

The Use of New Magnetic Resonance Imaging Techniques in Multiple Sclerosis

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Abstract

Background: Multiple Sclerosis (MS) is a chronic immune-mediated degenerative disease of the central nervous system (CNS), characterized by localized areas of inflammation, demyelination, axonal loss, and glial scar formation (sclerosis) in the brain and spinal cord. This study aimed to evaluate the role of advanced MRI techniques in assessing multiple sclerosis disease of the brain. **Methods:** This prospective study included 100 patients with multiple sclerosis. All studied cases were subjected to general and neurological examinations. Conventional MRI techniques included Axial T1WI, T2WI, FLAIR, and Sagittal FLAIR. Non-conventional MRI modalities included MRS, MTI, MTR, DTI, and SWI. **Results:** The mean CNR for Cube FLAIR was significantly greater than that for 2D FLAIR, with the statistical test result confirming this with a highly significant p-value (<0.001). The mean SNR for Cube FLAIR was substantially higher than that for 2D FLAIR, and the significance test result was also highly significant (p<0.001). SWAN detected CVS as positive in a higher percentage of cases (92%) compared to 2D FLAIR, which had a positive detection rate of 51%. **Conclusion:** Based on our results, Cube FLAIR is superior to the 2D FLAIR sequence used in multiple sclerosis

imaging. 2D FLAIR consistently detected more lesions compared to SWAN in the Centrum Semiovale Area, Subcortical U-Fibers, Periventricular Zone, and Pericallosal Region. Cube FLAIR showed a markedly higher SNR, with its mean SNR significantly higher than that of 2D

Keywords: Magnetic Resonance Imaging (MRI); Multiple Sclerosis (MS); Brain.

Introduction

Multiple Sclerosis (MS) is a chronic immune-mediated degenerative disease of the central nervous system (CNS) characterized by localized areas of inflammation, demyelination, axonal loss, and glial scar formation (sclerosis) in the brain and spinal cord. The disease typically begins in young adults, with onset occurring between the ages of 20 and 50 years. However, it may also affect children under 16 years of age and elderly individuals over 60 years of age. MS is three times more common in women than in men. The exact etiology and pathogenesis of the disease remain unknown, but it is believed to result from a combination of genetic, environmental, and immunological factors. Approximately 2.5 million people are affected globally, with an uneven distribution across the globe (1).

MS is pathologically characterized by the presence of multifocal, demyelinating white matter (WM) lesions that are disseminated in space and time. Each of these WM lesions is a focal region of inflammation, demyelination, oligodendroglial loss, reactive gliosis, and axonal degeneration (2).

Relapsing-Remitting MS (RRMS) is the most common type of MS, characterized by clearly defined attacks, also known as relapses or exacerbations, of new or worsening neurological symptoms, with intervals of remission in between (3). During remission, all symptoms may disappear, or some may persist and

become permanent. However, there is no apparent progression of the disease during these periods. RRMS can be active or inactive, and worsening or not worsening (4).

Primary Progressive MS (PPMS) is characterized by the worsening of neurological function (i.e., increased disability) from the onset of symptoms, with no early recurrence or recovery (5).

Magnetic resonance imaging (MRI) was formally included in the diagnostic work-up of patients presenting with a clinically isolated syndrome (CIS) suggestive of MS in 2001 by an international panel of experts. MS diagnosis requires demonstrating disease dissemination in space (DIS) and time (DIT) and excluding other conditions that can mimic MS through clinical and laboratory profiles. MRI offers three main applications in MS: first, in combination with characteristic symptoms, it provides earlier and more confident diagnosis than symptoms alone; second, it contributes to our understanding of the pathophysiology of MS and how pathophysiologic changes relate to clinical manifestations of the disease; third, it plays a role in monitoring the effects of therapies in clinical trials and has the potential to identify responses to therapy in individual patients (6).

Magnetization transfer (MT) MRI is a quantitative technique with the potential to provide additional information about the nature and extent of tissue damage

associated with this disease. Over the last ten years, MT MRI has enabled us to quantify the structural changes occurring within and outside lesions visible on conventional MRI (cMRI) scans, thereby providing a more accurate in vivo picture of the heterogeneity of MS and improving our ability to monitor disease evolution (7).

Diffusion imaging is based on the random movement of molecules through a fluid, known as diffusion. The diffusivity in brain tissue is lower than that of free water, referred to as the apparent diffusion coefficient (ADC). Restricted diffusion causes an increase in ADC values. Active MS plaques may demonstrate restricted diffusion on DWI/ADC. Analogous to MTI, DTI is sensitive to tissue injury and is abnormal in MS lesions and normal-appearing brain tissues. Poonawalla et al. reported that fractional anisotropy (FA) and mean diffusivity (MD) values were significantly higher in cortical lesions compared to healthy controls. DTI abnormalities have confirmed that brain damage in MS patients is not limited to focal and macroscopic lesions; it is also present in normal-appearing gray matter, even in the early stages of the disease. Abnormal gray matter diffusivity correlates with disease progression and cognitive impairment (8).

Susceptibility-weighted imaging (SWI) is a relatively new MRI sequence that uses the paramagnetic susceptibility effect of iron to demonstrate susceptibility differences between tissues. SWI

provides information about any tissue with a different susceptibility than its surroundings, such as deoxygenated blood, hemosiderin, ferritin, and calcium (9).

High-field (3 T) and ultra-high field (>7 T) MRI scanners are more sensitive for detecting T2 and gadolinium-enhancing lesions than 1.5 T MRI scanners. Higher-field imaging can improve the early diagnosis of MS. Specific pulse sequences, such as double inversion recovery (DIR) imaging, can further enhance the detection of cortical MS lesions in vivo but are technically challenging to execute. It has been reported that DIR imaging at higher fields captures a larger number of cortical lesions (10).

The purpose of this study was to evaluate the role of advanced MRI techniques in the assessment of multiple sclerosis disease of the brain.

Patients and methods

This prospective, non-controlled, non-randomized study included 100 patients with multiple sclerosis who were referred from the neurology department to the MRI unit. Written informed consent, approved by the Ethics Committee of Banha Faculty of Medicine, was obtained from all subjects (MS.15-9-2018). The study was conducted at Benha University Hospital from February 2022 to May 2023.

Inclusion Criteria: Patients with a confirmed diagnosis of multiple sclerosis,

specifically those with relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS), who were willing and able to tolerate MRI examination.

Exclusion Criteria: Patients were excluded if they had a very poor general condition, contraindications to MRI (e.g., old pacemakers, permanent hearing aids), high serum creatinine and impaired renal function that would preclude post-gadolinium MRI, known hypersensitivity to gadolinium, or were unable to tolerate the baseline MRI scan or if the scan was of inadequate quality for analysis due to excessive movement artifacts.

All studied cases were subjected to the following: Detailed history taking, including [age, gender, occupation, diagnosis, age at onset and disease duration]. General and neurological examination of the patients. Conventional MRI including [Axial T1WI, T2WI, FLAIR, Sagittal FLAIR]. Non-conventional MRI modalities [MRS, MTI, MTR, DTI, SWI].

MRI technique

The study was conducted using 3 Tesla and 1.5 Tesla MR machines with a Head-Neck 20 channel coil. The pre-contrast study included axial T1, T2, and FLAIR as well as sagittal CUBE FLAIR sequences. A susceptibility-weighted sequence (SWAN) was also obtained. If needed, post-contrast axial and sagittal T1 sequences were acquired 5 minutes after IV injection of Gadoterate Meglumine,

0.15 mL/kg (0.1 mmol/kg) body weight, with a maximum dosage of 20 mL. FSPGR sequences were then obtained. The total examination time, including conventional and non-conventional techniques, was approximately 50 minutes.

Statistical analysis

Statistical analysis was performed using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups using the unpaired Student's t-test. Qualitative variables were presented as frequency and percentage (%) and analyzed using the Chi-square test. A two-tailed p-value < 0.05 was considered statistically significant.

Results

Demographic Data

The mean age of the study subjects was approximately 35 years. Gender distribution within the study showed a higher proportion of females (62%) compared to males (38%). **Table 1**

Lesion Detection

Highly significant results ($p < 0.001$) were observed in the Centrum Semiovale Area, Subcortical U-Fibers, Pericallosal Region, and the total lesion count, indicating that Cube FLAIR is notably more effective in detecting lesions in

these areas. Additionally, the Periventricular and Infratentorial regions also showed significant differences with p-values of 0.017 and 0.033, respectively, although these were less pronounced compared to the other regions.

2D FLAIR consistently detected more lesions than FSPGR in the Centrum Semiovale Area, Periventricular Zone, Pericallosal Region, and the total lesion count, with highly significant results ($p < 0.001$). This indicates superior sensitivity of 2D FLAIR in these specific regions. However, in the Subcortical U-Fibers and Infratentorial Region, the differences were not statistically significant, with p-values of 0.051 and 0.215, respectively. **Table 2**

2D FLAIR also consistently detected more lesions compared to SWAN in the Centrum Semiovale Area, Subcortical U-Fibers, Periventricular Zone, and Pericallosal Region, with highly significant p-values (all $p < 0.05$), indicating greater sensitivity of 2D FLAIR in these regions. The most notable difference was observed in the Pericallosal Region, where the difference in lesion detection was extremely significant ($p < 0.001$). However, in the Infratentorial Region, the difference was not statistically significant ($p = 0.347$).

Table 3

Central Vein Sign (CVS) Detection

SWAN detected the Central Vein Sign (CVS) as positive in a higher percentage of cases (92%) compared to 2D FLAIR,

which had a positive detection rate of 51%. The statistical test result indicates a significant difference between the two imaging modalities in terms of CVS detection. **Table 4**

Case Studies

Case No. 1:

A 35-year-old male known to have relapsing-remitting multiple sclerosis (RRMS), currently on Gilenya, with an expanded disability status scale (EDSS) score of 1, and a family history (brother) of MS. Axial T2W FLAIR imaging (Image 1) shows multiple hyperintense MS plaques. Axial CUBE 3D FLAIR (Image 2) demonstrates better delineation of the plaques. SWAN 3D imaging (Image 3) shows the central vein sign (CVS) indicated by an arrow on the right. T1W post-contrast imaging (Image 4) clearly shows CVS, marked by an arrow on the left. Lastly, 3D FSPGR T1W post-contrast imaging (Image 5) highlights prominent periventricular lesions.

Case No. 2:

A 33-year-old female known to have multiple sclerosis, currently on teriflunomide. She had a history of upper and lower limb weakness three months prior, necessitating imaging to rule out new lesions. Axial T2W FS imaging (Image 1) shows a hyperintense MS plaque in the left centrum semiovale. Axial CUBE FLAIR imaging (Images 2 and 3) provides better delineation of MS plaques on both sides, particularly in the periventricular region. Sagittal CUBE

FLAIR imaging is shown in Image 4. Axial 3D post-contrast FSPGR imaging (Image 5) reveals hypointense MS

plaques, with at least one showing CVS (indicated by an arrow).

Table 1: Demographic data among study subjects

		Study subjects
		n=100
Age (years)	Mean ± SD	35.39 ± 9.39
Gender	Female	62(62.0%)
	Male	38(38.0%)

*: statistically significant as P value <0.05

Table 2: Comparison between 2D FLAIR and Cube FLAIR according to number of lesions detected in different brain regions and between 2D FLAIR and FSPGR according to number of lesions detected in different brain regions

		2D FLAIR	Cube FLAIR	Test Result
Centrum Semiovale Area	Median	15.00	21.00	p<0.001*
	(Min-Max)	(1.00-41.00)	(1.00-71.00)	
Subcortical U-Fibers	Median	6.50	8.00	p<0.001*
	(Min-Max)	(1.00-21.00)	(1.00-23.00)	
Periventricular Zone	Median	9.50	14.00	p=0.017*
	(Min-Max)	(2.00-31.00)	(2.00-31.00)	
Pericallosal Region	Median	3.00	4.00	p<0.001*
	(Min-Max)	(0.00-9.00)	(0.00-22.00)	
Infratentorial Region	Median	2.00	3.00	p=0.033*
	(Min-Max)	(0.00-11.00)	(0.00-11.00)	
		2D FLAIR	FSPGR	Test Result
Centrum Semiovale	Median	15.00	10.00	p<0.001*
	(Min-Max)	(1.00-41.00)	(0.00-41.00)	
Subcortical U-Fibers	Median	6.50	5.00	p=0.051
	(Min-Max)	(1.00-21.00)	(0.00-13.00)	
Periventricular Zone	Median	9.50	8.00	p<0.001*
	(Min-Max)	(2.00-31.00)	(0.00-23.00)	
Pericallosal Region	Median	3.00	2.00	p<0.001*
	(Min-Max)	(0.00-9.00)	(0.00-6.00)	
Infratentorial Region	Median	2.00	1.55	p=0.215
	(Min-Max)	(0.00-11.00)	(0.00-5.00)	

*: statistically significant as P value <0.05

Table 3: Comparison between 2D FLAIR and SWAN according to number of lesions detected in different brain regions.

		2D FLAIR	SWAN	Test Result
Centrum Semiovale Area	Median	15.00	10.41	p<0.001*
	(Min-Max)	(1.00-41.00)	(0.52-42.00)	
Subcortical U-Fibers	Median	6.50	5.18	p=0.030*
	(Min-Max)	(1.00-21.00)	(0.62-19.00)	
Periventricular Zone	Median	9.50	9.60	p=0.025*
	(Min-Max)	(2.00-31.00)	(1.35-21.21)	
Pericallosal Region	Median	3.00	1.95	p<0.001*
	(Min-Max)	(0.00-9.00)	(0.00-5.00)	
Infratentorial Region	Median	2.00	1.10	p=0.347
	(Min-Max)	(0.00-11.00)	(0.00-6.49)	

Table 4: Comparison between 2D FLAIR and SWAN according to detection of Central vein sign.

		FLAIR , T2	SWAN	Test Result
CVS	Negative	49(49.0%)	8(8.0%)	X2: 39.259, p=0.001
	Positive	51(51.0%)	92(92.0%)	

*: statistically significant as P value <0.05, CVS: Central vein sign

Case no 1

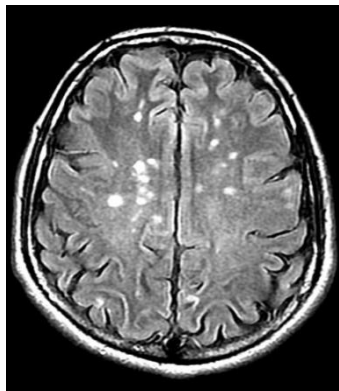


Image no 1

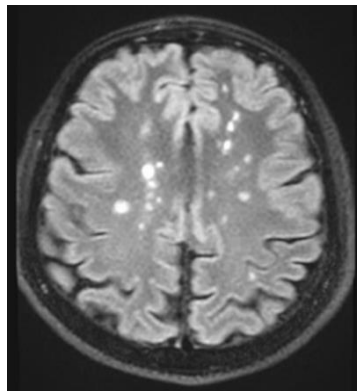


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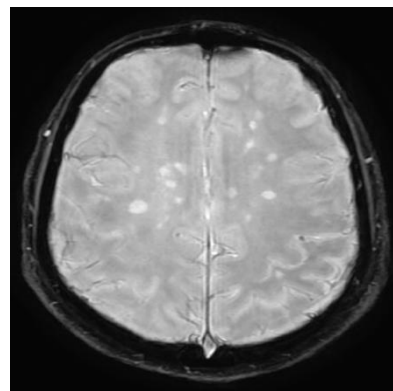


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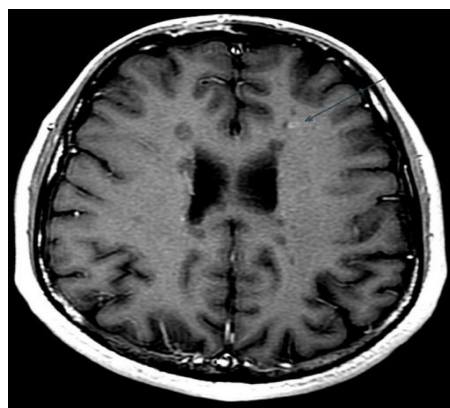


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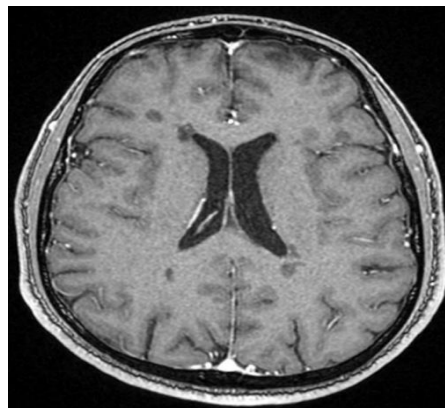


image no 5

Case no 2

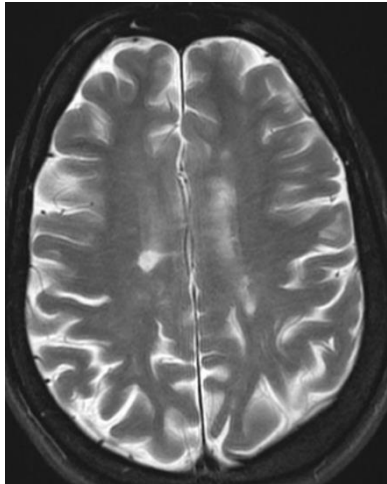


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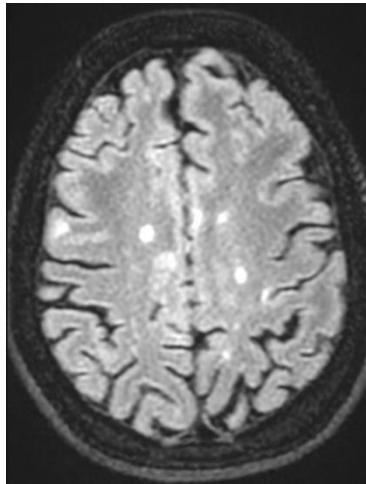


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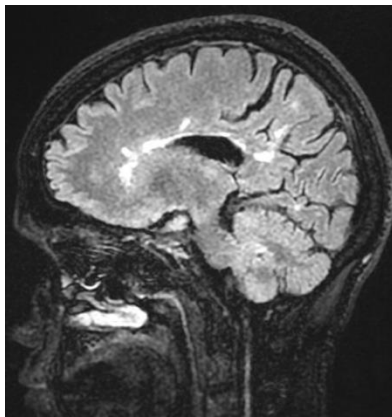


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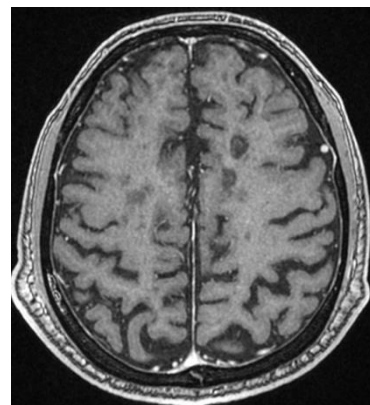


image no 5

Discussion

In this study, according to the demographic data of the study subjects, the mean age was approximately 35 years. Gender distribution showed a higher proportion of females (62%) compared to males (38%).

Comparable to our study, a study involving 30 MS patients reported that 86.7% were females and 13.3% were males, with ages ranging from 20 to 50 years, and a median \pm IQR of 25.00 \pm 25.00 years (11).

In the current study, the comparison between 2D FLAIR and Cube FLAIR was based on the number of lesions detected in different brain regions. Highly significant results ($p < 0.001$) were observed in the Centrum Semiovale Area, Subcortical U-Fibers, Pericallosal Region, and the total lesion count, indicating that Cube FLAIR is notably more effective in detecting lesions in these areas. Additionally, the Periventricular and Infratentorial regions also showed significant differences with p-values of 0.017 and 0.033, respectively, although these were less pronounced compared to the other regions.

A study performed on 20 selected MS patients included brain MRI using routinely used T2 and 2D FLAIR sequences, with an added 3D-FLAIR sequence. The 3D-FLAIR images were reformatted, and all images were blindly analyzed. Lesions were counted in each sequence and classified according to their location into supratentorial lesions, including periventricular, deep white matter, and juxta-cortical, and infratentorial lesions. Relative comparisons of lesion numbers on 3D-FLAIR versus 2D-FLAIR and T2 imaging were expressed as percentage gain or loss. The 3D-FLAIR sequence showed significantly more lesions compared to 2D FLAIR and T2 sequences in all locations (12).

According to this study, lesion detection between 2D FLAIR and FSPGR across different brain regions in multiple

sclerosis patients showed significant differences in most areas, except the Subcortical U-Fibers and Infratentorial Region. Highly significant results ($p < 0.001$) were noted in the Centrum Semiovale Area, Periventricular Zone, Pericallosal Region, and the total lesion count, with 2D FLAIR consistently detecting more lesions than FSPGR, indicating superior sensitivity in these specific regions. However, in the Subcortical U-Fibers and Infratentorial Region, the differences were not statistically significant, with p-values of 0.051 and 0.215, respectively.

A study compared the infratentorial lesion detection performance, observer performance, and signal and contrast properties between T2-weighted spin echo, 2D, and 3D fluid-attenuated inversion recovery. They noted that the number of lesions on 3D fluid-attenuated inversion recovery was significantly higher than those on 2D ($p < 0.001$) and T2-weighted spin echo ($p < 0.001$) (13).

Our findings demonstrate significant differences between 2D FLAIR and SWAN in lesion detection across multiple brain regions in multiple sclerosis patients, except in the Infratentorial Region. 2D FLAIR consistently detected more lesions compared to SWAN in the Centrum Semiovale Area, Subcortical U-Fibers, Periventricular Zone, and Pericallosal Region, with highly significant p-values (all $p < 0.05$), indicating a greater sensitivity of 2D FLAIR in these regions. The most notable difference was

observed in the Pericallosal Region, where the difference in lesion detection was extremely significant ($p < 0.001$). However, in the Infratentorial Region, the difference was not statistically significant ($p = 0.347$).

Parallel with our work, a study included 40 patients clinically diagnosed with MS according to McDonald criteria. Comparative studies between FLAIR and SWI sequences revealed a significant increase in the sensitivity and specificity of detection of periventricular lesions with the Central Vein Sign in the SWI sequence, with highly significant statistical difference ($p < 0.0001$) (14).

The findings of our study reveal that the comparison of lesion signal-to-noise ratio (SNR) between 2D FLAIR and Cube FLAIR demonstrates a highly significant difference, with Cube FLAIR showing a markedly higher SNR. The mean SNR for Cube FLAIR is substantially higher than that for 2D FLAIR, with a significant test result ($p < 0.001$).

Compatibly, a study sought to compare Cube, a 3D FLAIR sequence, to a standard 2D FLAIR sequence in multiple sclerosis (MS) imaging. The overall number of lesions found with Cube FLAIR was significantly higher than with 2D FLAIR ($N = 384$ vs. $N = 221$). The difference was mostly accounted for by supratentorial lesions ($N = 372$ vs. $N = 216$) while the infratentorial lesion counts were low in both sequences. SNRs and CNRs were significantly

higher in CUBE FLAIR with the exception of the CNR of lesion to gray matter, which was not significantly different (15).

In the present study, the comparison of white matter signal-to-noise ratio (SNR) between 2D FLAIR and Cube FLAIR revealed a significant enhancement with Cube FLAIR. The mean SNR for Cube FLAIR is considerably higher than that for 2D FLAIR, with a highly significant test result ($p < 0.001$).

In the current work, the signal-to-noise ratio (SNR) for gray matter between 2D FLAIR and Cube FLAIR was compared across a sample of 100 individuals. The results showed a pronounced improvement in SNR with Cube FLAIR, with its mean SNR significantly higher than that of 2D FLAIR. This substantial difference is statistically significant, as indicated by the test result ($p < 0.001$).

In agreement with our study, a study found that SNR for gray matter was significantly higher in Cube FLAIR than in 2D FLAIR ($P = 0.002$) (15).

According to our findings, Cube FLAIR demonstrates a significantly higher CSF SNR, with both mean and median values markedly exceeding those recorded with 2D FLAIR. The statistical significance of this improvement is robust, as indicated by the very low p-value (< 0.001).

Compatible with the present study, a study found that CSF SNR was

significantly higher in Cube FLAIR than in 2D FLAIR (P=0.028) (15).

Our results reveal that Cube FLAIR significantly outperforms 2D FLAIR in terms of mean CNR, which is more than double that of 2D FLAIR. This considerable improvement is statistically significant, as evidenced by the test result ($p < 0.001$). The results show only a slight difference in the mean and median CNR values between the two techniques, with Cube FLAIR showing a marginally higher mean CNR. However, this small difference is not statistically significant, as reflected by the p-value of 0.708.

Our study clearly demonstrated a substantial improvement with Cube FLAIR, which shows a much higher CNR compared to 2D FLAIR. The mean CNR for Cube FLAIR is significantly greater than that for 2D FLAIR, with the statistical test result confirming this with a highly significant p-value (< 0.001).

In line with our findings, a study examined 8 patients with MS at 3.0 T using a 2D FLAIR sequence and a single-slab 3D FLAIR sequence. They documented that in images acquired with the 3D FLAIR sequence, the lesions had significantly higher CNRs than in images acquired with the 2D FLAIR sequence (16).

The current study shows that SWAN detected CVS as positive in a higher percentage of cases (92%) compared to 2D FLAIR, which had a positive detection rate of 51%. The statistical test

result indicates a statistically significant difference between the two imaging modalities in terms of CVS detection.

In another study, 101 infratentorial lesions were detected on FLAIR, and 86% were centered by a vein. Fifteen MRIs from the non-MS group were analyzed, 19 lesions were visible on FLAIR, and 16% were positive for the CVS. They concluded that SWAN-venule detects infratentorial lesions and highlights the Central Vein Sign in MS plaques at 3T MRI. As occurs in the supratentorial brain, most infratentorial lesions are perivenular (17).

Conclusion

Based on our results, Cube FLAIR is superior to the 2D FLAIR sequence used in multiple sclerosis imaging. **2D FLAIR** consistently detected more lesions compared to **SWAN** in the Centrum Semiovale Area, Subcortical U-Fibers, Periventricular Zone, and Pericallosal Region. Cube FLAIR shows a markedly higher SNR. The results show a pronounced improvement in SNR with Cube FLAIR, with its mean SNR significantly higher than that of **2D FLAIR**. The results clearly demonstrate a substantial improvement with Cube FLAIR, which shows a much higher CNR compared to **2D FLAIR**.

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