The Role of Double Inversion Recovery Sequence in Detecting Gray Matter Lesions in patients with Multiple Sclerosis Using 3Tesla MRI

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ABSTRACT :

BACKGROUND:

In the recent time, the sequence used to delineate gray matter lesions is Double Inversion Recovery (DIR), with the use of this sequence in high magnetic field (3 Tesla machine).

OBJECTIVE:

To detect and localize gray matter lesions in patients with established multiple sclerosis using DIR sequence in 3 Tesla MRI. Also to compare the detection rate of white matter lesions by the use of DIR versus Fluid Attenuation Inversion Recovery (FLAIR) sequence.

PATIENTS AND METHODS:

A prospective study included 54 patients with established diagnosis of multiple sclerosis of more than 3 years duration was conducted from April 2014 to January 2015. The study was done in the MRI units of Al-Yarmouk Teaching Hospital and Al-Imamian Al-Kadhimian Medical City. All patients were examined with the following MRI imaging sequences: T2WI axial, T2 FLAIR sagittal and coronal, T1 axial and sagittal, DIR axial and coronal. T1 Sagittal and axial were repeated after giving IV contrast and examined after 30 minutes postcontrast. Gray matter lesions were classified according to Peterson and Bo model. Statistical analysis conducted by using Excel 2013 version.

RESULTS:

Fifty four patients with established diagnosis of MS (43 patients with relapsing remitting MS and 11 patients with secondary progressive MS) were included. Of the 54 patients, 39 patients (72.2%) patients have positive gray matter lesion. The 39 patients with positive gray matter lesions are classified as follows: 26 patients (66.5%) had sub-pial lesions, 9 patients (23%) had leucocortical lesions, 3 patients (7.5%) showed entirely cortical lesions, and finally the whole cortex is involved in 1 patient only (2.5%). The insular cortex was the most commonly involved region seen in 14 patients (35.8%), followed by the thalamic lesions. Among the 39 patients with positive 9 patients (16.5%) had additional deep nuclei lesions. Total number of lesions detected by DIR (320 lesions) was largely greater than the total number of lesions detected by FLAIR (185 lesions).

CONCLUSION:

DIR is a sensitive sequence for detection of gray matter lesion, DIR is more sensitive than FLAIR in detection of white matter lesions and cortical gray matter lesions are more commonly encountered than deep nuclei lesions.

KEY WORDS: double inversion recovery, gray matter lesions, multiple sclerosis, 3 Tesla MRI.

INTRODUCTION:

Multiple sclerosis (MS) is disabling chronic disease of the central nervous system that typically affects the white matter of the brain and spinal cord, mainly in a periventricular distribution [(1)]. Demyelination occurs in discriminative foci, termed plaques which range in size from a few millimeters to a few centimeters and are typically peri-venular [(2)].

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This perivenular distribution had led to a new theory about the pathogenesis of multiple sclerosis, which postulates that there is chronic intracerebral venous congestion at the venular level, resulting in "oozing" of blood around the adjacent myelin sheaths, with ferritin /hemosiderin deposition [3]. Multiple Sclerosis is the commonest worldwide demyelinating disease, affecting the central nervous system. It is by definition disseminated not only in space (i.e. multiple lesions), but also in time (i.e. lesions are of different ages) [1], Roughly, incidence is one person per thousand. Multiple sclerosis usually presents between the ages of 17 to 47 years, with a peak at approximately 35 years of age. There is a strong, well-known female preponderance with an F: M ratio of 2.5:1[4]. Role of imaging had extensively increased since introduction of MR imaging, since that time MRI had the major role in the triad for diagnosis as well as follow up of patients condition as a non-invasive tool that is extremely sensitive to detect new, in addition to the old plaques of MS, moreover, it was largely used to monitor disease response to medical treatment. Major sequences used for long time were T1 pre and post gadolinium injection, T2 axial and FLAIR in coronal and/or sagittal planes [5].

For a long time, MS was thought to be only a WM disease; yet, there is increasing evidence that virtually any GM structure is affected in an independent way from WM lesions [6]. Immunologic & histopathologic evidences have shown that cortical demyelination is quite prominent in the earlier stages of MS [7], they progress in time and space, as the WM lesion used to, Physical and psychological burden result from GM affection, so better imaging hints is at least essential. The advent in MRI had declared the importance of imaging in detection of these GM affections after long time of being in shadow [8]. Further work up used in the current time to detect and localize lesions that affect the gray matter of the central nervous system. Two dimensional Double Inversion Recovery (DIR) sequence depends on the same principle as FLAIR imaging, with the addition of a second 180 degree inversion pulse prior to the 90 degree exiting pulse, while in FLAIR, a single inversion 180 degree pulse is applied prior to the 90 degree exiting pulse [9]. That is to say , to suppress any signal coming from the cerebrospinal fluid as well as from the white matter and this will make the only visualized parts of the brain are gray matter regions [10].

AIMS OF THE STUDY:

To detect and localize gray matter lesions in patients with established multiple sclerosis (both cortical & deep nuclei affection) using the double inversion recovery (DIR) sequence in 3 Tesla MRI. The study also compared the detection rate of white matter lesions (both active & old plaques) by the use of DIR versus Fluid Attenuation Inversion Recovery sequence.

PATIENTS AND METHODS:

During the period from April 2014 to February 2015, 54 patients with established diagnosis of MS of more than 3 years duration (43 patients have Relapsing -Remitting, 11 patients have secondary progressive) were included in this cross sectional study. The 54 patients included in this study were 35 females and 19 males with ages range of 19-47 years (mean age: 33.5 years). The study was done in the MRI unite of Al- lmamain Kadhimain medical city and Al-Yarmouk Teaching Hospitals. All patients were referred to the MRI by neurologists with established diagnosis of MS for more than 3 years duration of illness.

Inclusion Criteria: Patients who matched the revised McDonald 2011 criteria to be classified as established MS cases of more than 3 years duration, relapsing remitting and secondary progressive subtypes included only and patients have at least one previous MRI study.

Exclusion Criteria: Patient with clinical history of less 3 years, patients who have no previous MRI brain, patients who have Clinically Isolated Syndrome (CIS), patients who have MRI findings of isolated spinal cord lesions, Lesions which appear as hyperintense on DIR, but less than 3 millimeters, patients with DM and patients with known vasculitis, such as systemic lupus and scleroderma.

Machine: The MR examinations were performed at a 3T whole-body MR system (Koninklijke electronics, Achieva Philips Medical Systems, Best, the Netherlands) using a 16-element phased array sensitivity-encoding (SENSE) head coil in supine position.

MRI protocols: All patients were examined in the supine position with the fallowing sequences:

1. T2 WI in axial plane (Field of view 230 mm. Matrix 256. Slice Thickness 5 mm. Voxel size 0.9/0.9/5 mm/Turbo factor 16/Repetition Time 4400 millisecond. Echo Time 100 millisecond. Number of signal averaged 1, Bandwidth/pixel (Hz) 184. Flip angle 90 degree. Acquisition time 2 minutes plus 20 seconds).
2. T2 FLAIR in coronal plane ((Field of view 230 mm, Matrix 256,Slice Thickness 5 mm, Voxel size 0.9/0.9/5 mm/Turbo factor 38/SENSE factor1.6/Repetition Time 6000 millisecond, Echo Time 220 millisecond, Number of signal averaged 1,Bandwidth/pixel(Hz) 287/Inversion Time:2800 milliseconds, Flip angle 90 degree, Acquisition time : 4 minutes).
3. T1 WI in axial and sagittal ((Field of view 230 mm, Matrix 256,Slice Thickness 5 mm, Voxel size 0.9/0.9/5 mm/Turbo factor 16/Repetition Time 600 millisecond, Echo Time 15 millisecond, Number of signal averaged 1,Bandwidth/pixel(Hz) 184,Flip angle 69 degree).
4. DIR in axial and coronal planes (Field of view 230 mm, Matrix 256, Slice Thickness 3 mm, Voxel size 0.9/0.9/5 mm/Turbo factor 16/Repetition Time 15600 millisecond, Echo Time 25 millisecond. Number of signal averaged 1, Bandwidth/pixel (Hz) 184. Inversion times 3400/340 milliseconds. Flip angle 90 degree. Acquisition time 3 minutes plus 20 seconds).

The usual axial T1, axial T2, sagittal FLAIR used, if new WM lesion suspected, we added Gadolinium-enhanced T1 axial after 30 minutes post-injection if the referring neurophysician suspects active new white matter plaque(s). Fifty patients were imaged using coronal GM sequence, four patients imaged with axial sections GM sequence.

DIR sequence implies the use of 2 consecutive inversions, the 1st with short inversion time (270-340 millisecond), followed by a second long inversion time (3000-3400 millisecond).

The imaging protocol included 22 contiguous axial sections of a T1, TSE/T2, coronal/sagittal FLAIR (5 mm slice thickness), while the DIR (34 coronal, 30 axial, 2mm slice thickness so as to reduce the volume averaging artifact & improve the final image quality).

In the DIR sequence, 2 different inversion pulses were applied. Both inversion times, TI 1 and TI 2 in our DIR sequence, were defined as the intervals between the respective 180° inversion pulse and the 90° excitation pulse, which means that the 2 inversion pulses are separated by TI 1 _ TI 2. These inversion times were calculated according to the formulas given by Turetschek et al [(11)]. Table 1 show the MRI parameters used.

Table 1: MRI parameters used in DIR, FLAIR and T2 TSE.

Parameter	DIR	FLAIR	T2/TSE
Field of view (mm)	230	230	230
Matrix	260	260	260
Section thickness (mm)	3	5	5
Voxel size (mm)	0.8x0.8x4	0.9x0.9x5	0.9x0.9x5
Repetition time (TR)(ms)	15600	6000	4400
Echo time(TE)(ms)	25	120	100
Inversion time(ms)	3400/340*	2800	Nil
Acquisition time (min sec)	3:20	4:00	2:20
Flip angle	90	90	90

Cortical lesion were always hyper intense on DIR not on FLAIR, for those lesions that are juxtacortical (hyperintense foci on DIR only), they were classified as mixed white matter/gray matter lesions if seen as hyper intense on FALIR as well.

Images were evaluated by 2 independent expert radiologists to decrease inter-observer error. Each single abnormality was agreed by consensus. Any lesion less than 3 mm was neglected. Then each lesion was measured in millimeter, and classified according to its location (Peterson Classification) (subpaial, leukocortical, whole cortical & entirely cortical). In our study, 5 topographic regions were selected, which are: The superior frontal gyrus, The inferior parietal gyrus, The amygdale, The thalamus and The insula.

Statistical analysis: Excel 2013 has been used to calculate the statistical tests, summate and analyze data.

RESULTS:

A total number of 54 patients with established diagnosis of Multiple Sclerosis were included in this study (43 patients with relapsing remitting MS and 11 patients with secondary progressive MS). Of the 54 patients, 39 patients (72.2%) patients have positive gray matter lesion (31 patients with relapsing remitting disease and 8 patients have secondary progressive disease), this finding is statistically significant (P value is 0.038) (table 2).

Table 2: Cortical GM lesions detected in clinical subtypes of MS in the 54 patients.

Clinical Subtype	No. of patients	Positive Gray matter lesions		P value
		No.	%	
Relapsing Remitting	43	31	57.4 %	0.038
Secondary Progressive	11	8	14.8 %	
Total	54	39	72.2%	

Females were more commonly affected than male with female to male ratio of 3: 1. of the 54 patients sample, there were 30 females (85%) out of 35 showed positive gray matter lesions, versus 9 males (47%) out of 19 showed gray matter lesions, and this was statistically significant finding (P value is 0.029).

According to Peterson and Bo classification, the 39 patients with positive gray matter lesions are classified as follows: 26 patients (66.5%) had sub-pial gray matter lesions, 9 patients (23%) had leucocortical lesions, 3 patients (7.5%) showed entirely cortical lesions, and finally the whole cortex is involved in 1 patient only (2.5%), as shown in table (3).

Table 3: Loco-regional GM lesions in MS patients with positive findings (39 patients).

Site of the lesion	Patients with positive gray matter lesion	
	No.	%
Subpial	26	66.5%
Leucortical	9	23 %
Entirely cortical	3	7.5 %
Whole cortex involved	1	2.5 %
Total	39	100%

From the above results, it is concluded that there is linear relationship between the clinical subtype of MS and the loco-regional distribution of the GM lesions, in that they show the same common subpial type incidence, followed by leucocortical then entirely cortical and finally the least common whole cortical pattern, in all these subtypes, secondary progressive MS show more prevalence of the GM lesions (P value was 0.018) as shown in figure (1).

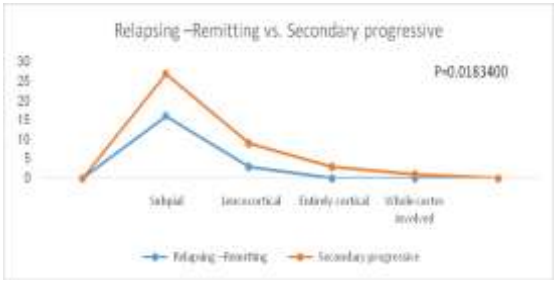

Figure1: Relationship between clinical & radiologic subtypes of GM lesions.

The insular cortex was the most commonly involved region seen in 14 patients (35.8%), followed by the thalamic lesions, seen in 10 patients (25.6%), then the inferior parietal gyrus, where 8 patients (20%) showed lesions in gray matter, followed by the superior frontal gyrus, seen in 6 patients (15.3%), and finally the amygdaloid cortex, where only 1 patient (2.5%) showed gray matter lesion as shown in table (4).

Table 4: Selected gray matter regions and the percent of GM lesions in them.

Region of interest	Patients with positive gray matter lesion	
	No.	%
Insular cortex	14	35.8%
Thalami	10	25.6 %
Inferior parietal gyrus	8	20.5 %
Superior frontal gyrus	6	15.3 %
Amygdaloid cortex	1	2.5 %
Total	39	100%

It was noted that all patients who show deep nuclei lesions also have cortical gray matter lesions but the reverse is not true. Of 39 patients who showed cortical gray matter lesions (72.2% of the sample), there were 9 patients (16.5%) had additional deep nuclei lesions. We did not find deep nuclei affection without co-existing cortical gray matter lesion as shown in Table (5).

Table 5: Topographic distribution of GM lesions (cortical versus deep nuclei).

Patients with +ve GM lesions	Areas of GM affection	%	P value
39/54	Intra-cortical lesions only	72.2 %	0.0203
9/54	Deep nuclei lesions in addition to intra-cortical lesions	16.5 %	

It was noted also that patients with MS without atrophic changes (43 patients), 29 of them showed gray matter lesions (67%), while those who have MS with atrophic brain changes (11 patients), 10 of them showed gray matter lesions (90%), as shown in Table (6).

Table 6: relation of GM lesions with atrophic brain changes.

brain atrophy	Total no. of patients	GM positive	% of GM lesions
No atrophic changes	43	29	67.4%
Various degrees of atrophy	11	10	90%

For purely white matter lesions, the number of lesions seen by DIR were 128 versus 96 lesions seen by FLAIR (P value=0.038).The purely gray matter lesions was almost not detected by FLAIR (1 lesion seen only) versus 85 seen by DIR (P value =0.0002). For mixed white and gray matter lesions, DIR detected a total of 107 lesions, while FLAIR detected 88 lesions only (P value=0.038). the total number of lesions detected by DIR (320 lesions) was largely greater than the total number of lesions detected by FLAIR (185 lesions). The detection rate of all the lesions by DIR (Total number of lesions seen by DIR/Total number seen in FLAIR) was nearly 99%, while that of FLAIR was 58 %.

Table 8: Relative comparison of DIR versus FLAIR in the detection of MS lesions.

Region	No. of lesions seen in		P value
	DIR	FLAIR	
Mixed WM/GM	107	88	0.038
Purely WM	128	96	
Purely gray matter	85	1	0.0002
Total	320	185	

The followings Figures (2, 3, 4 and 5) show MRI images of some patients with multiple sclerosis included in our study.

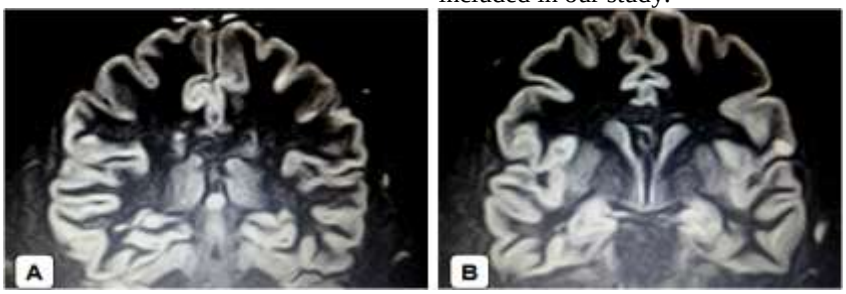

Figure 2: A: 36 years old female presented with Lt. sided hemiparesis, DIR shows sub-pial lesions in the left parietal convolutions. B: another 38 years old female presented with focal seizures, DIR shows typical whole cortical lesion in supra sylvian cortex on the left side.

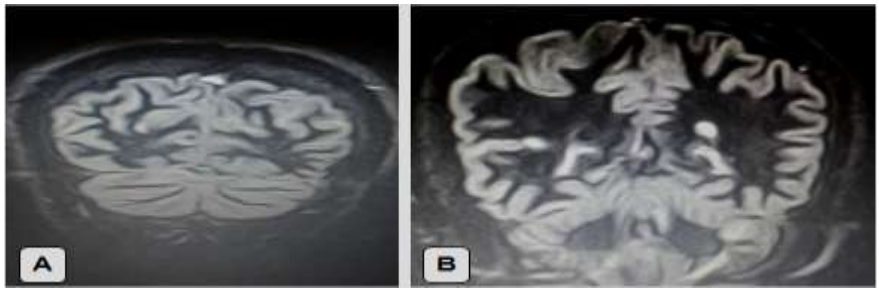

Figure 3: A: 32 years old male presented with Blurred vision, DIR shows leuco-cortical lesion in the right deep occipital convolution. B: another 32 years old male, DIR shows left thalamic lesion with right insular mixed W/G matter lesion.

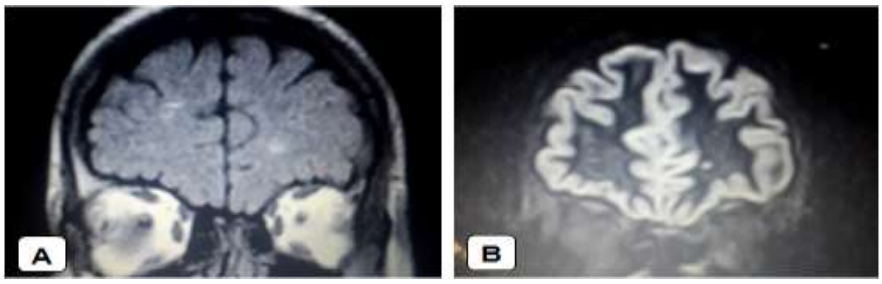

Figure 4: Shows how the DIR (image B) clearly depicts white matter lesion in case of questionable lesion on FLAIR (image B) seen in the Lt. deep inferior frontal area.

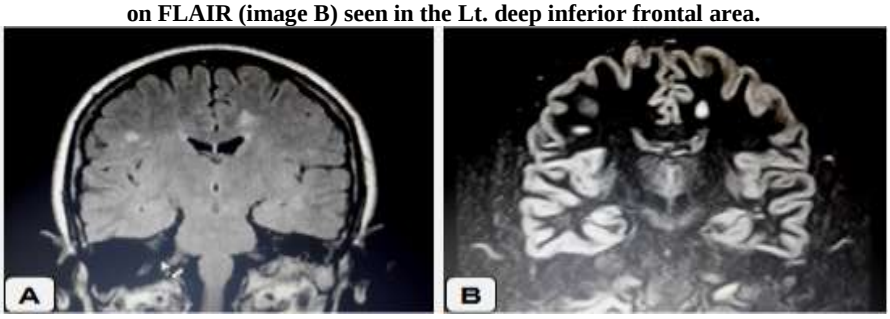

Figure 5: Shows the active white matter lesion seen by DIR (image B) was not detected by FLAIR (image A) in the Rt. upper parietal region.Notice also how elegantly the other 2 WM lesions are seen by DIR. Patient had multiple focal neurologic deficits.

DISCUSSION:

Histopathologic studies report that up to 60% of total MS lesions affect the cortical GM [12, 13] .Unfortunately; the sensitivity of conventional MR imaging techniques to detect cortical lesions remains poor compared with histopathologic studies [14-16]. Several years ago, a double inversion recovery pulse sequence (DIR) was introduced. This sequence provides 2 different inversion pulses, which attenuates the CSF as well as the whole white matter, thus achieving a superior delineation between gray and white matter [17]. High-field MR imaging at 3T allows the establishment of a fast and accurate DIR imaging protocol. In patients with suspected or definite MS, DIR brain imaging at 3T provides the highest overall sensitivity in the detection of MS lesions compared with the standard pulse sequences of FLAIR and T2-weighted TSE [18].

We included 54 patients with established Multiple Sclerosis with disease duration of more than 3 years, 43 of them have relapsing remitting clinical subtype of MS and 11 have secondary progressive clinical subtype. In our study 39 patients (72.2%) showed positive gray matter lesion-at least one lesion in each patient, each lesion should be hyper intense on DIR and greater than 3 mm to be regarded as positive.

In 43 patients with relapsing remitting multiple sclerosis (RRMS), 31 showed gray matter lesion (72%), while in those 11 patients with secondary progressive disease (SPMS), 8 patients (72.5%) showed gray matter lesion(s). P value = 0.038, this results were similar to that done by M.Calabrese et al [19] which is a longitudinal 2 years study done for 44 patients with RRMS and 31 patients with SPMS had shown that patients with SPMS have the highest rate of gray matter affection.

The occurrence of GM lesions is more common in females (30 out of 35 (85%), while only 9 male out of 19 males (47%) showed gray matter lesions, this result was in agreement with a previously reported study [4].

The topographic distribution of GM lesions in our study was highest in the sub-pial regions, the next commonest regions were the leucocortical, followed by the entirely cortical lesions, and the least affected regions were the holocortical (whole cortex involved). A study conducted by Emma C. et al [20] on 11 patients with established MS by use of DIR in 3 Tesla MRI, also show different results where 52% of lesions were sub-pial and 47% of lesions were leucocortical, this difference is possibly due to the smaller number of sample used in the mentioned study or the difference in disease duration or both.

For the cortical gray matter, the insular cortex was the most commonly involved region, followed by the inferior parietal gyrus, followed by the superior frontal gyrus. Similar results obtained by A. Prinster et al [21] but their study included the RRMS only, while in ours , we included SPMS as well.

For the affection of deep nuclei GM, It was concluded that all the patients who show deep nuclei lesions also have cortical gray matter lesions, but the reverse is not true. The commonest area of the deep nuclei affected was the thalamus, followed by the amygdaloid cortex. In a study done by N. Burgsland et al [22] showed the most apparent areas of affection were the caudate and thalamus, this slight difference occurred as we don't include the caudate in the ROI (regions of interest), instead ; amygdaloid region selected which usually show much less common affection in comparison to the caudate nucleus.

In our study it was noted that those who have brain atrophic changes showed more prevalence of GM lesions in comparison with those who had not brain atrophic changes (90% versus 67%). Leonora K. et al [23] found that in MS patients with a relatively long and homogeneous disease duration, GM atrophy is more marked than WM atrophy, and reflects disease subtype and disability to a greater extent than WM atrophy or lesions.

In our study DIR was more sensitive than FLAIR in detection of purely white matter lesions and mixed white and gray matter lesions with a total improvement in detection rate was 60% for pure white matter and 47% for mixed gray white matter lesions. A study done by Nelson et al [24] showed the improvement in detection rate by use of DIR for mixed white-gray matter lesions was 39%, and for juxtacortical lesions were 36%, this relative difference from our results might occurred due the difference in median age of the sample, may be attributed to the difference in voxel size used (for their study they used 2.2 mm voxel size, in our study 3 mm voxel size used), and also may be attributed to sample volume (their sample was 16 patients , ours was 54 patients).

The total number of lesions detected by DIR (320 lesions) was largely greater than the total number of lesions detected by FLAIR (185 lesions). The detection rate of all the lesions by DIR (Total number of lesions seen by DIR/Total number seen in FLAIR) was nearly 100%, while that of FLAIR was 58 %. Our results were appimatly similar to that done by M.P Wattjes et al [(25)].

There are many Limitations and Artifacts in our study: Flow related artifacts, mainly seen in the region of carotid bifurcation and basilar tip. These are seen as hyperintense signal areas in almost all patients. Flow compensation sequences and comparison with other sequences diminished this false positive result. CSF pulsation artifacts: mainly in the cerebellopontine angle and cerebral aqueduct, seen as hyperintense foci, they can't be eliminated by the DIR, but anatomical location and comparison with other sequences helped to reduce them. Juxtacortical small vessels may artifectually appear as hyperintense foci. Regions of allocortex was disregarded, as they inherently seen hyperintense signal intensity on DIR. Another limitation was that the section thickness of 3 mm used in our acquisitions likely resulted in partial-volume averaging across the cortical ribbon, this effect may either mask the presence of small cortical lesions or lead to a false classification of a given lesion as purely intracortical when, in fact, the lesion may have a subcortical extension. The partial-volume effect is a concern for almost all imaging studies of cortical lesions in the literature and can only be ameliorated by high-resolution imaging methods [(26)].

CONCLUSION:

In patients with MS: DIR is a sensitive sequence for detection of gray matter lesion, DIR is more sensitive than FLAIR in detection of white matter lesions and cortical gray matter lesions are more commonly encountered than deep nuclei lesions. Sub-pial lesions and Insular cortex are more commonly seen in patients with MS.

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