



Efficiency of Double Inversion Recovery (DIR) Sequence in the Evaluation of Supratentorial Cortical Lesions in Multiple Sclerosis

Gulhan Ertan^{1*}, Ozge Arici², Sila Ulus³, Baris Metin⁴

ABSTRACT

The aim of this study is to investigate if the three-dimensional (3D) double inversion recovery (DIR) sequence is superior compared to the 3D fluid-attenuated inversion-recovery (FLAIR) sequence in detecting intracortical, mixed, juxtacortical (JX), and deep grey matter (GM) lesions in multiple sclerosis (MS) patients. The correlation between intracortical lesion load and disability status was also investigated. Magnetic resonance imaging examinations of 24 patients (9 males, 15 females; mean age 34.4±12.0 (16-69) were retrospectively evaluated from our database. Lesions were counted and classified according to anatomic regions as intracortical, mixed, JX, and deep GM on the 3D DIR and FLAIR sequences. The incidence of lesions on the two sequences were identified and compared. The relationship between the number of lesions and type of MS, patient age, gender, duration of the disease, disability, the mean number of attacks per year and Expanded Disability Status Scale (EDSS) score was also investigated. More lesions were detected by the DIR sequence compared to the FLAIR sequence in all regions except for thalamus (11/12). The lesion detection superiority of DIR was statistically significant for intracortical lesions ($p<0.001$) and GM lesions (intracortical +mixed) ($p<0.001$). Lesion load of the JX area in the DIR sequence decreased as the disease duration ($r=-0.444$; $p=0.030$) and age ($r=-0.473$; $p=0.020$) increased. JX lesion load in the DIR sequence decreased as the number of attacks increased ($r=-0.602$; $p=0.002$). More mixed lesion load on the DIR sequence were found in cerebral atrophy group than in no cerebral atrophy group ($p=0.026$). EDSS score increased as the disease duration and number of attacks increased ($p=0.003$, $p<0.001$). There was no correlation between lesion location and EDSS score. The DIR sequence is superior to the FLAIR sequence in the detection of intracortical and GM lesions. Also, the mixed lesion load on the DIR sequence is correlated with cerebral atrophy.

Key Words: Multiple Sclerosis, Magnetic Resonance Imaging (MRI), Double Inversion Recovery (DIR) Sequence, Fluid-attenuated Inversion-recovery (FLAIR) Sequence, Cortical Lesion

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). Primarily involvement of the white matter (WM) is well known, however some recent histopathological and radiological studies have shown that cortical involvement occurs in MS patients as well (Calabrese *et al.*, 2007, Honce

et al., 2013, Geurts *et al.*, 2005, Seewann *et al.*, 2012, Sethi *et al.*, 2013). Actually cortical lesions may even appear before the classical WM lesions and therefore detection of these lesions are very important for diagnosis (Popescu *et al.*, 2011). Cortical lesions are also correlated to general disability and cognitive impairment. Harrison *et al.*, reported that cortical lesion load is related to

Corresponding author: Gulhan Ertan

Address: ¹Medipol University Mega Hospitals Complex, Department of Radiology, Istanbul Turkey; ²Medipol University Mega Hospitals Complex, Department of Neurology, Istanbul Turkey; ³Acibadem Mehmet Ali Aydinlar University School of Medicine, Department of Radiology, Istanbul Turkey; ⁴Uskudar University School of Medicine, Department of Neurology, Istanbul Turkey

e-mail ✉ ertan.akan@medipol.com.tr

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cognitive impairment and EDSS scores (Harrison *et al.*, 2015). Interestingly a recent revision to McDonald criteria recognized cortical lesions as an evidence for dissemination in time. However this modification also prompted the importance of detecting cortical lesions effectively. The success of conventional magnetic resonance imaging (MRI) sequences is limited in detecting cortical lesions. Fluid-attenuated inversion-recovery (FLAIR) sequence is the most common sequence used for imaging of MS patients. Although the FLAIR sequence detects cortical and subcortical WM lesions better than the other sequences, this sequence cannot differentiate the exact anatomical border between the cortex and the subcortical WM clearly (Geurts *et al.*, 2005). Double inversion recovery (DIR) is a relatively new sequence. This sequence requires, as the name implies, double inversion sequences for suppressing cerebrospinal fluid (CSF) and WM simultaneously using a combination of two inversion pulses (T1 and T2). Thus, the sequence significantly increases lesion conspicuity in both grey and WM (Bedell *et al.*, 1998).

Despite DIR sequence has been used in several studies to detect CLs (Calabrese *et al.*, 2009, Geurts *et al.*, 2011, Kolber *et al.*, 2015) the superiority of DIR to FLAIR is not clearly

established and Kolber *et al.*, did not report any difference between the two sequences in detecting CLs. DIR is a time-consuming sequence and has a high tissue absorption rate. Based on such disadvantages over FLAIR, one might think that its routine use in MS neuroimaging may not be justified (Geurts *et al.*, 2011). The aim of this study is to investigate whether or not the three-dimensional (3D) DIR sequence is superior compared to the 3D FLAIR sequence in detecting intracortical, mixed, juxtacortical, and deep GM lesions in MS patients. We also investigated the correlation between intracortical lesion load and disability status in these patients.

Methods

Patients

In this IRB-approved study, MRI examinations including 3D DIR and 3D FLAIR sequences of 24 patients (9 males, 15 females; mean age 34.4 ± 12.0 (16-69)) were retrospectively evaluated from our database between January 2014 and June 2017. 21 patients had relapsing remitting MS (RRMS) with MS according to the McDonald criteria, 1 patient had radiologically isolated syndrome (RIS), 1 patient had clinically isolated syndrome (CIS), and 1 patient had

Table 1. Patient demographics and clinical status

Patient	Gender	Age	MS Type	Cerebral Atrophy	EDSS	Disease Duration/Year	Number of Attacks
1	F	28	RRSM	-	2	10	8
2	F	22	RIS	+	0	2	1
3	F	36	RRSM	-	1	1	1
4	M	29	RRSM	+	1.5	12	2
5	M	23	RRSM	+	3	4	2
6	F	16	RRSM	+	1	1	1
7	F	22	RRSM	+	2	4	2
8	M	47	RRSM	-	2.5	5	2
9	F	69	SPMS	+	6.5	9	10
10	M	32	RRSM	+	1	1.5	2
11	F	27	RRSM	-	2	5	2
12	F	41	RRSM	+	5	10	7
13	F	20	RRSM	-	2	2	1
14	M	31	RRSM	-	1	1	1
15	F	47	RRSM	-	1	3	1
16	M	43	RRSM	-	2.5	1	2
17	F	41	RRSM	-	1.5	6	3
18	F	37	RRSM	-	2	5	4
19	M	25	RRSM	-	0	2	2
20	F	34	RRSM	+	2	7	2
21	F	31	CIS	-	1.5	2	1
22	M	36	RRSM	-	2	5	3
23	M	55	RRSM	+	5	10	5
24	F	33	RRSM	-	2.5	15	3

Abbreviations: MS, multiple sclerosis; EDSS, Expanded Disability Status Scale; F, female; M, male; RRSM, relapsing remitting MS; RIS, radiologically isolated syndrome; SPMS, secondary progressive MS; CIS, clinically isolated syndrome

secondary progressive MS (SPMS). Disease disability was evaluated by using EDSS (Expanded Disability Status Scale). Median Expanded Disability Status Scale (EDSS) at the time of scanning was 2.1 (0-6.5) and median duration of disease from the onset of symptoms was 5 years (range 1-15 years). In all patients; annual relapse rate was 1.9 (range 0.5-6). Patient demographics and clinical status are summarized in Table 1. The patients were not evaluated for cognitive status, but clinically all of the patients had cognitive complaints as forgetfulness.

MRI Acquisition

DIR and FLAIR scans were acquired on a 3T Achieva TX system (Philips healthcare, The Netherlands) with an 8 channel coil. Axial DIR was performed by using two different inversion pulses. The details of the DIR protocol were as follows: field of view, 250 mm; matrix, 208x207; slice thickness, 1 mm; no intersection gap; no parallel imaging; repetition time (TR) 5500 msec/echo time (TE) 250 msec, long inversion time, 2600 msec; short inversion time, 625 msec; number of signals acquired, 2; and acquisition time, 5 minutes 46 seconds. FLAIR sequences were matrix, 224x224; field of view, 280 mm; slice thickness, 1 mm; no intersection gap; TR 4800 msec/TE 274 msec, inversion time, 1650 msec; number of signals acquired, 2 and acquisition time, 4 minutes 52 seconds (3).

Image Analysis

Lesions were counted and classified according to anatomic regions as intracortical (only involving GM), mixed (involving GM and extending into the adjacent WM), and juxtacortical (WM lesions abutting but not entering the cortex) on the 3D DIR and FLAIR sequences. Lesions involving the deep GM were also counted separately. The incidence of cortical GM lesions on the FLAIR and DIR sequences were independently identified and compared. The relationship between the number of intracortical, mixed, juxtacortical, deep GM lesions and type of MS, patient age, gender, duration of the disease, disability, the mean number of attacks per year and EDSS score was also investigated.

Statistical Analysis

- Distribution of data was investigated with the Shapiro-Wilk test.
- The incidence of the cortical, juxtacortical, mixed, and deep GM lesions on the FLAIR and DIR

sequences were compared with Wilcoxon signed-rank test.

- Mann-Whitney U test was used to assess the comparison of lesion count between groups. Spearman's rho was used to evaluate the correlation between measurements.
- McNemar test was used to assess the correlation between DIR and FLAIR sequences regarding lesion detection.
- SPSS (Statistical Package for the Social Sciences) v.22 (Kaysville, Utah, USA) program was used for statistical analysis. Significance was evaluated as $p < 0.05$ levels.

Results

More lesions were detected by the DIR sequence compared to the FLAIR sequence in all regions except for thalamus (11/12). The lesion detection superiority of DIR was statistically significant for intracortical lesions ($p < 0.001$) and GM lesions (intracortical +mixed) ($p < 0.001$). Also, it was close to statistically significant for the mixed lesions ($p = 0.07$). There was no statistically significant difference between lesion detection capability of the two sequences in juxtacortical areas and deep GM lesions (Fig.1, 2).

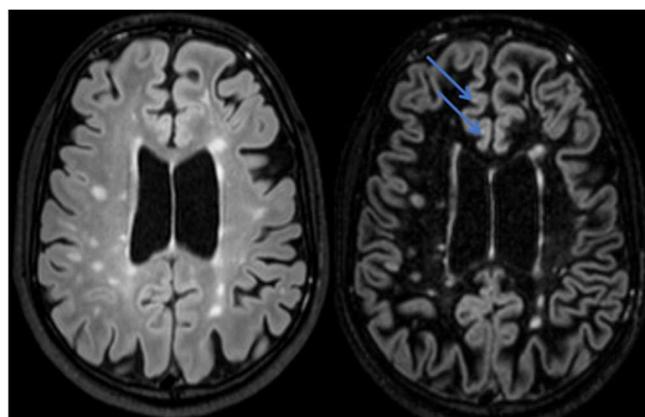


Figure 1. Axial FLAIR (left) and DIR (right) sequences; the intracortical lesions (arrows) seen on the DIR sequence are not visualized on the FLAIR sequence

The number of lesions detected by the DIR and FLAIR sequences in all regions, the ratio of the number of lesions detected by the DIR sequence compared to the FLAIR sequence, and the percentage of lesions detected by the FLAIR sequence compared to the DIR sequence are summarized in Table 2.

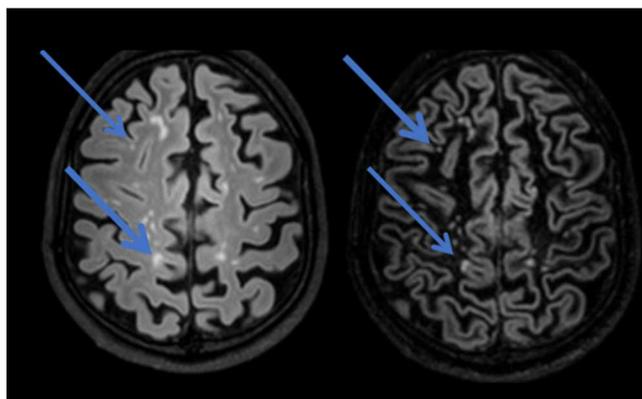


Figure 2. Axial FLAIR (left) and DIR (right) sequences; the plaques (top arrow) seen on the FLAIR sequence is seen as adjacent to the cortex, however it is located subcortical in the DIR sequence. The lesion (bottom arrow) seen on the FLAIR sequence is seen as juxtacortical, however it is located completely intracortical in the DIR sequence

Table 2. The number of lesions detected by the DIR and FLAIR sequences in all regions

	DIR	FLAIR	DIR/FLAIR*	FLAIR/DIR**	P
Intracortical	174	34	5.12	0.20	<0.001
Mixed	95	54	1.76	0.57	0.069
GM (IC+Mixed)	269	88	3.06	0.33	<0.001
JX	61	44	1.39	0.72	0.115
Caudat	3	0	---	0.00	0.180
BG	3	0	---	0.00	0.317
Thalamus	11	12	0.92	1.09	0.317
Total Deep GM	17	12	1.42	0.71	0.414

Abbreviations: Double inversion recovery, DIR; Fluid-attenuated inversion-recovery, FLAIR; GM, grey matter; IC, intracortical; JX, juxtacortical; BG, basal ganglia; *, ratio of the number of lesions detected by the DIR sequence compared to the FLAIR sequence; **, percentage of lesions detected by the FLAIR sequence compared to the DIR sequence

Table 3. Concordance between DIR and FLAIR for lesion detection

	DIR (%)	FLAIR (%)	DIR/FLAIR* (%)	FLAIR/DIR** (%)	p
Intracortical	20 (83.3)	12 (50.0)	10/12 (83.3)	10/20 (50.0)	0.039
Mixed	17 (70.8)	12 (50.0)	10/12 (83.3)	10/17 (58.8)	0.180
GM (IC+mixed)	24 (100)	16 (66.7)	16/16 (100)	16/24 (66.7)	---
JX	18 (75.0)	16 (66.7)	14/16 (87.5)	14/18 (77.8)	0.687
Caudat	2 (8.3)	0 (0.0)	---	0/2 (0.0)	---
BG	1 (4.2)	0 (0.0)	---	0/1 (0.0)	---
Thalamus	6 (25.0)	7 (29.2)	6/7 (85.7)	6/6 (100)	1.000
Total Deep GM	6 (25.0)	7 (29.2)	6/7 (85.7)	6/6 (100)	1.000

Abbreviations: Double inversion recovery, DIR; Fluid-attenuated inversion-recovery, FLAIR; GM, grey matter; IC, intracortical; JX, juxtacortical; BG, basal ganglia; *, ratio of the number of lesions detected by the DIR sequence compared to the FLAIR sequence; **, percentage of lesions detected by the FLAIR sequence compared to the DIR sequence

Table 3 summarizes the number of patients in which at least one lesion was detected by the two sequences, the percentage of number of lesions DIR detected when FLAIR detected at least one lesion, and the percentage of number of lesions FLAIR detected when DIR detected at least one lesion. Discordance was found only for the intracortical lesions. DIR was able to reveal at least one lesion in 83.3 % of the patients in which FLAIR detected at least one lesion, while FLAIR was able to reveal at least one lesion in 50.0 % of patients in which DIR detected at least one lesion.

There was inverse and weak correlation ($r=-0.444$; $p=0.030$) between disease duration and lesion load in the DIR sequence for JX area. Lesion load of the JX area in the DIR sequence decreased as the disease duration increased.

There was inverse and weak correlation between age and JX_DIR ($r=-0.460$; $p=0.024$) and JX_FLAIR ($r=-0.473$; $p=0.020$). The number of JX lesions decreased as the age increased.

There was inverse and moderate correlation between the number of attacks and JX_DIR ($r=-0.602$; $p=0.002$). JX lesion load in the DIR sequence decreased as the number of attacks increased significantly. No correlation was found for patients with higher cortical lesion load.

Cerebral atrophy was detected in 10/24 patients. More mixed lesion load on the DIR sequence were found in cerebral atrophy group than in no cerebral atrophy group ($p=0.026$).

There was a positive moderate correlation between EDSS score and disease duration ($r=0.585$; $p=0.003$), and number of attacks ($r=0.711$; $p<0.001$). EDSS score increased as the disease duration increased, and number of attacks in the same way. However, there was no correlation between lesion location and EDSS score.

The cerebral function score for EDSS in each patient was at least 1, and showed that the mental function was not normal for each patient.

Discussion

Conventional MRI sequences are unsuccessful in the detection of cortical lesions. However, previous MRI studies have shown increased cortical and subcortical lesion detection by using two-dimensional (2D) and 3D FLAIR imaging. Yet these sequences could not differentiate the exact anatomical border between the cortex and subcortical WM clearly (Bakshi *et al.*, 2001; Geurts *et al.*, 2005; Lazeron *et al.*, 2000; Moriarty

et al., 1999; Tan *et al.*, 2002; Tubridy *et al.*, 1998; Vural *et al.*, 2013). More recently, DIR sequences have been used to improve the sensitivity of MRI further in detecting cortical lesions. This technique simultaneously suppresses WM and CSF signals, using a combination of two inversion pulses. Thus, the contrast is due to the differences of T1 relaxation times between GM and CSF, as well as between grey and WM. The increased contrast between lesions and their surroundings provides visibility of cortical lesions (Bedell *et al.*, 1998). Some of the studies are based on 2D pulse sequences that have poor signal-to-noise ratio (SNR) and flow and pulsation artifacts. 3D DIR sequences allowing the acquisition of high resolution imaging with isotropic voxels and reducing flow artifacts might further increase the lesion count of cortical lesions (Geurts *et al.*, 2005).

In this study our main goal was to compare the cortical lesion detection power of a newer MR sequence (DIR) with the 3D FLAIR sequence in MS patients. Our secondary goal was to analyze the correlation between cortical lesion load and disability.

Previous studies examined intracortical lesions of MS and reported contradictory findings. Geurts *et al.* found a higher number of intracortical lesions with the DIR sequence than the FLAIR sequence (Geurts *et al.*, 2005). Vural *et al.* also reported similar results (Vural *et al.*, 2013). We also found that the DIR sequence was superior to the FLAIR sequence in detecting intracortical lesions. Results of our study revealed that the 3D DIR sequence depicted intracortical lesions five times more than the 3D FLAIR sequence. These findings are consistent with previous studies (Geurts *et al.*, 2005). In addition, Kolber *et al.* and Moraal *et al.* reported that the number of intracortical lesions detected using both DIR and FLAIR sequences was significantly higher, but they did not find a significant difference between the DIR and FLAIR sequences (Kolber *et al.*, 2015; Moraal *et al.*, 2008).

Our results regarding the relationship between CLs and other patient characteristics are also worthy of discussion. Calabrese *et al.* found a significant association between intracortical lesions and male gender (Calabrese *et al.*, 2007). However we did not find a gender effect on the number of CLs. This study also examined intracortical lesions in MS patients with DIR sequences and the frequency of intracortical lesion presence among the MS types. They found

that the number of intracortical lesions was higher in patients with secondary progressive MS (SPMS), but in our study comparison between the MS types was not done due to the majority of the patients being relapsing-remitting MS (RRMS).

Some of the previous studies found a positive correlation between the number of intracortical lesions and EDSS scores which is an indicator for disability (Calabrese *et al.*, 2007; Calabrese *et al.*, 2010; Mainero *et al.*, 2015). In our study, EDSS scores were higher in patients with long disease duration and more number of intracortical lesions. However, no correlation was found between lesion load and the EDSS scores in all regions. The reason for this could be that all patients included in the study had CL. Comparison with a CL negative group could identify the disability status better.

Besides intracortical lesions we also counted juxtacortical lesions. Some of the previous studies detected more JX lesions on the FLAIR sequence compared to the DIR sequence. Vural *et al.* reported a higher number of juxtacortical lesions with the FLAIR sequence than the DIR sequence, but no significant difference was found (Vural *et al.*, 2013). Morall *et al.* also detected more juxtacortical lesions with the FLAIR sequence than the DIR sequence, and similarly no significant difference was found (Moraal *et al.*, 2008). The reason of this may be the initial classification of these lesions as JX lesions on the FLAIR and the DIR sequence due to sharp delineation between the cortex and subcortical WM. Also, these lesions appear as touching the cortical areas on the DIR sequence and they could be categorized as mixed WM-GM lesions. Geurts *et al.* reported more juxtacortical lesion on the DIR sequence than the FLAIR sequence (Geurts *et al.*, 2005). In our study, we detected 1.76 times more JX lesions on the DIR sequence than the FLAIR sequence, but it was not statistically significant.

Regarding mixed lesions (i.e., GM-WM lesions) Geurts *et al.*, Vural *et al.*, Moraal *et al.* and Wattjes *et al.* found the highest number of mixed WM-GM lesions with the DIR sequence compared to the FLAIR sequence (Geurts *et al.*, 2005; Moraal *et al.*, 2008; Vural *et al.*, 2013; Wattjes *et al.*, 2007). In our study, 1.39 times more mixed lesions were detected on the DIR sequence than the FLAIR sequence, and this result was close to being statistically significant ($p=0.07$).

In contrast to cortical lesions in MS, studies on the detection of deep GM lesions have

been limited. A recent pathological study by Haider *et al.* have highlighted the significance of the caudate nucleus and hypothalamus as deep GM demyelinating lesions, an intermediate inflammation phenotype between low inflammatory cortical GM lesions and active WM lesions, and pathogenic processes of which include demyelination, neurodegeneration and accumulation of oxidative injury in deep GM pathology. Still cause of deep GM damage and their clinical significance remains unknown (Haider *et al.*, 2014). Geurts *et al.* found a higher number of deep GM lesions with the DIR sequence than the FLAIR sequence (Geurts *et al.*, 2005). Our study showed that more lesions were detected by the DIR sequence compared to the FLAIR sequence in deep GM regions except for thalamus. We found 1.42 times more deep GM lesions with the DIR sequence compared to the FLAIR sequence, but it was not statistically significant.

In MS patients, brain atrophy begins at disease onset in CIS and progresses throughout the course of the disease. While both GM and WM atrophy can occur, GM atrophy appears predominate. Some of the studies showed that GM atrophy increased progressively, but no change in the rate of WM atrophy was seen over time. These two entities are partially independent (Fisher *et al.*, 2008; Honce *et al.*, 2013). Some of the studies found that GM atrophy was significantly correlated with both physical and cognitive disability in MS (Fisher *et al.*, 2008; Honce *et al.*, 2013; Richard *et al.*, 2009; Seewann *et al.*, 2011). We could not assess the degree of GM and WM atrophy with computer assisted techniques due to the retrospective nature of the study. In our study cerebral global atrophy was present in patients with increased number of cortical lesions as well as in patients with no cortical lesions. However, when the groups with cerebral atrophy and no cerebral atrophy were compared, cerebral global atrophy was more common in patients with more mixed lesion load on the DIR sequence. There was no significant correlation between cortical lesion count and cerebral atrophy.

Disease duration also appears to be an important factor affecting the number of especially the JX lesions. In patients with long disease duration, JX lesion load on the DIR sequence was significantly lower. Also, there was an inverse correlation between age and JX lesion load on the DIR sequence; as age increases JX lesion count decreases. In patients with more attacks, we speculated that JX lesions are

decreasing in the course of the disease since JX lesion load is significantly lower on the DIR sequence.

Our study has some limitations. Most importantly, the patient number is low. Our image analysis of cortical lesions was limited to the classification of pure cortical, mixed and JX lesions. We did not try to classify cortical lesions further according to histopathological cortical lesion-classification. Moreover, advanced cognitive tests were not performed on the patients due to the retrospective nature of this study.

Conclusion

In conclusion, the DIR sequence is superior to the FLAIR sequence in the detection of intracortical and GM (intracortical+mixed) lesions and the mixed lesion load on the DIR sequence is correlated with cerebral atrophy. We also speculate that the JX lesions are decreasing in the course of the disease. We believe that further prospective studies will have a significant contribution to the clinic in explaining cognitive deficits due to GM involvement that may develop during the course of the disease.

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