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UTILITY OF 3D DOUBLE INVERSION RECOVERY SEQUENCES IN DETECTING SMALL GRAY AND WHITE MATTER LESIONS IN PATIENTS WITH MULTIPLE SCLEROSIS

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ABSTRACT **BACKGROUND:** Multiple sclerosis, once considered a white matter disease showed lesions in grey matter as well in histopathological studies. DIR (Double inversion recovery) sequence is valuable in the Magnetic resonance (MR) imaging workup of Multiple Sclerosis (MS) as it has improved lesion contrast in grey matter compared to the routine T2WI and FLAIR sequences used currently. DIR sequence may help to plan Disease Modifying drugs (DMDs) early and to assess the progression of disease after initiating DMDs.

AIM: The purpose of this study was to compare the ability of Double inversion recovery (DIR) sequence with the routine MR sequences in detecting lesions in MS patients and to examine the prospects of adding DIR sequence in routine MS imaging protocol.

MATERIALS AND METHODS: Seven patients with multiple sclerosis (MS) presented with clinical symptoms were included in this study. Imaging was done with a 1.5T MR system (MagnetomAera, Siemens, Germany) using 3D sequences of DIR (Double inversion recovery), fluid-attenuated inversion-recovery (FLAIR) and T2-weighted imaging (T2WI) sequences. The sensitivity of DIR was compared with the sensitivity of FLAIR and T2WI sequences in detecting MS lesions of different sizes in different anatomical locations in brain.

RESULTS: DIR sequence with a combination of two inversion pulses provided sufficient attenuation of both CSF and white matter and detected significantly higher overall load of lesions compared to the T2WI and FLAIR sequences. Also it detected more number of supratentorial white matter (WM) lesions in the juxta cortical regions compared to the FLAIR sequence which is considered the gold standard in imaging white matter. Due to better contrast between lesions and the surrounding grey matter in the DIR sequence, it revealed more number of intra cortical lesions (ICLs).

CONCLUSION: DIR showed better delineation between the white matter, grey matter and the multiple sclerosis lesions due to its remarkable image contrast in all anatomical locations particularly in the Juxtacortical and Intracortical location, thereby offering better clinical correlation and is of major prognostic relevance. Hence DIR should be included in the routine Multiple sclerosis MR imaging protocol.

KEYWORDS : Demyelination, MR imaging, brain, cortical

INTRODUCTION:

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system that affects young adults and is the important cause for neurological disability in young individuals. While the disease predominantly affects peri-ventricular white matter (WM), gray matter (GM) is also involved to some extent. Results of histo-pathological studies have shown that a considerable portion of the total cerebral lesion load in multiple sclerosis is located within the cerebral cortex and at the grey white matter interface (1, 2). Since Magnetic resonance (MR) imaging plays an important role in both diagnosis and disease monitoring in multiple sclerosis, more accurate estimation of number of lesions is essential. Presently available MR imaging sequences are not ideal for detecting smaller intracortical white matter lesions and for estimating lesion load. MR imaging in MS is performed with fluid-attenuated inversion-recovery (FLAIR), T2-weighted image (T2WI) and pre and post contrast T1 sequences. However, it is difficult to determine the exact anatomic border between the cortex and subcortical white matter on a FLAIR MR image which creates difficulties in judging whether lesions are juxta-cortical, mixed white matter–gray matter, or intra-cortical.

The double inversion recovery (DIR) sequence is a relatively novel imaging sequence which uses two inversion pulses before a turbo spin echo sequence to selectively image grey matter by simultaneously nulling both white matter and CSF (2). This allows optimal evaluation of the cerebral cortex, a portion of the brain which is inherently difficult to image because of its thin and folded structure and its close proximity to white matter and CSF, which have markedly different cellular properties. The purpose of our study was to prospectively compare the depiction of MS lesions by multislab 3D DIR, multislab 3D FLAIR, and T2-weighted spin-echo (SE) MR imaging sequences in patients with multiple sclerosis (4).

MATERIALS AND METHODS:

Patients

Seven patients with proven MS were included in the study comprising 3 males and 4 females, age ranging from 9 to 42 years. All patients had clinical symptoms of MS like optic neuritis, brain stem and spinal cord symptoms. Older age groups were not involved in this study to avoid confusion with age related white matter changes. Diabetics and hypertensives were also excluded from this study. All other concomitant neurological diseases causing similar symptoms were excluded by appropriate clinical and biochemical parameters. Informed written consent was obtained from all patients. Other neurological workup were completed. Institutional ethical committee clearance was obtained.

Image acquisition

MR Imaging of brain was done with a 1.5 Tesla MR system (Magnetom Aera, Siemens, Germany) using a standard head coil. Axial T2WI, FLAIR and DIR sequences were obtained using parameters as shown in **Table 1**. Post-contrast acquisitions were not performed. The contiguous axial sections of the T2WI, FLAIR and DIR sequences were performed with identical anatomical position, geometric, and resolution parameters. To perform DIR sequence, two different inversion pulses were applied with inversion times TI1 and TI2. The first inversion time has to be longer compared to the TI applied in the FLAIR sequence to provide better CSF signal nulling.

The long inversion time TI1 (3400 ms) is the interval between the first 180 degree inversion pulse and the 90 degree excitation pulse. The short inversion time TI2 (325 ms) is the interval between the second 180 degree inversion pulse and the 90 degree excitation pulse.

Table 1: **Various parameters applied in DIR, FLAIR and T2W MR imaging.**

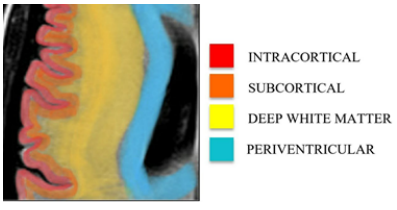
PARAMETERS	DIR	FLAIR	T2WI
Repetition time(m)	1100	6000	4000
Echo time(ms)	20	120	100
Inversion time(m)	3400/325	2000	-
Slice thickness(mm)	5	5	5
Field of view(mm)	230	230	230
Matrix	256	256	256
Voxel size	0.9	0.9	0.9
Number of signal averaging	2	2	2

DIR: Double inversion recovery, FLAIR: Fluid-attenuated inversion recovery, T2WI: T2-weighted imaging.

Image analysis

MS lesions are identified as foci of altered high signal intensity. The total number of lesions were counted in each of the 3 sequences separately and were assorted based on their anatomical location into (A) Infratentorial lesions, (B) Supratentorial (ST) Periventricular WM lesions which are contiguous with the margins of each lateral ventricle and located within 1 cm from the ventricular wall, (C) ST Deep WM lesions which are located more than 1 cm away from the ventricular wall, (D) ST Juxtacortical WM lesions which are abutting the cortex or located within 2 mm from the cortex and (E) ST Intracortical lesions (ICLs) as shown in **Figure 1.** The lesions in each anatomical location are further classified based on their size measurement as a)<2mm b)2-5mm c)5-10mm d)>10mm. Lesion size measurement is done by calculating mean maximum diameter of the lesion in all three dimensions.

Figure 1: Supratentorial anatomical locations for analyzing lesion load.



STATISTICAL ANALYSIS AND RESULTS

The lesions were analysed in the three different pulse sequences based on their anatomical location, size and number. The sensitivity of DIR sequence was compared with T2W and FLAIR sequence in identifying the MS lesions using Wilcoxon signed rank test. P value < 0.05 was considered as statistically significant. **Table 2** shows the comparison of lesion load and sensitivity of the three imaging sequences in the studied anatomical location. The total number of lesions detected in T2 weighted imaging is 176, in FLAIR imaging is 311 and in DIR imaging is 335.

DIR sequence was significantly superior to T2 (P=0.01) and FLAIR (P=0.01) sequences in the overall load measurement. There is no statistically significant difference between DIR, T2 and FLAIR sequences in depicting the infratentorial lesions. But in the supratentorial regions, DIR sequence showed significantly more number of Intracortical lesions (ICLs) when compared to T2 (P=0.01) and FLAIR sequences (P=0.01). MS lesion appearance in various anatomical regions in DIR sequence is shown **Figure 2.**

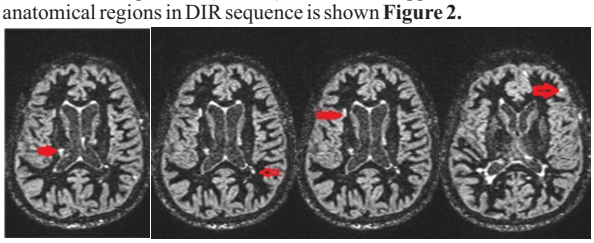


Figure 2: DIR sequence showing MS lesions in Supratentorial Periventricular WM, Deep WM, Juxtacortical WM and Intracortical GM.

	T2	FLAIR	DIR	DIR vs FLAIR P value	DIR vs T2 P value	T2 vs FLAIR P value
CORTICAL	2 (3.9%)	12 (22.6%)	39 (73.5%)	0.011	0.011	0.109
JUXTA-CORTICAL	17 (18.9%)	33 (36.7%)	40 (44.4%)	0.083	0.034	0.004
DEEP WHITE MATTER	76 (25%)	117 (38.7%)	109 (36%)	0.153	0.125	0.030
PERI-VENTRICULAR WHITE MATTER	74 (29.9%)	104 (35%)	119 (40%)	0.167	0.012	0.007
INFRA-TENTORIAL	7 (8.7%)	45 (56.2%)	28 (35%)	0.081	0.035	0.005

Further, DIR sequences demonstrated significantly more number of lesions with size measurement 2-5 mm when compared to the other two sequences. The lesion load in different ranges of size measurements in T2W, FLAIR and DIR sequences is shown in **Tables 3, 4 and 5** respectively.

Table 3: Lesion load measurement in T2WI sequence.

LOCATION	<2mm	2-5mm	5-10mm	>10mm
CORTICAL	0	0	2	0
JUXTACORTICAL	0	10	7	0
DEEP WHITE MATTER	0	59	11	6
PERIVENTRICULAR	4	35	31	4
INFRATENTORIAL	1	6	0	0

Table 4: Lesion load measurement in FLAIR sequence.

LOCATION	<2mm	2-5mm	5-10mm	>10mm
CORTICAL	0	10	2	0
JUXTACORTICAL	2	24	7	0
DEEP WHITE MATTER	4	89	16	8
PERIVENTRICULAR	4	45	49	6
INFRATENTORIAL	2	35	8	0

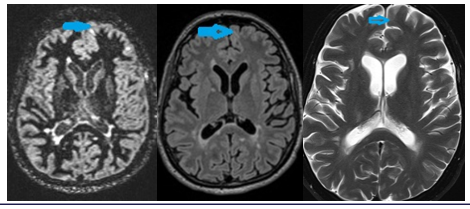
Table 5: Lesion load measurement in DIR sequence.

LOCATION	<2mm	2-5mm	5-10mm	>10mm
CORTICAL	4	30	5	0
JUXTACORTICAL	3	28	9	0
DEEP WHITE MATTER	1	92	10	6
PERIVENTRICULAR	4	61	48	6
INFRATENTORIAL	6	22	0	0

DISCUSSION:

Multiple sclerosis, once considered primarily as a disease of white matter has now been proved to involve grey matter as evidenced by the histo pathological studies. This property of cortical involvement has lead to the incorporation of intracortical and juxtacortical lesions in the recently revised diagnostic criteria for multiple sclerosis (3). In the past, the diagnosis of MS was based mainly on conventional multi sequence MR imaging protocols. Nowadays, FLAIR sequences have been incorporated into imaging protocols and guidelines for detecting brain lesions because of its CSF attenuation property. Recently established double inversion recovery imaging technique by using a combination of two inversion pulses provides a sufficient attenuation of WM in addition to CSF (4, 5). In the current study, DIR sequences significantly detected more overall load of lesions compared to the T2W and FLAIR sequences. Also it detected more supratentorial WM lesions in the juxtacortical regions compared to the FLAIR sequence which is being considered the gold standard in imaging white matter. In addition, DIR sequences revealed more intracortical (ICLs) compared to both T2W and FLAIR sequences in the present study. The increased conspicuity of an intracortical lesion in DIR sequence compared to T2W and FLAIR is shown in **Figure 3**.

Figure 3: DIR sequence demonstrating the pure intracortical nature of a MS lesion in the left frontal lobe which appears like a mixed grey white matter lesion in the routine FLAIR and T2 sequence.



Different studies have emphasized the greater benefit of DIR sequences in the detection of pure ICLs, which is due to better contrast between the lesions and surrounding GM in these sequences. This is explained by the slight attenuation of the signal of cortical grey matter in DIR sequence which leads to better distinction between pure intracortical and juxtacortical lesions. Similar observations of higher image contrast ratios in DIR compared to FLAIR and T2W sequences among cortical and WM lesions were reported in the literature. Further, histo-pathological studies have shown that abundant intracortical lesions are found in the patients with MS (6, 7). However in our study only fewer number of cortical lesions has been identified compared to other anatomical regions of brain which means that we still are unable to image few intracortical lesions using DIR sequence. Juxtacortical lesions identified by T2 and FLAIR sequences were actually mixed grey white matter lesions. In our study this is evidenced by reduced number of pure white matter lesions in DIR than FLAIR and an increased detection of juxtacortical lesions in DIR (8).

There is no significant difference between these techniques for the number of white matter lesions counted which means that there is no underestimation of white matter lesion load with DIR despite improved detection of intracortical lesions. DIR still has clinical values; it may find a role in improving the specificity of MS MRI diagnostic criteria or in unusual situations where there is a high index of suspicion that acute symptoms are due to new cortical lesion formation (9). When FLAIR sequence was used to detect lesion overload there was a poor correlation between imaging findings and clinical disability. Detection of new smaller cortical lesions in DIR will help in understanding the clinical presentation of MS patients better. For these reasons as well as our results we should encourage the routine use of DIR sequence in MS patients. We acknowledge the study limitations including the limited number of patients, the inclusion of only brain and not spinal imaging and not including size criteria for infratentorial lesions. But still statistical analysis based on the total number of lesions was considered sufficient.

CONCLUSION:

In patients with suspected or definite Multiple sclerosis, MR brain imaging with DIR sequence at 1.5T provides the highest overall sensitivity in the detection of lesions compared to the standard pulse sequences of FLAIR and T2. This higher sensitivity is especially obvious in the cortical and juxtacortical regions due to the higher image contrast between grey matter, white matter and MS lesions and therefore is of major prognostic relevance. Hence DIR sequence should be included in the routine Multiple sclerosis protocol.

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