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Fractional anisotropy measurements of the left dorsolateral prefrontal cortex for therapeutic response assessment after repetitive transcranial magnetic stimulation (rTMS) in relapsing remitting multiple sclerosis patients suffering from depression

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Abstract

Background: Multiple sclerosis (MS) is a major cause of neurological disability in adults. Depression is one of the most common psychiatric comorbidities in MS patients with negative impact on patients' quality of life. The aim of the study is to evaluate the role of diffusion tensor imaging (DTI) in monitoring the therapeutic response after high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) versus selective serotonin reuptake inhibitor (SSRI) therapy for relapsing remitting multiple sclerosis (RRMS) patients presenting with depression by measuring the fractional anisotropy of the dorsolateral prefrontal cortex (DLPFC) before and after treatment and also to assess the treatments' impact on patients' cognitive functions and depression.

Results: Fractional anisotropy (FA) only increased in rTMS group (0.44 ± 0.03 pre-rTMS vs 0.53 ± 0.05 post-rTMS, $P < 0.001$), but there were no significant changes in the SSRI group (0.44 ± 0.04 pre-SSRIs vs 0.45 ± 0.37 post-SSRIs, $P = 0.072$). Both rTMS and SSRI groups showed significant clinical improvement in Beck Depression Inventory (BDI) and Paced Auditory Serial Addition Test (PASAT) after either intervention (17.6 ± 3.25 pre-rTMS vs 10.6 ± 1.89 post-rTMS and 23 ± 6.36 pre-rTMS vs 24.87 ± 6.6 post-rTMS, respectively, $P < 0.001$; 17.67 ± 3.15 pre-SSRIs vs 0.6 ± 1.84 post-SSRIs and 23.8 ± 6.45 pre-SSRIs vs 25.07 ± 7.02 post-SSRIs, respectively, $P < 0.001$).

Conclusion: DTI is an ideal non-invasive tool for examining white matter integrity and can detect microstructural changes in the dorsolateral prefrontal cortex after rTMS and SSRI therapies for patients with MS and depression. FA increased only with rTMS denoting positive alteration in white matter microstructure. Both rTMS and SSRIs were equally effective in improving depression and cognition.

Keywords: Multiple sclerosis, Depression, Cognition, rTMS, SSRIs, Diffusion tensor imaging

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Background

Depression is one of the most common multiple sclerosis (MS) psychiatric comorbidities, having a lifetime prevalence that approaches 50%, which is three times the rate reported in the general population [1]. Despite its negative impact on patients' quality of life and their adherence to medications, depression in MS remains an underdiagnosed and undertreated symptom with no existing treatment guidelines [2].

A clear association between depression and cognitive impairment in physically healthy individuals has been previously described, and a similar association was also reported in MS patients, but it remains unknown if these impairments are reversible upon treatment of depression [3].

The dorsolateral prefrontal (DLPF) area has primarily been associated with executive functions and is considered a key node in attention networks. Besides, accumulating evidence also implicates it as an important neural substrate for depression and being the most accessible area for stimulation compared to other regions linked to depression pathophysiology [4]. Repetitive transcranial magnetic stimulation (rTMS) of DLPF cortex is considered a non-invasive alternative or adjunctive treatment for different types of depression disorders, including drug-resistant depression [5].

The diffusion tensor imaging (DTI) is a recent functional MR technique for detection of microstructure changes in the human brain. The FA (fractional anisotropy) is a DTI parameter which reflects the directionality of water molecule diffusion within the brain tissue [6]. Any abnormalities that lead to loss of axonal integrity and organization can reduce the normal FA values. Owing to the variable heterogeneous pathological changes of the brain tissue in MS patients, DTI has a higher specificity than conventional MRI sequences in the assessment of MS as it can detect microstructural changes in normal appearing white matter and normal appearing grey matter which is reflected as decrease in the FA and increase in the mean diffusivity which is beyond the capability of conventional MRI sequences [7, 8]. Several applications of DTI in MS patients were reported including grading of white matter injury, detection of microstructural changes in the normal appearing white matter, and normal appearing grey matter as well as lesions within the optic nerves and the spinal cord which is reflected as decreased FA that may precede the appearance of the lesion on conventional MRI sequences [8]. Several previous studies have discussed the role of DTI in multiple sclerosis patients with depression regarding the changes in the limbic system and DLPF which can be detected as altered FA values in the corresponding areas [9–11].

According to this background, we conducted our study to evaluate the possible effect of high-frequency rTMS versus selective serotonin reuptake inhibitor (SSRI) therapy on the microstructure of DLPF cortex using DTI in depressed relapsing remitting multiple sclerosis (RRMS) patients, and to furtherly assess the treatments' impact on patients' cognitive functions and depression. To our knowledge, previous imaging studies investigating the microstructural changes in the DLPF cortex in depressed MS patients after rTMS and SSRI therapy are lacking. Therefore, we aimed to investigate the role of DTI as a non-invasive tool for assessment of the therapeutic response in such patients.

Methods

This was an open label, parallel group, randomized study conducted on clinically depressed right handed RRMS patients diagnosed in accordance to the 2010 McDonald's criteria with Expanded Disability Status Scale (EDSS) scores of ≤ 5 , recruited from the Multiple Sclerosis Clinic, Neurology Department at our institution, between October 2015 and September 2017. Only patients who met the Structured Clinical Interview for DSM-IV (SCID-IV) criteria for depression were enrolled. Fifty-six patients were enrolled in the study, 26 were excluded (19 patients with Beck Depression Inventory (BDI) score ≥ 30 or ≤ 10 and 7 patients on interferon or steroid therapy). The final cohort is 30 patients (19 females and 11 males) divided into 2 equal groups, one receiving SSRIs and the other one receiving 3 rTMS sessions per week for 4 consecutive weeks. Mean patients' age in years was 29.3 ± 3.7 and 31.2 ± 4.7 for those receiving rTMS and SSRIs, respectively.

The study protocol was approved by the review board of our institution and conformed to the Helsinki declaration. Written informed consent was obtained from all participants prior to enrolment.

Exclusion criteria

Those with age < 18 years, current use of interferon or steroid therapies, Beck Depression Inventory-II (BDI) scores of ≤ 10 or ≥ 30 , pregnancy and history of seizures, and metallic implanted devices or foreign bodies were excluded.

Randomization, baseline assessment, and follow-up

Using computer-based randomization, patients who met the inclusion criteria were assigned to 2 groups, one receiving SSRIs and another receiving 3 rTMS sessions per week for 4 consecutive weeks. At baseline and 6 weeks following treatments, BDI to quantify depression severity and Paced Auditory Serial Addition Test (PASAT-B) for the assessment of cognitive functions were performed by four experienced neurologist with 20, 18, 12 and 10 years

of experience. DTI for left DLPF area was also performed at baseline and 6 weeks after therapy.

rTMS procedure

Left DLPF cortex rTMS was delivered using a Magstim Rapid® magnetic stimulator (Magstim Co. Ltd., Whitland, Dyfed, UK) at a frequency of 10 HZ in 10-s trains at 110% of the estimated motor threshold (MT). Twenty trains were given in each session with a 10-s inter-train interval with 100 stimuli and 80% of MT.

MR imaging and DTI

MRI scans were performed on a 1.5 Tesla unit (Achieva, Philips). A standard head coil was used. DTI obtained for all patients consisted of a single shot, spin-echo echo planar sequence in 12 encoding directions. A diffusion weighting factor of 800 s/mm² was used. The imaging parameters were as follows: TR 8000 ms, TE 67 ms, flip angle 90, matrix 112 × 110, FOV 210 mm, number of excitations 2, and slice thickness 2 mm. All images were transferred to a workstation (Philips Extended MR Workspace, 2.6.3.5) for post-processing. Grey scale FA maps and directionally encoded colour FA maps were obtained.

FA values were measured in the prefrontal white matter which was identified anterior and lateral to the corpus callosum and to the left of the midline. Freehand drawings of the regions of interest (ROIs) were made at the FA colour map overlaid on T2 or FLAIR images. Measurements were performed at normal appearing white matter without demyelinating plaques. The number of voxels for each ROI ranged between 6 and 8 (mean of 7 ± 0.081). MRI processing and interpretation were performed by three radiologists with 15, 14, and 13 years of expertise; each records the FA measurements independently, and then, the average of the three readings was recorded.

Statistical analysis

The collected data was revised, coded, tabulated, and introduced to a PC using Statistical package for Social Science (SPSS 20). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

Descriptive statistics: mean and standard deviation (± SD) were used to express the numerical data. Analytical statistics: Student *T* test was used to assess the statistical significance of the difference between two study group means. Chi-square test was used to examine the relationship between two qualitative variables. Correlation analysis (using Spearman's method) was used to assess the strength of association between two quantitative variables. The correlation coefficient denoted symbolically "rs" defines the strength (magnitude) and direction (positive or negative) of the linear relationship between two variables. Paired *t* test was used to assess the statistical significance of the difference between two means measured twice for the same study group.

Results

No significant differences were identified between the two treatment groups in terms of the demographics, clinical characteristics, and baseline BDI and PASAT scores (Table 1).

Fractional anisotropy (FA) only increased significantly in the rTMS group 6 weeks following treatment (0.44 ± 0.03 pre-rTMS vs 0.53 ± 0.05 post-rTMS, *P* < 0.001), but not in the SSRI group (0.44 ± 0.04 pre-SSRIs vs 0.45 ± .37 post-SSRIs, *P* = 0.072) (Figs. 1 and 2; Table 2).

Though baseline FA values in both study groups were comparable, rTMS was superior in improving FA values following treatment (Table 3)

Both rTMS and SSRIs demonstrated their efficacy in the improvement of depression and cognitive functions significantly as assessed by BDI and PASAT scores (17.6 ± 3.25 pre-rTMS vs 10.6 ± 1.89 post-rTMS and 23 ± 6.36 pre-rTMS vs 24.87 ± 6.6 post-rTMS, respectively, *P* < 0.001; 17.67 ± 3.15 pre-SSRIs vs 0.6 ± 1.84 post-SSRIs and 23.8 ± 6.45 pre-SSRIs vs 25.07 ± 7.02 post-SSRIs respectively, *P* < 0.001) (Table 4).

Discussion

Depression in MS patients adds substantially to the morbidity and mortality associated with this disease. TMS is a neurostimulatory and neuromodulatory technique which is based on the electromagnetic induction of an electric field in the brain [12].

Table 1 Demographics and baseline clinical characteristics of the study groups

	rTMS group (n = 15)	SSRI group (n = 15)	P value
Age, years (mean ± SD)	29.3 (3.7)	31.2 (4.7)	0.2
Gender, F/M	12/3	7/8	0.058
Disease duration in years (mean ± SD)	4.6 ± 2.2	3.6 ± 1.5	0.1
EDSS baseline scores (mean ± SD)	3.8 ± 1.4	3.2 ± 0.9	0.16
BDI baseline scores (mean ± SD)	17.6 ± 3.2	17.7 ± 3.2	0.96
PASAT baseline scores (mean ± SD)	23 ± 6.4	23.8 ± 6.4	0.74

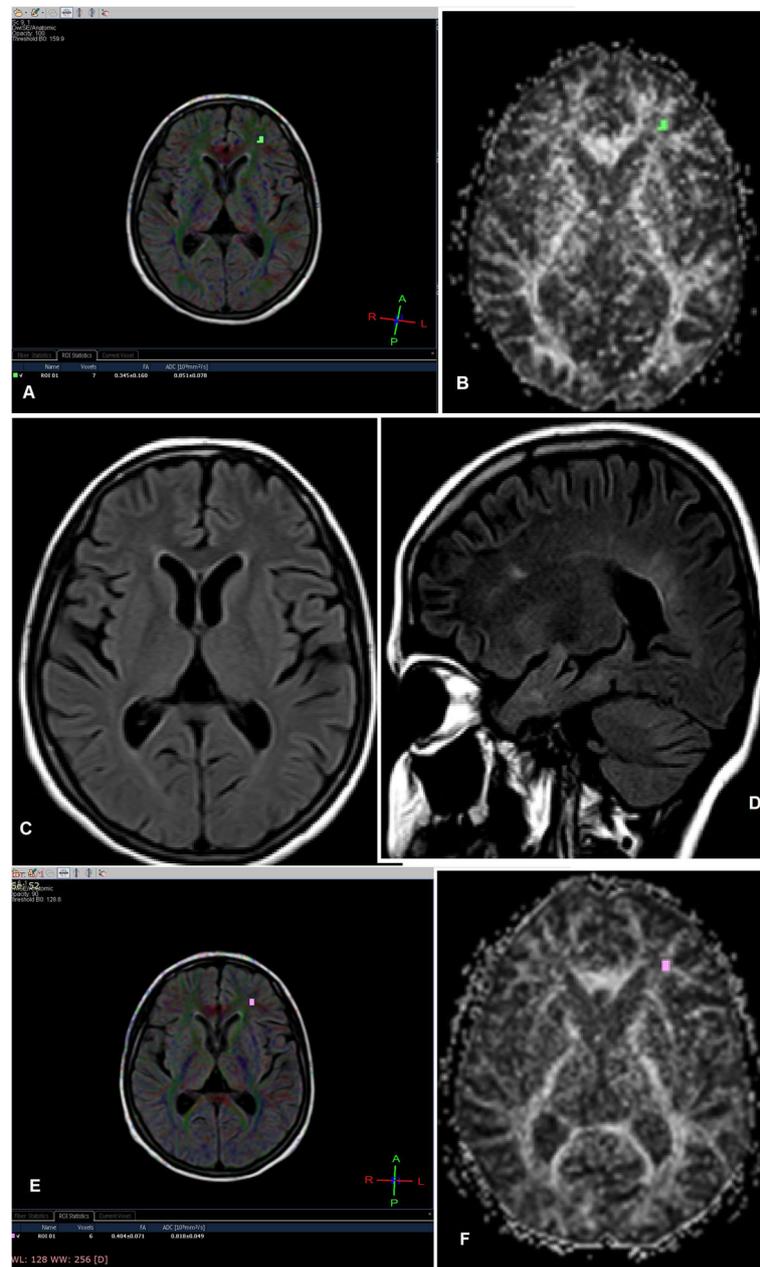


Fig. 1 A 26-year-old patient (BDI score 18). **a** Colour-coded FA maps overlaid on axial FLAIR and **b** grey scale FA map showing FA measurement in the left dorsolateral prefrontal white matter (0.345 ± 0.160). **c** Axial FLAIR and **d** sagittal FLAIR weighted images showing the periventricular high signal demyelinating plaques. The MRI examination 6 weeks following rTMS therapy. **e** Colour-coded FA maps overlaid on axial FLAIR and **f** grey scale FA map showing an increase in the FA value (0.404 ± 0.071)

FA has been found to be a sensitive measure of structural brain damage, as it can quantify the degree of water diffusion and reliably visualize the micro-structural status [13]. Numerous studies have reported reduced FA values in brains of patients with depression [14, 15]. In the current study, high-frequency repetitive transcranial magnetic stimulation (HF-rTMS)-treated patients had significantly higher post-

treatment FA values in left DLPF area compared to patients treated with SSRIs.

Liao et al. reported patients with treatment-resistant depression had reduced left middle frontal gyrus FA values, which significantly improved after 4 weeks of rTMS treatment which agreed with our results [16].

In the same context, May et al. found a significant structural alteration at the superior temporal cortex

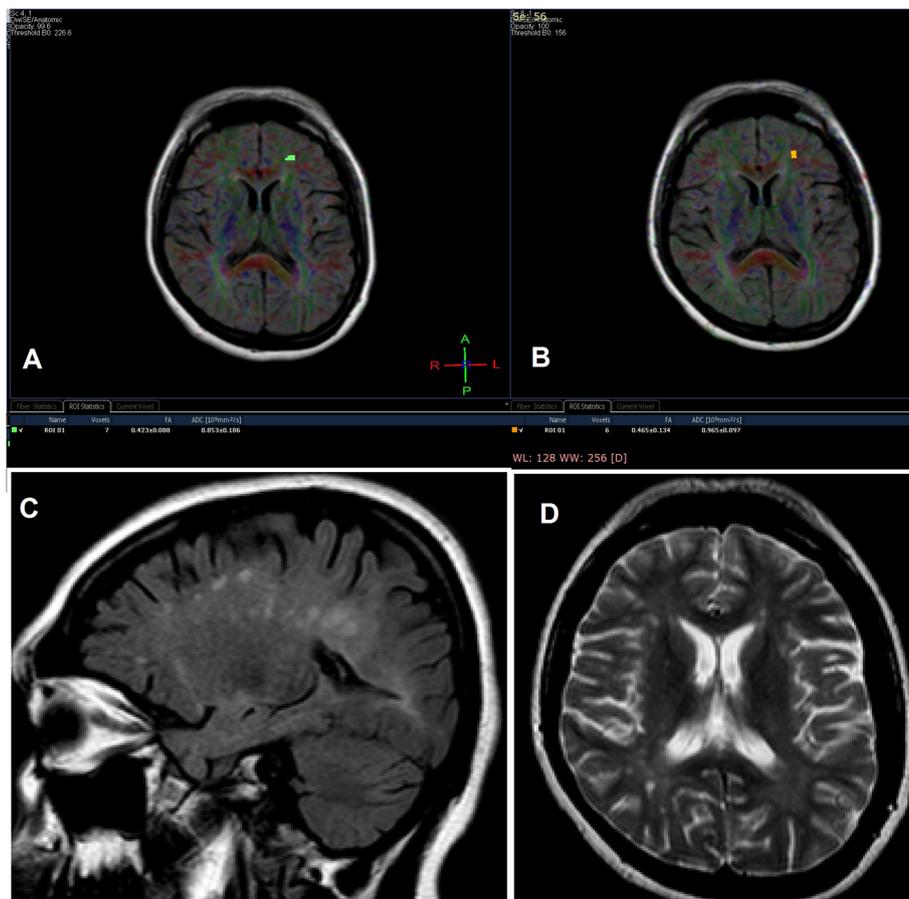


Fig. 2 A 30-year-old female patient (BDI score 13). **a** Colour-coded FA maps overlaid on axial FLAIR showing FA measurement in the left dorsolateral prefrontal white matter (0.423 ± 0.088). **b** The MRI examination 6 weeks following rTMS therapy showing an increase in FA value (0.465 ± 0.134). **c** Sagittal FLAIR and **d** axial T2 weighted images showing the bilateral cerebral white matter demyelinating plaques

reflected as increase in grey matter cortical evoked potential using voxel-based morphometry in regions of the brain stimulated with rTMS after 5 days of 1-Hz rTMS treatments at 110% motor threshold to the superior temporal gyrus [17]. Although these are different stimulated regions, using different rTMS parameters, and different imaging protocol from our study, it still supports the idea that rTMS can induce structural as well as functional changes.

One explanation for the selectively increased FA values after HF-rTMS is that the repeated rTMS induces a positive effect on the white matter organization for the side of the brain stimulated. White matter anatomical

connectivity changes following rTMS involve enhanced myelination, axonal and dendritic growth, and remodeling [18, 19]. Other potential mechanisms underlying sustained changes following rTMS is synaptic strength enhancement, through long-term potentiation and long-term depression that can last for several hours, days, or even weeks [20].

There has been limited research observing how white matter structures change after antidepressant treatment. On comparing FA values before and after administration of SSRIs, our study found no significant difference between pre- and post-treatment values. An explanation could be that SSRIs increase extracellular neurotransmitter activity thus modulating neuron activity in receptor-rich areas rather than inducing structural changes and that they appear to act more as symptom relievers rather than as normalizers of pathophysiologic causality [21].

In a study done by Avissar et al., resting state functional MRI was acquired in 27 patients suffering from depression and treated with rTMS over the left DLPF cortex. They measured the functional connectivity

Table 2 Left DLPF white matter FA values at baseline and 6 weeks after receiving rTMS and SSRIs

	At baseline	6 weeks after treatment	P value
	Mean ± SD	Mean ± SD	
rTMS group	0.44 ± 0.03	0.53 ± 0.05	< 0.001*
SSRI group	0.44 ± 0.04	0.45 ± 0.37	0.072

Table 3 Comparison between FA value before and after treatment

	rTMS group	SSRI group	P value	CI 95%
	Mean ± SD	Mean ± SD		
At baseline	0.44 ± 0.03	0.44 ± 0.04	0.915	
6 weeks after treatment	0.53 ± 0.05	0.45 ± 0.04	< 0.001*	(− 0.12 to − 0.05)
FA % of change	21.5% (10.9%)	3.1% (5.8%)	< 0.001*	(− 0.03 to 0.02)

between the frontal cortex and the corresponding striatal targets based on diffusion tensor imaging, and they concluded that higher functional connectivity between the dorsolateral prefrontal cortex (DLPFC) and striatum predicted better treatment response [22].

As for the clinical outcome, in the current study, patients who received either rTMS or SSRIs had a significant decrease in their BDI scores post-treatment, thus emphasizing the efficacy of rTMS in the same respect as the SSRIs in treating depression in RRMS patients.

In agreement with our results, George et al. observed that depression scores significantly decreased after treatment with rTMS [23]. In contrast, other studies did not show any benefit of rTMS in treatment of depression [24, 25].

No significant difference was found in this study when comparing therapeutic impact of rTMS on depression to that of SSRIs. This goes in accordance with Bares et al. who compared the efficacy of 1-Hz rTMS over the right prefrontal dorsolateral cortex with venlafaxine in the treatment of resistant depression; clinically relevant reduction of depressive symptomatology was found in both groups, and the rTMS results were comparable to that of venlafaxine [26].

Nevertheless, RRMS patients, in this study, showed significant improvement of their PASAT scores after receiving either HF-rTMS or SSRIs. This goes with Hulst et al. who investigated the effects of HF-rTMS of the right DLPF area on working memory performance and reported improved N-back accuracy following treatment [27]. In another study by Culang-Reinlieb et al., conducted on patients with major depressive disorder on SSRIs, verbal learning improvement was noticed regardless of the patients' response to therapy [28].

Table 4 BDI and PASAT scores before and after receiving rTMS and SSRIs

		At baseline	6 weeks after treatment	P value
		Mean ± SD	Mean ± SD	
rTMS group	BDI	17.6 ± 3.25	10.6 ± 1.89	< 0.001*
	PASAT	23 ± 6.36	24.87 ± 6.6	0.002*
SSRI group	BDI	17.6 ± 3.1	10.6 ± 1.84	< 0.001*
	PASAT	23.8 ± 6.4	25.07 ± 7.02	< 0.001*

Limitations of our study include relatively small group numbers and lack of placebo and sham rTMS arms to compare with both the SSRI and rTMS groups. Also the use of ROI measurements on FA maps is inherently limited when compared to voxel-based analysis such as TBSS; however, this depends on the software availability.

Conclusion

DTI is an ideal non-invasive tool for examining white matter integrity and can detect microstructural changes in the dorsolateral prefrontal cortex after rTMS and SSRI therapy for patients with MS and depression. FA increased only with rTMS denoting positive alteration in white matter microstructure. Both rTMS and SSRIs were equally effective in improving depression and cognition.

Abbreviations

BDI: Beck Depression Inventory; DLPF: Dorsolateral prefrontal; DLPF C: Dorsolateral prefrontal cortex; DSM: Diagnostic and Statistical Manual of Mental Disorders; DTI: Diffusion tensor imaging; EDSS: Expanded Disability Status Scale; FA: Fractional anisotropy; HF-rTMS: High-frequency repetitive transcranial magnetic stimulation; MS: Multiple sclerosis; PASAT: Paced Auditory Serial Addition Test; RRMS: Relapsing remitting MS; rTMS: Repetitive transcranial magnetic stimulation; SSRIs: Selective serotonin reuptake inhibitors

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Authors' contributions

TAH participated in the study design, manuscript editing, and MRI assessment. SFE is the editor of the manuscript and participated in the MRI assessment. HSS, NMS, and ANE shared in the clinical assessment and therapeutic procedures. MNS did the clinical assessment of the patients. BEM participated in the MRI assessment and the statistical analysis. MAE participated in the editing of the manuscript, data collection, clinical assessment, and the statistical analysis. The authors read and approved the final manuscript.

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Availability of data and materials

All the datasets used and analyzed in this study are available with the corresponding author on reasonable request.

Competing interest

The authors declare that they have no competing interest.

Ethics approval and consent to participate

Written informed consent was signed by all patients before the MRI examination. The study was approved by the medical committee of the Faculty of Medicine, Cairo University. Reference number is not available.

Consent for publication

All adult patients included in this research (> 18 years of age) gave written informed consent.

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