR 8,500 ms; TE 100,8 ms, 260 × 208 mm field of view, 128 × 128 mm matrix and 2 excitations). The acquisition time of DTI in each subject was 7.31 min. 16

Image analysis

The image analysis was performed according to previously described methods.¹⁷ Plain MRIs of the cervical spine

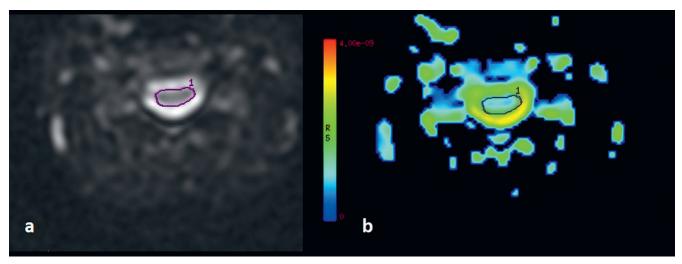


Fig. 1. Positioning of the regions of interest (ROI): a) b0 image and b) FA map. Each ROI was drawn manually over the entire axial cross-section of the cervical spinal cord, according to the most accurate axial b0 image

and brains of the 15 patients and 11 age-matched control subjects were analyzed by 2 independent readers (M.W. and J.B.), who were blinded to the clinical results. Image post-processing was done using the Functool software (GE ADW 4.6 workstation; GE Healthcare). Apparent diffusion coefficient (ADC) and fractional anisotropy (FA) axial maps were generated; FA and ADC values at the selected spine segments and brain regions were calculated based on these axial maps.

The regions of interest (ROIs) were drawn over the entire axial spinal cord cross-section, according to the most accurate axial B0 image¹⁷ at about half of the height of each vertebral body, as shown in Fig. 1.

All levels with significant artifacts were excluded from further analysis. The vast majority of artifacts were found at level C7; therefore, we decided to exclude all C7 levels from further evaluation. In total, 75 spinal segments were analyzed.

Diffusion tensor imaging measurements in the brain were performed by placing ROIs of 10 mm² in the following normal-appearing white matter regions: the right and left superior cerebellar peduncles (SCPR and SCPL), the right and left inferior cerebellar peduncles (ICPR and ICPL) and the right and left posterior limbs of the internal capsules (pyramidal cortico-spinal tracts (CSTs)) (PLICR and PLICL).

Clinical data

The type and duration of MS (duration of illness) were determined based on the patients' medical records. All patients underwent neurological examination, and their neurological deficit and level of disability were evaluated using the Expanded Disability Status Scale (EDSS).¹⁸ Functional tests¹⁹ were also performed to assess particular aspects of disability: the timed 25-foot walk (T25FW) for ambulation (the time needed to walk a distance of 25 feet,

with an average of the results from 2 trials) and the 9-hole peg test (9HPT) for manual dexterity (the time needed to insert 9 pegs into holes and remove them using one hand, with an average of the results from 2 consecutive trials for the dominant and non-dominant hand).

Statistical analysis

Comparisons of the FA and ADC values of the same cervical spinal cord levels among all groups were performed using Student's t-test and the Mann–Whitney test. Correlations between spinal cord DTI parameters and clinical results, as well as DTI values in selected brain regions, were estimated using Pearson's correlation coefficient. STATISTICA v. 10 software (StatSoft, Inc., Tulsa, USA) was used for statistical calculations; a p-value <0.05 was considered statistically significant.

Results

There were no significant differences in age (p = 0.66) or sex distribution between patients with MS and the control group.

Comparison of FA and ADC values in the spinal cord between patients with MS and the control group

The FA and ADC values at different levels (C1–C6) of the cervical spinal cord in patients with MS and controls, as well as statistical differences in these parameters between the 2 groups, are shown in Tables 1 and 2.

In the MS group, the mean FA values ranged from 0.570 (C6 level) to 0.644 (C3 level) and the mean ADC values ranged from 0.947 (C1 level) to 1.078 (C6 level) (\times 0.001 mm²/s). In the controls, the mean FA values ranged

Table 1. Mean FA values within the spinal cords of patients with MS and the control group

Cervical spine level	Mean FA in MS group	Mean FA in controls	p-value		
C1	0.635	0.641	0.884		
C2	0.639	0.708	0.047		
C3	0.644	0.694	0.023		
C4	0.604	0.636	0.425		
C5	0.599	0.650	0.062		
C6	0.570	0.632	0.068		

Statistically significant differences are marked in bold; MS – multiple sclerosis; FA – fractional anisotropy.

from 0.632 (C6 level) to 0.708 (C2 level) and the mean ADC values ranged from 1.009 (C3 level) to 1.058 (C4 level) (\times 0.001 mm²/s). Significantly lower FA values (p < 0.05) were found at levels C2 and C3 in patients with MS than in the control subjects (Table 1). There were no significant changes in ADC values between the studied groups (Table 2).

Correlations of DTI measurements in the spinal cord with outcomes of clinical evaluation in patients with MS

The outcomes of clinical evaluation of each patient are shown in Table 3. Correlations between mean DTI values in the spinal cord and clinical outcomes in the MS group are presented in Table 4.

Table 2. Mean ADC values within the spinal cords of patients with MS and the control group

Cervical spine level	Mean ADC in MS group				
C1	0.947	1.030	0.417		
C2	1.060	1.010	0.310		
C3	1.045	1.009	0.399		
C4	1.026	1.058	0.467		
C5	1.048	1.029	0.632		
C6	1.078	1.014	0.211		

FA – fractional anisotropy; ADC – apparent diffusion coefficient.

Significant negative correlations between the mean FA values in the spinal cord and the 9HPT test results were found at levels C4 and C5, for both the dominant and non-dominant hands.

There was also a significant negative correlation between FA values at level C6 and the 9HPT test results for the dominant hand. No significant positive correlations between mean FA values in the spinal cord and clinical results were observed.

Significant positive correlations between the ADC values in the spinal cord and the 9HPT test results for the non-dominant hand were found at levels C1, C2, C3, C4 and C6, and for the dominant hand at levels C4 and C6. The ADC values at levels C4 and C5 also positively correlated with a longer duration of illness. There were no significant negative correlations between the mean ADC values in the spinal cord and the clinical outcomes.

Table 3. Clinical evaluation of patients with MS

Patient	T25FW [s]	9HPT with dominant hand [s]	9HPT with non-dominant hand [s]	EDSS	Duration of illness [years]
1	5.6	19.6	21.3	1	3
2	5.3	21.3	20.6	1.5	7
3	4.9	20.5	22.4	3	11
4	4.0	16.6	17.2	3	5
5	4.2	23.6	28.9	1.5	8
6	6.1	21.5	27.3	4	5
7	7.1	31.7	32.5	1.5	14
8	4.8	33.2	31.4	2	8
9	5.2	29.1	29.3	3.5	15
10	6.4	19.3	21.4	2.5	3
11	4.6	20.2	21.7	2.5	10
12	5.4	21.5	19.2	2	3
13	5.2	18.1	16.6	2	5
14	4.0	19.2	19.1	1.5	6
15	5.7	19.8	17.3	2.5	3
Median	5.2	20.5	21.4	2.0	6.0

T25FW – timed 25-foot walk test; 9HPT – 9-hole peg test; EDSS – Expanded Disability Status Scale.

Cervical spine level		T25FW		9HPT, dominant hand		9HPT, non-dominant hand		EC	OSS	Duration of illness	
		PCC	p-value	PCC	p-value	PCC	p-value	PCC	p-value	PCC	p-value
C1	FA	-0.5412	0.086	-0.2914	0.385	-0.4049	0.217	-0.4199	0.198	-0.0756	0.825
	ADC	0.4674	0.147	0.4371	0.179	0.6382	0.035	0.3044	0.363	0.1898	0.576
63	FA	0.1809	0.595	-0.2524	0.454	-0.5221	0.099	-0.0977	0.775	-0.256	0.447
C2	ADC	0.3854	0.242	0.47	0.145	0.6613	0.027	0.2189	0.518	0.1284	0.707
60	FA	-0.2639	0.433	-0.483	0.132	-0.555	0.076	-0.3941	0.230	-0.2735	0.416
C3	ADC	-0.009	0.979	0.5829	0.060	0.6373	0.035	0.3232	0.332	0.4583	0.156
C4	FA	-0.1142	0.738	-0.8626	0.001	-0.7529	0.007	-0.0811	0.813	-0.5435	0.084
C4	ADC	0.1294	0.705	0.8897	0.001	0.8287	0.002	0.041	0.905	0.6583	0.028
C.F.	FA	-0.0863	0.801	-0.8467	0.001	-0.7209	0.012	-0.0654	0.848	-0.4814	0.134
C5	ADC	-0.0573	0.867	0.0534	0.876	0.3643	0.271	0.5587	0.074	0.1901	0.576
66	FA	-0.2115	0.533	-0.6287	0.038	-0.4551	0.160	0.2392	0.479	-0.212	0.531
C6	ADC	-0.1285	0.707	0.7331	0.010	0.6859	0.020	-0.1958	0.564	0.7921	0.004

Table 4. Correlations between mean DTI values in the spinal cord and clinical outcomes in patients with MS

Statistically significant differences are marked in bold; C1–C6 – levels of the cervical spinal cord; FA – fractional anisotropy values; ADC – apparent diffusion coefficient values; EDSS – expanded disability status scale score; T25FW – timed 25-foot walk test; 9HPT – 9-hole peg test; PCC – Pearson correlation coefficient.

Correlations between mean DTI parameters in the spinal cord and selected white matter tracts

Within the white matter tracts, the mean FA values ranged from 0.570 to 0.658, and for selected white matter locations the values were as follows: ICPR - 0.57; ICPL - 0.64; SCPR - 0.59; SCPL - 0.60; PLICR - 0.65; and PLICL - 0.66 (Table 5).

Significant positive correlations were found between the mean FA values in SCPR and the FA values in the spinal cord at level C2, between FA values in ICPL and FA values in the spinal cord at levels C4 and C5, and between FA values in PLICL and FA values in the spinal cord at level C6, which means that spinal FA values were lower in patients with lower FA values in the cerebral white matter tracts. Within the brain regions which were analyzed, the mean ADC values ranged from 0.71 to 1.26, and for the selected locations the values were as follows: ICPR - 0.87; ICPL - 0.77; SCPR - 1.26; SCPL - 1.11; PLICR - 0.71; and PLICL - 0.72.

Significant positive correlations were found between the mean ADC values in PLICR and the ADC values in the spinal cord at levels C1, C3 and C4, between the ADC values in PLICL and the ADC values in the spinal cord at levels C2 and C3, and between the ADC values in ICPL and the ADC values in the spinal cord at level C4, which means that ADC values in the spinal cord were higher in patients with higher ADC values in the cerebral white matter tracts.

There were no significant negative correlations found between ADC values in the spinal cord and ADC values in the examined brain regions.

Table 5. Correlations between me	an FA values in the spinal	cord (levels C1 to C6) an	d brain white matter tracts
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Cervical spina level	ICPR FA		ICPL FA		SCPR FA		SCPL FA		PLICR FA		PLICL FA	
FA value	PCC	p-value	PCC	p-value	PCC	p-value	PCC	p-value	PCC	p-value	PCC	p-value
C1 FA	0.128	0.708	0.1733	0.610	0.3392	0.307	0.135	0.692	0.0724	0.833	0.4236	0.194
C2 FA	-0.0937	0.784	0.4463	0.169	0.6157	0.044	0.4477	0.167	0.3157	0.344	0.1656	0.627
C3 FA	0.1592	0.640	0.295	0.378	0.0674	0.844	-0.1179	0.730	-0.012	0.972	0.2659	0.429
C4 FA	0.1959	0.564	0.6405	0.034	0.2448	0.468	-0.209	0.537	0.1347	0.693	0.193	0.570
C5 FA	0.215	0.526	0.6381	0.035	0.2697	0.423	-0.1817	0.593	0.284	0.397	0.3444	0.300
C6 FA	0.2397	0.478	0.2797	0.405	-0.1359	0.690	-0.4744	0.140	0.4093	0.211	0.6947	0.018

Statistically significant differences are marked in bold; C1–C6 – levels of the cervical spinal cord; FA – fractional anisotropy values; SCPR/SCPL – right/left superior cerebellar peduncles; ICPR/ICPL – right/left inferior cerebellar peduncles; PLICR/PLICL – right/left posterior limbs of internal capsules; PCC – Pearson correlation coefficient.

Cervical spinal level	ICPR ADC		ICPL ADC		SCPR ADC		SCPL ADC		PLICR ADC		PLICL ADC	
ADC value	PCC	p-value	PCC	p-value	PCC	p-value	PCC	p-value	PCC	p-value	PCC	p-value
C1 ADC	0.2717	0.419	0.1413	0.679	0.0607	0.859	-0.3826	0.246	0.652	0.030	0.489	0.127
C2 ADC	0.3103	0.353	0.2404	0.476	0.1777	0.601	-0.2385	0.480	0.5552	0.076	0.6661	0.025
C3 ADC	-0.0518	0.880	0.5132	0.106	0.0808	0.813	-0.5963	0.053	0.8303	0.002	0.7517	0.008
C4 ADC	0.1448	0.671	0.6652	0.026	-0.1176	0.731	-0.5598	0.073	0.7026	0.016	0.4697	0.145
C5 ADC	-0.3967	0.227	-0.02	0.953	-0.2161	0.523	-0.3959	0.228	0.579	0.062	0.4795	0.136
C6 ADC	-0.087	0.799	0.4599	0.155	-0.4038	0.218	-0.5568	0.075	0.5435	0.084	0.1459	0.669

Table 6. Correlations between mean ADC values in the spinal cord (levels C1 to C6) and the brain

Statistically significant differences are marked in bold; C1–C6 – levels of the cervical spinal cord; ADC – apparent diffusion coefficient values; SCPR/SCPL – right/left superior cerebellar peduncles; ICPR/ICPL – right/left inferior cerebellar peduncles; PLICR/PLICL – right/left posterior limbs of internal capsules; PCC – Pearson correlation coefficient.

Discussion

Because MS onset mainly occurs in young adults, and due to the long-term and highly variable course of the disease, there is a need to diagnose and possibly predict at an early stage the extent of damage to the CNS and its clinical consequences. ²⁰ Early DTI changes reflect microstructural changes found at almost the cellular level, and FA value could potentially be a noninvasive biomarker for detecting subtle axonal lesions which may precede focal demyelination likely appearing later on as MS plaques on T2 sequences.

In this study, we investigated quantitative DTI indices such as FA and ADC values, measured at different levels of normal-appearing cervical spinal cords and in selected normal-appearing cerebral white matter tracts. This data correlated with functional measures of the degree of overall disability (EDSS), ambulation (T25FW) and manual dexterity (9HPT). Spinal cord atrophy is a well-known contributor to disability^{3,21}; however, the conventional indices of spinal cord atrophy reflect tissue loss that is more likely to be irreversible. Measuring DTI parameters within a normal-appearing spinal cord may have the advantage of detecting potentially reversible changes which are not visible on conventional MRI scans.

Significant differences in FA values between patients with MS with normal-appearing spinal cords and controls were found at spinal levels C2 and C3. These results are in agreement with previous DTI studies showing decreased FA values in both normal-appearing spinal cords and in T2-visible lesions in the spinal cords of subjects with MS.^{6–10} On the other hand, we found no significant differences between the ADC values of the studied groups. Lower FA values in MS reflect axonal impairment, which corresponds to functional discontinuity of the axons and, by definition, is a more specific measurement than ADC, which increases due to the inflammatory/demyelinating processes. Therefore, our results may suggest that the axonal loss within the spinal cords of patients with MS is more pronounced than the inflammatory-demyelinating

component. The other mechanism which could contribute to the lower FA values is Wallerian degeneration. However, the patients have no visible demyelinating lesions in the spinal cord — only the brain lesions; therefore, it seems rather unlikely.

Our results suggest a correlation between ADC values at levels C4 and C6 and the duration of illness, since the spinal ADC values appear to be higher in patients with a longer duration of illness. This may reflect increasing neuronal damage with a longer duration of disease.

In the next part of our study, we analyzed FA and ADC values of the spinal cord as related to various measurements of disability in the course of MS. Our data showed significant FA and ADC correlations with manual dexterity, as measured with the 9HPT. Particularly pronounced correlations were found between the higher ADC values in the spinal cord and manual dexterity at the levels of C1, C2, C3 and C6. Correlations between FA values and manual dexterity parameters were found only at levels C4 and C5.

Walking dysfunction is a relatively common problem in patients with MS, yet there is still a poor understanding of the possible neuronal substrate of walking. ^{4,5,14} In this study, we did not find any significant correlations of DTI parameters in the spinal cord with the timed 25-foot walk test (T25FW) or the Expanded Disability Status Scale (EDSS). The EDSS score is strongly affected by ambulation ability, so the lack of correlations for both the EDSS and the T25FW is consistent. Our results seem to suggest that a loss of neuronal integrity within the cervical spinal cord is associated with greater impairment in manual dexterity than in walking ability.

The vast majority of available studies investigating the relationships between clinical parameters and DTI changes in patients with MS are primarily focused on the brain and not on the spinal cord. Hubbard et al. ¹⁴ evaluated different DTI values of the corticospinal tract, including mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD) and FA and their relationships with ambulation test scores (the T25FW and the 6-minute walk test). ¹⁴ Although they found some significant correlations

between the walking test results and RD and AD values, none were observed for FA values in the corticospinal tract, which seems to be consistent with our results.

Additionally, we investigated the relationships between DTI values in the spinal cord and corresponding pathways in the brain. A significant correlation was observed between lower FA values in the inferior cerebellar peduncle (ICP) and at levels C4 and C5 of the spinal cord. Such an association may suggest neuronal disintegration along the posterior spinocerebellar tract, running predominantly through the ICP. A significant correlation was also noted between the lower FA values in the superior cerebellar peduncle (SCP) and level C2 of the spinal cord, which in turn may be related to changes in the integrity of the anterior spinocerebellar tract.^{22,23} A considerable positive correlation was found between ADC values within the ICP and level C4 of the spinal cord, with corresponding higher ADC values in both regions. Although this correlation was found only at 1 level, it might suggest the involvement of the spinocerebellar tracts by disease, which could contribute to MS-related disability.

Our study also revealed correlations between ADC values within the spinal cord (levels C1, C2, C3 and C4) and in both posterior limbs of the internal capsules (PLICs). This association may depend on the anatomical structure of the pyramidal tracts, as more than half of their fibers terminate in the cervical spinal cord to supply the upper extremities. In comparison to other studies which evaluated cervical spinal cord changes at 1 or 2 levels of the cervical spinal cord, 9,34–36 our study provides an assessment of pathological changes within a wider range of the cervical spinal cord (levels C1 to C6), which renders a more comprehensive look into changes that may contribute to clinical dysfunction.

As a preliminary report, our study features a number of limitations. The small sample size is likely to limit the statistical significance of the findings. Additionally, the use of ROIs encircling the cross-sectional area of the spinal cord- instead of particular columns - might have possibly created a bias in the observed structure-function relationships, although we believe this approach provides us with a more comprehensive view of spinal cord changes, assessing both white matter and grey matter. This approach has been already discussed in the literature, including our previous experience.¹⁷ Besides, it has been shown that MS affects both white matter and grey matter; therefore, the impairment of all spinal cord structures is calculated with our method. The involvement of the spinal cord grey matter (GM) in MS had already been recognized by the turn of the 20th century, which is discussed in a study by Schlaeger et al.²⁴ Other authors have reported a similar reduction of both grey matter and white matter cross-sectional cervical cord areas in advanced, progressive MS, with a predominance of GM loss.^{26–33}

Nevertheless, the results seem to be interesting and to encourage further investigation. They suggest the need to explore spinal cord-specific pathological processes, mainly

with regard to clinical disability in patients with a normalappearing spinal cord on plain MRI. Studies on a larger base of material, using an improved DTI evaluation protocol, may improve our understanding of the inflammatory and neurodegenerative processes underlying disability in MS.

Conclusions

Our preliminary findings show significant differences in FA values between the normal-appearing spinal cords of patients with MS and healthy controls. These may suggest that the structural loss within the spinal cords of patients with MS is of greater importance than the inflammatory-demyelinating component. The initial loss of neuronal integrity within the cervical spinal cord seems to influence manual dexterity more than walking function. Further studies are necessary to establish the role of DTI measures as biomarkers of the subtle alterations in the spinal cord integrity of patients with MS and their clinical and prognostic relevance.

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