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ORIGINAL ARTICLE

# Microvascular abnormalities in normal appearing brain tissue in cases of RR-MS using Susceptibility Perfusion MRI

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## ABSTRACT

**Background:** To prospectively determine hemodynamic changes in the normal-appearing white matter (NAWM) of patients with relapsing-remitting multiple sclerosis (RR-MS) comparing with normal healthy individuals by using dynamic susceptibility contrast material-enhanced perfusion magnetic resonance imaging.

**Methods**: This study was a single-center, comparative cross-sectional study, recruited 46 consecutive male patients between April 2024 to October 2024. Conventional MR imaging and dynamic susceptibility contrast-enhanced T2*-weighted MR imaging were performed in 23 male patients with relapsing remitting multiple sclerosis- and 23 healthy control cases. Absolute cerebral blood volume (CBV), absolute cerebral blood flow (CBF), and mean transit time (MTT) were determined in different regions of the brain including the frontal white matter and the periventricular white matter, to compare perfusion measurements between patients with relapsing remitting multiple sclerosis patients and control healthy individuals.

**Results**: We applied our study on 46 patients, was divided into two groups: Cases Group (n=23) and Control Group (n=23), mean age 31.87±6.13 with the same inclusion and exclusion criteria. The 23 cases were classified according to the disease duration as we found that 73.9% of our patients were diagnosed with MS from > 5 years.

We found significant differences between the RR-MS patients and healthy controls regarding the CBF in the periventricular NAWM (p= 0.002) but not in frontal WM (p> 0.085) and We also found significant differences between the RR-MS patients and healthy controls regarding the CBV in both periventricular (p= 0.029) and frontal NAWM and (p=0.022).

**Conclusion** As we compared between the mean values of the cerebral blood value, cerebral blood flow in relapsing remitting multiple sclerosis Patients Group and Control healthy Group, we observed that control individuals had higher CBF and CBV values in both periventricular and frontal NAWM. This finding strengthens the hypothesis that MS may have a vascular origin

**Keywords:** Cerebral microcirculation, Neurovascular impairment, Hemodynamic MRI, Vascular Perfusion, Relapsing Remitting Multiple Sclerosis

## INTRODUCTION

Chronic demyelinating diseases are a group of neurological disorders that involve the progressive damage or loss of myelin, the protective sheath around nerve fibers. This damage impairs nerve function and can lead to various physical, cognitive, and sensory symptoms. Myelin is essential for the efficient transmission of electrical signals in the nervous system, so when it's damaged, communication between nerves is disrupted [1].

Chronic demyelinating disease affecting oligodendrocytes, axons, and myelin, it is known as multiple sclerosis (MS). MS is said to have made a substantial contribution to the increasing neurologic impairment despite its highly varied clinical course [1].

Since MS-related acute inflammatory white matter (WM) lesions manifest as focal hyperintensities on T2WI, conventional magnetic resonance imaging (cMRI) has become an essential diagnostic and monitoring technique (Brisset et al., 2021). But regrettably, the cMRI focal lesions only show a portion of the illness [2].

Historically, changes in MR Perfusion have been recognized as an important aspect of the disease progression in both NAWM and the MS plagues [3].

Dynamic susceptibility contrast Perfusion WI allows for the evaluation of key parameters typically affected in brain tissue, that includes the CBV, absolute CBF and MTT [4].

PWI is utilized extensively in MS to assess perfusion in MS plaques and its contralateral NAWM region or investigate connection between MR perfusion and clinical history in various brain areas standardized to hippocampi. thereby motivating many research teams to look for brain perfusion biomarkers that could be applied to managing and tracking the progression of multiple sclerosis [4,5].

Limited studies were conducted on microvascular abnormalities and complications in the Egyptian population with MS. Therefore, the main goal of our study was to prospectively check any white matter hemodynamic changes or microvascular abnormalities in cases of RRMS and compare these findings with healthy control group using DSCE perfusion MRI.

## METHODS

### Study design and Patients

This study was a comparative cross-sectional study, single-center study recruited 46 consecutive male patients between April 2024 to October 2024. They were referred from the Neurology Department to the Radiology Department in our institution. Official permission was acquired from the faculty ethical committee before we began with a reference number **479 on 20 April 2024**, and an informed consent. We adhered to the Declaration 0f Helsinki's ethical principles. And the study followed the STARD reporting guidelines.

**The flow chart of the study**, from proposal writing to final thesis writing, starting month was April 2024, the first two months we took the ethical approval and wrote the introduction and planned the study, then we have collected the patients' data in the following 4 months, then we analyzed the results and wrote the paper in October 2024.

**Inclusion criteria** Any adult male patient (age > 18 y) who was diagnosed clinically as RRMS patient (according to McDonald's Criteria).

**Exclusion criteria** were

- Patients with other neurological, systemic, or autoimmune disorders
- Patients who have claustrophobia

- Patients with contraindications of MRI either absolute or relative (such as metallic stents, artificial heart valves, cardiac pacemakers, or joint prostheses other than titanium ones) or Gadolinium (Gd) based contrast media (renal failure not on dialysis or allergy).
- Suboptimal MRI images.
- Patients didn't complete or refused to take contrast.

A total of 46 eligible male cases met our inclusion criteria, 23 case with RRMS & 23 control cases (mean age was 31.8 years; age range was 18-40 years).

All eligible patients were illuminated about nature, the main aim of the study and ensure confidentiality.

All of them underwent full history taking, general and local Neurological examination.

**Imaging procedure**:

**Preparation (Prior to MRI):**

- Every patient was requested to remove any metallic objects and was questioned again about any absolute or relative contraindications to MRI.
- All patients were told about the length of the examination and the need to maintain stillness.
- We checked the body weight for every Patient to calculate the amount of contrast (Gadovist / Magnevist) needed, we need 0.1 mmol for each kg.

18G IV cannula was inserted into the antecubital fossa to provide contrast,

**Position:** Supine position.

**Scanning** was done using a sixteen channel sensitivity encoding neurovascular coil on 1 ½ Tesla closed scanner (Philips Achieva).

**MRI technique**

Initially, a T1 scout image in a sagittal plane was taken to verify the patient's exact position and to serve as a reference to the subsequent slices. Then, non-enhanced axial images were acquired using multiple pulse sequences (T1, T2 and FLAIR). Following that, DCSE imaging was performed using these parameters: slice thickness 5 mm, FOV 220 *189 *126 $mm^3$, Matrix 244*168, TR/TE = 614/15 msec, and an acquisition time of 1 minute and 45 seconds. This was done after an intravenous contrast injection (Rate of injection was five ml/sec contrast then we injected a 20 ml saline bolus also at the same rate. All the collected images were captured at one-second intervals (we captured 60 images).

**Post-processing Perfusion analysis:**

All captured images were then transferred to the workstation that is supplied by the manufacturer to measure all perfusion parameters in multiple areas where we put the regions of interest in NAWM at the level of periventricular region and frontal NAWM, then we got a mean value for each parameter (CBV, CBF and MTT).

The ROIs were placed after revising the cMRI Images by two experienced radiologists with >10 years' experience in Neuroimaging reporting, yet to be sure that lesions were not included in the ROI. We took five measurements and calculated the average CBV, CBF, and MTT. All the ROIs were same size (radius = 1.8 mm) and carefully positioned to avoid any vascular structures. The ROI location was consistent across all examined patients, placed at the same section in each case.

The perfusion measurements were obtained by the two experienced radiologists simultaneously to rule out interobserver and preclude intra-observer variation & hence

reduce the variability as to the location of ROI placement between patients, each patient data set was reviewed by both radiologists at the same time.

***Statistica1 Analysis***

- The collected data were assessed and evaluated by the SPSS version 23.0. For parametric (normally distributed) data, all the results were presented as mean ± SD& range, while non-parametric (non-normally distributed) variables were presented as median with interquartile range (IQR). Quantitative variables were also expressed as percentages and counts. The normality of the data was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests.
- The Independent T-Test of significance was used when we were comparing between 2 different means.
- ANOVA& Post Hoc test: Tukey's test was used for comparison between >2 means &between different Inconsistent respectively.
- We used CHI-square test to compare different qualitative data groups.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was thought to be significant if the probability values were as follows

➢ P-value <0.05 → S.
➢ P-value <0.001 → HS.
➢ P-value > 0.05 → IS.

*S= Significant **HS=Highly Significant ***IS=In Significant

## RESULTS

This study was a comparative cross section study. We applied our study on 46 patients, was divided into two groups: Cases Group (n=23) and Control Group (n=23), mean age 31.87±6.13 with the same inclusion and exclusion criteria (Table 1). The 23 cases were classified according to the disease duration as we found that 73.9% of our patients were diagnosed as MS from > 5 years (Table 2). We found significant differences between the RR-MS patients and healthy controls regarding the CBF in the periventricular NAWM (p= 0.002) but not in frontal WM (p> 0.085) and We also found significant differences between the RR-MS patients and healthy controls regarding the CBV in both periventricular (p= 0.029) and frontal NAWM and (p=0.022) (Table 3).

These obtained findings seemed to raise the suggestion that microvascular impairment may play a role in the pathogenesis of MS. As it was widely recognized that inflammation can lead to microvascular damage through various mechanisms, for example Cytotoxic T-Cells may directly identify their target antigen on the luminal surface of brain blood vessels and then a subsequent apoptosis of the endothelial cells and activation of the clotting cascade may lead to thrombosis. Furthermore, inflammation-related edema may cause localized tissue swelling, which can disrupt microcirculation.

Table (1): Demographic data of Cases Group and Control Group

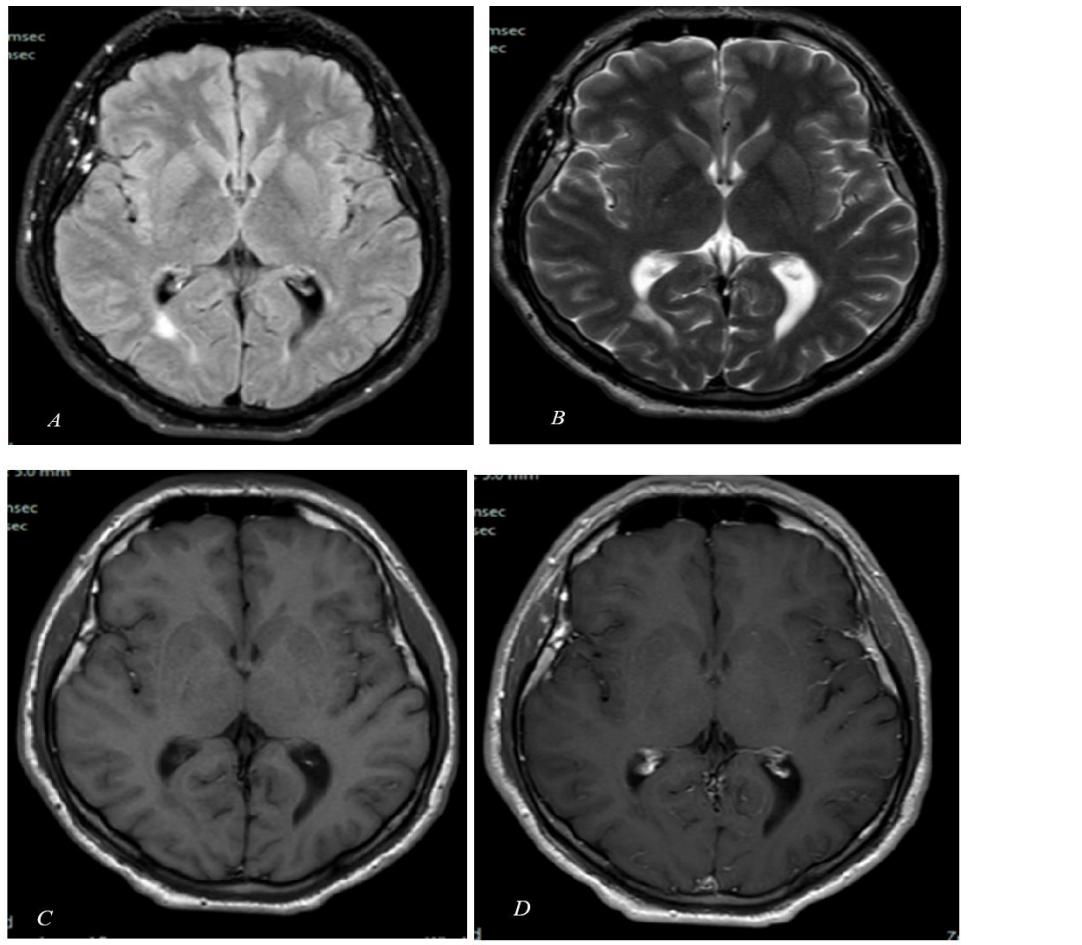
| **Demographic data** | | **Cases Group (n=23)** | **Control Group (n=23)** | **Test value** | **p-value** |
|---|---|---|---|---|---|
| **Age "years"** | Mean±SD | 31.87±6.13 | 31.04±5.83 | 0.219 | 0.642 |
| | Range | 20-40 | 21-40 | | |
| **Sex** | Male | 23 (100.0%) | 23 (100.0%) | 0.000 | 1.000 |

Table (2): Disease duration (years) distribution among study group. This table shows that 6 patients (26.1%) were ≤5 years and 17 patients (73.9%) were >5 years.

| **Disease duration (years)** | **No.** | **%** |
|---|---|---|
| 2-5 years | 6 | 26.1% |
| 5-10 years | 17 | 73.9% |
| Range | 2-10 | |
| Mean±SD | 7.26±2.54 | |

Table 3 CBV, CBF and MTT measurements in 2 different areas in white matter (frontal and periventricular regions)

| ROI in the white matter (n. of each group=23) | Frontal white matter | | Peri-Ventricular White matter | |
|---|---|---|---|---|
| | Control group | RR_MS patients | Control group | RR_MS patients |
| CBF values (ml/min/100 g) | 44.87 ± 0.85 SD | 33.68 ± 1.84 SD | 42.7 ± 1.7 SD | 34.57± 1.77 SD |
| CBV values (% units) | 3.38 ± 0.23 SD | 2.54 ± 0.23 SD | 3.23 ± 0.59 SD | 2.54± 0.13 SD |
| MTT values (in seconds) | 4.47 ± 0.28 SD | 4.50 ± 0.25 SD | 8.6 ± 3.0 SD | 4.48± 0.9SD |



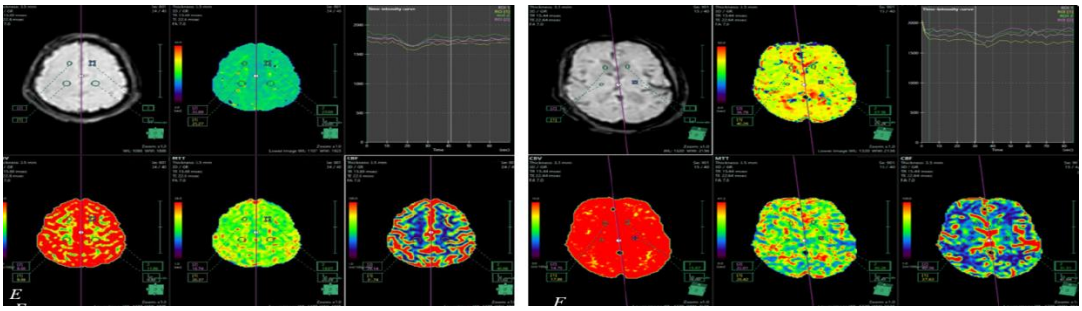
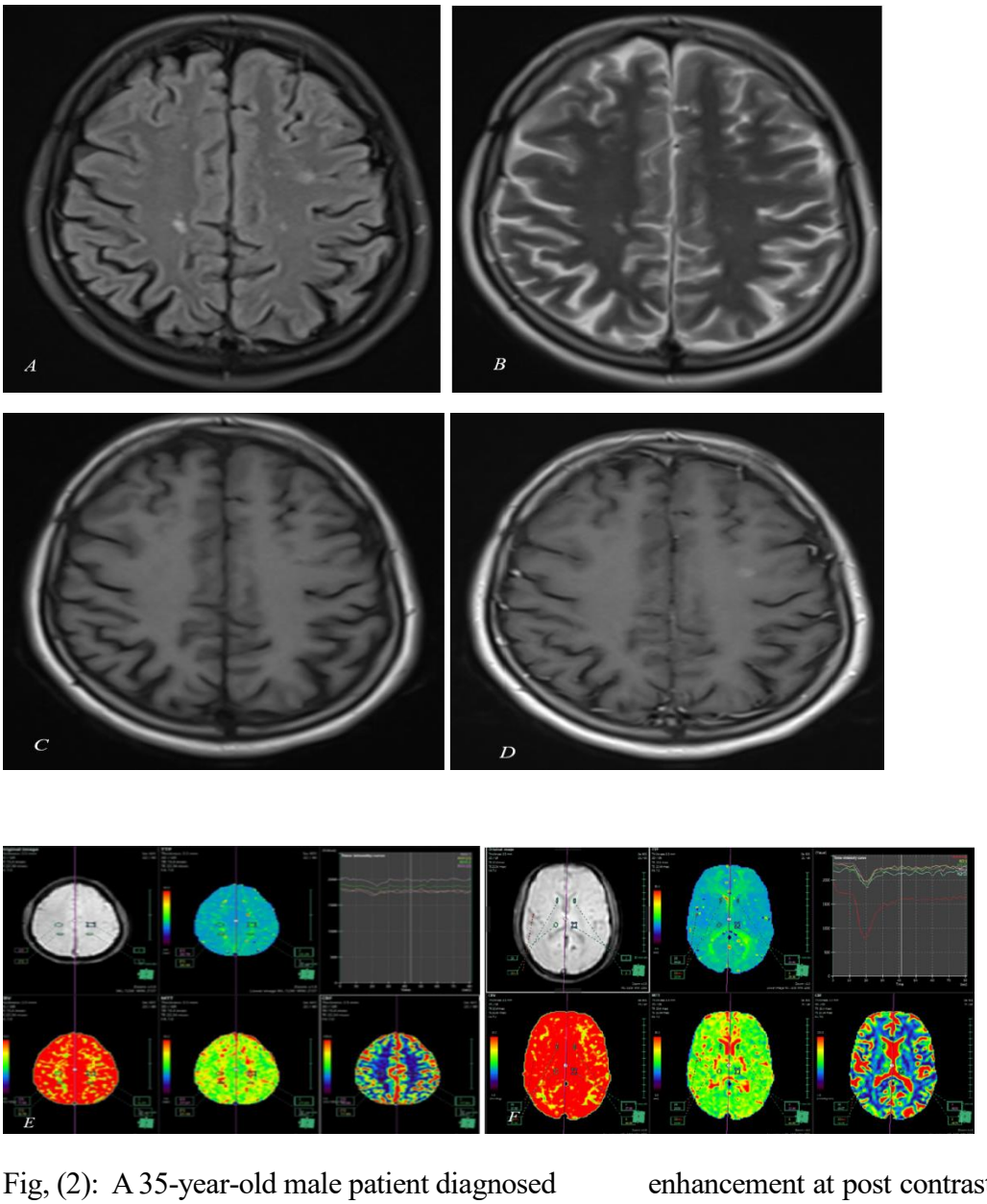
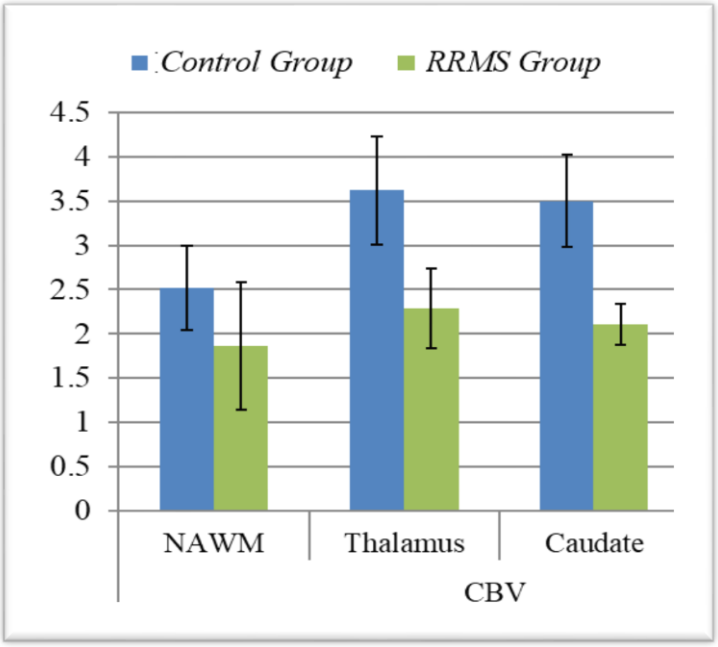




Fig.1 A 30-year-old male patient diagnosed from 1 year ago as MS. He is now complaining from left side numbness and blurring of vision. with EDSS 3months after attack is 3 (mild to moderate disability) & MSSS is 7.93. cMRI revealed a Single Right side Well-defined periventricular WM (PVWM) MS lesion seen displaying high SI at both Axial FLAIR (A) & T2 WI (B) and iso-intense on Axial T1 WI (C). The plaque shows no significant enhancement in the post contrast Axial T1 WI (D). Post processing Perfusion parameters: (E-F): The mean value of CBF measures 19.6 ml/100g/min. in NAWM and 32.2 ml/100g/min in NAGM, The mean value of CBV measures 1.89 ml/100g/min in NAWM and 1.8 ml/100g/min in NAGM. While the mean value of MTT is 4.97 sec in NAWM and 4.1 sec in NAGM.




Fig, (2): A 35-year-old male patient diagnosed from 6 years ago as RRMS. He is now complaining from progressive right upper and lower limb numbness, EDSS 3 months after the attack was 3 (minimal disability) & MSSS is 5.38. cMRI show Multiple bilateral well-defined supraventricular WM MS lesions displaying high SI at both Axial FLAIR (A) & T2 WI (B) and isointense on Axial T1 WI (C). Some of these plaques show significant enhancement at post contrast images (D). Post processing Perfusion parameters: (E-F): The mean value of CBF measures 26.5 ml/100g/min. in NAWM and 32.5 ml/100g/min in NAGM, the mean value of CBV measures 2.2 ml/100g/min in NAWM and 2.9 ml/100g/min in NAGM. While the mean value of MTT is 5.39 sec in NAWM and 4.66 sec in NAGM

**Illustrative cases fig. 1 & 2**




Fi g. 1 CBV measurements

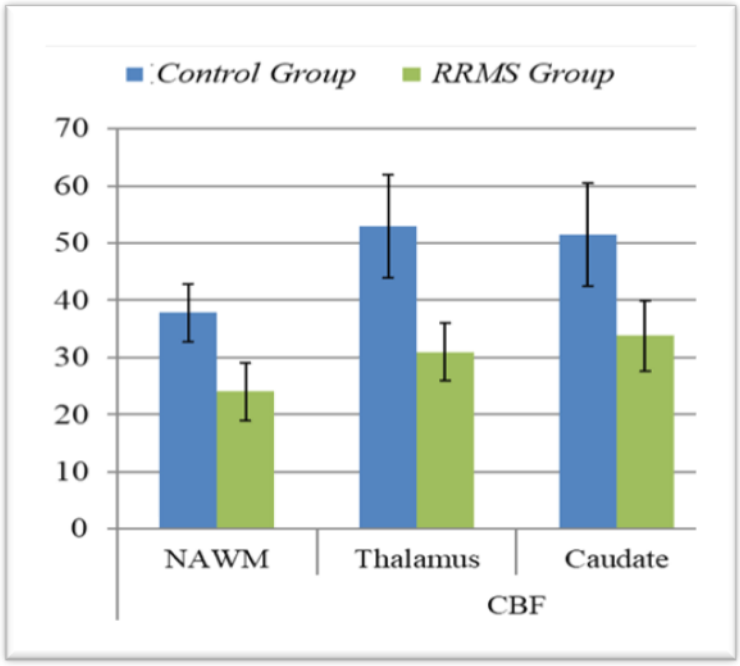



Fig. 2 CBF measurements

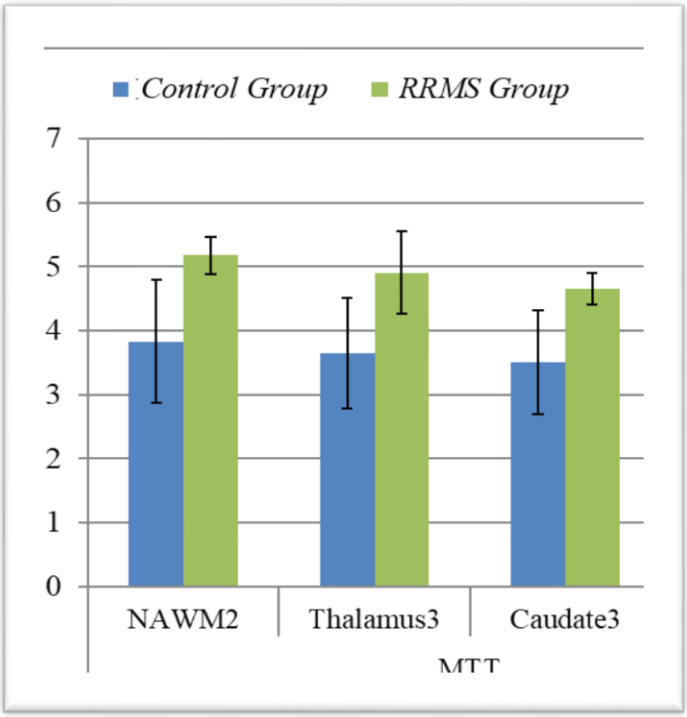



Fig. 3 MTT measurements

## DISCUSSION

Multiple sclerosis is a familiar neurological condition worldwide and a major cause of non-traumatic neurological impairment in middle aged adults across many countries. The disease is primarily marked by a variety of processes,such as inflammation, demyelination,neurodegeneration, remyelination, and axonal repair, which occur in variable combinations and at various stages as the disease progresses [6,7].

MRI had a very important role in MS, highlighting the importance of an initial MRI within the first 6 months and fo11ow up scans every 12 months. These exams can detect any newly developed T2 plaques and identify areas of active inflammation using contrast based enhanced T1 WI where enhancing MS plaques considered a recognized indicator of inflammatory changes occurred in MS lesions [8].

Although activity & progression are closely linked to each other, but they are typically analyzed separately as Disease activity is characterized by relapses clinically and hence plaques changes observed in neuro-imaging, and it is as while Progressions' of tissue damage driven by inflammation, as noted by Daumer et al. in 2009, while progression is thought to be closely linked to increasing neurologic dysfunction, that was noted and represented by neurodegenerative processes by Tillema, et al. in 2016 [9, 10].

Based on the current criteria, Thompson et al. in 2018 evaluated therapeutic outcomes and assessed active disease by performing MR imaging to determine lesion load, which includes the number of newly detected plaques or the increase in volume of existing lesions, as well as detecting blood-brain barrier (BBB) dysfunction through Gd enhancement. Wattjes et al. in 2015 highlighted that perfusion parameters are commonly calculated to monitor MS patients, as they reflect BBB dysfunction and the inflammatory response. Di Filippo et al. in 2010 also emphasized these parameters in their research [8, 11,12].

Dynamic susceptibility contrast-enhanced perfusion MR imaging is a robust and high-powered tool for depiction of any cerebral microvascular hemodynamics.

In our study, we found that Perfusion MRI can detect changes in the NAWM as we found that there was a significant reduction of the CBF and CBV in the periventricular and frontal NAWM even before any significant abnormal lesion

development and that strongly suggested that there was an early microvascular impairment that could play a role in the disease's progression.

Previous studies done by Law, et.al. in 2004 have also noted similar perfusion abnormalities in NAWM in cases of RRMS at the level of the lateral ventricle, including significantly reduced CBF & CBV with significant prolonged MTT compared with cerebral perfusion parameters in normal patients [3].

Studies done by Inglese et al. in 2008 have also showed consistent findings of lower CBF and CBV in patients suffering from RRMS compared to healthy individuals, yet they found that there were more reduced parameters in PPMS compared to RRMS, particularly in the periventricular NAWM, thalamus, caudate head, and frontal NAWM [13].

In 2021, Haacke et.al. and Haller et.al, have summarized the relationship between CBV & CBF in the circumstance of MS and it co-exist vascular changes, and concluded that the Vascular Changes in MS resulting from inflammation (causing vasodilation) and venous occlusion (causing reduced flow), and hence it would likely decrease CBF and increase MTT [14,15].

Further studies were done by Lapointe et.al in 2018, Doche et.al in 2017, and Varga et.al in 2009 reported that in RRMS cohorts, decreases perfusion in NAWM and NAGM as well as in patients with CIS, they noted that there was a regional CBF decrease in either PV-NAWM or deep GM compared with healthy individuals. CBV and MTT were found to be elevated relative to healthy individuals in NAWM and deep GM [16,17,18].

In our study, after adjustment of the patient's age & sex, we observed that in the control individuals, the periventricular NAWM perfusion parameters were significantly higher than the same calculated parameters in patients with RR-MS as we found that the mean CBF = 42.7 ± 1.7 ml/min/100 g and mean CBV = 3.23 ± 0.59 %, while in RR-MS patients the mean CBF in periventricular NAWM was 34.57± 1.77 and the CBV in was 2.54± 0.13, these findings strengthen the hypothesis that MS may have a vascular origin, as periventricular regions are more susceptible to conditions that affect the cerebral microvasculature. Further support for a vascular pathogenesis in MS as Lapointe et.al in 2018 & Towler et al in 2000 mentioned in their studies in that field, involving patients with optic neuritis who later suffered from MS, where their research explores the potential vascular mechanisms behind multiple sclerosis (MS), highlighting retinal and cerebral vascular abnormalities in the disease. In MS, vascular changes like fluorescein leakage, perivenous sheathing, and retinal peri phlebitis can occur independently of myelin and oligodendrocytes. These changes suggest a vascular origin for some of the disease's progression. Studies have suggested that inflammation of cerebral veins, often found within MS lesions, could be an early phase in lesion formation. Chronic ischemia from vasculitis might also lead to diffuse brain dysfunction [16].

Another important finding of this study was thecorrelation between regional hemodynamic impairment in both frontal & periventricular regions and clinical disability. This provides further evidence that tissue changes undetectable on cMRI may be functionally relevant. Future research incorporating cognitive assessments might reveal a stronger connection to hemodynamic dysfunction.

**Clinical significance**

Perfusion MRI studies in MS have demonstrated that CBV & CBF are altered even in the normal appearing MRI brain tissue and that may reflect an underlying damage not visible with conventional imaging. The question remains whether these perfusion abnormalities are early indicators of lesion formation, a separate phenomenon, or a consequence of metabolic changes due to demyelination.

The vascular involvement hypothesis in MS, particularly in terms of ischemia and hypoxic-like injury, could have significant implications for treatment. Studies indicate that therapies targeting inflammation, such as statins, might not only reduce inflammation but also improve tissue perfusion by affecting vascular tone in the small vessels supplying NAWM.

**Summary and explanation of the results**

In summary, our study supports the hypothesis that RRMS may involve a vascular component, with vascular inflammation and ischemia providing the development and progression of the MS disease. Further investigation is also needed to understand these mechanisms and their potential for therapeutic intervention.

**Therapeutic Implications**:

The study raises the possibility that therapies targeting vascular involvement (e.g., statins, which have anti-inflammatory and cholesterol-lowering effects) could play a role in managing MS by improving perfusion and reducing inflammation in the brain.

**Limitations and Future Directions**:

- All our patients are males.
- The study acknowledges limitations, including the potential effects of control group conditions (such as headaches) on perfusion measurements, the possible impact of immunomodulatory treatment on vascular parameters, and technical challenges with perfusion imaging (e.g., errors due to bolus delays or dispersion).
- Future research is still needed to highlight these limitations and further investigate the role of vascular changes in MS. Longitudinal studies may help clarify how perfusion abnormalities relate to disease progression and whether they could serve as predictors for MS outcomes.

**Conclusion**

Microvascular abnormalities in NAWM are an important, though often underrecognized, feature of RRMS. These changes may contribute to disease pathology, even in the absence of visible lesions on traditional MRI, and they may play a role in the early stages of MS and its progression. Advancing imaging techniques and more understanding of the possible vascular and cellular mechanisms that can cause the disease and could provide valuable insights into early disease detection.

**Conflict of Interest:** None

**Financial disclosure:** None

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## Citation

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