# Comparison of Double Inversion Recovery and FLAIR Sequences in Diagnosing Multiple Sclerosis Infratentorial Plaques

**Gulhan Ertan[1]*, Barış Metin[2]**

**ABSTRACT**

Fluid–Attenuated Inversion Recovery (FLAIR) is the most commonly used sequence in routine practice for MS. Recent studies employ alternative sequences such as Double Inversion Recovery (DIR) in addition to conventional MRI techniques. In this study we compared these two sequences for their sensitivity in detecting infratentorial lesions in MS. A total of 24 patients with 3D DIR and 3D FLAIR sequences were included in this study. Plaques were classified according to their localization such as brainstem and cerebellar plaques. The relationship between number of infratentorial plaques and age, gender, MS type, disease duration, average annual number of attacks, cerebellar atrophy existence and EDSS score was also analyzed. DIR sequence detected higher number of lesions compared to FLAIR sequence in brainstem (59 vs 45 plaque in 24 cases) and cerebellum (50 vs 25 plaque in 24 cases). In detecting cerebellar lesions, superiority of DIR sequence compared to FLAIR sequence was statistically significant (p=0.049). Patients with longer disease duration had less cerebellar lesion load in FLAIR sequence at a statistically significant rate. Patients with longer disease duration and higher number of attacks had higher EDSS scores. There was no relationship between brainstem plaques number of cerebellum plaques and EDSS score. Comparing groups with and without cerebellar atrophy, cerebellar atrophy was also more frequent in patients with higher level of cerebellar lesion load in DIR sequence (p=0.028). Our findings suggest that DIR sequence is superior to FLAIR sequence in detecting cerebellar lesions. Cerebellar lesion load detected in DIR sequence was correlated to cerebellar atrophy. For this reason, especially during early period of disease, DIR sequence may be more useful than FLAIR sequence in distinguishing definite MS from clinical isolated syndromes and also for determining atrophy risk.

**Key Words:** Multiple Sclerosis, Double Inversion Recovery (DIR) Sequence, Infratentorial Plaque

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## Introduction

Multiple sclerosis (MS) is the most common demyelinating disease of the central nervous system. According to McDonald criteria used in the diagnosis of MS, it is crucial, for diagnosis, to show the dissemination in time and space of MRI findings (McDonald *et al*., 2001). At this point, it should be noted that detection of especially cortical and infratentorial lesions that are not easy with conventional techniques and this results in acceleration of diagnostic process (Geurts *et al*., 2005; Wattjes *et al*., 2007).

Double Inversion Recovery (DIR) sequence is a relatively new MRI sequence. Difference of DIR sequence from FLAIR (Fluid-Attenuated Inversion Recovery) sequence is the use of a second inversion pulse.

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**Corresponding author**: Gulhan Ertan
**Address**: [1]Department of Radiology, Istanbul Medipol University School of Medicine, Istanbul, Turkey; [2]Department of Neurology, Uskudar Jniversity School of Medicine, Istanbul, Turkey
**e-mail** ✉ ertan.akan@medipol.com.tr
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This sequence is the combination of FLAIR and STIR (Short Time Inversion Recovery) sequences (Turetschek *et al*., 1998). DIR sequence suppresses white matter and cerebrospinal fluid (CSF) simultaneously and increases visibility of lesions in gray matter and white matter (Bedell *et al*., 1998). Many studies have conducted on its superiority especially in detecting cortical MS plaques (Geurts *et al*., 2011; Ertan *et al*., 2018; Tubridy *et al*., 1998). However, there are limited numbers of studies conducted on efficiency of this technique in detecting infratentorial lesions, and dissimilar results were reported in these studies (Elnekeidy *et al*., 2014; Moraal *et al*., 2008; Wattjes *et al*., 2007).

FLAIR sequence that is the most commonly used method in routine practice in MS imaging. In this study we compared FLAIR and DIR sequences in diagnosing number of infratentorial plaques. Besides comparison of detection rates, the relationship between lesion load and age, gender, MS type, disease duration, average annual number of attacks, cerebellar atrophy existence and Expanded Disability Status Scale were also analyzed.

## Methods

MRI images of patients who were monitored with MS diagnosis in our hospital during 2014-2017 were examined retrospectively. A total of 24 patients with 3D DIR and 3D FLAIR sequences were included in this study. Local Ethics Committee approved the study protocol.

37.5% (9/24) of patients included in the research were male, and 62.5% (15/24) of them were female, and mean age was 34.38 ± 12.05 (16-69). While mean age of males was 35.67±10.67, the mean was 33.60±13.11 for females. The group difference for gender was not significant (p=0.694). Median value of disease duration was 5 years (1-15), and median value of EDSS score was 2 (0-6.5).

Plaques were classified based on their localization as brainstem (mesencephalon, pons, bulbus) and cerebellar (cerebellar hemispheres, cerebellar peduncle) plaques. The numbers of plaques in the DIR and FLAIR sequences were counted separately by two physicians, a neuroradiologist and a neurologist, blinded to the clinical findings and to the lesion count in the other sequence. Hyperintense signals observed in the FLAIR and DIR images were considered lesions. Lesions were counted as single lesion when there was no obvious signal chance between them, otherwise they were accepted as confluent lesions and counted individually.

Cerebellar atrophy was classified as present / absent. Visually, presence of parenchymal volume loss, prominence in cisterns and fissures, enlargement in sulcus and ventricles was evaluated as cerebellar atrophy.

The relationship between number of infratentorial plaques and age, gender, MS type, disease duration, average annual number of attacks, cerebellar atrophy existence and EDSS score was analyzed.

### *Imaging parameters*

All MR imagings were performed with a 3T MR device (Philips Achieva TX, Philips Healthcare, Best, Netherlands).

### *DIR sequence*

Parameters: TR/TE 5500/250 ms, Inversion Time (ms) : 2600/625 cross-section thickness: 1 mm, FOV: 250x250 mm, matrix 208x207, voxel size 1.2 mm, NSA (Number of Signal) averaging: 2

### *FLAIR sequence*

Parameters: TR/TE 4800/274 ms, Inversion Time (ms): 1650, cross-section thickness: 1 mm, FOV: 280x280 mm, matrix 224x224, voxel size 1.1 mm, NSA (Number of Signal) averaging: 2.

### *Statistical Analysis*

DIR and FLAIR comparison in terms of number of plaques was conducted with Wilcoxon test. DIR and FLAIR concordance in terms of plaque detection was tested with McNemar test. Spearman's Rho correlation analysis was used to analyse correlation among measurements. Statistical comparisons were conducted with SPSS v.22 package software, and significance level was taken as 0.05.

## Results

37.5% (9/24) of patients included in the research were male, and 62.5% (15/24) of them were female, and mean age was 34.38 ± 12.05 (16-69). While mean age of males was 35.67±10.67, the mean was 33.60±13.11 for females. The group difference for gender was not significant (p=0.694). Median value of disease duration was 5 years (1-15), and median value of EDSS score was 2 (0-6.5).

Brainstem plaques were detected in 10/24 patients in DIR sequences and 13/24 patients in FLAIR sequence. 18/24 patients had clinically

brainstem involvement. Oculomotor impairment was the most common symptom for brainstem involvement. Cerebellar plaques were detected in 15/24 patients in DIR sequence and 12/24 patients in FLAIR sequence. 9/24 patients had clinical cerebellar involvement. Cerebellar ataxia was the most common symptom in these patients.

### *The detection rates of brainstem and cerebellar plaques by DIR and FLAIR sequences*

While 59 plaques in brainstem were detected in DIR sequence, 45 plaques were detected in FLAIR sequence. DIR sequence detected 1.31 times more lesions compared to FLAIR sequence (Figure 1).

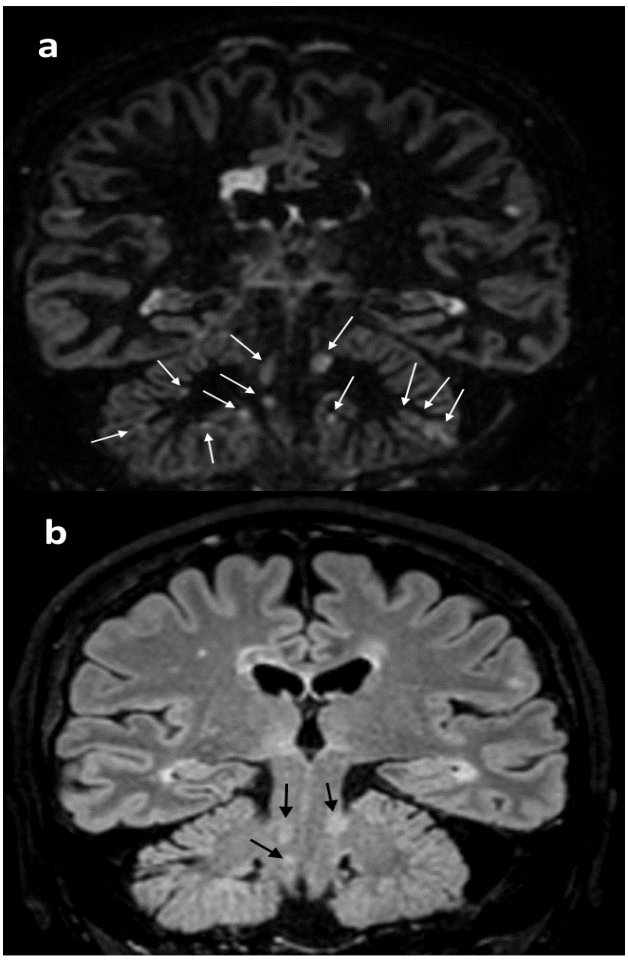


**Figure 1.** Brain stem and cerebellar lesions are much more numerous and more prominently seen in the coronal DIR image (a) than in the coronal FLAIR image (b)

While 50 plaques in cerebellum were detected in DIR sequence, 25 plaques were detected in FLAIR sequence (Figure 2). DIR sequence detected 2 times more lesions compared to FLAIR sequence. (Table 1-2).

**Table 1.** Number of plaques as per localization in DIR and FLAIR sequences

| Localization | DIR | FLAIR |
|---|---|---|
| Mesencephalon | 11 | 3 |
| Pons | 31 | 31 |
| Bulbus | 17 | 11 |
| Cerebellar peduncle | 11 | 8 |
| Cerebellar hemispheres | 39 | 17 |

**Table 2.** Number of brainstem and cerebellar plaque incidences in DIR and FLAIR sequences and detection rates of DIR and FLAIR sequences relative to each other

| | DIR | FLAIR | DIR/FLAIR | FLAIR/DIR | P |
|---|---|---|---|---|---|
| Brainstem | 59 | 45 | 1.31 | 0.76 | 0.670 |
| Cerebellum | 50 | 25 | 2.00 | 0.50 | ***0.049*** |

***DIR:*** *Total number of plaques detected in DIR sequence,* ***FLAIR:*** *Total number of plaques detected in FLAIR sequence,* ***DIR/FLAIR:*** *Plaque detection rate of DIR sequence compared to FLAIR sequence,* ***FLAIR/DIR:*** *Plaque detection rate of FLAIR sequence compared to DIR sequence*

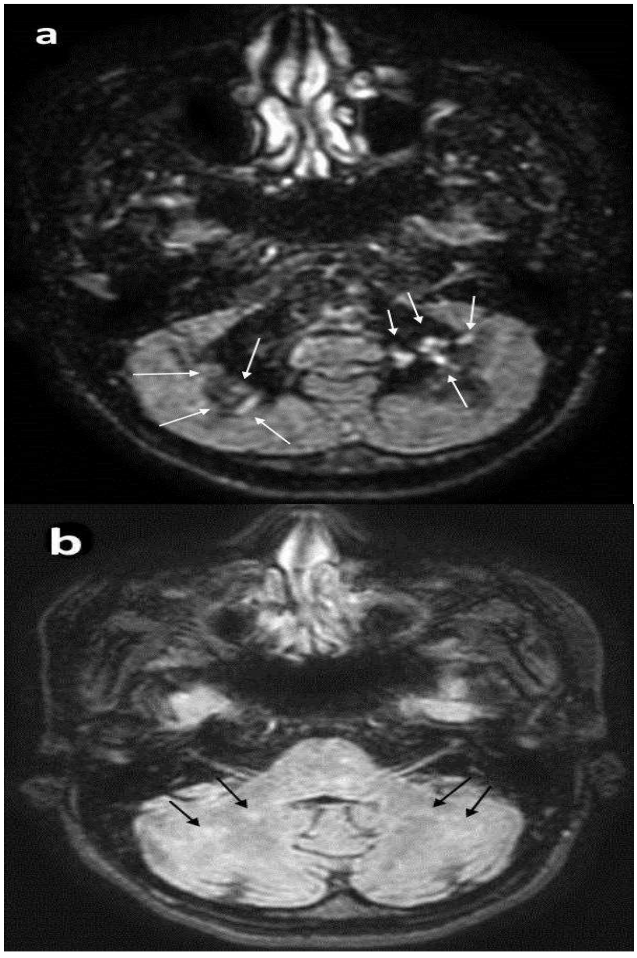


**Figure 2.** Cerebellar lesions are much more numerous and more prominently seen in the axial DIR image (a) than in the axial FLAIR image (b).

DIR sequence detected higher number of lesions compared to FLAIR sequence in brainstem and cerebellum. In detecting cerebellar lesions, superiority of DIR sequence compared to FLAIR sequence was statistically significant (p=0.049).

### *The concordance between DIR and FLAIR sequences in terms of number of lesion detections*

While DIR sequence detected at least one lesion in brainstem in 41.7% of 24 patients, this ratio was 54% in FLAIR sequence. DIR sequence also detected at least one lesion in 76% of patients for whom FLAIR sequence had detected at least one lesion previously. In all of the patients for whom DIR sequence had detected at least one lesion, FLAIR sequence also detected at least one lesion.

While DIR sequence detected at least one lesion in cerebellum in 62.5% of 24 patients, this ratio was 50% in FLAIR sequence. DIR sequence also detected at least one lesion in 83.3% of patients for whom FLAIR sequence had detected at least one lesion previously. In 66.7% of the patients for whom DIR sequence had detected at least one lesion, FLAIR sequence also detected at least one lesion.

**Table 3.** Number of patients with at least one brainstem and cerebellar plaque incidence in DIR and FLAIR sequences and detection rates of DIR and FLAIR sequences relative to each other

| | DIR % | FLAIR % | DIR/FLAIR % | FLAIR/ DIR % | P |
|---|---|---|---|---|---|
| Brainstem | 10 (41.7) | 13 (54.2) | 10/13 (76.9) | 10/10 (100) | 0,250 |
| Cerebellum | 15 (62.5) | 12 (50.0) | 10/12 (83.3) | 10/15 (66.7) | 0,453 |

***DIR:*** *Number of patients with at least one lesion detected in DIR sequence,* ***FLAIR:*** *Number of patients with at least one lesion detected in FLAIR sequence,* ***DIR/FLAIR:*** *Rate of number of patients with at least one lesion detected in DIR sequence to those with at least one lesion detected in FLAIR sequence,* ***FLAIR/DIR:*** *Rate of number of patients with at least one lesion detected in FLAIR sequence to those with at least one lesion detected in DIR sequence*

Brainstem plaques were detected in FLAIR but not DIR sequences in 3/24 patients, while the number of detected brainstem plaques was higher on DIR versus FLAIR. This result is due to the fact in 3 patients, hyperintensities assessed as plaque on FLAIR sequence could not be confirmed in any sequence including DIR sequence. These hyperintensities detected in FLAIR but not DIR considered as false positive.

There was a weak negative correlation (r=-0.436; p=0.033) between disease duration and number of plaques detected in cerebellum in FLAIR sequence. Patients with longer disease duration had less cerebellar lesion load in FLAIR sequence at a statistically significant rate. Patients with longer disease duration (r=0.585; p=0.003) and higher number of attacks (r=0.711; p<0.001) had higher EDSS scores. There was no relationship found between brainstem, number of cerebellum plaques and EDSS score.

Comparing groups with and without cerebellar atrophy, cerebellar atrophy was also more frequent in patients with higher level of cerebellar lesion load in DIR sequence (p=0.028).

## Discussion

Since brainstem and cerebellum have important vital function, they are clinically described "eloquent" localizations. Especially in the early stages of MS disease, infratentorial lesions may assist in distinction of clinical isolated syndrome from clinically definite MS in terms of McDonald criteria (McDonald *et al*., 2001). In addition, incidence of infratentorial lesion initially in MS is indicative of negative prognosis (McDonald *et al*., 2001; Minneboo *et al*., 2004).

Wattjes *et al*. report that infratentorial lesion load is an important factor for predicting long-term disability. Accurate detection of these plaques is critical in treatment decision and thus may be important for decreasing long-term disability. Our results showed that DIR is more sensitive than FLAIR for detecting infra-tentorial lesions. Thus, performing DIR sequence early in the course of disease and especially for clinically isolated syndrome may be useful for establishing the diagnosis and guiding treatment. Our results are consistent with earlier studies reporting that FLAIR sequence may not be sensitive for infratentorial plaques. However, it should be taken into account that FLAIR protocols have improved significantly over years and newer protocols may yield better results as reported by studies (Bakshi *et al*., 2001; Gawne-Cain *et al*., 1997; Wattjes *et al*., 2007).

Previously, Moraal *et al*., did not found a difference between FLAIR and DIR sequence for detecting infratentorial lesions (Moraal *et al*., 2008). Vural *et al*. also did not find a statistically significant difference in average number of plaques detected in DIR and FLAIR sequences in infratentorial localization (Vural *et al*., 2013). Wattjes *et al*. however, found that DIR was superior to FLAIR (Wattjes *et al*., 2007). Similar to our findings, in studies conducted by Geurts *et al*. and Elnekeidy *et al*. higher numbers of plaques were detected in DIR sequence in infratentorial localization as compared to FLAIR sequence (Elnekeidy *et al*., 2014; Geurts *et al*., 2005).

In our study, we detected 1.3 times more number of plaques in brainstem in 3D DIR sequence compared to 3D FLAIR sequence. In addition, 2 times more plaques were detected in cerebellum in DIR sequence compared to FLAIR

sequence. When compared the number of the detected lesions per patients with the 2 sequences in detecting number of cerebellar lesions, superiority of DIR sequence as compared to FLAIR sequence was statistically significant. In some of the previous studies, it was argued that the superiority of lesion detection with DIR sequence was due to artifacts that tend to occur in posterior fossa. Artifacts monitored in the form of high signal intensity in DIR sequence and detected in periaqueductal localizations especially in posterior fossa, periventricular white matter and brainstem were attributed to transependymal CSF effusions (Geurts *et al*., 2005). Besides, other monitored artifacts are "ribbon like" hyperintensities. These artifacts are known with their bilateral incidence, symmetrical form, characterized by change of shape in consecutive sections (Calabrese *et al*., 2007). In our cases, no artifacts were found on DIR sequences in posterior fossa.

Mechanism of brain atrophy occurring in MS disease have not been understood thoroughly yet. In MS, demyelination and neurodegeneration causing axonal loss inside and outside of plaques in white matter and neuronal loss in gray matter are thought to be implicated in atrophy. Brain atrophy is important in that it is an indicator of inflammation and neurodegeneration, which in turn reflects the severity, and progression of disease in MS (Lassmann *et al*., 2007). Edwards *et al*. (Edwards *et al*., 1999), in their study, reported a decline in cerebellum and brainstem volumes in 15 MS patients compared to healthy controls. Cerebellum volumes were found to be correlated with disease duration and disability scores. On the other hand, a weak correlation was found between brainstem volumes and disability scores. This finding was explained with the less severe loss of axon and myelin in brainstem or relatively compensated axon loss with an increase in gliosis, remyelination and extracellular length. In our research, while the MRIs were not analyzed with voxel-based volumetric methods, cerebellar atrophy, characterized with presence of parenchymal volume loss, clarification of cistern and fissure, clarification of sulcus and ventricular expansion was frequent in patients with high cerebellar lesion load detected in DIR sequence. But there was no significant correlation between disability scores and cerebellar atrophy. In our study, we did not visually detect brain stem atrophy in patients.

The shortcomings of the study are relatively limited number of patients and lack of cognitive testing for analyzing the relationship between cognitive decline and lesion load. The latter was due to the retrospective nature of the study.

## Conclusions

Our findings suggest that DIR sequence is superior to FLAIR sequence in detecting cerebellar lesions. For brainstem lesions, although FLAIR detected more patients with brainstem involvement, this difference did not reach significance. Cerebellar lesion load detected in DIR sequence was correlated to cerebellar atrophy. For this reason, especially during early period of disease, DIR sequence may be more useful than FLAIR sequence in distinguishing definite MS from clinical isolated syndromes and also for determining atrophy risk.

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