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Original Research Paper

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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

AIM: The aim of this study was to compare the sensitivity of 3D sequences of double inversion recovery (DIR) with fluid attenuated inversion recovery(FLAIR) & T2 weighted imaging in early detection of small cortical and white matter lesions in patients with multiple sclerosis.

MATERIALS AND METHODS: Seven patients of multiple sclerosis (MS) with 364 supratentorial lesions 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 image (T2WI) sequences. The sensitivity of DIR was compared with the sensitivity of FLAIR and T2WI sequences.

RESULTS: Double inversion recovery imaging technique by using a combination of two inversion pulses provides a sufficient attenuation of both CSF and the white matter (WM) and significantly detected more overall load of lesions compared to the T2W and FLAIR sequences. Double inversion recovery (DIR) sequence similarly detected more supratentorial white matter (WM) lesions in the juxta cortical regions compared to the FLAIR sequence which was considered the gold standard in this region. Due to better contrast between lesions and the surrounding GM in the DIR images DIR sequences revealed more intra cortical lesions(ICLs) .

CONCLUSION: DIR showed better delineation between the white matter, grey matter, and the lesions of multiple sclerosis due to its image contrast in all anatomical locations. DIR sequence is valuable in the imaging workup of MS as it can detect more MS lesions compared to the T2W and FLAIR sequences DIR helps to plan Disease Modifying drugs (DMDs) early and to detect the progression of disease after initiating DMDs. Hence DIR sequence should be included in the routine MR protocols of MS patients especially to answer the question about intra-cortical and juxta-cortical MS lesions.

KEYWORDS :

INTRODUCTION:

Multiple sclerosis is an inflammatory demyelinating disease of the central nervous system that usually affects young adults and is the important cause for neurological disability in young individuals[1]. While the disease predominantly affects periventricular white matter, gray matter is also involved to an extent in multiple sclerosis[1,2]. 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 or at the grey white matter interface. [2,3]Since MR imaging plays an important role in both diagnosis and disease monitoring in multiple sclerosis more accurate estimation of number of lesions is essential[3]. Presently available magnetic resonance (MR) imaging is not ideal for detecting intra-cortical & smaller white matter lesions and lesion load[4]. MR imaging in MS is performed with fluid-attenuated inversion-recovery (FLAIR), T2-weighted image (T2WI) and pre and post contrast T1 sequences. However, the exact anatomic border between the cortex and subcortical white matter will be difficult to determine on a FLAIR MR image, which creates difficulties in judging whether lesions are juxta-cortical, mixed white matter–grey matter, or intra-cortical[5].

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 white matter and CSF[6]. This allows optimal evaluation of the cerebral cortex, a portion of the brain which is inherently difficult to image because of the thin and folded structure as well as the close proximity of white matter and CSF, which have markedly different cellular properties[6,7]. The purpose of our study was to prospectively compare the depiction of intra-cortical lesions by using a multislab 3D DIR, a multislab 3D FLAIR, and a T2-weighted spin-echo (SE) MR imaging sequence in patients with multiple sclerosis.

MATERIALS AND METHODS:

Seven proved multiple sclerosis patients were included in the study comprising 3 males and 4 females age ranging from 9 to 42 years. Older age groups were not involved in this study inorder to avoid confusion with age related white matter changes. The lesions in basal ganglia and thalamus were not included in this study. In our study there was total 28 infra tentorial lesions out of which 18 were depicted by DIR, 22 by FLAIR & 24 by T2 sequences which was difficult to further charecterise into different sizes hence infratentorial lesions were not further evaluated in our study. Diabetic and hypertensives were also excluded in this study (TABLE 11). All other concomitant neurological diseases causing similar symptoms were excluded by appropriate clinical and biochemical parameters. Informed written consent was obtained from all patients. Institutional ethical committee clearance was obtained.

A brief cognition assessment was done using Mini mental state examination (MMSE) and screening battery specific for cognition impairment in MS (BICAMS). BICAMS -entire battery needs only 15 minutes to complete and requires no specialist/equipment in cognition assessment [8]. BICAMS is composed of –**Symbol digit modality test-** processing speed and working memory,**California verbal learning test II** – for verbal memory/ immediate recall,**Brief visuospacial memory test revised (BVMT)-**visual memory/immediate recall[8].MMSE is a 30 point questionnaire which examines functions including registration, attention and calculation, recall, language, ability to follow simple commands and orientation [8].

TABLE 1
PATIENT CHARACTERISTICS AND RADIOLOGICAL FEATURES:

	P1	P2	P3	P4	P5	P6	P7
AGE	23	20	40	35	40	28	32
SEX	F	F	F	M	M	M	F
PERSENTINGCOMP	Rt HEMIPARESIS	BIL CEREBELLAR R>L	VISUAL	ONLY SENSORY	VISUAL &RT HEMIPARESIS	ONLY SENSORY	Lt HEMIPARESIS
DURATION	ONE YR	4 MONTHS	5 YRS	2YRS	5 MONTHS	3 YEARS	1 YEAR
EXAMINATION	NO DEFECIT	R CEREBELLAR SIGNS	BILINO(WEBINO)	DISEMINATED SENSORY DEFECIT	NO DEFICIT	DISEMINATED SENSORY DEFECIT	NO DEFICIT
MMSE	30/30	30/30	27/30	25/30	30/30	30/30	28/30
BICAMS SDMT CVLT BVMTR RESULT	 1/126 10/16 7/12 IMPAIRED	 2/130 11/16 10/12 IMPAIRED	 4/132 12/16 10/12 IMPAIRED	 Fatigued 12/16 6/12 IMPAIRED	 4/131 14/16 8/12 IMPAIRED	 150/150 16/16 12/12 NORMAL	 3/132 13/16 7/12 IMPAIRED
CORTICAL LESION	18	1	2	3	2	0	7
SUBCORTICAL LESIONS	20	4	3	5	3	2	19
DEEP WHITE MATTER LESIONS	30	19	17	26	25	6	19
PERI VENTRICULAR LESIONS	44	7	4	37	16	4	21
TOTAL	112	31	26	71	46	12	66

MR IMAGING:

Imaging was done with a 1.5T MR system (MagnetomAera, Siemens ,Germany) using a standard head coil. 3D sequences of Axial T2-weighted image (T2WI), FLAIR, and DIR sequences were obtained with identical anatomical position, geometric, and resolution parameters(TABLE 2). Post-contrast acquisitions were not included in our study. To perform DIR sequence, two different inversion pulses were applied (TI1 and TI2), representing intervals between the 180 degree inversion pulse and the 90 degree excitation pulse. Considering that the DIR has two inversion times, the first inversion time has to be prolonged compared to the TI in the FLAIR sequence to provide better CSF signal nulling.[6,7]

TABLE 2: MRI PARAMETERS:

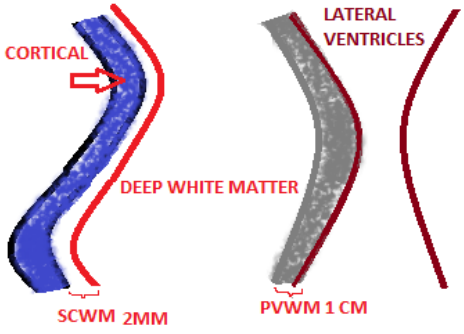
PARAMETERS	DIR	FLAIR	T2WI
Repetition time(m)	1100	6000	4000
Echo time(ms)	20	120	100
Inversion time(m)	3400/325	2000	-
Slice thickness(mm)	1	1	1
Field of view(mm)	230	230	230
Matrix	256	256	256
Voxel size	0.9	0.9	0.9
Number of signal averaging	2	2	2

DIR: Double inversion recovery, FLAIR: Fluid-attenuated inversion recovery, T2WI: T2-weighted images. The long inversion time TI1 (3400 ms) is defined as the interval between the first 180degree inversion pulse and the 90 degree excitation pulse. The short inversion time TI2 (325 ms) is defined as the interval between the second 180degree inversion pulse and the 90 degree excitation pulse.

IMAGE ANALYSIS:

MS lesions were identified as foci of altered high signal intensity . These lesions were counted in each of the 3 sequences separately and classified according to their location into (A) infra tentorial lesions, (B) WM lesions; including (a) periventricular lesions (PVWML as WMLs contiguous with the margins of each lateral ventricle within 1 cm from the ventricle), (b) deep WM lesions (in the deep WM1 cm from the ventricle) and (c) juxtacortical WM lesions (in the WM but abutting the cortex and within 2 mm from the cortex), and finally (d) intracortical lesions (ICLs) as described in (FIGURE 1).[9]The lesions in each anatomical location is further classified based on the lesion measurement as a)<2mm b)2-5mm c)5-10mm d)>10mm.Lesion size measurement is done by calculating mean maximum diameter of lesions in all three dimensions. (length*breadth*height/3).

FIGURE 1a:



SCWM - SUB CORTICAL WHITE MATTER
PVWM - PERI VENTRICULAR WHITE MATTER

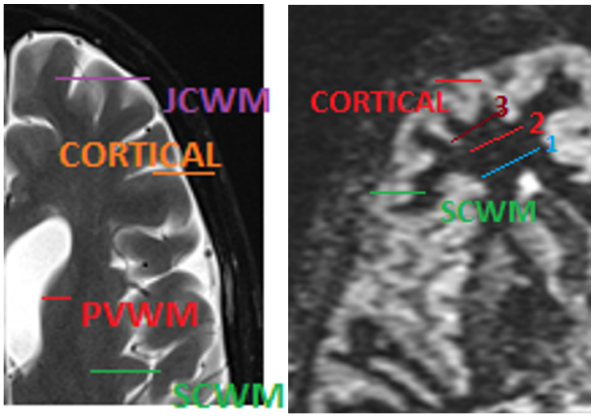
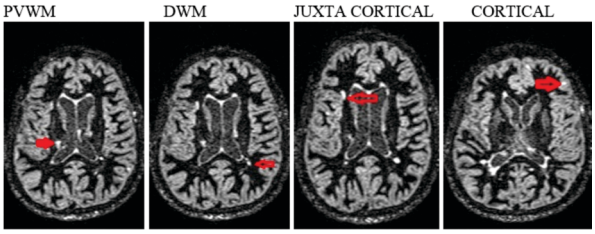


FIGURE 1b:T2W image

DIR image showing better cortical and juxta Cortical delineation .
1-periventricular white matter
2-deep white matter
3-subcortical white matter

FIGURE 1c:



PVWM- PERIVENTRICULAR WHITE MATTER, DWM-DEEP WHITE MATTER.

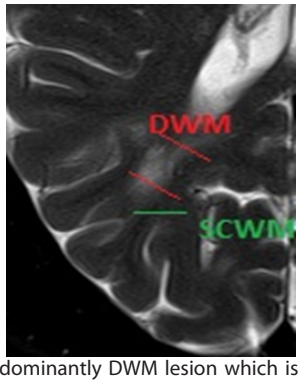


FIGURE 1d: Predominantly DWM lesion which is seen extending into the SCWM. The lesion is included in the DWM.

STATISTICAL ANALYSIS:

The lesions were analysed based on their location , size & number . The collected data was analysed with IBM.SPSS Statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis and percentage analysis were used. To find the significant difference between the bivariate samples in Paired groups the McNemar test was used as the outcome is dichotomous. For the multivariate analysis in the repeated measures the Friedman test was used. In both the above statistical tools the probability value .05 is considered as significant level. ** Highly Significant at P ≤ 0.01, * Significant at P ≤ 0.05 & # No Significant at P > 0.05.The lesions were analysed by two different radiologist with 20 and 15 years experience. The resultant data was analysed by a statistician using inter rater agreement statistic kappa with 95% confidence interval .The overall inter observer concordance between radiologist for the counting of lesions was very good with kappa value of 0.901.

RESULTS:

Total number of lesions detected in T2 weighted imaging is 147(40.38%), FLAIR imaging is 289(79.39%) and DIR imaging is 322 (88.46%).(FIGURE :3)

DIR sequence was significantly superior to T2 (P=0.01) and FLAIR (P = 0.01) sequences regarding the overall MS plaque load detection. There is no statistical difference between DIR,T2 and FLAIR sequences in depicting the infratentorial lesion.(TABLE 11)

DIR sequences significantly showed more number of lesions in the supratentorial regions when compared with T2 sequences and FLAIR sequences (P-0.0005) (TABLE 5).The lesions were further categorized according to their anatomical location and sizes. DIR sequences significantly detects smaller lesions of <2mm and 2-5mm size when compared to the T2W sequence and FLAIR sequence .(TABLE 6). DIR sequences significantly showed more number of lesions in the cortical region (100%) when compared with T2 sequences(6.06%)and FLAIR sequences(36.36%) (TABLE 7) .DIR sequences significantly showed more number of lesions in the juxtacortical region (98.2%) when compared with T2 sequences(25%)and FLAIR sequences(85.7%) (TABLE 8) .DIR sequences significantly showed more number of lesions in the periventricular region (98.49%) when compared with T2 sequences(54.13%) and FLAIR sequences(78.19%) (TABLE 10) .FLAIR sequence was superior to DIR and T2 sequence for detecting deep white matter lesions.(TABLE 9)

TABLE 3:
LESION LOAD AND COGNITIVE IMPAIRMENT

LESION DISTRIBUTION	COGNITIVE DYSFUNCTION IN MS PATIENTS(6 PATIENTS)	NORMAL COGNITION (1 PATIENT)	P VALUE
CORTICAL LESIONS	5.5	0	
SUBCORTICAL LESIONS	9	2	
DEEP WHITE MATTER	22.6	6	
PERIVENTRICULAR LESIONS	21.5	4	
TOTAL LESION	58.6	12	

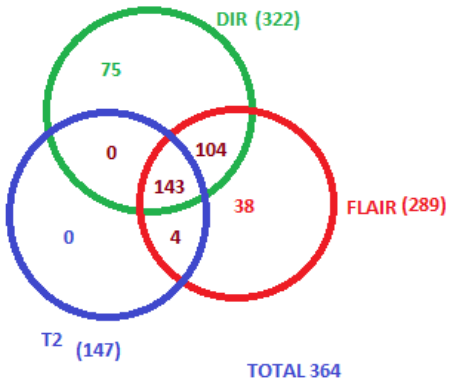


FIGURE 3: SUPRATENTORIAL PLAQUE DETECTION IN MR IMAGING

TABLE 4: LESION LOAD MEASUREMENTS &COMPARISION OF DIR versus T2 & FLAIR IMAGING FOR DEPICTING LESIONS:

	TOTAL LESIONS(364)	% of lesions detected	P VALUE (DI RVs FLAIR & T2)
DIR	322	88.46	0.0005**
FLAIR	289	79.39	
T2	147	40.38	

** Highly Significant at P ≤ 0.01.

TABLE 5: SUPRATENTORIAL PLAQUE DISTRIBUTION:

	T2	FLAIR	DIR	TOTAL
CORTICAL	2	12	33	33(9.06%)
SUBCORTICAL	14	48	55	56(15.3%)
CENTRAL DEEP WHITE MATTER	49	132	114	142(39.01%)
PERIVENTRICULAR WHITE MATTER	72	104	131	133(36.5%)
TOTAL	147	289	322	364

TABLE 6: SIZE OF MS PLAQUE:

	T2	FLAIR	DIR	Total LESIONS	P value (DIR Vs FLAIR & T2)
<2mm	0	7	16	16(4.39%)	0.000
2-5mm	88	196	248	252(69.2%)	0.000
5-10mm	37	85	76	84(23.07%)	0.06
>10mm	7	7	7	12(3.29%)	-

0.000- highly significant, >0.05-not significant.

TABLE 7:
CORTICAL LESIONS:

	<2mm	2-5mm	5-10mm	>10mm	TOTAL (33)	% OF LESION LOAD
T2	0	0	2	0	2	6.06%
FLAIR	0	10	2	0	12	36.36%
DIR	3	27	3	0	33	100%
TOTAL	3	27	3	0	33	
P VALUE (DIRVs FLAIR & T2)	0.018 *	0.0005**	0.368 #	-	0.0005**	

** Highly Significant at P ≤ 0.01, * Significant at P ≤ 0.05 & # No Significant at P > 0.05

TABLE 8:
SUBCORTICAL LESIONS:

	<2mm	2-5mm	5-10mm	>10mm	TOTAL (56)	% OF LESION LOAD
T2	0	7	7	0	14	25%
FLAIR	2	34	12	0	48	85.7%
DIR	5	38	12	0	55	98.2%
TOTAL	5	39	12	0	56	
P VALUE (DIRVs FLAIR & T2)	0.05 #	0.0005**	0.23#	-	0.0005**	

** Highly Significant at P ≤ 0.01, * Significant at P ≤ 0.05 & # No Significant at P > 0.05

TABLE 9:
DEEP WHITE MATTER LESIONS:
** Highly Significant at P ≤ 0.01, * Significant at P ≤ 0.05 & # No Significant at P > 0.05

	<2mm	2-5mm	5-10mm	>10mm	TOTAL (142)	% OF LESION LOAD
T2	0	35	13	1	49	34.5%
FLAIR	4	105	22	1	132	92.95%
DIR	4	96	13	1	114	80.28%
TOTAL	4	105	22	1	142	
P VALUE (FLAIR VsDIR& T2)	0.38#	0.0005**	0.002**	-	0.0005**	

TABLE 10:
PERI VENTRICULAR LESIONS:

	<2mm	2-5mm	5-10mm	>10mm	TOTAL (133)	% OF LESION LOAD
T2	3	47	11	11	72	54.13%
FLAIR	3	43	47	11	104	78.19%
DIR	4	69	47	11	131	98.49%
TOTAL	4	71	47	11	133	
P VALUE (DIRVs FLAIR & T2)	0.039 *	0.0005**	0.36#	-	0.0005**	

** Highly Significant at P ≤ 0.01, * Significant at P ≤ 0.05 & # No Significant at P > 0.05.

TABLE 11: Infratentorial lesions:

TOTAL NO OF LESIONS	T2	FLAIR	DIR	P value (DIR Vs FLAIR & T2)
48	38	45	30	0.36#

#-Not significant

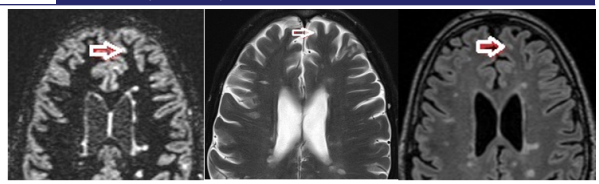


FIGURE 4: Axial DIR T2 and FLAIR images. It is hard to determine whether the lesion is pure cortical or mixed grey white matter or juxtacortical in T2 & FLAIR images .DIR due to better contrast demonstrates pure cortical nature of these lesions.

DISCUSSION:

Multiple sclerosis a disease of white matter has now been proved to involve grey matter as evidenced by the histo pathological studies[10].This property of cortical involvement has lead to the incorporation of cortical & juxtacortical lesions in the diagnostic criteria for multiple sclerosis[11]. Gray matter (GM) involvement is detected even in early stages of MS and Gray matter atrophy occurs at a faster rate than WM atrophy. Gray matter lesions may be mild or extensive and occurs independently of WM lesions. GM lesions may be the earliest manifestation of MS and may be the predictor of progression to MS[11].The presence of at least one cortical lesion at clinically isolated syndrome onset can identify patients at risk of conversion to clinically definite MS and has been added as a diagnostic criterion for MS[12,13].Previous studies have shown strong association between GM involvement and global or selective cognitive disabilities in MS.Cognitive deficits such as information processing speed, time for recall, attention deficits are better explained with cortical GM lesion.[14]Pathology is different from WM lesions in that Gray matter lesions are less inflammatory with less macrophage and lymphocyte infiltration, significant axonal transection and neuronal loss.[15]

All of our patients had cortical lesion without physical disability signs. MMSE was normal for all of them except one due to illiteracy. BICAMS – showed cognitive deficits despite normal MMSE. Results of previous studies in which FLAIR MR was used to determine juxta cortical lesion count or load did not specifically focus on correlating lesion counts with clinical and neuropsychologic measures but merely showed the possible improvement in detection of intracortical lesions. In our study six out of seven patients had impaired BICAMS score. All of these 6 patients had large number of cortical and total lesion load which proves association between cortical and total lesion load and cognitive impairment (TABLE 2 & 3).

In the past, the diagnosis of MS was based mainly on conventional multi sequence MR imaging protocols. FLAIR sequences, have been considered as gold standard 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 both CSF and the white matter (WM)[16].In the current study, DIR sequences significantly detected more overall load of lesions(88.46 %) compared to the T2W(40.38%) and FLAIR(79.39%) sequences(TABLE 4).

In our study Cortical lesions forms 9.06% of total lesion load out of which 9.09% of total cortical lesions are <2mm in size. DIR sequence detected 100% of these cortical lesions whereas T2 and FLAIR sequences were able to detect only 6.06 and 36.36 % of cortical lesions respectively(TABLE 7). Therefore DIR was better to detect small cortical lesions. Different studies emphasized the greater benefit of DIR sequence in the detection of pure ICLs, compared to the T2W and FLAIR sequences, which is explained by the better contrast between lesions and the surrounding GM in the DIR images. This is explained by the slight attenuation of the signal of cerebral cortex in the DIR images and the better distinction between pure cortical and juxtacortical lesions[17]. Histo pathological studies has shown that abundant intracortical lesions are found in MS patients brain (even amount to larger than 59%) [4,10]. However in our study DIR sequence has depicted only 9.09 % of cortical lesions which means that few intracortical lesions can still be not visualised

with DIR imaging. The findings in this study of increased numbers of lesions detected are in accordance with the results of Jeroen J. G. Geurts et all [19] at 3D DIR imaging in the cortical grey matter (lesions with low contrast on T2- weighted images).

69.2% of total lesion load in our study are 2-5mm size(TABLE 6) representing major burden of lesions. Out of 69.2% lesions 98% were detected by DIR ,53.84% by FLAIR and 24.17% by T2 with p value of 0.000 which is highly significant.(TABLE 6).Therefore incorporation of 3D DIR in imaging of patients with MS will improve the detection of smaller lesions and lesion load.

Besides the increased sensitivity to intracortical lesions, the second major advantage of 3D DIR imaging is its apparent potential to enable better distinction between juxtacortical lesions, and purely intracortical lesions. Subcortical lesions identified by T2 & 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(80.28%) than FLAIR(92.95%) and an increased detection of juxtacortical lesions in DIR(98.2%) (TABLE 8). Relatively small differences between techniques were found for the numbers of white matter lesions counted (periventricular and deep white matter).There is no significant difference between these techniques for the total number of white matter lesions counted which means that there is no underestimation of white matter lesion load with DIR despite 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 [18]. Previously when FLAIR image was used to detect lesion overload there used to be poor correlation of clinical disability. Detection of even smaller lesions in DIR will help in better understanding of physical & clinical problems encountered by MS patients. For these reasons as well as our results we should encourage the routine use of DIR in MS patients .

Some artifacts seen in DIR images includes areas of high signal intensity at the posterior fossa, choroid plexus, and periaqueductal brainstem region ,probably as a result of transependymal CSF effusion has lead to reduced detection of infratentorial lesions.[16]Other artifacts could be identified as linear hyperintensities commonly located in extra-cortical regions but they are bilateral or symmetrical, and their shapes change in contiguous sections, which helps in delineating them from MS lesions in the supratentorial region.[16]

In our study small sample volume for clinical assessment is a limitation. Contrast and diffusion characteristics of the lesion were not analysed. Spinal cord lesions were not included . The current study does not differentiate acute and chronic lesions seperately. Few nonspecific white matter changes not related to MS may be included as lesions.

CONCLUSION:

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

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