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EVALUATION OF WHITE MATTER IN PATIENTS WITH MULTIPLE SCLEROSIS THROUGH DIFFUSION TENSOR MAGNETIC RESONANCE IMAGING

Rachel E. Maia de Andrade[1], Emerson L. Gasparetto[2,3], Luiz Celso Hygino Cruz Jr.[1,3], Fabiana Brito Ferreira[3], Roberto Cortês Domingues[3], Edson Marchiori[4], Romeu Cortês Domingues[5]

ABSTRACT - *Objective*: To study the white matter of patients with multiple sclerosis (MS) with diffusion tensor magnetic resonance (MR) imaging (DTI). *Method*: Forty patients with clinical-laboratorial diagnosis of relapsing-remitting MS and 40 age- and sex-matched controls, who underwent conventional and functional (DTI) MR imaging, were included in the study. The DTI sequences resulted in maps of fractional anisotropy (FA) and regions of interest were placed on the plaques, peri-plaque regions, normal-appearing white matter (NAWM) around the plaques, contralateral normal white matter (CNWM) and normal white matter of the controls (WMC). The FA values were compared and the statistical treatment was performed with the Mann-Whitney U test. *Results*: The mean FA in plaques was 0.268, in peri-plaque regions 0.365, in NAWM 0.509, in CNWM 0.552 and in WMC 0.573. Statistical significant differences in FA values were observed in plaques, peri-plaque regions and in NAWM around the plaques when compared to the white matter in the control group. There was no significant difference between the FA values of the CNWM of patients with MS and normal white matter of controls. *Conclusion*: Patients with MS show difference in the FA values of the plaques, peri-plaques and NAWM around the plaques when compared to the normal white matter of controls. As a result, DTI may be considered more efficient than conventional MR imaging for the study of patients with MS.

KEY WORDS: diffusion tensor imaging, fractional anisotropy, normal-appearing white matter, multiple sclerosis.

Avaliação da substância branca em pacientes com esclerose múltipla através de ressonância magnética com imagens por tensor de difusão

RESUMO - *Objetivo:* Estudar a substância branca de pacientes com esclerose múltipla (EM) através de imagens de ressonância magnética (RM) por tensor de difusão (DTI). *Método:* Foram avaliados 40 pacientes com diagnóstico clínico-laboratorial de EM remitente-recorrente e quarenta controles pareados por idade e sexo, os quais foram submetidos à RM convencional e funcional (DTI). As seqüências de DTI resultaram em mapas de anisotropia fracionada (FA) e as regiões de interesse foram posicionadas nas placas, regiões peri-placas, substância branca aparentemente normal (SBAN) ao redor das placas, substância branca normal contra-lateral (SBNC) e substância branca normal do grupo controle (SBC). Os valores de FA foram comparados e a análise estatística foi realizada utilizando o teste Mann-Whitney U. *Resultados:* A média de FA nas placas foi 0,268, nas regiões peri-placas 0,365, na SBAN 0,509, na SBNC 0,552 e na SBC 0,573. Foram observadas diferenças estatisticamente significativas nos valores de FA nas placas, regiões peri-placas e na SBAN ao redor das placas quando comparados com a SBC. Não houve diferença entre os valores de FA na SBNC dos pacientes com EM e na SBC. *Conclusão:* Pacientes com EM demonstram diferença nos valores de FA nas placas, peri-placas e SBAN ao redor das placas quando comparados com a SBC. Assim, o DTI pode ser considerado mais eficiente do que as seqüências de ressonância magnética convencional no estudo dos pacientes com EM.

PALAVRAS-CHAVE: imagem por tensor de difusão, anisotropia fracionada, substância branca aparentemente normal, esclerose múltipla.

Department of Radiology of the University of Rio de Janeiro (UFRJ) and CDPI - Clínica de Diagnóstico por Imagem, Rio de Janeiro RJ, Brazil: [1]Radiologist and Master of Science Student of the Department of Radiology, UFRJ; [2]Associated Professor of the Department of Radiology, UFRJ; [3]Radiologist of the CDPI - Clínica de Diagnóstico por Imagem, Rio de Janeiro RJ, Brazil; [4]Professor of the Departments of Radiology, UFRJ and University Fluminense, Niteroi RJ, Brazil; [5]Radiologist and Director of the CDPI - Clínica de Diagnóstico por Imagem, Rio de Janeiro RJ, Brazil.

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Dr. Emerson L. Gasparetto - Hospital Universitário Clementindo Fraga Filho da UFRJ - Rua Professor Rodolpho Paulo Rocco 255 - 21941-913 Rio de Janeiro RJ - Brasil. E-mail: egasparetto@gmail.com

Magnetic resonance (MR) imaging has become increasingly important as an additional tool for the diagnosis and follow-up of patients with multiple sclerosis (MS)[1-10]. Several parameters have been suggested for the classification of MR imaging criteria to predict conversion to multiple sclerosis. Barkhof criteria[1] - later modified by Tintoré et al.[2], are the most commonly employed in clinical practice. In addition, McDonald criteria consider the idea of dissemination in space and time of the lesions, what can be evaluated with MR imaging[3]. The study of T2-weighted images on conventional MR imaging is, however, very limited. The main problem is related to the low specificity, since inflammation, edema, demyelination, gliosis and axonal loss are represented by areas of high signal on this sequence[3]. In addition, conventional MR imaging has also shown low ability to detect and quantify the extension and severity of microscopic injuries on the normal-appearing white matter (NAWM)[4-7] surrounding plaques, particularly in early phases of the disease[8-10].

Diffusion tensor imaging (DTI) is a new MR imaging technique that in addition to investigate the magnitude of water diffusion in the tissues, allows the study of its direction. This is an important advantage since the highly directional organization of myelinated white matter results in a high degree of anisotropic diffusion in these tracts[11-14]. Diminished anisotropic diffusion and fractional anisotropy (FA), on the other hand, are expected in diseases in which axon integrity or myelination are affected[10,15,16].

More recently, several studies have shown an increasing importance of the DTI for the evaluation of MS patients, particularly analyzing microstructural alterations in the NAWM[5,6,13,16-18]. Brain regions with normal signal on T1- and T2-weighted images have demonstrated abnormal values of fractional anisotropy. In addition, the alterations detected on DTI seem to relate better with clinical deterioration comparing to the conventional MR imaging findings.

The present study aimed to study the normal-appearing white matter of patients with MS thought DTI, comparing the fractional anisotropy values in these regions with control patients.

METHOD

This prospective study was conducted from October 2003 to February 2005. We studied the brain MR imaging of 40 patients (14 men and 26 women, mean age 32.6 years) with clinical and laboratory diagnosis of relapsing-remitting MS[1,2]. The age- and sex-pared control group included forty volunteers (14 men and 26 women, mean age 30 years), with no clinical evidence of neurological disease and with normal conventional brain MR imaging. All patients signed informed consent and the Institutional Review Board of our institution approved the study.

The exams were performed in a 1.5T scanner (Symphony Avanto, Siemens, Germany), with 8-channel head coil. All patients were submitted to the conventional MR imaging protocol, including T2-weighed sequences (repetition time (TR)=4410 ms, echo time (TE)=98 ms, field of view (FOV)=240 mm, matrix=320X320 mm and 3-mm section thickness with 30% of interval); FLAIR sequence (TR= 9950 ms, TE=100 ms, FOV=220 mm, matrix=256X256 mm and 5-mm thickness section with 35% of interval) and T1-weighed sequences with magnetization transfer (MT) before and after intravenous administration of gadolinium (TR=635 ms, TE=9.4 ms, FOV=240 mm, matrix=256X256 mm and 5-mm section thickness with 35% of interval).

The DTI sequence employed a gradient pulse in six different directions, with 5-mm section thickness and 1.5 mm interval, FOV of 230 mm, matrix of 128X128 mm and six excitations. The images were transferred and post-processed in an independent workstation, using the software DTI Task Card developed by the Massachusetts General Hospital, Martinos Center-MIT/MGH (Boston, Massachusetts, USA) to determine the anisotropy index. We defined the FA as the anisotropy index to allow comparison with other studies, because most of them have used this index[19,20].

The same observer placed regions of interest (ROIs) of the same size (5 pixels) on the white matter plaques, on the normal-appearing white matter (NAWM) peri-plaque and near to the plaque (radius of 1cm) and on the contra-lateral normal white matter (CNWM) (Fig 1). All plaques were chronic and were defined as lesions hyperintense on T2-weighed and FLAIR images and isointense or hypointense in T1-weighed images, without contrast enhancement. Patients with acute symptoms and signals of acute plaques (peri-plaque edema and contrast enhancement) were not included in the study. The NAWM was defined as and area of white matter with normal signal of all sequences of the conventional MR imaging. In the control group, four ROIs were placed on the periventricular white matter in both hemispheres.

The statistical treatment was performed with the Mann-Whitney U test, a non-parametric *t* test, using Gaussian two-tail approximations. P values of less than 0.05 were considered statistically significant.

RESULTS

The fractional anisotropy showed increasing values on the plaques, peri-plaque regions, NAWM around the plaques, CNWM and normal white matter of the controls (WMC), retrospectively (Table 1) (Fig 2).

The comparison between the FA values measured patients with MS and control group showed significant differences in the following: plaque versus peri-plaque ($p<0.0001$), NAWM ($p<0.0001$), CNWM ($p<0.0001$) and NM WMC ($p<0.0001$); peri-plaque versus NAWM ($p<0.0001$), CNWM ($p<0.0001$) and WMC

Table 1. Values of fractional anisotropy on the different locations of patients and controls.

	Plaque	Peri-plaque	NAWM	CNWM	WMC
Mean FA	0.268	0.365	0.509	0.552	0.573
±SD	±0.085	±0.080	±0.085	±0.096	±0.048

FA, fractional anisotropy; SD, standard deviation; NAWM, normal-appearing white matter; CNWM, contra-lateral normal-appearing white matter; WMC, normal white matter of controls.

Table 2. Values of p when comparing the FA between the different locations in both study and control group.

	Plaque	Peri-plaque	NAWM	CNWM	WMC
Plaque		p<0.0001	p<0.0001	p<0.0001	p<0.0001
Peri-plaque	p<0.0001		p<0.0001	p<0.0001	p<0.0001
NAWM	p<0.0001	p<0.0001		p=0.0353	p=0.0002
CNWM	p<0.0001	p<0.0001	p=0.0353		p=0.7161
WMC	p<0.0001	p<0.0001	p=0.0002	p=0.7161	

NAWM, normal-appearing white matter; CNWM, contra-lateral normal-appearing white matter; WMC, normal white matter of controls.

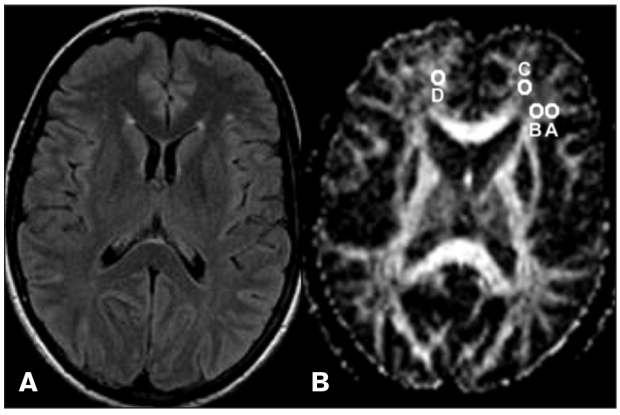

Fig 1. Axial FLAIR (A) and FA map (B) MR imaging demonstrating the position of the ROIs in the patients with MS, including the plaque (A), NAWM peri-plaque (B) and around the plaque (C) and contra-lateral NAWM (D).

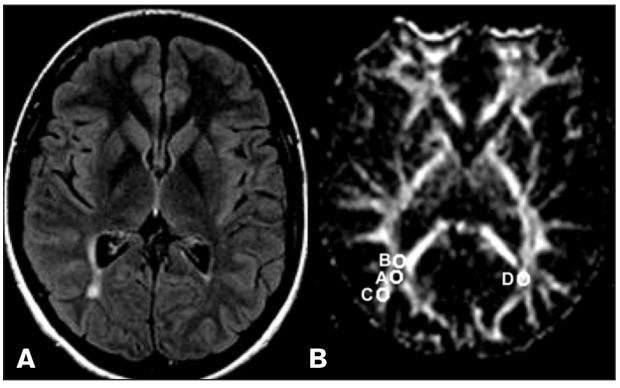

Fig 2. Axial FLAIR (A) MR imaging showing a plaque adjacent to the posterior horn of the right lateral ventricle. The FA map (B) demonstrates the position of the ROIs with the following values of fractional anisotropy: A=0.255; B=0.385; C=0.515 and D=0.565.

(p<0.0001); and NAWM versus CNWM (p=0.0353) and WMC (p=0.0002). There was no significant difference when comparing the FA values of CNWM and WMC (p=0.7161) (Table 2).

DISCUSSION

We compared the FA values in different regions of white matter between 40 MS patients and 40 healthy adult controls. Our results have showed that not only the plaques present reduced fractional anisotropy, but also the peri-plaque region and the white matter around the plaque, both of then demonstrating normal signal intensity of T2-weighted images.

Diffusion tensor imaging provides visualization of white matter microstructure and fiber organization that is not accessible with other imaging modalities. The diffusion ellipsoid obtained from DTI provides a quantitative assessment of the magnitude of water diffusion and its direction within the image voxel. In brain white matter, the motion of water molecules can be hindered by the presence of structural barriers created by the highly organized myelinated axonal fiber tracts. Therefore, water diffusion is much greater along the fibers than across the fiber. This information can be quantified by deriving quantitative scalar indices, such as mean diffusivity and fractional anisotropy, which have significant clinical value for the cellular level integrity of highly ordered white matter tissue. Unlike conventional MR imaging, DTI provides a unique method of imaging contrast and quantification that may allow better understanding

of the pathophysiology of MS-related white matter damage that would also be useful for monitoring disease progression and treatment effects[13,14,16].

Our results showed that DTI sequence is able to detect involvement of NAWM surrounding plaques, supporting previous reports. Guo et al.[5] analyzed NAWM surrounding plaques in 26 MS patients and in a control group, comparing FA and ADC values to estimate abnormalities of the white matter. They observed that FA values were significantly lower in plaques than in peri-plaque regions, NAWM and in the control group. Tievsky et al.[17] compared the ADC and FA in acute and chronic plaques of 12 patients in different stages of MS, showing that FA values were lower in acute plaques than in peri-plaques, chronic plaques and NAWM. In a study reported by Filippi et al.[19] involving 78 patients, lower FA values were observed in the NAWM of MS patients than in the white matter of control individuals. Rocca et al.[21] reported diffuse and subtle abnormalities in the NAWM of 20 MS patients, observing decreased FA values in the patients when compared to normal control individuals. Although there is still a lack of studies with correlation between DTI and pathological findings in patients with MS, previous histological observations support the hypothesis of extension of the MS lesions beyond the plaques[7,10,13].

The mechanisms underlying the apparent extension of the MS lesion beyond the plaques seen in T2-weighed images are not yet completely understood. Although MS is primarily characterized by myelin loss, histological evaluations have suggested that axonal lesions as well as neuronal loss may contribute to the pathogenesis of the disease[22,23]. *Post-mortem* studies have also shown significant axonal loss in NAWM of MS and suggested a contribution of this feature to the clinical presentation of the patients[7,10]. Probably, a complex process involving perivascular inflammation, astrocyte proliferation, myelin loss and axonal destruction is responsible for the lesions seen in patients with MS[3,17]. This process, mainly the myelin loss and direct interruption of axonal fibers, results in higher mobility of water molecules through fibre tracts, resulting in a decrease of FA values not only on the plaques, but also on the NAWM.

In conclusion, our study supports previous reports of abnormal FA values in the abnormal and normal-appearing white matter of patients with multiple sclerosis. We observed lower FA values in the plaques than in the peri-plaques, NAWM around the plaques and white matter of the controls group. There was no significant difference between the FA values of the white matter contra-lateral to the MS plaques when compared with the white matter of the control group. As a result, we suggest that DTI is more sensible in identifying and demarcating plaque limits than conventional MR sequences. Consequently, this technique is becoming a promising imaging tool for patients with multiple sclerosis.

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