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DIFFUSION TENSOR IMAGING OF THE CERVICAL SPINAL CORD OF PATIENTS WITH RELAPSING-REMISING MULTIPLE SCLEROSIS

A study of 41 cases

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Abstract – **Objective:** To evaluate the fractional anisotropy (FA) values of the multiple sclerosis (MS) plaques and normal-appearing cervical spinal cord (NASC) by diffusion tensor MRI imaging (DTI). **Method:** Forty-one patients with relapsing-remising MS and 37 controls were evaluated. All MRI exams were performed using a conventional protocol, as well as diffusion tensor MR imaging. Regions of interest were placed within the spinal cord lesions and in the normal appearing spinal cord adjacent to the plaque. **Results:** The FA values were statistically reduced in the plaques compared to the surrounding NASC and to equivalent location in controls. A reduction in FA values was also observed in the spinal cord of MS patients without visible lesions on T2WI. **Conclusion:** We observed reduced fractional anisotropy in the demyelinating plaques and in the NASC of MS patients, corroborating the hypothesis that the histological extension of the MS lesions is more severe than the abnormalities seen in the conventional MRI sequences.

KEY WORDS: multiple sclerosis, magnetic resonance imaging, diffusion tensor imaging.

Imagens por tensor de difusão da medula cervical de pacientes com esclerose múltipla remitente-recorrente: estudo de 41 casos

Resumo – **Objetivo:** Avaliar os valores da anisotropia fracionada (FA) em pacientes com esclerose múltipla (EM) nas placas e na medula espinhal aparentemente normal (MEAN). **Método:** Quarenta e um pacientes com EM remitente-recorrente e 37 controles foram examinados. Todos os exames foram realizados com protocolo convencional, assim como imagens por tensor de difusão. Regiões de interesse foram definidas nas placas da medula espinhal e na MEAN ao redor das placas. **Resultados:** Os valores de FA estavam significativamente reduzidos nas placas, comparados à MEAN ao redor e às regiões equivalentes dos controles. Redução dos valores de FA também foi demonstrada na medula espinhal de pacientes com EM sem lesões visíveis nas imagens de RM pesadas em T2. **Conclusão:** Observamos redução dos valores de anisotropia fracionada nas placas de desmielinização e na MEAN, corroborando a hipótese de que a extensão histológica das lesões na EM é maior que as alterações de sinal vistas nas seqüências convencionais de ressonância magnética.

PALAVRAS-CHAVE: esclerose múltipla, ressonância magnética, imagens por tensor de difusão.

The involvement of the spinal cord is a common finding in patients with multiple sclerosis (MS). Post-mortem and magnetic resonance (MR) imaging studies have shown cord lesions in up to 90% of these patients[1-4]. In addition, the cord involvement is likely to contribute to the level of disability, particularly locomotor impairment, which is

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one of the main clinical hallmarks of the disease[1,2]. However, correlation between severity of the lesions seen on conventional MR imaging and clinical disability was not yet achieved. This divergence could represent the inability of conventional MR imaging to quantify accurately the degree of cord tissue damage[3]. Post-mortem studies have shown that the cord damage is more extensive than the macroscopic lesions seen on conventional MR imaging[4]. In addition, histopathologic studies have demonstrated spinal cord lesions in patients with defined diagnosis of MS, but with normal spinal MR imaging[5]. Moreover, advanced MR imaging techniques, such as diffusion tensor imaging (DTI), have shown involvement of the brain white matter in areas with normal signal on conventional MR imaging[6-8].

The diffusion tensor imaging requires the measurement of the MR signal with diffusion sensitization along six or more non-collinear directions. It allows the determination of three perpendicular eigenvectors, whose magnitudes are given by three corresponding eigenvalues. Various mathematical combinations of these three vectors allow the derivation of a number of diffusion indices. The main advantage of using diffusion tensor indices in clinical studies is that they are reliable, quantitative, and objective measures of the diffusion properties in the human brain. In white matter, water molecules diffuse preferentially in the direction parallel to axons. This property, termed diffusion anisotropy, may be quantified by the fractional anisotropy (FA) indices. FA increases with anisotropy and provides the most detailed spatial depiction of anisotropic areas[9,10].

Several studies have been investigating the spinal cord of patients with multiple sclerosis using DTI[11-14]. The results have demonstrated that the cervical cord FA values are significantly lower in MS patients compared to controls. In addition, FA and mean diffusivity values have correlated with the degree of disability in these patients. However, there is still a lack of studies investigating the DTI findings in MS plaques and normal-appearing spinal cord (NASC) (no abnormal signal on T2-weighted MR images) of patients with multiple sclerosis.

The aim of this study was to assess the fractional anisotropy values of the MS plaques and normal-appearing cervical spinal cord in patients with MS using diffusion tensor MR imaging.

METHOD

Population

We retrospectively studied a cohort of 41 patients with MS (31 female and 10 male, mean age 33.4 years-old) and 37 age- and sex-matched healthy volunteers (28 female and nine male, mean age 31 years-old). All patients had the relapsing-remising form of MS and the diagnosis of was defined based on McDonald's criteria[15]. All patients had been receiving medication for various periods of time when the MR imaging data was acquired. The patients and controls signed informed consent and the institutional review board approved the study.

MR imaging

The exams were performed in a 1.5T scanner (Magnetom Avanto, Siemens, Germany), with 8 channels head coil. All patients underwent the conventional MR imaging protocol, including sagittal T1-weighted images (repetition time (TR)/echo time (TE) 4410/98ms, field of view (FOV) 240 mm, matrix 320×320 mm and slice thickness 3 mm with 30% of interval), sagittal T2-weighted images (TR/TE 4410/98 ms, FOV 240 mm, matrix 320×320 mm and slice thickness 3 mm with 30% of interval) and axial T2*-weighted images (TR/TE 4410/98 ms, FOV 240 mm, matrix 320×320 mm and slice thickness 3 mm with 30% of interval).

The DTI sequences employed gradient pulses in twelve different directions in the axial (TR/TE 3200/80 ms, FOV 225×225 mm, matrix 128×128 mm, slice thickness 3 mm with 30% of interval) and sagittal planes (TR/TE 2800/90 ms, FOV 280×280 mm, matrix 192×192 mm, slice thickness 3 mm with no interval).

DTI processing

The DTI data was post-processed using DTI Task Card software (Massachusetts General Hospital, Boston, United States), and FA maps were calculated. For the placement of regions of interest (ROI), the patients with MS were divided in two groups: group one (n=29) patients with areas of high signal on T2-weighted images (plaques) in the cervical spinal cord and group two (n=12) patients with no evidence of abnormal signal on T2-weighted images in the cervical spinal cord. In the group one the ROIs were placed on the plaques, around the plaques and on the NASC distant more than 10 mm from the plaque, using sagittal FA maps (mean size of the ROI 0.30 mm^2) (Fig 1). In the controls of group one the ROI was positioned on the center of the spinal cord at the level of C2–C3, and included most of the cord tissue at this level. In the group two and its controls, four ROIs were placed at the level of C2–C3 in every patient on the following regions: right anterior horn, right posterior horn, left anterior horn and left posterior horn (mean size of the ROI 0.08 mm^2) (Fig 2).

Statistical analysis

Regarding the group one, which included patients with MS and abnormal spinal cord MR imaging, the statistical analysis compared the FA values of the plaque, periplaque and NASC with the values obtained at the central region of the controls' spinal cord at the level of C2–C3. In the group two, which included patients with MS and normal spinal cord MR imaging, the comparison considered the FA values of study and control groups that were measured on different regions of the spinal cord (right anterior horn, right posterior horn, left anterior horn and left posterior horn) at the level of C2–C3. The statistical treatment was performed with the exact Mann-Whitney test, and P values of less than 0.05 were considered statistically significant.

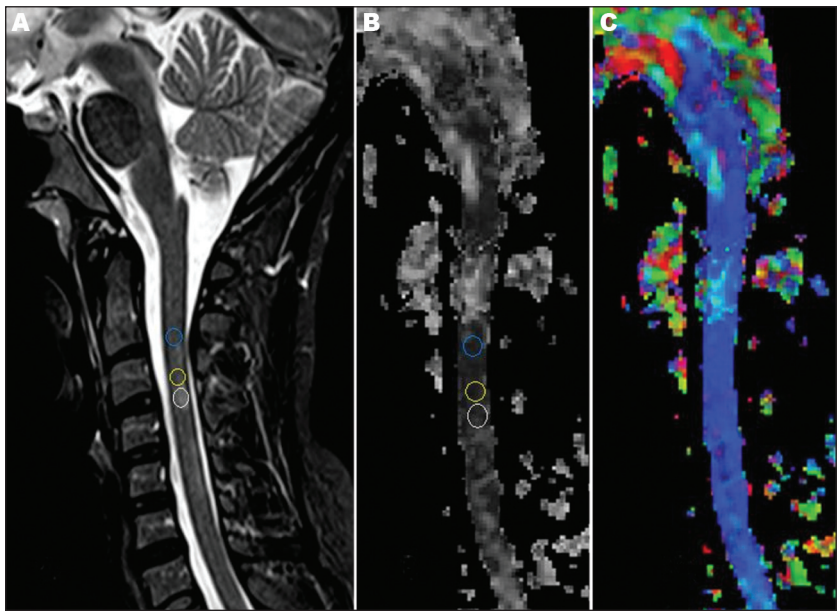

Fig 1. 32-year-old female patient with MS. Cervical spine MRI showing sagittal STIR [A], FA map [B] and FA color map [C]. In A and B, the placement of the ROIs is demonstrated in the plaque (white), NASC around the plaque (yellow) and NASC more than 1cm from the plaque (blue). Note the artifacts in the FA and FA color maps above the blue ROI, which are common in the DTI of the spinal cord.

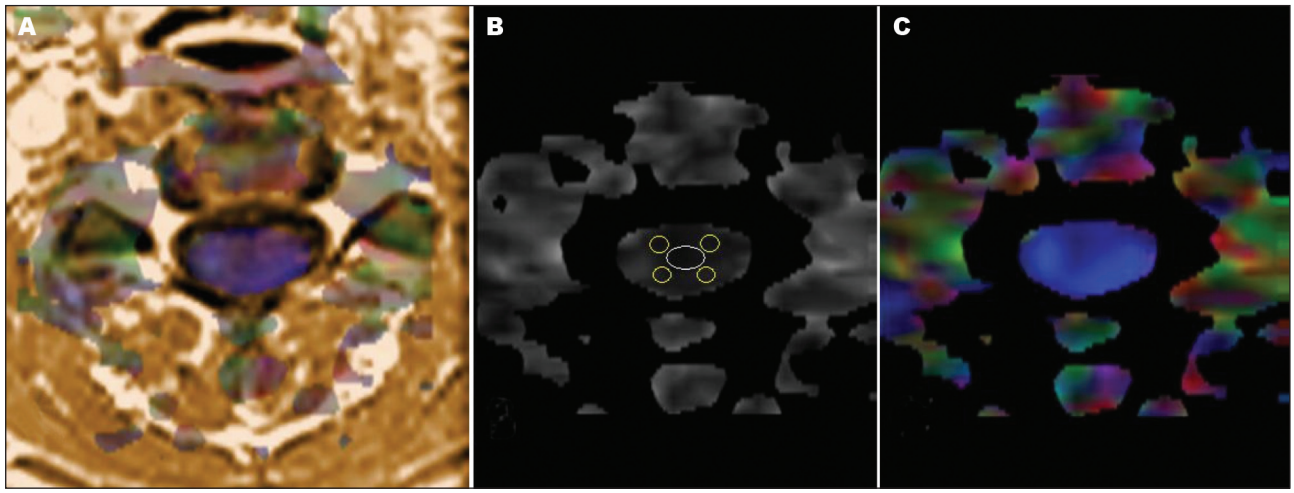

Fig 2. 28-year-old female patient with MS. Cervical spine MRI showing axial T1 fused with FA color map [A], FA map [B] and FA color map [C]. In B, the position of the ROIs is demonstrated. An ROI was drawn in the center of the spinal cord (white) for guiding the placement of the ROIs in the right anterior, right posterior, left anterior and left posterior horns (yellow) of the spinal cord.

Table 1. Mean FA values of cervical spinal cord of MS patients with abnormal signal on T2-weighted MR imaging.

	Topography in the cervical spinal cord			
	Plaque	Periplaque	NASC	Controls
FA mean values ± SD	0.435 ± 0.036	0.572 ± 0.042	0.629 ± 0.024	0.735 ± 0.057

FA: fractional anisotropy; SD: standard deviation; NASC: normal-appearing spinal cord.

RESULTS

The FA values obtained thought DTI of the cervical spinal cord of patients with MS, who showed abnormal high signal on T2-weighted images (plaques) are shown in the Table 1. The FA values were significantly lower in the plaques compared to the periplaque region, NASC and controls ($p<0.001$). In addition, the FA values in the periplaque region were also lower than the NASC and controls ($p<0.001$). Finally, the FA mean values in the NASC were lower than the values obtained in the control group ($p<0.05$).

The Table 2 shows the FA values of the cervical spinal cord of patients with MS, who had normal conventional MR imaging. The FA values obtained in all the regions of

Table 2. Mean FA values of cervical spinal cord of MS patients with normal signal on T2-weighted MR imaging.

	Topography in the cervical spinal cord			
	Left anterior horn	Right anterior horn	Left posterior horn	Right posterior horn
MS patients	0.603 ± 0.090	0.616 ± 0.080	0.652 ± 0.087	0.611 ± 0.089
Control group	0.715 ± 0.062	0.704 ± 0.061	0.752 ± 0.069	0.759 ± 0.067

Fractional anisotropy mean value ± standard deviation, MS: multiple sclerosis

NASC of patients with MS were significantly lower than controls ($p<0.05$). Comparing only the patients with MS and NASC, there was no significant difference between the FA values obtained in the posterior and anterior horns at the level of C2–C3 ($p>0.05$).

DISCUSSION

In this study, we retrospectively evaluated a cohort of 41 patients with relapsing-remising MS and compared the DTI findings with an age- and gender-matched control group. Similar to other studies[11-14], in this series the fractional anisotropy in the plaques, periplaque region and NASC more than 10 mm distant from the plaques was significantly lower than controls. Also, the FA values obtained in our series were robust and comparable to the previous studies[11]. In addition, when evaluating the FA of the NASC at the level of C2–C3, both anterior and posterior horns showed reduced FA values. However, no significant differences were seen when comparing the fractional anisotropy of the anterior and posterior horns.

Multiple sclerosis is a chronic inflammatory disease that causes demyelination and axonal loss in both brain and spinal cord. Spinal cord lesions demonstrated with MR imaging have been included in revised McDonald criteria of MS[15], ascertain that these findings can be used to demonstrate disease dissemination in time and space. MS spinal cord abnormalities may consist of focal well-demarcated or diffuse poorly demarcated lesions, and up to 97% of the MS patients demonstrate spinal cord abnormalities on MR imaging[16]. Currently, spinal cord MR imaging studies focus on the presence of lesions visible on T2, short tau inversion recovery (STIR) or proton density sequences, which are secondary to demyelination[17]. However, previous authors have failed to prove the relation between the spinal cord MR imaging abnormalities on the conventional sequences and the clinical disability[16,18,19]. Advanced MR imaging techniques, such as proton spectroscopy and diffusion tensor imaging, have also been studied with some success when aiming to demonstrate a correlation between the imaging findings and the clinical status[20]. Also, the DTI have demonstrated fractional anisotropy abnormalities in the brain white matter[7,8] and in the spinal cord[11,12], even in regions with normal signal on T2-weighted images, defining the well-known terms called "normal appearing white matter" and "normal appearing spinal cord".

The diffusion tensor imaging is a recent MR imaging technique that allows measurement of magnitude and directionally of water diffusion in tissue, providing a quantitative method for assessment of the integrity of white matter fiber tracts[9,10]. Previous studies with DTI have demonstrated reduced fractional anisotropy in the demyelinating plaques as well as in the normal appearing white matter in the brain of MS patients, despite any abnormality in the conventional MR imaging sequences, including T2-weighted image and FLAIR[6-8].

Several authors had evaluated the spinal cord of patients with multiple sclerosis using diffusion tensor MR imaging[11-14]. Agosta et al.[13] investigated 24 patients with progressive MS and demonstrated reduction of the cross-sectional area and average cord fractional anisotropy. However, the DTI parameters showed no correlation with conventional and DTI MR findings in the brain. They suggested that the DTI of the cervical cord could quantify the extent of the diffuse cord pathology in MS, but these findings are independent of the brain damage. Hesseltine et al.[12] studied 24 patients with relapsing-remising MS, measuring the FA in the anterior, posterior, lateral and central areas of the normal appearing cervical spinal cord at the level of C2–C3. The fractional anisotropy was reduced in the lateral, posterior and central regions, and the authors suggested that the DTI could be useful in detecting spinal cord occult lesions, predicting clinical course and monitoring disease progression. In addition, Ohgiya et al.[11] also demonstrated reduction of the fractional anisotropy in the C2–C3, C3–C4 and C4–C5 spinal cord levels in 21 patients with MS. The mean FA was 0.441 in the plaques, 0.542 in the NASC and 0.739 in the controls. Thus, these studies point to the potential use of the diffusion tensor MR imaging for the evaluation of the spinal cord plaques and NASC of patient with MS, mainly for identification of occult lesions and probably for the evaluation of disease progression.

Although initial reports suggest advantages of DTI in the evaluation of spinal cord in MS patients, they are single-center preliminarily results and should be cautiously interpreted. The DTI has several technical limitations, mainly related to low signal-to-noise ratio and movement artifacts associated to breath and pulsation. Also, the technical limitations of the spinal cord DTI are even more important, as there is a small amount of tissue (spi-

nal cord) contributing for the signal and a large amount of tissue (bone and liquor) causing artifacts. Finally, a limitation of our study was the selection of patients with MS referred from different physicians, and thus being submitted to diverse treatments. As a result, we couldn't make correlations between the DTI data and treatment response or follow-up. Nevertheless, these initial results are promising and needs further investigations.

In conclusion, DTI seems to offer the possibility of adding important information for the evaluation of MS patients. In this series of relapsing-remising MS patients, we observed reduced fractional anisotropy in the demyelinating plaques and in the NASC, corroborating the hypothesis that the histological extension of the MS lesions is more severe than the abnormalities seen in the conventional MR imaging sequences. While the spinal cord MR imaging is improving and gaining importance in the clinical evaluation of MS patients, improvements in the MR imaging acquisition and analysis are welcome to provide even more sensible imaging evaluation of the spinal cord. The method herein assessed is capable to depict subtle and diffuse changes in the microarchitecture of spinal cord in MS patients despite any visible lesions in the conventional MR sequences. As a result, fractional anisotropy measurement makes possible the assessment of early stage spinal cord involvement. Further studies can confirm the role of this advanced MR imaging technique for predicting the real extension of the demyelinating disease, as well as for evaluating the disease progression and treatment response.

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