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Research Article

Dual Inversion Recovery Magnetic Resonance Imaging's Diagnostic Value for Estimating the Overall Load of Multiple Sclerosis Lesions and its Anatomical Distribution

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ABSTRACT

Background: In young adults, multiple sclerosis is a prevalent chronic inflammatory demyelinating condition. It is characterized by white matter affection, but many individuals also have significant gray matter involvement. A double inversion recovery pulse pattern was recently proposed to improve the detectability of multiple sclerosis lesions.

Objectives: To evaluate the diagnostic value of double inversion recovery sequence in the detection of cortical and white matter multiple sclerosis plaques in different brain anatomical locations.

Subjects and methods: A total of 37 patients with an established diagnosis of multiple sclerosis were included in this cross-sectional study. Brain MRI was done using double inversion recovery, T2 and FLAIR sequences. The number of lesions was counted and compared in the three sequences.

Results: Dual Inversion Recovery sequence was highly significant and superior to both T2 and FLAIR sequences ($P < 0.001$) in depicting the lesions regardless of anatomical distribution. Dual Inversion Recovery was significantly superior to T2 ($P =<0.001$) and FLAIR ($P =<0.001$) in detecting lesions in cortical and juxtacortical. However, Dual Inversion Recovery shows less periventricular and deep white matter lesions in comparison to T2 and FLAIR sequences.

Conclusion: The Dual Inversion Recovery sequence detected more multiple sclerosis lesions in cortical, subcortical and infratentorial than the traditional T2W and FLAIR sequences. It also demonstrated greater delineation between the white matter, grey matter, and multiple sclerosis lesions, which became more easily visualized.

Introduction

The most prevalent chronic inflammatory demyelinating disease of the central nervous system is multiple sclerosis (MS) which is a common cause of neurological disability in middle-aged and young adults resulting in both physical and neurocognitive disability (1,2). It

is characterized by central nervous system (CNS) inflammation and demyelination, along with varying degrees of axonal and neuronal damage. (3).

MS primarily affects the white matter (WM), however abnormalities in the grey matter (GM) have been reported in recent clinical autopsy studies (4, 5). Imaging cortical lesions is difficult to comprehend particularly with traditional magnetic resonance imaging (MRI) protocols (6). Because of their tiny size and low contrast with surrounding normal gray matter, intracortical lesions (ICLs) are difficult to detect with conventional MRI (7, 8).

A double inversion recovery (DIR) pulse sequence was introduced several years ago. This sequence generates two unique inversion pulses that attenuate the cerebrospinal fluid (CSF) and the whole of the white matter, providing a superior distinction of the gray and white matter. (9, 10). It has successfully been used to detect focal cortical lesions in MS and other neurological disorders, and has considerably improved the identification of intracranial lesions (ICLs) in vivo (11).

Pathologically, multiple sclerosis is distinguished by the formation of focal-often periventricular-scattered regions of demyelination, as well as reactive gliosis, axonal injury, and neuronal degeneration (12). While the condition primarily affects the periventricular areas, calloso-septal interface, cerebellum, brainstem, and basal ganglia.

The McDonald criteria are used to diagnose multiple sclerosis (MS), which calls for objective evidence of lesions dispersed in time and space, either clinically or radiologically, as well as the elimination of other conditions that may mimic MS based on their clinical and laboratory profiles (13). In addition to clinical presentation (i.e., a clinical event suggestive of a first attack of multiple sclerosis or disability progression suggestive of primary progressive multiple sclerosis) and CSF analysis (i.e., showing oligoclonal bands) (14), the 2017 revisions of the McDonald criteria on multiple sclerosis diagnosis (15) reinforced the importance of brain and spinal cord MRI exams in certain instances.

The diagnostic, prognostic, and monitoring worth of MRI in individuals with multiple sclerosis is well established (16). The role of MRI in the diagnosis of MS is substantial, MRI protocols are divided into two separate categories: "conventional" and "advanced". The conventional protocols include T1- weighted pre-and post-gadolinium contrast, T2-weighted and fluid-attenuated inversion recovery (FLAIR) pulse sequences, at 1.5T magnetic field strengths in the brain and spinal cord. T2-weighted and FLAIR sequences are the commonest sequences utilized for brain MRI. T2-weighted sequences seem to be the highest sensitivity for detecting lesions in the brainstem and cerebellum, but FLAIR is more sensitive for detecting periventricular and cortical/juxtacortical lesions (17).

By comparing a DIR sequence with FLAIR and T2 WI in various anatomical locations of the CNS, our work aimed to estimate the diagnostic utility of a DIR sequence in MS lesions detection.

Subjects and Methods
Ethical considerations and study design
A prospective study was conducted in the period from November 2022 to May 2023, which included 37 patients (17 male and 20 female) underwent brain MRI of known cases of MS disease in different genders and age groups (They had already received a multiple sclerosis diagnosis in accordance with the 2017 revised McDonald Criteria). All patients were referred by well qualified neurologist (experience of more than 15 years) from the Neurology Department / outpatient clinic of Multiple Sclerosis (not assessed by disability status scale (DSS) because we are not studying the correlations between the MS and the physical disabilities) to the MRI unit of the radiology department at Al Shaheed Ghazi Al Hariri hospital/medical city. The study had been approved by the local ethical committee of the college of medicine – University of Baghdad. All patients were informed to obtain their consent before the exam and their information were used in this study. The data were collected and interpreted by two well qualified radiologist with experience of 3 - 7 years.

Inclusion criteria: Adult patients with definitive diagnosis of multiple sclerosis coming for regular follow up or have acute exacerbation of symptoms. Fortunately, all the obtained images quality were sufficient to be studied.

Exclusion criteria:
• Patients with cardiac pacemakers and those who are claustrophobic are absolute contraindications to MRI.
• MS patients who also have a concurrent neurological disease.
• Patients have no MRI detectable CNS lesions due to remission.
• Any patient with current or past medical history of neoplastic, vascular, or immunological CNS illnesses.

Image acquisition and MRI interpretation
1.5 T MR imaging scanner (Philips Achieva nova, dual 16 channel, Netherlands) was used to perform brain MRI in which all patients were scanned in supine position with standard circularly polarized head coil. T2W, FLAIR, and DIR sequences were performed in axial sections. The parameters are summarized in Table 1.

Table 1: parameters of MRI sequence

Parameter	DIR	FLAIR	T2W
TR (ms)	14000	6000	1000
TE (ms)	25	120	110
TI (ms)	3400/325**	2000	
Slice thickness(mm)	3	3	3
FOV (mm)	300	300	300
Matrix size	350	350	350
Voxel size	0.7,0.8,4	0.7,0.8,4	0.7,0.8,4
NSA	2	2	2
Time(minutes)	5:22	2:06	1:22

*TR: repetition time, TE: echo time, TI: inversion time, FOV: field of view, NSA: number of signal averaging.

**TI1 (3400 ms) is the time interval between the initial 180° inversion pulse and the 90° excitation pulse. The second 180° inversion pulse and the 90° excitation pulse are separated by the short inversion time TI2 (325 ms).

The number of high signal intensity lesions in the brain that were at least 3 mm in size were tallied in each of the three pulse sequences; hyperintense lesions were only counted once when they showed on multiple contiguous slices. Their location was documented and classified into supratentorial (cortical, juxtacortical, DWM, and periventricular) and infratentorial lesions.

Statistical analysis:

Raw data were tabulated using Microsoft Excel 2016, which were later imported via the IBM Statistical Package for Social Sciences version 26 (IBM-SPSS v.26) to conduct descriptive statistics, normality testing (Shapiro–Wilk test), and inferential hypothesis tests, including the Spearman's rank-order correlation, paired (Wilcoxon signed-rank test) and unpaired testing (Mann–Whitney U test), and the Analysis of variance (ANOVA) with post-hoc pairwise comparisons. The Bonferroni correction was used to reduce the type I errors due to multiple comparisons. An alpha (α) value of 0.05 was considered the cut-off margin for statistical significance, corresponding to a 95% confidence interval (95%).

Multiple brain lesions were analyzed using different pulse sequences (DIR, 2D-FLAIR, and T2). The relative comparison of the number of MS brain lesions observed on DIR versus 2D-FLAIR and T2 imaging was represented as a percentage of gain or loss in the number of detected brain lesions.

Results

A total of 37 patients with established diagnosis of MS were included in this study. The patients included 20 (54.05 %) females and 17 (45.95%) males. The age ranges from 17 to 64 years.
The total number of lesions detected was 4754. 1605 on T2W, 1353 lesions on FLAIR and 1797 lesions on DIR. DIR sequence was highly significant and superior to both T2 and FLAIR sequences (P < 0.001) in detecting the lesions regardless to anatomical distribution (Table 2) , (Figusre 1 and 2).

Table 2: Correlations of total detected lesion in the three MRI sequences (T2, FLAIR and DIR).

Parameters	Number of lesions	P-value
DIR total detected lesion	1797	0.000*
T2 total detected lesion	1605	0.000*
FLAIR total detected lesion	1353	0.000*

*Correlation is significant at the 0.05 level (2-tailed)

DIR sequence demonstrated significantly more cortical, subcortical, periventricular and infratentorial lesions when compared to T2 (P <0.001) and less in regards to DWM (P<0.001 {to the side of the T2}). DIR sequence also revealed significantly more cortical, subcortical and infratentorial lesions when compared with FLAIR (P <0.001) and less in regards to Periventricular and DWM lesion (P < 0.001 {to the side of Flair}) (Figure 1, 3, 4, and 5) (Table 3).
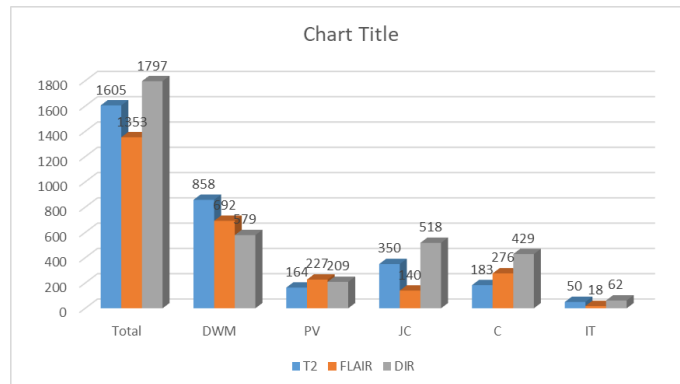

Figure 1: The total number of lesions were detected in the five anatomical regions on DIR, T2 and FLAIR

*DWM: deep white matter, PV: periventricular, JC: juxtacortical, C: cortical, IT: infratentorial, FLAIR: fluid attenuation inversion recovery, DIR: double inversion recovery.

Table 3: The statistical correlation of DIR in relation to T2 and FLAIR sequences presented in different anatomical locations

Parameters	Mean	SD	P-value
DIR-IT	1.68	1.749	
T2-IT	1.35	1.602	0.001*
FLAIR-IT	0.49	0.804	<0.001*
DIR-PV	5.65	5.594	
T2-PV	4.43	4.640	<0.001*
FLAIR -PV	6.14	5.197	<0.001*
DIR-DWM	15.65	12.530	
T2-DWM	23.19	20.487	<0.001*
FLAIR -DWM	18.70	13.180	<0.001*
DIR-JC	11.59	9.679	
T2-JC	9.46	8.494	<0.001*
FLAIR -JC	7.46	6.131	<0.001*
DIR-C	14.00	10.783	
T2-C	4.95	4.034	<0.001*
FLAIR -C	3.78	2.359	<0.001*

* The result was significant at P-value <0.05.
*IT: infratentorial, PV: periventricular, DWM: deep white matter, JC: juxtacortical, C: cortical, DIR: double inversion recovery.
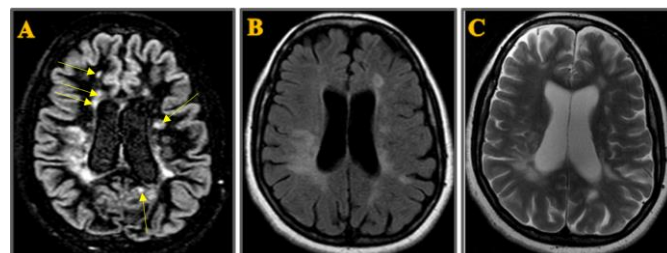

Figure 2: A 40-year's-old female patient with RRMS. Axial brain MRI show more MS lesion load depicted on DIR [Arrows refers to the lesions detected only by DIR], (A) compared with FLAIR (B) and T2(C) images
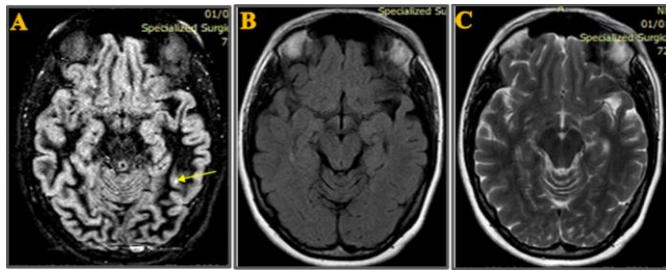
Figure 3: A juxtacortical lesion in the left temporal region in brain MRI of a patient with MS. The lesion is clearly identified at DIR (A) but not seen at FLAIR (B) or T2(C)
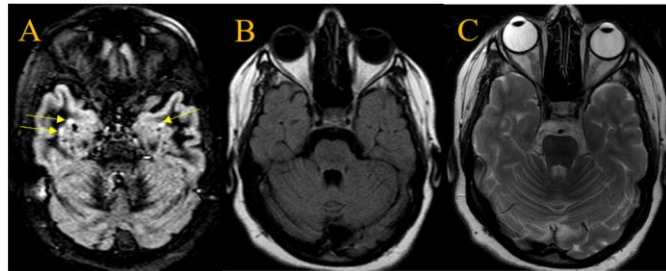

Figure 4: A 32 year's old female with Relapsing Remitting MS [RRMS]. Axial brain MRI show a small cortical lesion (yellow arrow) at the right temporal lobe which easily visualized on DIR (A) with better contrast and lesion delineation than T2 (C), the lesion is not visualized at FLAIR (B) and T2 (c)
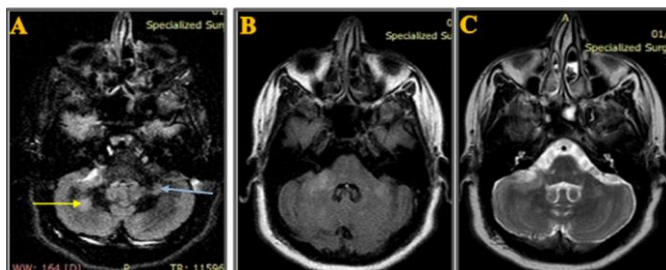

Figure 5: Infratentorial lesions in axial brain MRI of a 22 years old female with relapsing remitting MS. There is a lesion in the right cerebellar hemisphere (yellow arrow) that is more clearly seen at DIR (A), than T2 (C), the lesion is poorly seen at FLAIR (B). Another smaller lesion (blue arrow) is seen in the left cerebellar hemisphere at DIR (A) but not in T2 (C) or FLAIR

Discussion

MS has long been thought to be a white matter disorder; however, a growing amount of data has pointed to the involvement of grey matter in the pathophysiology of MS in the past few years (4, 18). Recognizing GM involvement in the disease process resulted in the inclusion of cortical / juxtacortical lesions in the most recent revised 2017 McDonald's criteria for diagnosis of MS (19). Recent research has found that the extent of GM damage closely corresponds with progression of the disease as well as the degree of physical impairment and cognitive disorders (20).

T2W is a sensitive sequence in detecting infratentorial lesions, while FLAIR is extremely sensitive in detecting supratentorial brain lesions, especially in the periventricular WM and juxtacortical regions, due to CSF attenuation (10). However, unlike the DIR sequence, these sequences lack the ability to precisely define the borders that circumscribes the cortex from subcortical WM (6, 21). When two inversion pulses are combined, the double inversion recovery sequence offers appropriate attenuation of both CSF and

WM. This resulted in a higher contrast ratio and greater distinction of gray and white matter, as well as a high sensitivity in identifying periventricular brain lesions that was similar to FLAIR imaging, the gold standard in this field (22).

In this study both conventional (T2, FLAIR) and DIR sequences were used to produce brain imaging sequences for MS patients. Compared to T2 WI and FLAIR, the total number of identified lesions was significantly greater in DIR, and the studies done by Elnekeidy et al (21) and Abidi et al (23) showed similar results.

In the supratentorial region a less lesion number were identified on DIR than T2 and FLAIR in different white matter locations. DIR revealed significantly more lesions in the periventricular WM when compared to T2 WI as the results of Abidi et al (23), but in contrary for the FLAIR sequence where shown also by Hamed W et al (24) and Elhussein N et al (26) work. However, DIR showed less deep WM lesions than T2 and FLAIR sequences, in accordance to the study conducted by Hamed W et al (24), and in controversy to the study done by Elnekeidy et al (21). In the juxtacortical region DIR was also superior to T2 and FLAIR in detecting more lesions. This was similar to the results of studies published by Elnekeidy et al (21), Abidi et al (23)and Yousra M. et al (27), but differing from the outcomes of Simon B et al (25) which show more juxtacortical lesions on T2 and FLAIR than on DIR. The reason was due to many of these lesions were tabulated as juxtacortical on both T2 and FLAIR images while they were scored as pure cortical or mixture of grey-white matter lesions on DIR leading to a relatively decreased numbers of juxtacortical lesions detected on DIR images.

All 37 patients who participated in this study had cortical lesions based on the DIR study. The DIR sequence was highly significant at detecting cortical lesions more than T2 and FLAIR in which the lesions were usually non-visualized and that was identical to the outcomes listed by Elnekeidy et al (21), Hamed W et al (24), Mahmoud M et al (28) and Ahmed S et al (29).

This is because lesions and surrounding normal GM have a larger contrast ratio in DIR images, which is revealed by mild attenuation of the cerebral cortex signal in DIR. and the sharp demarcation between gray and white matter which allows for a better delineation between juxtacortical and pure cortical lesions (6,25).

Almutairi A et al (30) compared MS lesion load in DIR, FLAIR and T2WI using 3T MR imaging scanners. They detected greater number of lesions in the cortical and juxta cortical regions; which were similar to the results done at 1.5 T MR Scanner used in this study. Further studies comparing 1.5 T and 3 T MRI scanner may recommended to evaluate the beneficial value of using the 3 T equipment instead.

Performing DIR sequence is a useful strategy that could influence the diagnosis and treatment decision at the MS onset particularly in patients with CIS. The improved lesion identification at DIR would be extremely beneficial in suspected MS cases, allowing the diagnosis to be changed from "possible" to "definite" MS as it will complete the criteria of "dissemination in space and time" (22). Furthermore, it can aid in the detection of patients at risk of developing aggressive MS. who will need more aggressive therapies like natalizumab (13).

In this study there were some DIR-related artifacts. In the extra-cortical areas, some of bilateral high-signal ribbon-like artifacts were present due to the effect of cerebral cortical vessels. The detection of their anatomical location, variable appearance in continual sections and other MRI sequences including T1WI or FLAIR can help to differentiate lesions from artifacts. Other artifacts were identified at

the choroid plexus and posterior fossa, which might be caused by CSF pulsation or by venous sinuses and larger vessels.

Despite the long acquisition time of DIR (5:22 minutes) relative to the shorter time of conventional sequences (2:06 minutes in FLAIR, 1:22 minutes in T2), the results in this study were very promising in detecting higher lesion load with highest contrast on DIR in all brain anatomical locations

Limitation for this study include the small sample study due to the exclusion criteria, by which many patients with remission have no detectable MRI lesion.

Conclusion

Due to its ability to identify more MS lesions, the DIR sequence is useful in the MS imaging analysis in most of anatomical regions than the traditional T2W and FLAIR sequences. This higher lesion detection promotes the usefulness of MRI in the follow up and monitoring of multiple sclerosis patients.

The DIR sequence advised to be included in regular MRI investigations of patients with MS, particularly to resolve problems about intra-cortical and juxtacortical lesions. It is critical to pay close attention to the identification of even a single new gray matter lesion particularly cortical lesions as they can cause cognitive and physical disability.

Further studies recommended to be done using 3 Tesla MRI machine; larger sample size; and signal intensity statistical measurements of different MRI sequences.

Conflict of Interest

Authors declare no conflict of interest.

Data availability

Data are available upon reasonable request.

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