ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

# Susceptibility Weighted ImagingEnhanced byGadoliniumin Multiple Sclerosis: Optimizing the Recognition of Central Venous Sign for Different Magnetic ResonanceImagingSequences

**Sara M. Rady[1], Hossam M. Abdelrahman[1], Ahmed Mohamed Alsowey[1],**

**Heba A. E. Mohamed[1]**

**[1]Radiodiagnosis Department, Faculty of Medicine, Zagazig University, Egypt**

**Correspondence:** sararady9292@gmail.com.

## ABSTRACT

**Background:**Gadolinium SWI is anew MR imaging that has recently been reported to be effective in the evaluation of several neurologic disorders, including demyelinating diseases**.**
**Aim of the study:**Compare between Gadolinium-Enhanced Susceptibility Weighted Imaging sequence(Gd-SWI) and pre contrast Susceptibility Weighted Imaging performance in MS plaques in the brain esp. in enhancing of central venous sign.
**Method**: The study was done in Zagazig University Hospitals.This study has been conducted on 24 patients clinically and radiologically proven MS cases for MRI diagnosis and follow up, the patients were referred from the Neurology Department and Multiple Sclerosis clinic at Zagazig University Hospitals, to Radio Diagnosis Department, Magnetic Resonance Imaging (MRI unit), Zagazig University Hospitals, over a period of 11 months starting from August 2020 to July 2021.
**Results:**There was statistically significance higher ability of post-contrast SWI to demonstrate lesions with positive central vein than pre-contrast SWI and in contrast there was statistically significance decrease on number of homogenous hypointense lesions with post contrast than pre-contrast while regarding scattered hypointense dots and peripheral hypointense rim, they were more obvious by post contrast than pre contrast but not different enough to be significant and also isointense lesions not seen were more among pre-contrast than post-contrast.
**Conclusion**: Our study has proven the role of post GD –SWI in detection of central vein sign better than pre-GD SWI; it facilitated the visibility of small veins that already seen in pre-contrast SWI.
**Keywords:**Gadolinium-Enhanced, Magnetic Resonance Imaging, Multiple sclerosis, Susceptibility Weighted Imaging.

## I. INTRODUCTION:

Multiple sclerosis (MS) is one of the neurological diseases that mainly affect young adults and it is chronic disabling demyelinating autoimmune disease. It is considered a multifactorial condition whichmaybe caused by the interaction among environmental, immunologic and geneticfactors; predominantly it is characterized by these independent processes ofinflammation, demyelination, neurodegeneration,remyelination and repair of the

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

axons in different multifocal combinations at different stages of disease progression. MS is the main reason for nontraumatic neurologic disability in young adults in many countries,and it is considered one of the most common neurologic disorders in the world [1, 2].

Magnetic resonance imaging(MRI) has become the best technique for in vivo imaging of several disorders, Combined with its noninvasiveness. It produces contrasts according to different tissues. nowadays, MR imaging is used in all work-up processes of MS as it contributes in the evaluation of the activity of disease, helps to safely exclude potential differential diagnosis, facilitates earlier diagnosis and also contributes in the evaluation of potential complications linked to the treatment [3, 4]**.**

One of the most important relatively new MR imaging techniques is Susceptibility-weighted imaging (SWI) which is being implemented in clinical practice currently besides conventional T1- and T2-weighted imaging methods, which are already used in MR imaging scanners that are commercially available. A central vein inside white matter lesions have been investigated by a number of studies. SWI images have detected the “central vein sign,” as a promising imaging biomarker of inflammatory demyelination, adding specificity to the diagnosisof MS[5].

it is demonstrated a presence of non-confluent lesions 3 mm in length with 1 central vein as a specific and sensitive discriminator of patients with relapsing-remitting MS from control individuals with benign white matter lesions [6, 7]**.**

Hosseini et al also conducted a study that proved a hypointense rim around MS lesions as an MS adjunct imaging biomarker, which may be used with the central vein sign as a radiologic sign to distinguish MS from other benign white matter lesions [8]**.**

Furthermore, information is provided by SWI about any tissue that has a different susceptibility than its surrounding structures, such as calcium, ferritin, hemosiderin and deoxygenated blood (which are exhibited by the T2* effect) [9]**.**

The vein Signal loss on SWI can be increased by Gadolinium-based contrast media (CM). The CM increased the contrast between the central vein and the parenchyma allowing as well the detection of the vein not visible on the same SWI sequence acquired before CM injection.

In light of this background, this study designed to investigate the accuracy of the Gd-SWI sequence to detect central venous sign in MS plaques in the brain by comparing it with the performance of pre contrast SWI sequence.

## II. PATIENT AND METHODS:

***Patients****:*

This study has been conducted on 24 patients (16 females and 8males, their age ranging from 20- 42 years with the mean age 26.33), they were divided into two groups: 8 active cases and 22 inactive cases clinically and radiologically proven MS cases for MRI diagnosis and follow up, the patients were referred from the Neurology Department and Multiple Sclerosis clinic at Zagazig University Hospitals, to Radio diagnosis Department, Magnetic Resonance Imaging (MRI unit), Zagazig University Hospitals, over a period of 11 months starting from August

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

2020 to July 2021. The study was conducted with institutional review based board (IRB) approval and written informed consents were taken from all patients.

***Inclusion Criteria:***

Series of patients with a defined MS diagnosis or suspicious to have MS according to the 2017 revised McDonald Criteria, any age group is included and both sexes, and also Patient acceptance.

***Exclusion criteria***

Patients with very bad general condition, Patients unwilling to complete the study, Contraindications to magnetic resonance imaging (MRI) (e.g. cochlear implants, metallic foreign bodies, cardiac pacemaker, ferromagnetic aneurysm clips), Patients with suspected unavailability throughout the study, and also Patients with other neurologic disease or brain SOL.

***Methods:***

All patients were subjected to the following:

1- ***Full history taking:***

A. Personal history (name, age, occupation…)

B. Present history (complaints): hemiparesis, numbness, seizures, tremors and visual disturbance.

C. Past history of neurological manifestations.

2- ***Laboratory investigations:***

Kidney functions tests.

3- ***General and neurological examination of the patients:***

(Carried out by referring clinician)

4- ***MR Imaging including:***

Conventional magnetic resonance imaging including T1WI, T2WI and FLAIR, Gadolinium enhanced MR imaging, Diffusion Weighted Imaging and ADC map, and also Susceptibility Weighted Imaging (SWI)

***MR Imaging Techniques:***

***Preparation:***

A. (16G) IV cannula will be established.
B. All patients were asked to get rid of any metallic subjects as well as they were asked about any contraindication to MRI examination (artificial heart valve, cardiac pacemaker, metallic stents or joint prosthesis except that made of titanium). The patients were informed about the duration of the examination, the position of the patient and the importance of being motionless.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

***Technique:***

**Position:** supine position.

**Scanning:** All data will be acquired on a 1.5 T closed scanner (Philips Achieva) using a 16-channel sensitivity encoding neurovascular coil.

**Sagittal volumetric FLAIR images** thatwere used for brain lesion detection (acquisition time, 8 minutes and 31 seconds; slice thickness, 0.7mm; FOV, 220 x 220 x 180mm3; and matrix, 184 x 184; TR/TE/TI,7.000/263/ 2.300 ms).

**Gd-SWI data**alsowere acquired with a flow-compensated 3D gradient echo method (slice thickness, 1mm; matrix, 160 x 172x100; FOV, 200 x 211x 150mm3; TR/TE,52/12ms; voxel size, 1.25 x 1.24 x 3.0 mm3; flipangle10°; acquisition time, 3minutes and 20seconds).

**The 2D-T1 spin-echo (SE) sequence**was acquired using the following parameters: (acquisition time, 1 minute and 45 seconds; 25 slices; slice thickness, 5 mm; FOV, 220 x 189 x 126 mm3; matrix, 244 x 168; TR/TE, 614/15 ms) was also obtained before and after intravenous administration of 0.1 mmol/kg of Gd (Gadovist [gadobutrol]); Bayer Schering Pharma, Berlin, Germany). The order of acquisition of the post contrast sequences was uniform in all studies. Firstly, the SWI sequence was acquired, followed by the T1 SE.

**Diffusion Weighted MR Imaging (DWI):**The imaging sequence for DWI was a multi-section single shot spin echo EPI sequence (TR/TE/NEX: 4200/140 ms/I) with diffusion sensitivities of b values =0, 500 and 1000 s/mm2. The diffusion gradients were applied sequentially in three orthogonal directions (X, Y & Z directions). The total acquisition time was 80 sec, Sections of 5mm thickness, interslice gap of 1mm, FOV 240mm and a matrix of 128x256 were used for all images.

Three types of images were obtained: orthogonal, trace, and ADC maps. The MRI software calculated ADC maps automatically and included in the sequence. ADC was measured in different regions of interest (ROI) [on the lesions and in Normal Appearing White Matter (NAWM)]. The ADC values were expressed in $10^{-3}mm^2/sec$.

We computed trace (D) by summing ADC x, ADC y, and ADC z on a pixel-by-pixel basis after assuming that the diffusion sensitization produced by the imaging gradients in our sequence was negligible. We then divided trace (D) by three to obtain the orientationally averaged ADC. We measured the orientationally averaged water diffusion coefficient in plaques of MS patients. Measurements of ADC values were done in ROIs within the lesions.

**Statistical Analysis:**

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. According to the type of data, the following tests were used:

All quantitative data were expressed as mean (M) ± Std. Deviation (SD) unless otherwise indicated. Independent samples t test was used for checked differences in continuous measurements .

Chi-square test (or Fisher's exact test where appropriate) was used for comparing qualitative variables. ROC curve was used to obtain the best cutoff point of ADC value according to the following principle: the sensitivity plus specificity had a biggest number .

Diagnostic indices (sensitivity, specificity, and accuracy) were calculated, and then compared with McNemar X2 test .

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Parameters with P < 0.05 were considered significant and all tests were two tailed.

## III. RESULTS:

**Table (1):Clinical types of the lesions**

| Clinical types | The studied group No = 24 | (%) |
|---|---|---|
| **** Active*** | **8** | **33.3 %** |
| - Progressive | 1 | 12.5 % |
| - Non progressive | 7 | 87.5% |
| **** Inactive*** | **16** | **66.7 %** |
| - Progressive | 2 | 12.5 % |
| - No progressive | 14 | 87.5 % |

In this table two thirds of the studied group (66.7 %) had inactive lesions and one third (33.3 %) had active ones with (12.5 %) of both active and inactive lesions were progressive.

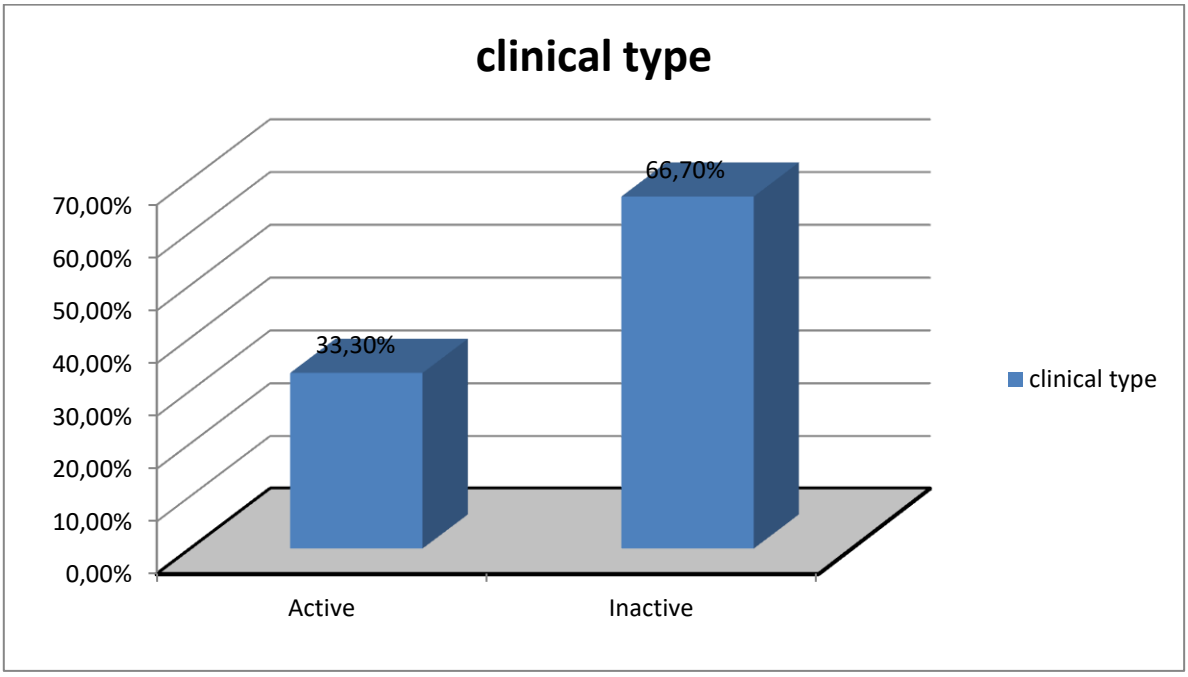


**Figure (1):** Bar chart for the clinical types of the lesions among the studied g

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

**Table (2): Clinical presentation among the studied group**

| Clinical presentation | The studied group | |
|---|---|---|
| | No = 24 | (%) |
| Lumbar weakness | 15 | 62.5 % |
| Hemiparesis | 10 | 41.7 % |
| Numbness | 6 | 25.0 % |
| Visual troubles | 6 | 25.0 % |
| Memory loss | 1 | 4.2 % |
| Tremors | 1 | 4.2 % |
| Generalized weakness | 5 | 20.8 % |
| Loss of sensation | 2 | 8.3 % |
| Loss of concentration | 4 | 16.7 % |
| Dysarthria | 2 | 8.3 % |
| Urine incontinence | 1 | 4.2 % |

* Many patients had more than one clinical presentation.

Lumbar weakness was the commonest clinical presentation (62.5%) of the studied group followed by hemiparesis (41.7 %) then visual troubles and numbness (25.0 %) for each and lastly generalized weakness and loss of concentration (20.8 % and 16.7) respectively, loss of sensation and dysarthria (8.3 %) for each one and finally urine incontinence, memory loss and tremors (4.2 %) for each.

**Table (3): Number of hyper intense lesions by $T_2$& flair**

| $T_2$& flair | The studied group |
|---|---|
| | No = 24 |
| hyper-intense lesions No | 381 |
| (range/one patient) | (2 – 72) |

*This table shows that the number of hyper intense lesion was 381 lesions ranged from 2 lesions to 72 per one patient.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

**Table (4): Comparing pre and post contrast non-enhanced lesions by SWI**

| Lesions | Pre-contrastNo. (range/one patient) | Post-contrast No. (range/one patient) | X2 | P. value |
|---|---|---|---|---|
| Lesions with positive central vein | 109 (0-33) | 132 (0-33) | 5.4 | **0.02*** |
| Scattered hypointense dots | 3 (0-3) | 4 (0-4) | 0.2 | 0.6 |
| Peripheral hypointense rim | 4 (0-1) | 5 (0-1) | 0.17 | 0.6 |
| Homogenous hypointense lesions | 152 (0-17) | 112 (0-12) | 6.5 | **0.01*** |
| Isointense lesion not seen | 99 (0-17) | 95 (0-17) | 0.01 | 0.9 |

*There was statistically significance higher ability of post-contrast SWI to demonstrate lesions with positive central vein than pre-contrast SWI and in contrast there was statistically significance decrease on number of homogenous hypointense lesions with post contrast than pre-contrast while regarding scattered hypointense dots and peripheral hypointense rim, they were more obvious by post contrast than pre contrast but not different enough to be significant and also isointense lesions not seen were more among pre-contrast than post-contrast.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

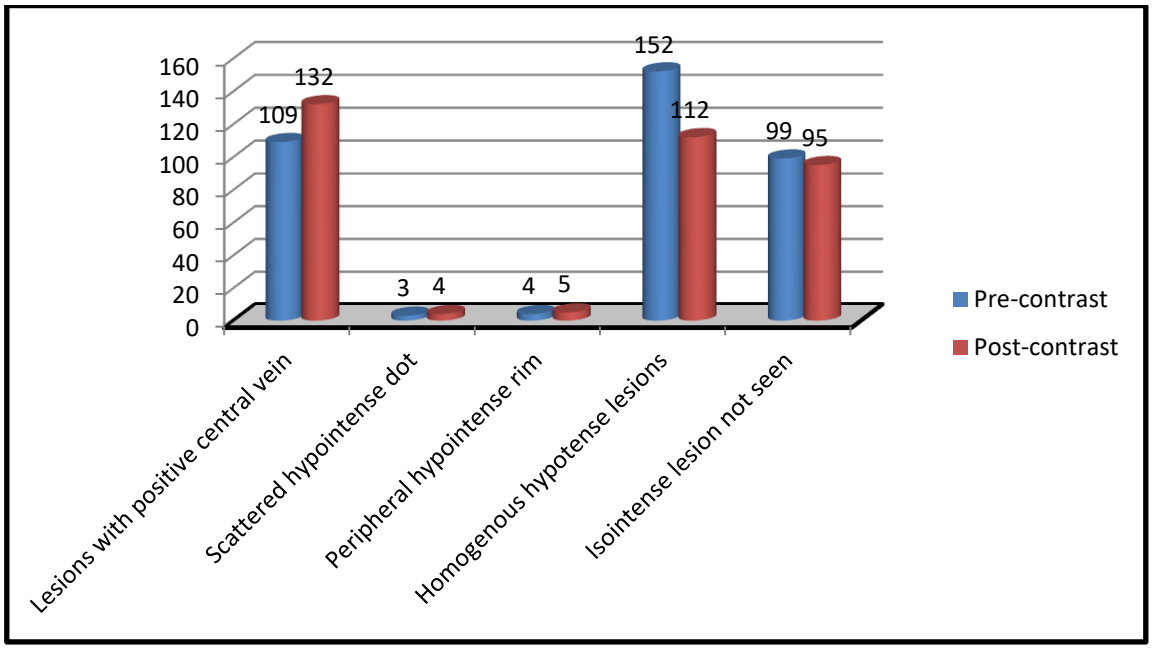


**Figure (2):** Bar chart for the pre and post contrast non enhanced lesions by SWI among the studied group.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

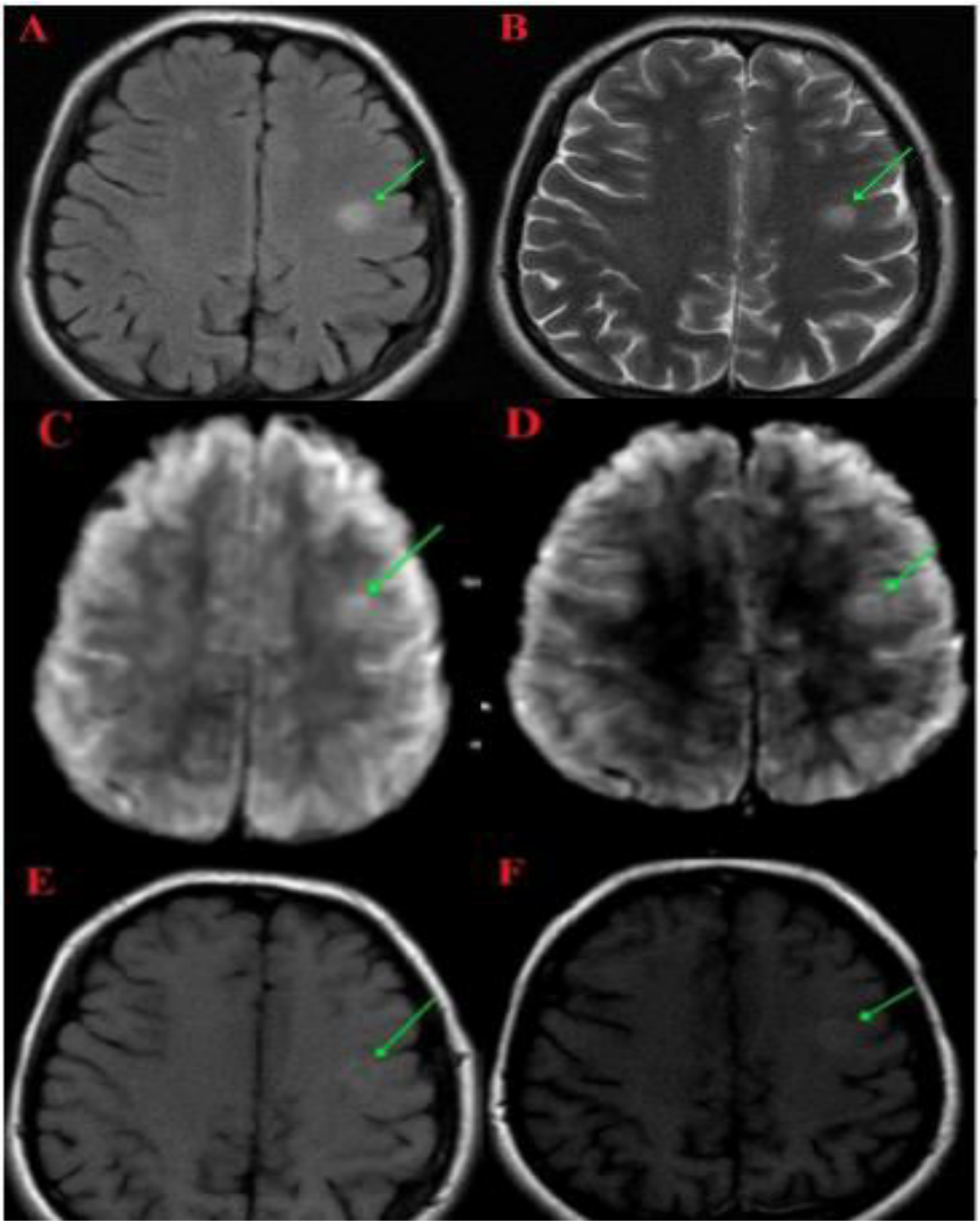


**Figure (3):** A 24-year-old male patient, presented with lumber weakness and numbness of three months duration. **(The initial MRI) A & B):** axial FLAIR and Axial T2WI:show left subcortical white matter hyperintense plaques,**C):** Axial pre contrast Susceptibility Weighted Images (SWI): Show white matter hyperintense plaques,**D):** Axial post contrast Susceptibility Weighted Images (SWI): Showwhite matter hyperintense plaques with central vein sign supporting diagnosis of MS,**E & F):** Axial T1WI (pre and post contrast study): The both show white matter isointense plaques that are difficult to be seen. The clinical and the radiological findings are consistent with inactive demyelinating disease (MS).

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

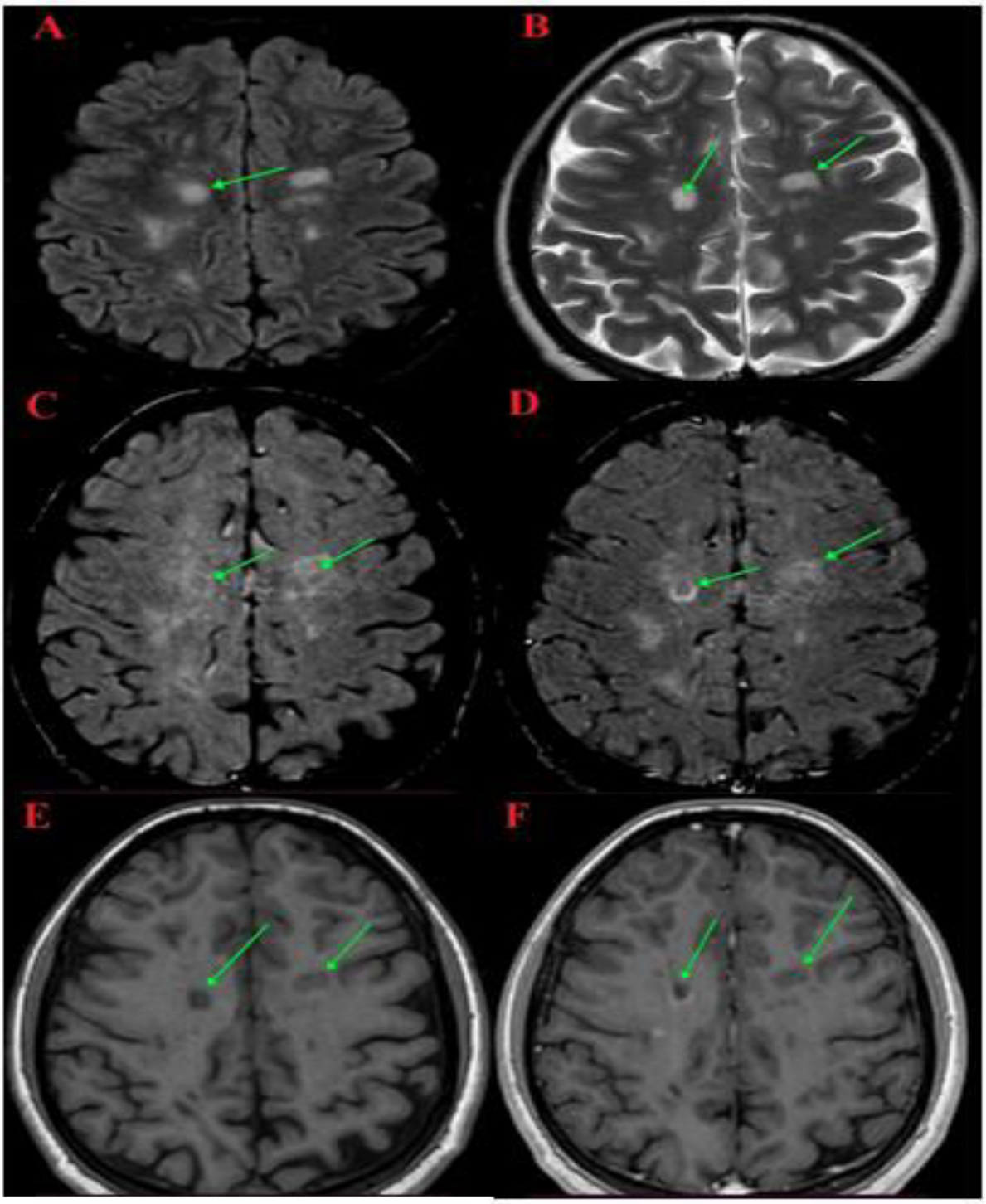


**Figure (4):** A 22-year-old female patient, presented with Hemiparesis, lumber weakness and numbness of two weeks duration. **(The initial MRI) A & B):** axial FLAIR and Axial T2WI: Show bilateral subcortical white matter hyperintense plaques, **C):** Axial pre contrast Susceptibility Weighted Images (SWI): Shows white matter hyperintense plaques with central vein sign supporting diagnosis of MS, **D):** Axial post contrast Susceptibility Weighted Images (SWI): Shows multiple white matter hyperintense plaques, the largest on the right side show ring shape enhancement and two central vein sign supporting diagnosis of MS. that is characterized more obvious by the GD-SWI sequence more than pre contrast SWI, **E & F):** Axial T1WI (pre and post contrast study): The both shows white matter hypointense plaques that show ring enhancement in post contrast T1WI. The clinical and the radiological findings are consistent with active demyelinating disease (MS).

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

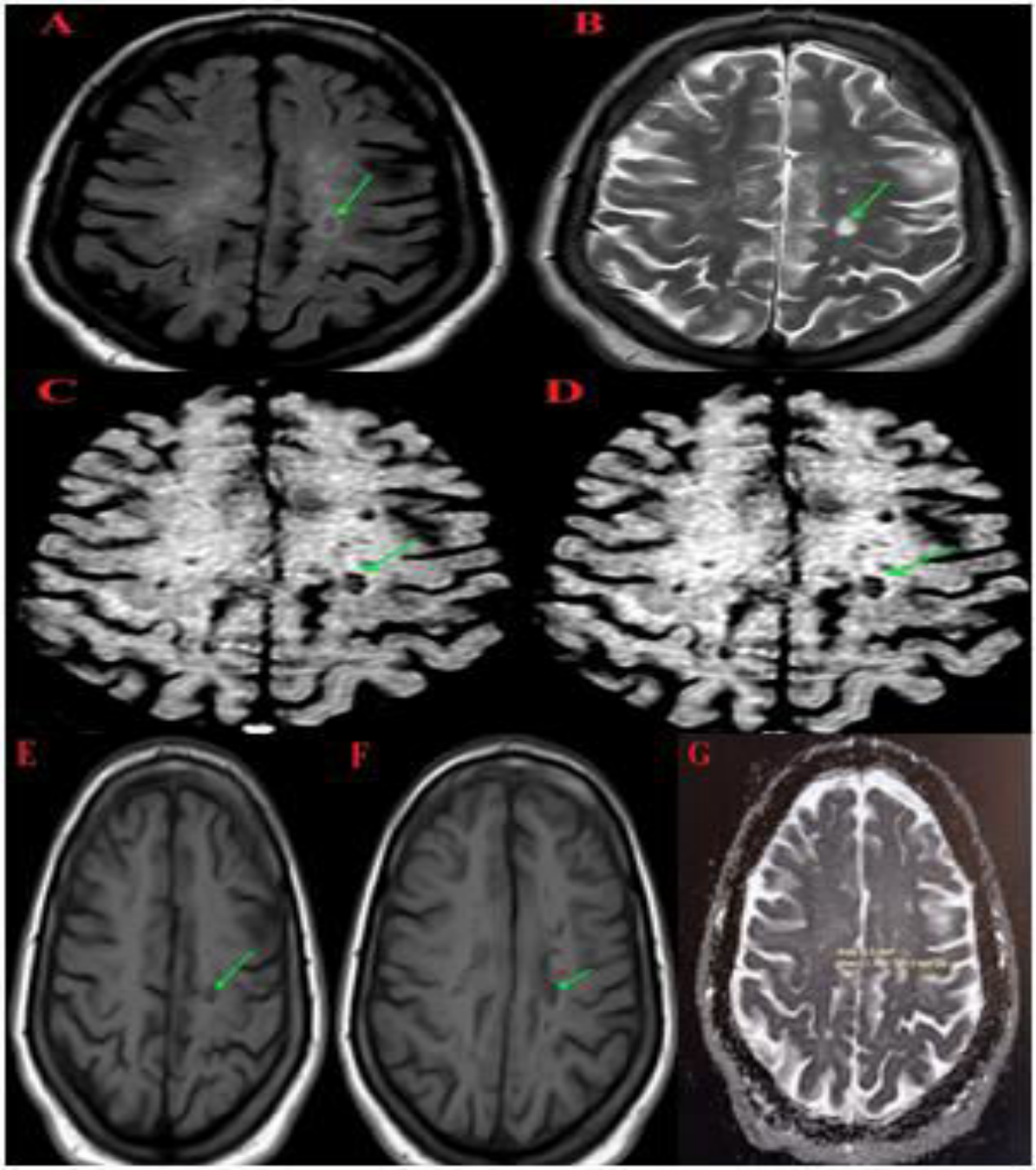


**Figure (5):** A 42-year-old female patient, who had a past history of chronic RRMS, 3 years duration. Recently, she developed further neurological deficits in the form of presented with right hemi-paresis, lumber weakness, numbness and generalized weakness with progressive deterioration 3 months' duration. **(The initial MRI) A & B):** axial FLAIR and Axial T2WI: Show large left sub cortical white matter hyperintense plaques, **C & D):** Axial Susceptibility Weighted Images (SWI) (pre and post contrast study): Shows characteristic scattered hypointense dots inside the plaque (arrows) which demonstrate iron deposition inside the lesion, **E & F):** Axial T1WI (pre and post contrast study): shows subcortical white matter hypointense plaques, **G):** ADC map: The plaques are hyperintense on ADC map (G). The ADC value of MS plaque of (NEL) on the left side (ROI1) is elevated = 1.469 X 10-3 $mm^2$/ second. The clinical and the radiological findings are consistent with secondary progressive case of multiple sclerosis. The current MRI revealed progressive course of the MS disease in the form of elevation of the ADC value of the old plaques and presence of scattered hypointense dots inside the plaque in GD-SWI sequence.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

## IV. DISCUSSION:

MS is the main reason for nontraumatic neurologic disability in young adults in many countries, and it is considered one of the most common neurologic disorders in the world. Predominantly it is characterized by the independent processes of, inflammation, demyelination, neurodegeneration, remyelination and repair of the axons in different multifocal combinations at different stages of disease progression [1, 2].

Magnetic Resonance Imaging has an important role in MS evaluations and indicates a necessity for an initial examination in (1st 6 months) and follow-up examinations every 12 months to assess the presence of new T2 lesions and to search for foci of active inflammation using the post gadolinium T1 sequence. MS plaque enhancement with gadolinium (Gd) is a well-established marker of MS lesion inflammation [10].

One of the most important relatively new MR imaging techniques is Susceptibility-weighted imaging (SWI) which is being implemented in clinical practice currently besides conventional T1- and T2-weighted imaging methods, which are already used in MR imaging scanners [5].

Our study has investigated a central vein inside white matter lesions in SWI sequence, the "central vein sign," detected by SWI can be considered as a promising imaging biomarker of inflammatory demyelination, adding specificity to the diagnosisof MS.

This was in agreement with ***Tallantyre EC, Dixon JE, and Donaldson I, et al. (2011)*** who reported the sensitive role of SWI sequence in diagnosis of MS by detection of central vein sign [5].

Our study has also investigated a hypointense rim around MS lesions as an adjunct imaging biomarker for MS, inside white matter lesions in SWI sequence, the "hypointense rim sign," detected by SWI can be considered as a promising imaging biomarker of inflammatory demyelination, adding specificity to diagnosis of MS.

This was in agreement with A study conducted by ***Hosseini et al. (2018)***, also demonstrated a hypointense rim around MS lesions as an adjunct imaging biomarker for MS, which may be used with the central vein sign as a radiologic sign to differentiate MS from other benign white matter lesions [8].

Our study has also investigated the role of post GD –SWI in detection of central vein sign better than pre-GD SWI; it facilitated the visibility of small veins already seen in pre-contrast SWI.

This was in agreement with a study conducted by Pietro Maggi et al. (2015) that reported that gadolinium seems to improve the visibility of veins inside multiple sclerosis WM lesions when using SWI, and this appears to be remarkably conspicuous when the lesion itself is visibly contrast enhancing on the same SWI sequence[11].

Our study included 24 patients, 8 active and 16 inactive cases proven as MS patients clinically and radiologically, fulfilled the inclusion criteria. They were 16 females and 8 males; their ages were ranged from 20-42 years with the mean age 26.33 years.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

The twenty-four patients with well-documented definite or clinically probable MS were examined with cMRI and advanced MRI techniques (diffusion weighted MR imaging & Susceptibility-weighted imaging (SWI)).ADC values measurements were obtained for selected areas of white matter plaquesthat show scattered hypointense dots or hypointense rim in SWI.

Our study has shown that the plaques with scattered hypointense dots on SWI had a significantly higher mean ADC values than the other isointense plaques in both enhancing and non-enhancing lesions, seen more in chronic 2ry progressive cases.

These results were also in agreement with multiple studies which have demonstrated that iron accumulates within macrophages and microglia at the edges of these lesions, generating rims [12, 13]. A current study investigated iron accumulation at the edge of MS lesionsby using 7-T post-mortem MRI. The authors demonstrated that thehypointense rim detected on SWI was correlated histologically with iron accumulation in macrophages and microglia expressing the pro-inflammatory markers CD86 and p22phox at the edge of slowly expanding lesions, whereas non-rim lesions demonstrated a tendency to shrink over time [14]. The authors concluded that the presence of iron rims on SWI sequence might be a sign of progressive tissue injury and might serve as a marker of a disease activity in MS patients [14]. It is possible that hypointense rim lesions are specific for MS and not seen in other pathologies. Future researches could address this more.

## V. CONCLUSIONANDRECOMMENDATIONS:

Our study has concluded the role of post GD –SWI in detection of central vein sign better than pre-GD SWI; it facilitated the visibility of small veins already seen in pre-contrast SWI.

Gadolinium-Enhanced Susceptibility Weighted Imaging in Multiple Sclerosis: Optimizing the Recognition of Active Plaques better than T1WI and facilitate visibility of central venous sign better than pre-contrast SWI and should be used as a part of MRI protocol for MS diagnosis.

**Funding:** No funding was received for this study.

**Data Availability Statement:** The data presented in this study are available on request from the corresponding author.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. ***Cristiano E, Rojas JI. (2017)*** Multiple sclerosis epidemiology in Latin America: an updated survey. MultScler J ExpTranslClin 3(2): DOI: 10.1177/2055217317715050.
2. ***Ebers GC. (2008)*** Environmental factors and multiple sclerosis. Lancet Neurol 7:268–77.
3. ***Sicotte NL. (2011)*** Magnetic resonance imaging in multiple sclerosis: the role of conventional imaging. Neurol Clin 29:343–56.
4. ***Rovira A, Wattjes MP, Tintore´ M, et al; (2015)*** MAGNIMS study group-evidence based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

sclerosis—clinical implementation in the diagnostic process. Nat Rev Neurol 11:471–82.

5. ***Tallantyre EC, Dixon JE, Donaldson I, et al. (2011)***Ultra high field imaging distinguishes MS lesions from asymptomatic white matter lesions. Neurology 76:534–39.
6. ***Sati P, Oh J, Constable RT, et al; (2016)*** NAIMS Cooperative. The central vein sign and its clinical evaluation for the diagnosis of multiple sclerosis: a consensus statement from the North American Imaging in Multiple Sclerosis Cooperative. Nat Rev Neurol 12:714–22.
7. ***Sparacia G, AgnelloF,Gambino A, et al. (2018)*** Multiple sclerosis: high prevalence of the "central vein" sign in white matter lesions on susceptibility-weighted images. Neuroradiol J 31:356–61.
8. ***Hosseini Z, Matusinec J, Rudko DA, et al. (2018)*** Morphology-specific discrimination between MS white matter lesions and benign white matter hyper intensities using ultra-high-field MRI. AJNR Am J Neuroradiol 39:1473–79.
9. ***Mittal S, Wu Z, Neelavalli J, et al. (2009)***Susceptibility-weighted imaging: technical aspects and clinical applications, Part2.AJNR Am J Neuroradiol 30:232–52.
10. ***Wattjes MP, Rovira A `, Miller D, et al; (2015)*** MAGNIMS study group. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis establishing disease prognosis and monitoring patients. Nat Rev Neurol 11:597–606.
11. ***Maggi P, Mazzoni LN, Moretti M, Grammatico M, Massacesi L.(2015)***SWI enhances vein detection using gadolinium in multiple sclerosis. ActaRadiol Open. 2015 Mar 18;4(3):2047981614560938. Doi: 10.1177/2047981614560938. PMID: 25815209; PMCID: PMC4372566.
12. ***FrischerJM,Weigand SD, Guo Y, Kale N, Parisi JE, Pirko I, et al.*** Clinical and pathological insights into the dynamic nature of the white matter multiple sclerosis plaque. Ann Neurol. (2015) 78:710–21. doi: 10.1002/ana.24497
13. ***Bagnato F, Hametner S, Yao B, van Gelderen P, Merkle H, Cantor FK, et al.*** Tracking iron in multiple sclerosis: a combined imaging and histopathological study at 7 Tesla. Brain. (2011). 134(Pt 12):3602–15. doi: 10.1093/brain/awr278.
14. ***Dal-Bianco A, Grabner G, Kronnerwetter C, Weber M, Hoftberger R, Berger T, et al.*** Slow expansion of multiple sclerosis iron rim lesions: pathology and 7 T magnetic resonance imaging. ActaNeuropathol. (2017) 133:25–42. doi: 10.1007/s00401-016-1636-z.