Usefulness of Contrast-Enhanced Double Inversion Recovery T2 FLAIR in multiple sclerosis disease: a preliminary experience in 40 patients

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Aims and objectives

Multiple sclerosis (MS) is one of the most common disabling neurologic disease of young adults involving the central nervous system\textsuperscript{1,2,3}. Cerebrospinal fluid (CSF) tests and MRI have expanding roles in the early diagnosis of MS\textsuperscript{2,3}. Contrast-enhanced brain MRI is a part of baseline evaluation of suspected and clinically definite MS patients who have shown brain lesions in precontrast MR studies. Active MS lesions are associated with focal disruption of the blood-brain barrier (BBB) due to perivascular inflammation and injection of contrast leads to significant shortening of T1-relaxation time of these lesions with subsequent increased signal intensity. Generally, in clinical practice, evaluation of enhancement of acute lesions is usually made in early contrast-enhanced T1-weighted images (CE-T1WI)\textsuperscript{4} but different studies demonstrate that delayed T1-weighted images (20 minutes to 1 hour after contrast administration) in MS patients can add valuable information respect to early CE-T1WI\textsuperscript{4,7}. A few recent studies focusing on different disease entities involving central nervous system have attracted our attention by indicating that injection of gadolinium can intensify T1 effect on fluid-attenuated inversion-recovery (FLAIR) images leading to increased signal intensity of lesions in this sequence\textsuperscript{8,17}. Some of these studies have proposed a major role for contrast-enhanced (CE)-FLAIR and (CE) Double Inversion Recovery (DIR) T2-FLAIR images in depicting leptomeningeal carcinomatosis, cranial nerve metastasis, small subdural hematomas, and other extra-axial lesions and also a complementary role for detecting intracranial tumors and metastases besides CE-T1W images\textsuperscript{8,18}. The aim of this study was to assess the diagnostic value of CE DIR T2-FLAIR for the detection of cortical or juxcortical lesions or new active plaque in the different identified phases of the Multiple Sclerosis (MS) disease and to find out if this proposed additional sequences can add any diagnostic information regarding number, size, location, and degree of enhancement of lesions respect to the routine CE-T1W images.
Methods and materials

Subjects: The institutional review board approved this prospective study in which all subjects provided written informed consent. A total of 40 patients admitted to our institution between January and November 2017 with clinically definite MS disease according to the criteria of McDonald et al. were enrolled into the study and underwent brain MRI. All examinations were performed using 3 T MR scanner. These patients attended the outpatient neurology department of our center due to new-onset symptoms that were not present previously or because they needed brain MRI during their follow-up course. Exclusion criteria for entrance into the study were pregnancy, breastfeeding, a history of allergy and adverse reaction to contrast media, and current asthma. In addition, recent use of corticosteroids or other immunosuppressives (within previous month) was considered an exclusion criterion. Patients with concomitant disease involving brain parenchyma (including ischemia and stroke, vasculitis, and viral infections) were also excluded of the study. Written informed consent was obtained from the patients before participation in the study, which was approved by the local committee on ethics.

MRI Acquisitions: All MRI examinations was carried out with use of one MRI unit in our department (3T MR scanner Philips Ingenia Best, Netherlands) using a 15-channel receive head coil. All precontrast and postcontrast images of the brain were taken with slice thickness of 5 mm and interval gap of 1 mm, 256X256 image matrix and 24X18 cm field of view not including axial T1 MP-RAGE, SWI and DIR T2-FLAIR sequences. Precontrast images included axial T1 MP-RAGE (8° flip angle, 7.1 ms TR, 3.0 ms TE, 900 ms TI, 2400 ms TD, 24x18 FOV, 1.2 slice thickness, 256x256 matrix and 1 NEX), axial DIR T2-FLAIR (90° flip angle, >4000 ms TR, 50 ms TE, TI1=3400 and TI2=325 ms, 24x18 FOV, 1.2 slice thickness, 256x256 matrix and 1 NEX), axial T1W images (TR 225 ms/TE 2.5 ms, FOV 220 mm, slice thickness 5 mm, voxel size 0.7 3 0.7 3 5.0 mm), axial and coronal spin-echo T2-weighted images (TE/TR 110/3500 ms), axial DWI (TR 5,300 ms/TE 68 ms/ b 0/1,000 s/mm2, FOV 220 mm, slice thickness 4 mm) and axial FLAIR images (TE/TI/TR 100/2000/6000 ms). Axial images were acquired aligned with the inferior borders of the corpus callosum. Brain iron accumulation has been shown histologically in MS and recently, an iron increase from 24% to 39.5% was reported in the deep gray matter in MS patients compared to control subjects. For this reason as biomarker we assessed the presence of iron deposition along the rims of chronic lesions using SWI sequence (slab of 64 slices of 3 mm thickness, no gap, a field of view (FOV) of 220 mm, an acquisition matrix of 384 X 256, a TR/TE of 85.2/32.6 ms, NEX 2 and a flip angle of 20°) and its SWI phase image. Afterward, the contrast agent, gadoterate meglumine Gd-DOTA (Dotarem; Guerbet, France) was injected into the antecubital vein at the dose of 0.1 mmol/kg body weight for all patients. Ten minutes after the injection of contrast material, postcontrast images were taken including axial DIR T2-FLAIR (CE DIR T2-FLAIR), axial T1W images and axial T1 MP-RAGE (CE-MP-RAGE) images, with the same scan techniques as precontrast images.
Evaluations: Pre and Postcontrast images of each patient were reviewed by two experienced neuroradiologists. They were asked to determine the number of enhancing lesions and also location, size, degree, and pattern of enhancement of each lesion in each sequence independently. The results were entered into a special chart for subsequent analysis. The lesions were separated by their location into six different groups, including subcortical, paraventricular, centrum semiovale, callosal, brain stem, and cerebellar. The size of the lesions was measured according to their largest dimension. The degree of enhancement was determined subtracting the intensity signal value of the ROI placed surrounding the lesion showed in CE DIR T2-FLAIR sequence from the value assessed positioning ROI on the same lesion in the same precontrast image. The degree of enhancement in CE- T1W images and T1 MP-RAGE(CE-MP-RAGE) image were evaluated by the same method. The pattern of enhancement was also evaluated by dividing the lesions into different groups with homogeneous, nonhomogeneous, ring-like, central, or centripetal patterns of enhancement. Any discrepancies between the two reviewers were resolved by consensus.

Data Analysis: Statistical analysis was conducted using SPSS Version 11.5 for Windows (SPSS Inc., Chicago, IL). Determination and comparison of sensitivities of different sequences for detecting lesions (by their number) were done by \( \chi^2 \) test. Evaluation of the difference in the degree of enhancement and size of lesions in acquired sequences was done by T test.
Results

Number of Lesions: Forty patients who met the inclusion criteria mentioned were included in this study. None of these patients had no criteria for exclusion from the study (Table 1). The mean age of the patients was 29.7 years with an age range of 17 to 45 years old; 25 of the patients were female and 15 were male. Eleven out of 40 patients had no active plaques in post contrastographic sequences being in remitting phase; SWI confirmed only the presence of iron storage as disease biomarker in white matter. The remaining 29 patients had at least one enhancing brain lesion in the routine CE-T1W and CE-MP-RAGE and/or in our added sequences. A total number of 83 enhancing lesions were detected in 29 patients of the study (2.9 lesions per patient). The total number of enhancing lesions, detected in CE-T1W and CE-MP-RAGE images was 51 lesions (61.4% of total) in 18 patients which means 11 patients had no enhancing lesions in this sequence. All these lesions showed an enhancement in the post-contrast DIR T2-FLAIR sequence while DIR T2-FLAIR images showed 32 (38.5%) new enhanced lesions in 11 patients for a total of 83 lesions (100%) highlighted with the use of post contrast sequence (Table 2).

Degree of Enhancement: Mean ± SD of degree of enhancement of 51 lesions lesions (61.4% of total) enhanced in CE-MP-RAGE and CE-T1W were 377±49.5 while in all 83 lesions enhanced in CE DIR T2-FLAIR sequence was 243±38.5 with statistical difference between the two groups\(p<0.01\). Compared with CE-MP-RAGE and CE-T1W, 32 lesions (38.5%) had a greater degree of enhancement in CE DIR T2-FLAIR with a Mean ± SD of 286±32.5 (Table 2) (Figure 1).

Size of the Lesions: Mean SD of the size of the lesions commonly enhanced in all sequences was 9.5 ± 4.7 mm in the greatest diameter in the CE-MP-RAGE and CE-T1W images, while it was 10.1 ± 5.5 mm in CE-FLAIR images. The results of the study are summarized in Table 2.

Lesion Location: Thirty-nine of the total 83 enhancing lesions were in the periventricular region (46.9%); 23 were located in the subcortical and cortical region (27.1%), 17 were in the centrum semiovale (20.4%), and the rest (4.8%) were in the brain stem and cerebellum. Of 32 lesions that were not enhanced in CE-MP-RAGE or CE-T1W images but enhanced in CE-DIR T2-FLAIR, 19 were in the periventricular region (59.3%), 4 were in the subcortical and cortical (12.5%), and the rest were in the centrum semioval and brain stem. The number of enhancing lesions in all acquired sequences, differentiated by their location, is summarized in Table 3.

Pattern of Enhancement of Lesions: Forty-two of the total 51 lesions enhanced in CE-T1W or CE-MP-RAGE images showed a homogeneous enhancement (82.3%), 7 showed ring enhancement pattern of enhancement (13.7%), and the other 2 lesions (3.9%) were centrally or nonhomogeneously enhanced. Fifty-nine of the total 83 lesions enhanced in CE-FLAIR images showed a homogeneous pattern of enhancement (72%),
15 showed ring enhancement (19%), and the other 9 lesions (9%) were centrally or non-homogeneously enhanced (Table 4).

**Diagnostic performance of CE-FLAIR in detecting new enhancing lesions:** Diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CE-DIR T2-FLAIR and CE-MP-RAGE/CE-T1W are detailed in Table 5. The results of our study indicate a sensitivity of 97.7% was achieved for this sequence in our study, which shows a 25.3% increase in sensitivity compared with CE-T1WI (72.4%).
Fig. 1: (a,e,i) Axial DIR pre contrast T2-FLAIR images of 37 years old women at different slices of brain show multiple areas of altered signal intensity respectively and in particular in the left prefrontal cortical-subcortical lobe, white matter adjacent to the right trigone of the lateral ventricle and white matter near the left temporal horn. Axial DIR post contrast T2-FLAIR images (b,f,l) at the same pre contrast slices show slight enhancement of the same lesions highlighted in pre contrast DIR FLAIR images. (c,g,m) Axial SWI images of the same slices show some iso-hypointense micro spots near the noted lesions. (d,h,n) Axial post contrast MPRAGE T1 did not show enhancing of the highlighted lesions.

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Table 1. Characteristics of patients with multiple sclerosis

<table>
<thead>
<tr>
<th></th>
<th>Overall(40)</th>
<th>CIS(5)</th>
<th>RRMS(24)</th>
<th>PPMS(5)</th>
<th>SPMS(6)</th>
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<tbody>
<tr>
<td>Age</td>
<td>29.7</td>
<td>26.7</td>
<td>34.7</td>
<td>42.1</td>
<td>46.1</td>
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<tr>
<td>Female</td>
<td>25</td>
<td>3</td>
<td>18</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Mean disease duration(years)</td>
<td>6</td>
<td>-</td>
<td>4</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>EDSS median</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Interferon β</td>
<td>30/40</td>
<td>2/5</td>
<td>20/24</td>
<td>3/5</td>
<td>5/6</td>
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<tr>
<td>Natalizumab</td>
<td>6/40</td>
<td>0/5</td>
<td>1/29</td>
<td>3/7</td>
<td>2/8</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>5/40</td>
<td>0/5</td>
<td>3/29</td>
<td>1/7</td>
<td>1/8</td>
</tr>
<tr>
<td>Remitting</td>
<td>14/40</td>
<td>0/5</td>
<td>11/29</td>
<td>1/7</td>
<td>2/8</td>
</tr>
<tr>
<td>Relapsing</td>
<td>35/40</td>
<td>5/5</td>
<td>19/29</td>
<td>6/7</td>
<td>5/8</td>
</tr>
</tbody>
</table>

Table 1

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Table 2. Number of patients, total number of enhancing lesions and lesion characteristics in different pulse sequences

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>CE-MP-RAGE and CE- T1W</th>
<th>CE-DIR T2-FLAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with enhancing lesions</td>
<td>29/40</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Total number of enhancing lesions</td>
<td>83</td>
<td>51/83</td>
<td>83</td>
</tr>
<tr>
<td>Mean degree of enhancement</td>
<td>304 ± 42.3</td>
<td>377 ± 49.5</td>
<td>243 ± 38.5</td>
</tr>
<tr>
<td>Mean size of the lesions</td>
<td>9.8 ± 5.1 mm</td>
<td>9.5 ± 4.7 mm</td>
<td>10.1 ± 5.5 mm</td>
</tr>
</tbody>
</table>
Table 2

Table 3. Number and percentage of enhancing lesions in all acquired sequences differentiated by their location

<table>
<thead>
<tr>
<th>Location</th>
<th>Paraventricular</th>
<th>Subcortical and Cortical</th>
<th>Centrum Semiovale</th>
<th>Brain Stem</th>
<th>Cerebellum</th>
<th>Corpus Callosum</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE-MP-RAGE and CE- T1W</td>
<td>24</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>8</td>
<td>51</td>
</tr>
<tr>
<td>CE-DIR T2-FLAIR</td>
<td>42</td>
<td>14</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>13</td>
<td>83</td>
</tr>
</tbody>
</table>

Table 3

Table 4. Pattern and percentage of enhancing lesions in all acquired sequences

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Homogeneous</th>
<th>Non - homogeneous</th>
<th>Ring - like</th>
<th>Central</th>
<th>Centripetal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE-MP-RAGE and CE- T1W</td>
<td>42(82.3%)</td>
<td>1(1.9%)</td>
<td>7(13.7%)</td>
<td>1(1.9%)</td>
<td>0</td>
<td>51</td>
</tr>
<tr>
<td>CE-DIR T2-FLAIR</td>
<td>59(72%)</td>
<td>4(4.8%)</td>
<td>15(19%)</td>
<td>4(4.8%)</td>
<td>1(1.2%)</td>
<td>83</td>
</tr>
</tbody>
</table>

Table 4
Table 5. Diagnostic Performance of CE-MP-RAGE and CE-FLAIR in detecting new enhancing lesions in relapsing phase

<table>
<thead>
<tr>
<th></th>
<th>CE-MP-RAGE and CE- T1W</th>
<th>CE-DIR T2-FLAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>AUC(95% CI)</td>
<td>95.7 (96.1–97.4)</td>
<td>98.7 (97.3–99.5)</td>
</tr>
<tr>
<td>Sensitivity(95% CI)</td>
<td>71%</td>
<td>97%</td>
</tr>
<tr>
<td>Specificity(95% CI)</td>
<td>64%</td>
<td>89%</td>
</tr>
<tr>
<td>Accuracy(95% CI)</td>
<td>68%</td>
<td>93%</td>
</tr>
<tr>
<td>NPV(95% CI)</td>
<td>83.2 (82.2–84.5)</td>
<td>95.7 (94.1–96.7)</td>
</tr>
<tr>
<td>PPV(95% CI)</td>
<td>93.6 (92.1–94.8)</td>
<td>98.3 (97.1–99.4)</td>
</tr>
</tbody>
</table>

Table 5

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Conclusion

Any lesions are seen on noncontrast FLAIR or T2W images of MS patients, then gadolinium-enhanced images are needed to determine the presence of active enhancing lesions. Furthermore subclinical disease activity may be detected in an asymptomatic patient by means of gadolinium-enhanced MRI. Perivascular inflammation has been thought to play a primary role in the disruption of the BBB, in myelin breakdown, and in the formation of new lesions. Transient breakdown of the BBB in acute MS lesions allows intravenous gadolinium contrast agents to enter these active lesions, causing marked shortening of the T1 relaxation time of neighboring water protons. As a result, contrast agents locally increase the signal from active MS lesions in T1-weighted images. According to routine MRI protocols for MS patients, if any lesions are seen on precontrast FLAIR and/or T2W images, then gadolinium-enhanced axial T1W images are also acquired. In our results, although CE-T1WI obtained a sensitivity of 71% in detection of enhancing MS lesions 97% was achieved for CE-DIR T2-FLAIR sequence, which shows a 25.3% increase in sensitivity compared with CE-T1WI. The mean degree of enhancement of lesions commonly enhanced in in CE-MP-RAGE and CE-T1W was 377±49.5 while in all lesions enhanced in CE-FLAIR sequence was 243±38.5 with statistical difference between the two groups(p<0.01). Compared with CE-MP-RAGE and CE-T1W, 32 lesions(38.5%) had a greater degree of enhancement in CE-DIR T2-FLAIR with a Mean ± SD of 286±32.5 probably due to vasogenic oedema of this type of lesions. The mean size of the lesions was 9.5 ± 4.7 mm in the greatest diameter in the CE-MP-RAGE and CE-T1W images, while it was 10.1 ± 5.5 mm in CE-DIR T2-FLAIR images without no statistically significant difference between the two groups(p>0.001). FLAIR is an inversion recovery sequence of MRI that produces heavily T2-weighted images with CSF signal suppression. This is done by using inversion recovery scheme and acquiring the image data after a time delay (which is the inversion time), when the longitudinal magnetization of the signal from CSF is zero. Any other tissue with T1 relaxation time similar to CSF (such as water) then also appears strongly attenuated, but FLAIR also has mild T1-weighting which means T1-relaxation time of lesions also contributes to making signal in this sequences and that is the main reason that gadolinium-containing lesions show increased signal intensity (enhancement) in FLAIR images. Although a great deal of research performed in the past decade on the role of FLAIR sequence in delineating MS lesions has shown very promising aspects and great sensitivity of this sequence, to the best of our knowledge, no study has a large number of patients for evaluating the role of DIR T2-FLAIR in imaging enhancement of lesions in MS. It is obvious that detecting new enhancing lesions in CE-DIR T2-FLAIR in patients who had no enhancement in T1WI resulted in a relevant change in their clinical management. The results indicate that CE-FLAIR images are reliable sequences for depicting enhancing brain MS lesions and are significantly more sensitive than CE-T1WI or CE-MP-RAGE (P<0.001). Statistically significant less degrees of enhancement of lesions in CE-DIR T2-FLAIR images compared with T1WI or CE-MP-RAGE (P<0.001) can be partly attributed
to T2-weighting of these lesions contributing to increased signal intensity in the CE-
DIR T2-FLAIR images. This might be assumed as a drawback in comparing degrees
of enhancement of lesions in T1W and FLAIR images, as T1W images cannot use
this property of lesions. However, it can guide the radiologist for better delineation of
enhancing lesions. Increased size of the lesions in FLAIR images is also assumed to be
due to perilesional edema appearing as high signal intensity zone around the lesion. On
the basis of study data, our suggestion is to consider CE-DIR T2-FLAIR and CE-T1W as
part of evaluation of postcontrast brain MRI in MS patients.
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