CLINICAL STUDIES

The clinical value of deep gray matter 3T MRI perfusion in patients with multiple sclerosis

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ABSTRACT

Background. Multiple sclerosis (MS) is a common neurological disorder between adults. Magnetic resonance imaging (MRI) is the imaging modality of choice, new MRI techniques helped in more accurate assessment of the disease extent, activity and severity. In dynamic susceptibility contrast (DSC), the perfusion of the lesions as well as normally appearing white and gray matter of the brain have been assessed.

Objective. To highlight the role of MRI perfusion of the deep gray matter in multiple sclerosis patients and its relation to their clinical disability and cognitive impairment

Methods. 40 patients with MS were enrolled in this study, they were divided into two groups (group A with mild clinical disease and preserved cognitive functions, and group B with marked clinical disease and cognitive functions impairment) they were divided according to their clinical disability and cognitive impairment assessed by experienced neurologist, Additional 20 healthy controls were included.
Perfusion parameters including cerebral blood volume(CBV), cerebral blood flow (CBF) and mean transit time (MTT) of the deep gray matter were compared for healthy controls and for the study groups.

Results. The perfusion values of the thalamus, putamen and caudate were significantly changed in group B that shows marked decrease in CBV and CBF and increased MTT compared with group A and the controls, With respect to group (A), there was no significant difference between the patients and controls

Conclusion. The decrease of perfusion of the deep gray matter in patients with MS is associated with the severity of the disease and cognitive impairment.

Keywords: multiple sclerosis, dynamic susceptibility contrast, deep gray matter perfusion

List of abbreviations

AIF – arterial input function
CBV – cerebral blood volume
CBF – cerebral blood flow
CI – cognitive impaired
CP – cognitive preserved
DSC – dynamic susceptibility contrast
GM – gray matter
MMSE – mini mental status examination
MoCA – Montreal cognitive assessment

MRI – magnetic resonance imaging
MS – multiple sclerosis
MTT – mean transit time
NAGM – normally appearing gray matter
NAWM – normally appearing white matter
PPMS – primary progressive multiple sclerosis
RRMS – relapsing remitting multiple sclerosis
SPMS – secondary progressive multiple sclerosis
WM – white matter

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INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated inflammatory demyelinating disease leading to neuronal dysfunction and disability [1].

MS is characterized by development of acute inflammatory white matter lesions that call plaques [1] and are visible on conventional MRI [2].However, it is now well-recognized that these plaques represent only an aspect of the disease [3].

In the last few decades, emerging advanced quantitative MRI modalities have detected micro pathological alterations even in the normal appearing white and gray matter of MS patients [4]. Furthermore, cortical lesions and gray matter (GM) perfusion changes have been defined as significant features of the disease [5] and as predictor for cognitive dysfunction in MS [6].

In DSC MRI, the tissue perfusion is assessed by evaluation of a series of rapidly repeated T2*-weighted MR images resulting from the first pass of a contrast agent bolus through the tissue, the first pass of a paramagnetic contrast through the capillary bed after rapid intra-venous injection induces local magnetic field heterogeneousities leading to fast dephasing of proton spins and lead to a transient drop in signal intensity which is approximately proportional to the instantaneous concentration of contrast agent in tissue [7].

The semi-quantitative parameters can be derived from the signal intensity attenuation curve. The transformation into the contrast concentration curve allows quantitative evaluation of the following parameters: CBV which is defined as the fraction of tissue volume occupied by blood (ml/g); MTT defined as the average time the contrast agent travels through the vascular bed of the brain tissue and CBF is defined as the volume of blood passing through a defined amount of brain tissue per minute (ml/g/min) [8]. The absolute quantification of the physiological parameters is strongly dependent on the arterial input function AIF [9].

METHODS
Study population

40 patients had undergone MR imaging between Jan 2021 and August 2022, studies were performed at Kobri El-Koba military hospital using 3 Tesla MR machine. All patients were subjected to full history taking, general and neurological examination

The mean age of the patients was 35±14 years. The patients had a mean disease duration of 5±3 years The patients were divided into two main groups (20 for each one) according to their clinical disability and cognitive impairment (group A that includes patients with mild disease course, no disability and preserved cognitive functions and group B that includes pa-

tients with marked disease course , disability and impaired cognitive functions), Additional 20 normal control cases in the same age group were included in the study, the disability scores and cognitive impairment were assessed by single experienced neurologist blind to the MR findings using the expanded disability scoring status (EDSS) and other cognitive assessment tests like mini mental status examination (MMSE) and Montreal cognitive assessment (MoCA)

Group (A) patients were all relapsing remitting patients.

Group (B) patients were 11 secondary progressive, 7 primary progressive and 2 relapsing remitting patients.

Image acquisition

Magnetic resonance imaging

The MRI examinations were performed to all the patients. They were done on a 3 Tesla super conducting system using a head coil of the appropriate size.

Protocol of MRI

The protocol included transverse dual echo T2-weighted (TR/TE: 3500/120msec), non-enhanced T1-weighted (TR/TE: 500/14 msec), and FLAIR imaging (TR/TE/TI: 11000/140/2800 msec).

Before scanning, an 18- or 20-gauge intravenous access was placed in the ante-cubital fossa for contrast injection

Enhanced MR was performed in transverse plane using a T2* sequence and images

Dynamic susceptibility contrast

The images were acquired during the first pass of a standard dose (0.1mmol/kg) bolus of GD. Contrast was injected at a rate of 5 ml/s, followed by a 20-mL bolus of saline also at a rate of 5ml/s. A total of 60 images were acquired at 1-second intervals.

Image post processing

All the images were transferred to the workstation supplied by the manufacturer.

Deconvolution of the measured tissue concentration with the arterial input function which was found manually, before deconvolution gamma variate functions were applied to reduce noise and correct any leakage secondary to blood brain barrier disruption

Quantitative values of MTT, CBV and CBF were calculated in regions of interest in the following brain regions bilaterally: the thalami, putamen and head of caudate

Regions of interest were placed in the same positions in patients and controls (Figure 1).
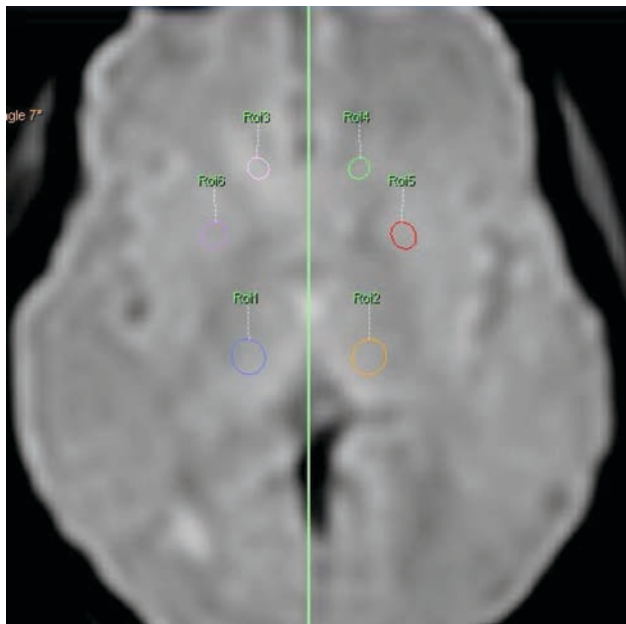
FIGURE 1. Regions of interest were placed in the caudate, lentiform and thalami bilaterally

Statistical analysis

Analysis was performed using SPSS version 21, normality of data was assessed by Shapirow Wilk test. Quantitative data were presented by mean +/- SD median, range and interquartile range. It was evaluated by Kruskal Wallis test. The P value was considered significant at level of < 0.05 and highly significant at level of 0.001.

RESULTS

The main findings in our study are:
– Marked reduction in CBV in group B in comparison to the group A and controls at the three regions (caudate, lentiform and thalami bilaterally) P value < 0.001 at the three locations bilaterally.
– Marked reduction in CBF in group B in comparison to the group A and controls in the three regions (caudate, lentiform and thalami bilaterally) P value < 0.001 at the three locations bilaterally.
– Increased MTT in group B in comparison to group A and controls at the three regions (caudate, lentiform and thalami bilaterally) P value < 0.001 at the three locations bilaterally.

Although there are some reduced perfusion values in group A in comparison to the controls yet no significant changes regarding CBV and CBF compared to the controls

No MTT changes in group A in comparison to controls,

p value for MTT = 1 at all locations
P value for CBV at thalamus = 0.494
P value for CBF at thalamus = 0.603
P value for CBV at caudate = 0.381
P value for CBF at caudate = 0.425
P value for CBV at lentiform = 0.053
P value for CBF at lentiform = 0.053

TABLE 1. Relation between the three groups regarding thalami measures

	control group (n=20)	Group A (n=20)	Group B (n=20)	Kruskal Wallis test
CBV (ml) Mean ± SD. Min. – Max. Median (IQR)	3.7± 0.17 3.4 – 4.0 3.7 (3.6 – 3.9)	3.4 ± 0.50 2.3 – 4.0 3.5 (3.225-3.8)	1.5± 0.26 1.0 – 1.8 1.4 (1.3 – 1.7)	**41.549**
p1 = 0.494 p2 <0.001* p3 = <0.001*				
CBF (ml/100gm/min) Mean ± SD. Min. – Max. Median (IQR)	56.2±2.54 51.0 – 60.0 55.75 (54.0 -58.5)	51.4 ± 8.16 33.0 – 60.0 53.0 (48.5-57.5)	19.2±4.13 13.3 – 28.0 21.0 (15.6-21.75)	**41.129**
p1 = 0.603 p2 <0.001* p3 = <0.001*				
MTT(seconds) Mean ± SD. Min. – Max. Median (IQR)	4.0 ± 0.00 4.0 – 4.0 4.0 (4.0 – 4.0)	4.0± 0.06 4.0 – 4.2 4.0 (4.0 – 4.0)	4.8± 0.26 4.2 – 5.0 4.8 (4.5-5.0)	**51.753**
p1 = 1.000 p2 <0.001* p3 = <0.001*				

*P1 (between group A and C)
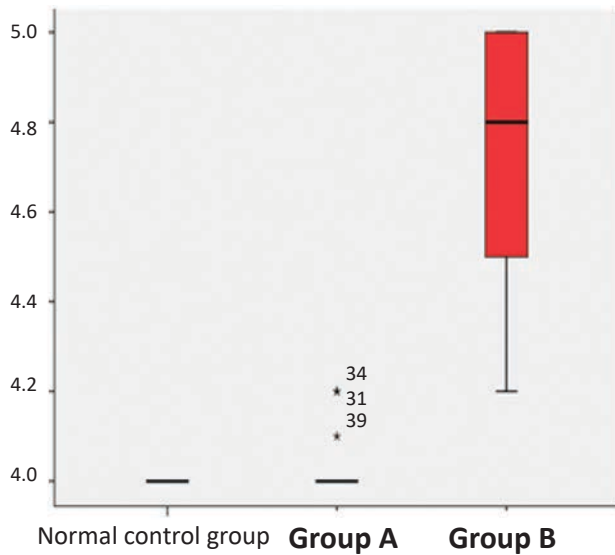*P2 (between B and C)
*P3 (between B and A)

FIGURE 2. Box and Whisker plot for relation between the three groups regarding thalami MTT (on the left)
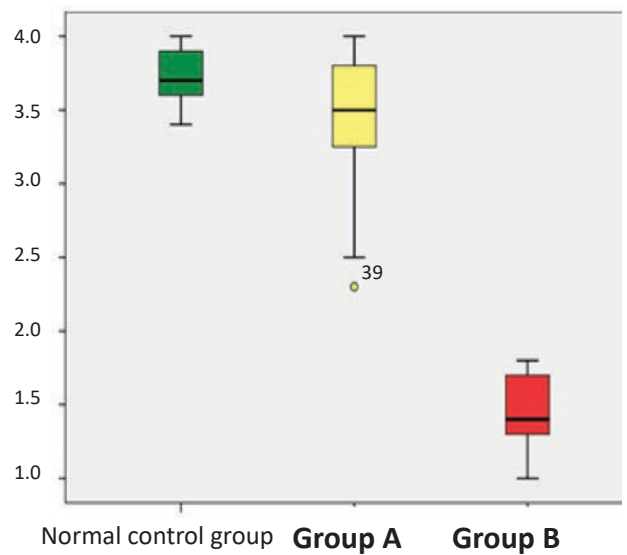

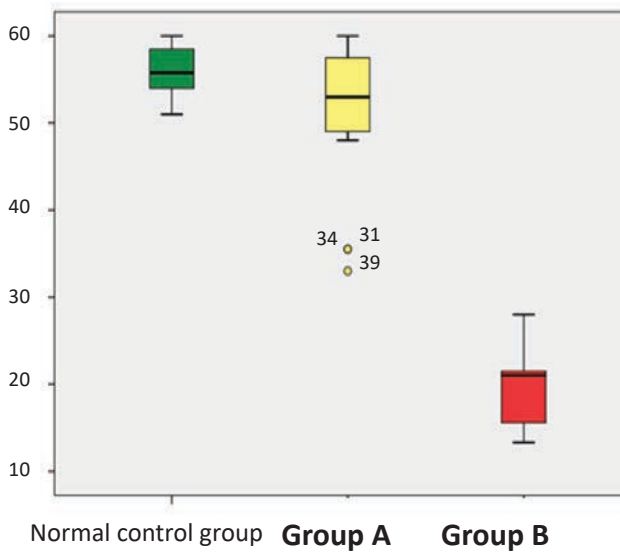**FIGURE 3.** Box and Whisker plot for relation between the three groups regarding thalami CBV (middle)

FIGURE 4. Box and Whisker plot for relation between the three groups regarding thalami CBF (on the right)

TABLE 2. Relation between the three groups regarding head of caudate measures

|	control group (n=20)	Group A (n=20)	Group B (n=20)	Kruskal Wallis test
CBV (ml)				
Mean ± SD.	3.7± 0.17	3.4 ± 0.50	1.7± 0.20	41.946
Min. – Max.	3.4 – 4.0	2.3 – 4.0	1.0 – 1.9	
Median (IQR)	3.7 (3.525 – 3.8)	3.5 (3.225-3.775)	1.7 (1.6 – 1.8)	
p1 = 0.381 p2 <0.001* p3 = <0.001*				
CBF (ml/100gm/min)				
Mean ± SD.	55.9±2.63	50.9 ± 7.99	22.7± 5.03	41.053
Min. – Max.	51.0 – 60.0	33.0 – 60.0	13.3 – 38.0	
Median (IQR)	55.75 (53.25-57.5)	53.0 (48.5-57.125)	21.5 (20.25-24.75)	
p1 = 0.425 p2 <0.001* p3 = <0.001*				
MTT(seconds)				
Mean ± SD.	4.0 ± 0.00	4.0 ± 0.03	4.7± 0.27	53.103
Min. – Max.	4.0 – 4.0	4.0 – 4.1	4.2 – 5.0	
Median (IQR)	4.0 (4.0 – 4.0)	4.0 (4.0 – 4.0)	4.8 (4.5-5.0)	
p1 = 1.000 p2 <0.001* p3 = <0.001*				
*P1 (between group A and C) *P2 (between B and C) *P3 (between B and A)				
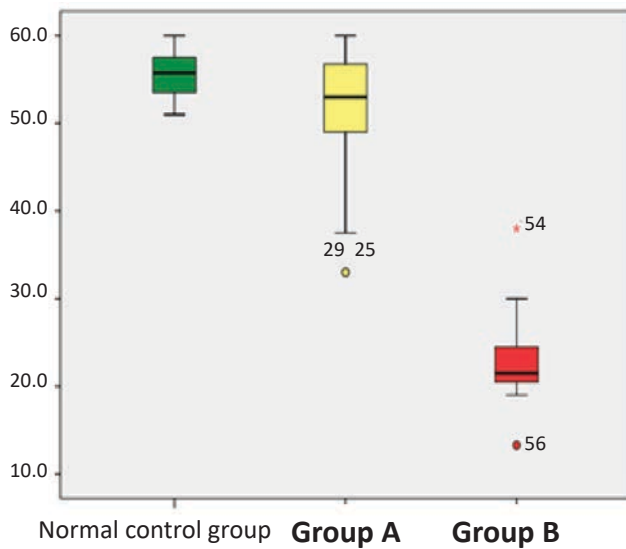
FIGURE 5. Box and Whisker plot for relation between the three groups regarding caudate CBF (left)
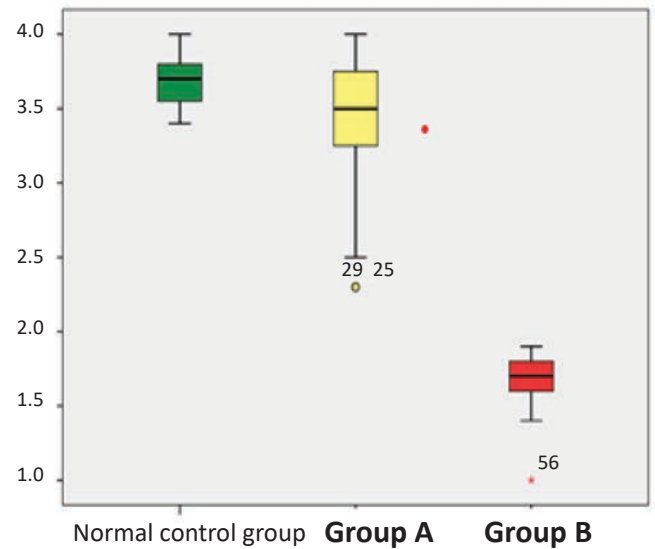

FIGURE 6. Box and Whisker plot for relation between the three groups regarding caudate CBV (middle)
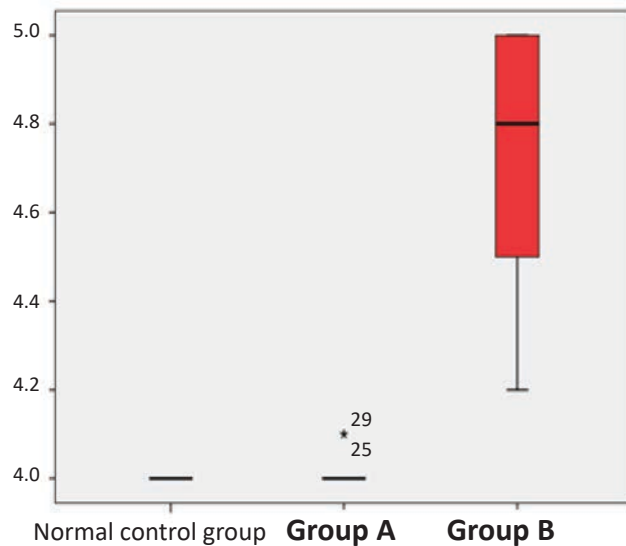

FIGURE 7. Box and Whisker plot for relation between the three groups regarding caudate MTT (right)

TABLE 3. Relation between the three groups regarding lentiform measures

	control group (n=20)	Group A (n=20)	Group B (n=20)	Kruskal Wallis test
CBV (ml)				
Mean ± SD.	3.8± 0.17	3.3 ± 0.54	1.6± 0.28	**45.270**
Min. – Max.	3.5 – 4.0	2.3 – 4.0	1.0 – 1.9	
Median (IQR)	3.9 (3.7 – 4.0)	3.4 (3.2-3.775)	1.7 (1.4 – 1.8)	
p1 = 0.053 p2 <0.001* p3 = <0.001*				
CBF (ml/100gm/min)				
Mean ± SD.	57.9±2.38	49.8 ± 8.87	22.9±4.88	**45.242**
Min. – Max.	53.0 – 60.0	33.0 – 60.0	13.3 – 30.0	
Median (IQR)	59.0 (56.0-60.0)	51.0 (48.0-57.125)	24.0 (21-26.5)	
p1 = 0.053 p2 <0.001* p3 = <0.001*				
MTT(seconds)				
Mean ± SD.	4.0 ± 0.00	4.0 ± 0.07	4.7± 0.30	**46.701**
Min. – Max.	4.0 – 4.0	4.0 – 4.2	4.0 – 5.0	
Median (IQR)	4.0 (4.0 – 4.0)	4.0 (4.0 – 4.0)	4.65 (4.425-5.0)	
p1 = 1.000 p2 <0.001* p3 = <0.001*				

*P1 (between group A and C)
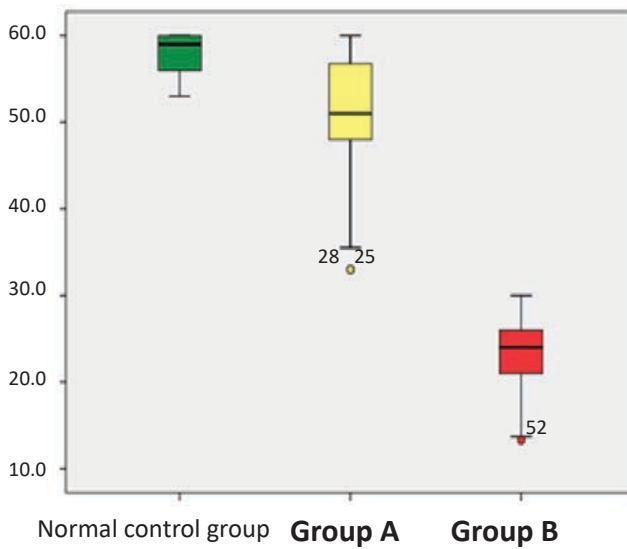*P2 (between B and C)
*P3 (between B and A)

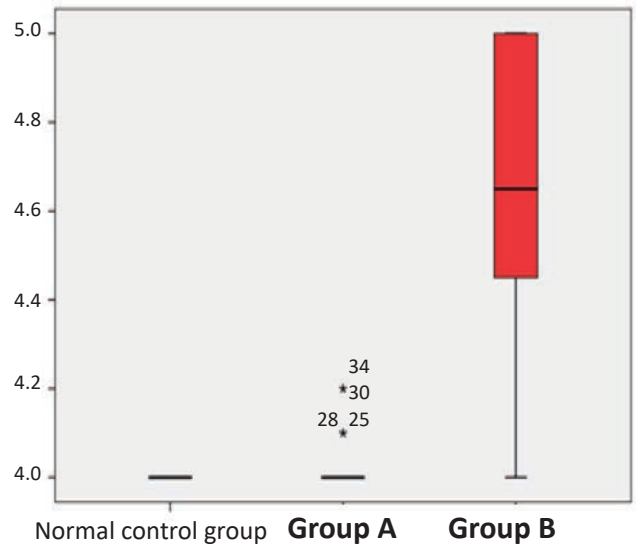**FIGURE 8.** Box and Whisker plot for relation between the three groups regarding lentiform MTT (middle)

FIGURE 9. Box and Whisker plot for relation between the three groups regarding lentiform CBF (left)
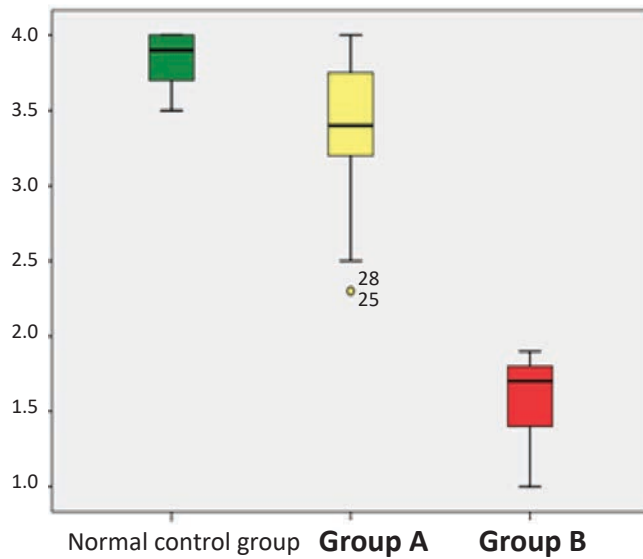

FIGURE 10. Box and Whisker plot for relation between the three groups regarding lentiform CBV (right)
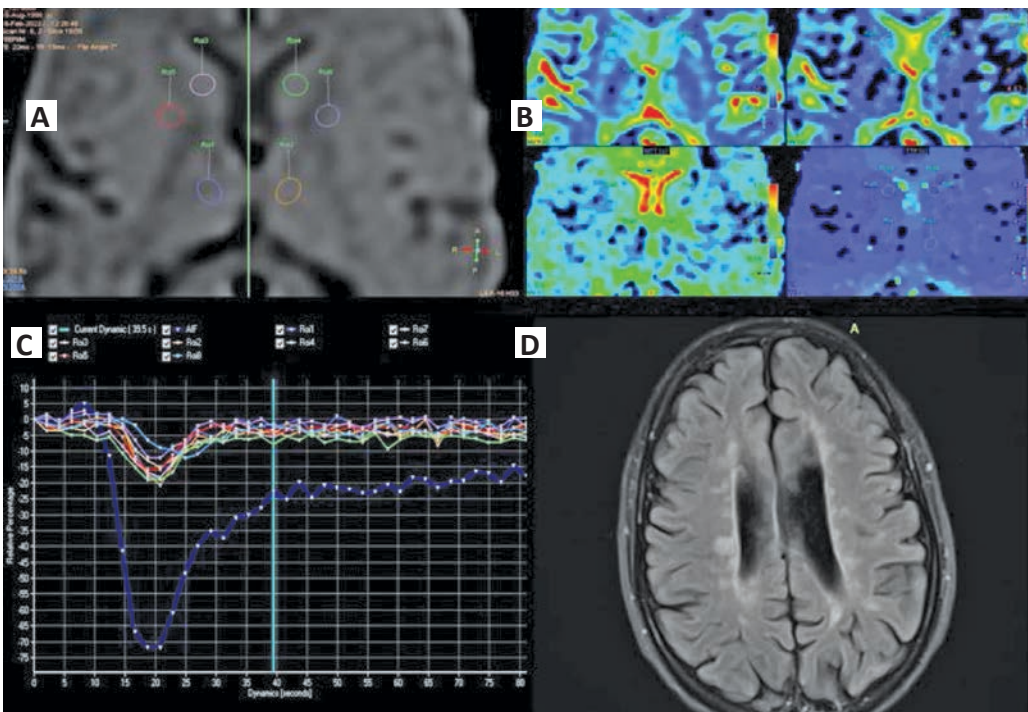

FIGURE 11. 35 years old female patient with clinical diagnosis of SPMS complaining of concentration and memory problems (A) regions of interest on caudate, lentiform and thalamus bilaterally. (B) Color maps. (C) Time attenuation curve (D) axial FLAIR showing multiple MS plaques

TABLE 4. CBV, CBF and MTT values of caudate, lentiform, thalamus bilaterally, showing marked decrease in CBV and CBF values and increased MTT

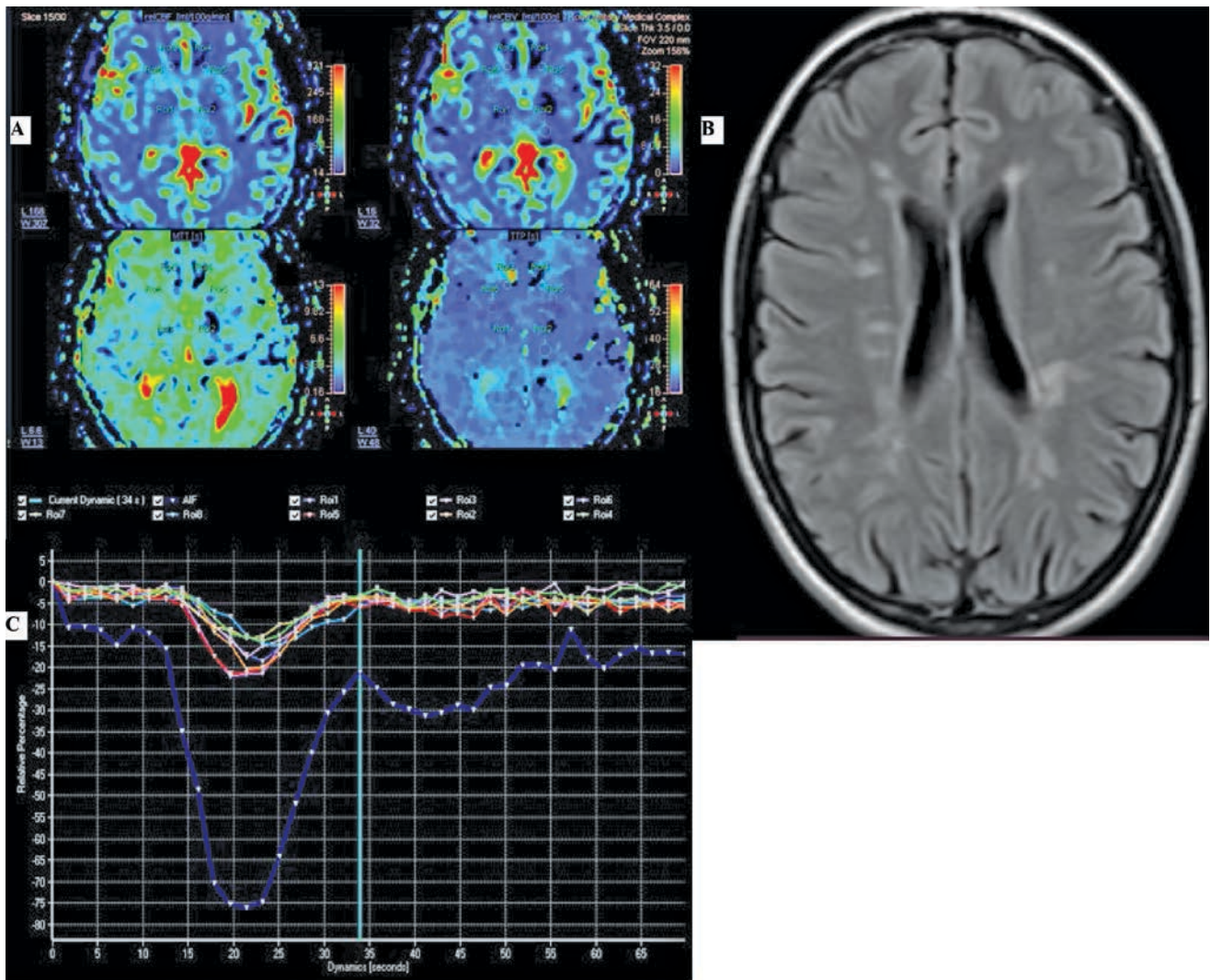|	RT thalamus	LT thalamus	RT caudate	LT caudate	RT lentiform	LT lentiform
CBV ml/ 100gm	1.5	1.1	1.2	1.7	1.5	2
CBF ml/100gm/min	20	15	16	24	21	27
MTT s	4.5	4.5	4.5	4.2	4.3	4.4

FIGURE 12. 34 years old female patient with clinical diagnosis of SPMS complaining of severe fatigue, memory, and concentration troubles and limbs weakness.
(A) color maps (B) Axial FLAIR showing multiple MS plaques(C) Time attenuation curve

TABLE 5. CBV, CBF and MTT of caudate, lentiform and thalamus bilaterally showing marked decrease in CBV and CBF values and increased MTT

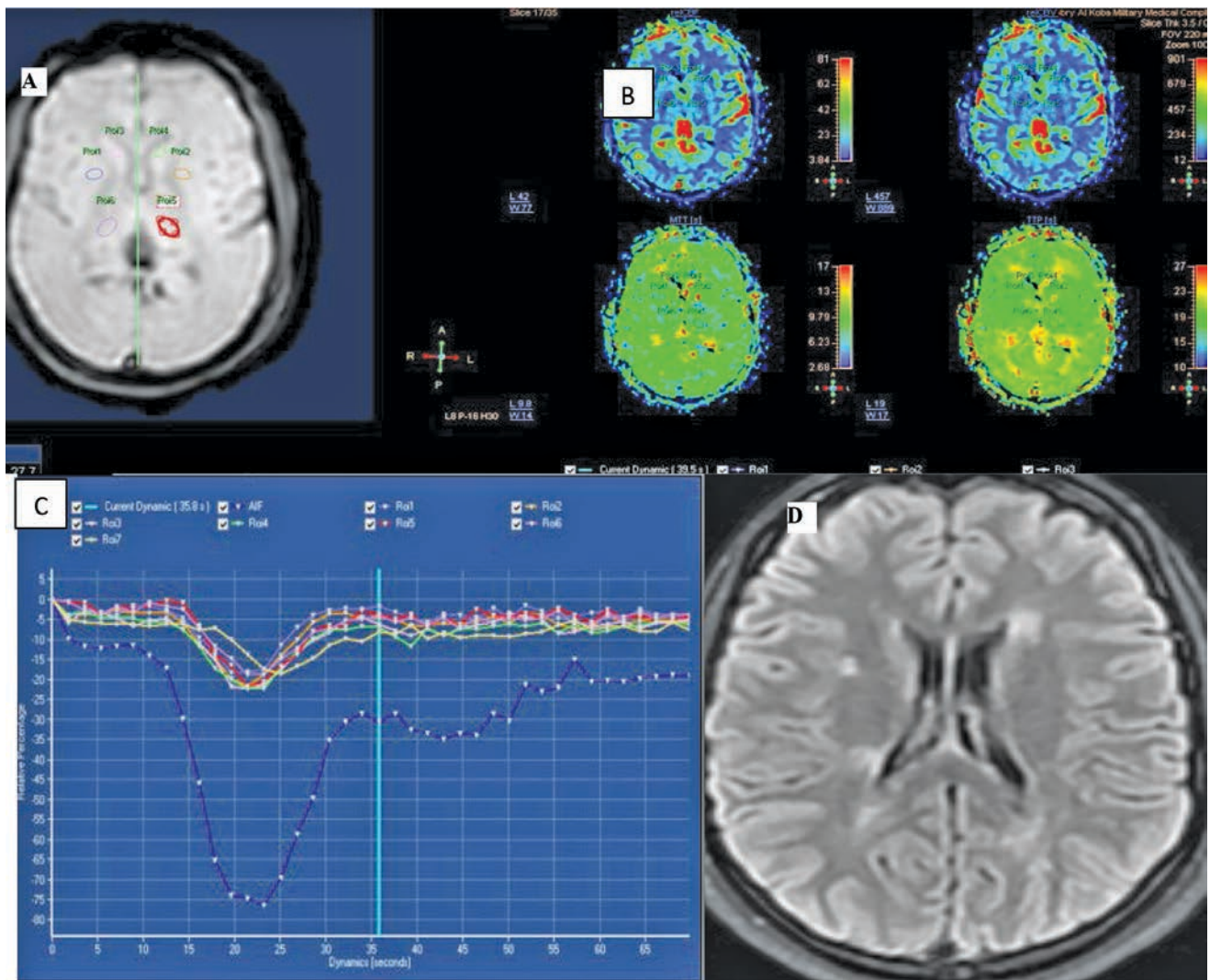|	RT thalamus	LT thalamus	RT caudate	LT caudate	RT lentiform	LT lentiform
CBV ml/ 100gm	1.5	1.1	1.2	1.7	1.5	2
CBF ml/100gm/min	20	15	16	24	21	27
MTT s	4.5	4.5	4.5	4.2	4.3	4.4

FIGURE 13. 32 years old male patient with clinical diagnosis of RRMS of 2 years duration complaining of headache and feet numbness.
(A) regions of interest on caudate, lentiform and thalamus bilaterally. (B) Color maps. (C) Time attenuation curve (D) axial FLAIR showing few MS plaques

TABLE 6. CBV, CBF and MTT of caudate, lentiform and thalamus bilaterally showing marked decrease in CBV and CBF values and increased MTT

	RT thalamus	LT thalamus	RT caudate	LT caudate	RT lentiform	LT lentiform
CBV ml/ 100gm	3	3.2	3	3	2.9	3.3
CBF ml/100gm/ min	45	48	45	45	44	50
MTT s	4	4	4	4	4	4

DISCUSSION

This study was conducted to evaluate the value of (DSC MR Perfusion) in assessing the deep gray matter perfusion changes and its relation to the patient's clinical disability and cognitive impairment

In our study, the most remarkable findings were reduction of CBV, CBF and increased MTT in deep gray matter of the patients with high levels of disability and cognitive impairment.

The second one is no significant changes in the MR perfusion values in mildly affected patients compared to the control group

Studies were done using 1.5 T scanners; Amann, et al., 2012 [10]. and (Sowa et al., 2017) [11] reported lower perfusion of white and gray matter in case of higher physical disability, that agrees with our study that detected positive relation between lower perfusion values of the gray matter and high physical disability

Amann et al., 2012 also reported that benign MS presented hypoperfusion in only small GM areas that disagreed with our study that shows no significant perfusion changes in mild MS cases compared to the controls, these small changes may be due to difference in disease duration, T2 lesions load and the age of the patients

The trend reported by studies performed at 1.5T scanners was confirmed by studies at 3T that consistently showed significant lower perfusion in PPMS than in RRMS (Adhya, et al., 2006) [12] (Inglese, et al., 2008) [13] (Doche et al., 2017) [14] (Zhang et al., 2018) [15] and (Garaci et al., 2012) [16] Specifically, significant CBF and CBV reduction in PPMS with respect to RRMS was reported in thalamus and caudate head (Inglese, et al., 2007).

Multiple studies showed relationship between MS physical assessment scores and CBF and/or CBV (Adhya et al., 2006) (Inglese et al., 2007) (Doche et al., 2017) (Zhang et al., 2018) and mean transit time (Paling et al., 2014) [17]. Specifically, either a significant (Adhya et al., 2006; Doche et al., 2017; Zhang et al., 2018) or a trend for negative correlation (Inglese et al., 2007) between EDSS (expanded disability status scale) and CBF/CBV was reported.

This was in agreement with our study that negatively correlates the EDSS with the perfusion values (CBF and CBF).

Doche et al. (2017) also showed a significant correlation between thalamic CBF and the cognitive functions impairment. Thus, symptoms worsening were associated with decreased CBF/ CBV (Doche et al., 2017; Zhang et al., 2018) that correlates with our study that shows significant correlation with the cognitive impairment and perfusion values.

Nonetheless, one study reported both negative and positive correlation between EDSS and CBF in diffuse GM areas (Zhang et al., 2018). The discrepancies between Zhang's and other studies findings may be ascribed to the differences in the methodological approach.

The studies reporting an association between severity of physical disability and transit time (Paling et al., 2014 and Sowa et al., 2017) showed prolonged transit time associated with higher EDSS in different regions of NAWM and DGM. This is in agreement with our study.

Papadaki, et al., 2014 [18] reported an inverse correlation between memory and CBV within several regions that are involved in memory functions (i.e.

left frontal NAWM, bilateral thalami, right caudate and corpus callosum) that was in agreement with our study regarding the caudate and thalami perfusion changes.

Schoonheim et al., 2015 [19] showed strong association between cognitive dysfunction and perfusion alterations within deep GM, and prominently in the thalamus.

Also, memory assessed with Brief Visuospatial Memory Test was observed to be correlated with thalamus hypoperfusion in MS patient Debernard et al., 2014 [20].

In addition, compared to cognitively preserved RRMS and SPMS, cognitively impaired patients presented with lower perfusion in the thalamic medial dorsal nuclei (Vitorino et al., 2016) [21] or in the thalamic pulvinar nuclei (Francis et al., 2013; Hojjat et al., 2016) [22,23]. Beside thalamus, also caudate nucleus displayed altered perfusion in cognitively impaired RRMS and SPMS patients (Francis et al., 2013 ; Hojjat et al., 2016), these are in line with our study.

Prolonged MTT was observed in whole WM, cortical GM and normal-appearing GM (this part specifically is with agreement with our study (Hojjat et al., 2016).

Declarations:

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