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Comparison of Double Inversion Recovery and Conventional Magnetic Resonance Brain Imaging in Patients with Multiple Sclerosis and Relations with Disease disability

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Key words: adult, brain, magnetic resonance imaging, multiple sclerosis

SUMMARY – Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system, predominantly affecting the white matter, but also the grey matter. Aim of this study was to detect MS lesions with double inversion recovery (DIR), fluid-attenuated inversion recovery (FLAIR) and T2-weighted magnetic resonance (MR) techniques and determine the sensitivity of these techniques, and the correlation between the number of lesions and expanded disability scale (EDSS) scores. Thirty-four patients with MS (20 females and 14 males) were included in this study. DIR and conventional MR (T2-A, FLAIR) sequences were obtained. Lesions were counted and classified as belonging to one of seven anatomical regions: cortical, juxtacortical, deep grey matter, deep white matter, mixed white matter-grey matter, periventricular white matter and infratentorial. The correlation between lesion number and EDSS scores was investigated. DIR images showed more intracortical and mixed white matter-grey matter lesions in comparison with both FLAIR and T2 sequences (p=0, p=0 respectively). There was a significant difference between mean lesion numbers at the juxtacortical region, obtained with DIR and T2-weighted images (p = 0.002). The total number of lesions obtained with all methods was similar. DIR brain imaging had the highest sensitivity in the detection of cortical and mixed white matter-grey matter lesions, compared with FLAIR and T2 sequences. In addition, the lesions obtained with DIR images were more easily visualized.

Introduction

Multiple sclerosis (MS) is the most common chronic inflammatory demyelinating disease of the central nervous system, resulting in both physical and neurocognitive disability. MS typically affects the white matter, but recent clinical autopsy studies have also reported changes in the grey matter. Magnetic resonance imaging (MRI) has played a very important role in elucidating the pathophysiology, diagnosis and treatment of MS. T1- and T2-weighted conventional MRI images reveal islands of demyelinating plaques, more frequently found in white matter than grey matter. Autopsy studies have also demonstrated inflammatory and pathological changes in MS, which are not present in regions of demyelinating plaques but appear as islands in MRI sequences and are present almost throughout the brain, encompassing both the white and grey matter and appearing macroscopically normal. Thus, the inability to demonstrate such changes using conventional MRI sequences reflects the technical insufficiency of these classical techniques. Conventional magnetic resonance imaging (MRI) does not show any histopathological characteristics apart from an association between specific T2-weighted images of hyperintense lesions (demyelinating plaques) and inflammation with gadolinium uptake. These considerations have necessitated the de-
development of new techniques to obtain a better understanding of MS pathophysiology. Such novel techniques include fluid−attenuated inversion recovery (FLAIR) and double inversion recovery (DIR). Although FLAIR has been used in a routine clinical setting, DIR is more frequently used in experimental studies, although it has recently started to enter clinical use.

The FLAIR sequence is a sequence that suppresses the signal of cerebrospinal fluid (CSF) with a reverse cycle (inversion recovery) pulse and a high time Echo (TE values increase) T2-weighted SE sequences, but not in FLAIR sequences, since their T2 relaxation times are different. The DIR sequence was developed by Redpath and Smith. It differs from FLAIR in its utilization of a second inversion pulse. These images have hybrid features of FLAIR and a short time inversion recovery (STIR). Both the white and grey matter play a clear role in the physical and neurocognitive disability of MS patients. However, a sufficient correlation has not been demonstrated between conventional MRI findings and disability, which is mostly due to the inability to demonstrate all of the histopathological changes present in MS in vivo using classical MR images. In particular, lesions located at the junction of the grey matter-CSF, grey matter−white matter (juxtacortical areas) and white matter−CSF could not be visualized in conventional MR sequences because of the signal suppression of the grey matter by signals from both the white matter and CSF as well as the absence of sufficient contrast. Signals from the CSF are suppressed in FLAIR sequences so that lesions in the parenchymal areas, which are in juxtaposition to the CSF, become more prominent. However, this approach still cannot reveal lesions in the junction of the grey and white matter. In addition, signals from the white matter should be suppressed to detect these lesions. Because the DIR technique can better accomplish this suppression, it is thought that MS plaques located in the grey matter are more easily delineated using DIR. The disturbances in consciousness, cognitive and psychic changes and epileptic fits observed in MS patients in clinical practice cannot be explained by the changes in white matter observed in conventional MR sequences. This is most likely due to the inability of classical MR techniques to detect grey matter lesions. Thus, the detection of grey matter lesions will play an important role in our understanding of both the physical and neurocognitive disability observed in MS patients.

We aimed to detect grey matter lesions not adequately observed using conventional MRI in patients with MS. If present, we sought to determine the relationship between these lesions and the expanded disability status scale (EDSS) scores.

Material and Methods

This study was approved by the ethics committee of our hospital, and informed consent was obtained from all participating patients. A total of 34 patients with relapsing–remitting multiple sclerosis (RRMS) were evaluated and treated in our clinic. A detailed neurological examination of all patients was performed. Conventional cranial and cervical MRI and DIR images were obtained from patients with RRMS after a remission of three months, and their functional capacities were evaluated with the EDSS. The presence of a neurological disturbance, according to a subjective patient report or objective observation, of at least 24 hours in duration was considered a new attack. The patients were discharged after treatment of the attack, and follow-up evaluations were performed. Patients who did not exhibit a new attack within three months of follow-up (i.e., who were in remission for three months) were asked to return to the clinic, and a new MRI was performed and an EDSS score was determined.

All of the patients’ MR sequences were obtained with a 1.5 T super-conductive magnet (Philips Achieva) with a standard head coil of 8-16 channels. Transverse T2-weighted (TR: 5291 ms; TE: 110 ms, matrix: 300×212, NEX: 2, slice thickness: 5 mm, section width: 1 mm; exposure time: 1.10 min) and FLAIR (TR: +1000 ms, TE: 120 mS, TI: 2000 ms, matrix: 264×149, NEX: 2, slice thickness: 5 mm, section width: 1 mm, exposure time: 1.30 min) sequences were obtained, according to the conventional MRI protocol. Three-dimensional DIR images were obtained with the following technical features: TR, +1000 ms; TE, 120 ms; TI, 2000 ms; matrix, 264×149; NEX, 2; slice thickness, 5 mm; section width, 1 mm; and exposure time, 1.30 min. Radiological evaluations of the obtained sequences were performed by two physicians, a
neuroradiologist and a neurologist, blinded for the clinical findings and paraclinical test results. All of the hyperintense signals observed in the T2, FLAIR and DIR images were considered lesions. In contrast, the hyperintense signals originating from the sinuses or major vessels or from signals extending as an extracortical strip were considered to artifacts and not lesions. The detected lesions were divided according to seven anatomical regions: cortical, juxtacortical, deep white matter, deep grey matter, mixed white matter-grey matter, periventricular white matter, and infratentorial regions. The lesion numbers according to the regions were determined. In addition, T2-weighted spinal images of all patients were obtained. The evaluation of a spinal lesion was classified as “present” or “absent” and not as a lesion count.

The statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) version 15.0 software. Two independent group t tests were performed on the data, according to parametric test pre-conditions. In addition, a Mann Whitney U-test was performed on the data, which did not meet with parametric test pre-conditions. An independent one-way analysis of variance and the Kruskal Wallis test were used to compare variables with three or more groups. The Tukey test was used in multiple comparisons of variables, which were significant in the one-way analysis of variance. The Dunn test was used following the Kruskal Wallis test results. Repeated measurements were analyzed with an analysis of variance of dependent groups, and the Friedman test was used if p≤0.05, which was considered the statistical significance level.

**Results**

Thirty-four consecutive patients with RRMS were included in this study. There were 20 (58.8%) female and 14 (41.2%) male patients, with a mean age of 38 ± 20 years. The upper and lower age limits for the female and male patients were 18 to 49 years and 20 to 58 years, respectively. Spinal lesions were observed in 22 out of 34 MS patients (64.7%) (9 out of 14 male patients [64%] and 13 out of 20 female patients [65%]). Demographic, clinical and radiological characteristics and the EDSS scores of the MS patients are presented in Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Some demographic, clinical and radiological characteristics and EDSS scores of patients with multiple sclerosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minimum</strong></td>
<td><strong>Maximum</strong></td>
</tr>
<tr>
<td>Patient age (year)</td>
<td>18</td>
</tr>
<tr>
<td>Duration of illness (year)</td>
<td>1</td>
</tr>
<tr>
<td>EDSS score</td>
<td>0</td>
</tr>
<tr>
<td>Lesion number with T2</td>
<td>6</td>
</tr>
<tr>
<td>Lesion number with FLAIR</td>
<td>8</td>
</tr>
<tr>
<td>Lesion number with DIR</td>
<td>6</td>
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</table>
Comparison of Double Inversion Recovery and Conventional Magnetic Resonance Brain Imaging in Patients... G. Varal

Figure 2 A lesion of mixed white matter–grey matter location, which is seen in the DIR image (A) but cannot be seen in FLAIR (B) or T2-weighted images (C).

Figure 3 Two lesions of juxtacortical location prominent in the DIR (A) and FLAIR (B) images.

T2, FLAIR and DIR images of MS lesions of one patient are shown in Figures 1 to 5. The lesion distributions in the seven anatomical regions and the mean lesion numbers obtained by T2-weighted, FLAIR and DIR images of MS patients are shown in Table 2. The mean number of lesions in the cortical region with DIR was significantly higher than the mean number of lesions detected with T2 and FLAIR (p = 0.00 and p = 0.00, respectively). The mean number of lesions detected with DIR in the juxtacortical region was significantly higher than the mean number of lesions detected with T2 (p = 0.002). The mean number of lesions detected in the deep white matter with T2 and FLAIR were higher than the mean number of lesions detected with DIR (p = 0.022 and p = 0.027, respectively). The mean number of lesions detected with DIR in the mixed white matter–grey matter was significantly higher than the mean number of lesions detected with T2 and FLAIR (p = 0.000 and p = 0.000, respectively). The mean number of lesions detected in the periventricular white matter with FLAIR was significantly higher than the mean number of lesions detected with DIR (p = 0.000). The mean number of lesions detected by T2 in the infratentorial region was significantly higher than the mean number of lesions detected with DIR (p = 0.001). There was no significant difference between the mean number of lesions detected in the infratentorial region with DIR or FLAIR (p = 0.802). The statistical comparisons between the different groups are shown in Table 3.

There was a significant correlation between the number of periventricular white matter lesions in the T2-weighted images and the EDSS scores (r = 0.463, p = 0.006). In addition, there was a significant correlation between the number of lesions detected with DIR in the juxtacortical and periventricular white mat-
Table 2: Lesions distributions in seven anatomical regions and mean lesion numbers obtained by T2-weighted, FLAIR and DRR images of MS patients.

| Z   | T2          | T2          | T2          | T2          | T2          | T2          | T2          | T2          | T2          | T2          | T2          | T2          | T2          | T2          | T2          | T2          | T2          | T2          | T2          | T2          | T2          | T2          | T2          |
|-----|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| C   | JC          | DWM         | DGM         | MWM         | GM          | PVWM        | JWM         | JWM         | JWM         | JWM         | JWM         | JWM         | JWM         | JWM         | JWM         | JWM         | JWM         | JWM         | JWM         | JWM         | JWM         | JWM         | JWM         | JWM         |
| 1   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   |
| 2   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   |
| 3   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   |
| 4   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   |
| 5   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   |
| 6   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   |
| 7   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   | 0.1 ± 0.9   |

Mean ± standard deviation.
Discussion

This study obtained brain imaging sequences of patients with MS using both conventional (T2, FLAIR) and DIR. We investigated the number of lesions with each sequence and the relationship between the number of lesions in each sequence and the EDSS scores.

Interestingly, only a few previous studies have examined this topic and have reported contrasting results. Moraal et al. compared the lesion burden detected with DIR, FLAIR and T2-weighted imaging and found that the highest number of intracortical lesions was de-
ected with DIR. In addition, they suggested that the number of intracortical lesions detected using both DIR and FLAIR techniques was significantly higher, but they did not detect a significant difference between the DIR and FLAIR images. Our study found a higher number of intracortical lesions detected with DIR compared to both FLAIR and T2. In line with our study, Geurts et al.\textsuperscript{18} examined the number of intracortical lesions in MS patients and detected a higher number of lesions with DIR sequences than both FLAIR and T2 sequences, where the gain was 152\% and 538\%, respectively. Moreover, Calabrese et al.\textsuperscript{24} investigated the number of intracortical lesions with DIR in 380 patients, including 163 RRMS, 101 SPMS and 116 clinical isolated syndrome patients. They found intracranial lesions (ICL) in 58\% of these patients. The number of ICLs was higher in patients with SPMS compared to patients with clinical isolated syndrome and patients with RRMS. Patients with ICLs also exhibited higher EDSS scores. There was a significant correlation between the number of ICLs and the EDSS scores. Moreover, there was also a significant association between ICLs and male gender. Our study only found a significant correlation between juxtacortical lesions and the EDSS scores. Calabrese et al.\textsuperscript{24} also indicated that grey matter (i.e., cortical) lesions showed different inflammatory characteristics from white matter lesions and that these lesions resolved faster and displayed active remyelination that stabilized over time. In addition, they indicated that grey matter damage may contribute to the development of disability. It is well-established that ICLs are more easily detected in postmortem tissues by immunohistological examination, although very few of these lesions may be revealed using conventional MRI sequences. The employment of DIR sequences should not be omitted in the detection of intracortical lesions. Although this sequence shows fewer ICLs than immunohistological methods, the sensitivity of DIR may provide additional biological information, which cannot be obtained through ex vivo investigations.

Moraal et al.\textsuperscript{20} also reported the ability to detect the highest number of juxtacortical lesions with T2-weighted images and the detection of the lowest number of lesions with DIR images. However, there were no statistically significant differences between these two groups. Geurts et al.\textsuperscript{18} reported the detection of the highest number of juxtacortical lesions with T2 and the detection of the lowest number of lesions with FLAIR. In our study, we visualized the highest number of juxtacortically located lesions with FLAIR images and the lowest number with T2, but no significant difference between the number of lesions obtained with DIR and FLAIR was observed, although DIR detected significantly more lesions than T2. Moreover, Wattjes et al.\textsuperscript{19} reported that the highest number of juxtacortical lesions was detected with FLAIR and that the lowest number was detected with T2 sequences. There was no statistically significant difference between DIR and FLAIR or T2. Although our results are consistent with the findings of Wattjes et al.\textsuperscript{19}, we also reveal that DIR detected significantly more lesions than T2.

Moraal et al.\textsuperscript{20} reported the detection of the highest number of mixed white matter–grey matter lesions with DIR and no differences between the detection of the mixed white matter–grey matter lesion burden with DIR and FLAIR. However, the number of lesions detected using these two methods was significantly higher than that revealed with T2-weighted images. In a study conducted by Geurts et al.\textsuperscript{18}, the highest number of mixed white matter–grey matter lesions was found with DIR; the lowest, with T2. In line with with this study, we also detected the highest number of mixed white matter–grey matter lesions with DIR sequences; the number of lesions detected was significantly higher with DIR than with T2 or FLAIR. Wattjes et al.\textsuperscript{19} also found that DIR visualized the highest number of mixed white matter–grey matter lesions and that T2 revealed the lowest number, but no statistically significant difference in the number of lesions was detected with either DIR and FLAIR or DIR and T2. We detected 57 lesions with DIR, two lesions with FLAIR and seven lesions with T2. Moraal et al.\textsuperscript{20} also detected the highest number of lesions with DIR, which was significantly higher than that visualized with T2. However, in their study, the number of lesions detected with FLAIR was lower than that detected by T2.

Three-dimensional DIR imaging has a few advantages, including higher sensitivity for intracortical lesions and an enhanced ability to discriminate between mixed white matter–grey matter, juxtacortical and pure intracortical lesions. Although T2-weighted MRI is a sensitive technique, the discrimination between these three lesion types may prove difficult with T2. Our study found a significantly higher number
of both juxtacortical and mixed white matter–grey matter lesions with DIR. Although DIR is superior to T2 within these two regions, 89.1% of the total number of lesions in these three regions were found to be juxtacortical, and 3.3% of the lesions were observed in the mixed white matter-grey matter. In comparison, with DIR, these percentages were 40.2% and 8.4%, respectively. These results suggest that some of the lesions, which were assessed as juxtacortical with T2, may be classified as mixed lesions with DIR. Because the difference in contrast between the white and grey matter is minimal, it is difficult to differentiate mixed white matter–grey matter lesions from purely intracortical or juxtacortical lesions. The contrast obtained with 3D DIR sequences is thought to be sensitive in its ability to identify cortical lesions. Although DIR is sensitive, Calabrese et al. reported that DIR detected a lower number of cortical lesions compared with histopathological methods and may have specifically missed subpial lesions. Furthermore, DIR sequences may be affected by current artifacts, which mask its ability to visualize the lesions.

Moraal et al. also reported that the highest number of lesions was detected with FLAIR images in the periventricular white matter region and that no significant difference was observed between FLAIR and DIR. However, both DIR and FLAIR revealed more lesions than T2-weighted images. In contrast, Geurts et al. and Wattjes et al. reported the ability to visualize the highest number of periventricular lesions with DIR. Our study detected the highest number of periventricular lesions with FLAIR and found that DIR did not detect more lesions than T2.

Moraal et al. found the highest number of lesions and a statistically significant difference in the deep white matter with FLAIR and the lowest number with DIR. However, they did not report a significant difference between T2 and DIR within this region. Geurts et al. reported the highest number of deep white matter lesions with FLAIR and the lowest number with T2. Wattjes et al. also reported visualization of the highest number of deep white matter lesions with FLAIR, equal numbers with DIR and T2, and no statistically significant differences in the number of lesions detected between DIR and FLAIR or between DIR and T2. Similarly, we detected the highest number of lesions with FLAIR and the lowest number with DIR. Furthermore, we also found that the number of lesions detected was significantly higher with FLAIR and T2 than with DIR.

Geurts et al. reported a higher number of deep grey matter lesions detected with DIR compared to those detected with both FLAIR and T2 sequences. Moraal et al. reported no significant differences between the number of deep grey matter lesions visualized with DIR, FLAIR or T2 images. Our study also failed to find a significant difference between these sequences in the detection of deep grey matter lesions.

Moraal et al. found a similar number of lesions in the infratentorial region with DIR, FLAIR and T2 images. Geurts et al. reported the detection of more lesions with DIR in the infratentorial region compared to both T2 and FLAIR. Wattjes et al. detected the highest number of infratentorial lesions with DIR and the lowest with FLAIR and found a statistically significant difference in the number of lesions detected between DIR and FLAIR and between DIR and T2. However, our findings were not similar to any of the above-mentioned studies. Wattjes et al. suggested that the infratentorial lesion burden had an important prognostic value in determining long-term disability. Previous studies have indicated that a short echo duration in DIR sequences may decrease sensitivity in the detection of lesions. In addition, DIR sequences may be affected by current artifacts, which may lead to misclassification of some actual lesions as artifacts. This may be due to differences in the detection of infratentorial lesions with DIR.

Moraal et al. also reported the detection of the highest number of lesions with FLAIR and the lowest number with T2 compared with the total lesion burden determined by DIR, FLAIR and T2-weighted imaging. In addition, no significant differences were found between DIR and FLAIR and between DIR and T2, although significant differences were observed between FLAIR and T2. Furthermore, Geurts et al. found that the total number of lesions detected was higher for DIR than for FLAIR or T2. In addition, Wattjes et al. revealed that the highest number of lesions was detected with DIR and that the lowest was detected with T2, and a statistically significant difference in the number of lesions detected was observed between DIR and FLAIR and between DIR and T2. We detected the highest number of lesions with DIR and FLAIR and the lowest number with T2 sequences. However, we did not find a significant difference in the number of lesions...
detected between DIR and FLAIR and between DIR and T2. These results are consistent with those obtained by Moraal et al. but differ from the results of Wattjes et al. 19.

Neema et al. 25 conducted a study with 97 MS patients and reported a significant association between the hypointensity of deep grey matter and the progression of disability. However, they were unable to find a significant association between the global hyperintense lesion number and clinical progression. This finding suggests that the neurodegenerative and destructive aspects of MS, which include involvement of the deep grey matter, may have a closer association with disability compared with white matter inflammation and demyelination. Furthermore, the T2 hyperintense lesions are insufficient to fully account for the underlying pathology observed in MS and the disclosure of the clinically related but diffuse occult disease.

In a study conducted by Ciccarelli et al. 26, the lesion burden detected with FLAIR was 34% greater than that obtained with T2, which resulted in a mild correlation with the EDSS scores. However, this correlation was not more robust than the mild correlation detected between T2 and the EDSS scores.

Calabrese et al. 27 also reported a positive correlation between the intracortical lesion number and EDSS scores with the DIR technique. They found that the number and volume of cortical lesions were higher in patients who showed clinical deterioration in the follow-up evaluation compared to the patients who did not. In addition, they reported a correlation between cortical lesion volume and both the EDSS scores and change in EDSS scores over time.

Our study examined the relationships between EDSS scores and the lesion numbers detected in seven anatomical regions with DIR, FLAIR and T2 sequences. We found a positive correlation between the number of lesions detected with DIR in the juxtacortical and periventricular white matter regions and the EDSS scores. However, a correlation was only found between the periventricular white matter lesions detected with T2 and the EDSS scores. We were unable to find a correlation between the lesion numbers detected with FLAIR sequences in seven anatomical regions and the EDSS scores. Of the total number of lesions, a significant correlation with the EDSS scores was found only with the number of cerebral T2 lesions. Thus, the absence of a correlation between the total DIR lesion burden and the EDSS scores may have resulted because 51% of all lesions detected with 3D DIR were classified as cortical and the EDSS, which primarily measures ambulatory capacity, was limited in evaluating cortical function.

Histopathological studies have also demonstrated generalized myelin and axonal involvement in MS, in addition to the lesion regions detected with both DIR and non-conventional MRI sequences. From this perspective, studies investigating only the correlation between the lesion burden and disability, such as our study, are a priori insufficient. Thus, the EDSS would be useful in the primary detection of disability, although it has its limitations.

Taken together, we found that the DIR technique is more sensitive in the detection of a higher number of lesions in patients with MS, the enhancement of imaging these lesions, and the determination of their anatomical localizations compared with conventional MRI techniques (T2, FLAIR). Although we disclosed a significant correlation between the lesions in a few anatomical locations and the EDSS scores, we were unable to find a significant correlation between the total lesion burden and the EDSS scores. Therefore, the DIR technique may be used in routine application to visualize lesions in patients with MS in order to develop practical batteries of tests to detect cognitive losses not readily observed in EDSS scores and are thus frequently missed, which may increase patients’ physical disability.

**Conclusion**

DIR brain imaging had the highest sensitivity in the detection of cortical and mixed white matter-grey matter lesions compared with FLAIR and T2 sequences. In addition, the lesions observed with DIR images were more easily visualized.
References


Progressive Multifocal Leukoencephalopathy Presenting as IRIS in an AIDS Patient
A Case Report and Literature Review

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Key words: progressive multifocal leukoencephalopathy, IRIS, magnetic resonance imaging, AIDS, HIV

SUMMARY – Progressive multifocal leukoencephalopathy causes an infection of the central nervous system by JC virus (JCV), a polyomavirus that destroys oligodendrocytes and their myelin processes. Here, we describe a patient with AIDS who developed a progressive multifocal leucoencephalopathy with the clinical and neuroimaging characteristics of the immune inflammatory reconstitution syndrome. Unlike other opportunistic infections, this disease can present when CD4 T cell counts are higher than those associated with AIDS and also when patients are receiving combined antiretroviral therapy. Clinical suspicion of this form of the disease is based on clinical examination that shows focal neurological deficits associated with magnetic resonance imaging findings. The histopathological examination of brain biopsy smears and the identification of JCV in cerebrospinal fluid or brain tissue are definitive for the diagnosis.

Introduction

Progressive multifocal leukoencephalopathy (PML) is an opportunistic subacute demyelinating infection of the central nervous system (CNS) first described by Aström et al. in 1958.¹ The etiological agent is a DNA polyomavirus, called JC virus (JCV) with tropism for oligodendrocytes and myelin protein. Before the pandemic of AIDS, PML was a rare disease, but it now occurs in up to 7% of these patients without combined antiretroviral therapy (ART).²

The classic clinical presentation of PML includes subacute to chronic focal neurological deficits depending on the location of the lesions. The typical magnetic resonance imaging (MRI) findings of PML are white matter lesions in different brain areas, predominantly the parieto-occipital lobes. They are usually hyperintense in T2-weighted and FLAIR sequences and hypointense in T1-weighted scans in relation to the white matter involvement, without contrast enhancement and no mass effect.³ However, a small proportion of patients present the inflammatory form of the disease defined radiologically by the presence of contrast enhancement, perilesional edema and mass effect on the middle line structures.⁴

We describe an AIDS patient who developed an unusual form of PML presenting as an immune inflammatory reconstitution syndrome (IRIS) with a brain cerebral mass lesion at MRI.

Case Report

A 29-year-old heterosexual man was referred to the Infectious Diseases Department at F.J. Muñiz Hospital with a three-month history of headache and generalized tonic-clonic seizures. He had a diagnosis of HIV infection when he developed Pneumocystis Jirovecii pneumonia and disseminated cryptococcosis. He completed therapy with cotrimoxazol and amphotericin B and was started on AZT/3TC/atazanavir/ritonavir and secondary prophylaxis with cotrimoxazol three times weekly and fluconazol 200 mg/daily.
Progressive Multifocal Leukoencephalopathy Presenting as IRIS in an AIDS Patient

M. Corti

Figure 1. Brain MRI revealed a single right, large cortico-subcortical temporo-parieto-occipital area of demyelination, hypointense in T1 with perilesional edema and mass effect (arrow).

Figure 2. Axial MRI brain scan shows the lesion hyperintense in FLAIR, with mass effect on the middle line structures and collapse of the occipital ipsilateral ventricular prolongation (arrow).

Figure 3. Histopathological examination of stereotactic brain biopsy revealed oligodendrocytes with large intranuclear inclusions and large, “bizarre” astrocytes with hyperchromatic nuclei, named reactive astrocytes. These findings were consistent with a diagnosis of progressive multifocal leukoencephalopathy.

Figure 4. Axial MRI brain scan post-treatment showing a right sequelar cortico-subcortical parieto-occipital image, hypointense in T1 compatible with a minimal sequelar gliosis (arrow).

Figure 5. MRI brain scan after treatment shows a resolution of the described lesion.
On physical examination he was afebrile, fully conscious and oriented with left hemiparesis and headache and signs of intracranial hypertension. The remaining physical examination was normal. A CD4 T cell count was 126 cell/µL. Brain MRI revealed a single right, large cortico-subcortical temporo-parieto-occipital area of demyelination, hypointense in T1 and hyperintense in T2-weighted and FLAIR, with perilesional edema and mass effect on the middle line structures and contrast enhancement (Figures 1 and 2). Antitoxoplasma gondii therapy was started without clinical response after two weeks. At this time, a stereotactic brain biopsy was performed; histopathological examination revealed multifocal and microscopic foci of demyelination, hyperenlarged oligodendroglial nuclei containing abnormal inclusions and enlarged bizarre astrocytes with lobulated and hyperchromatic nuclei (Figure 3). These findings were consistent with a diagnosis of PML. Detection of JCV in biopsy smears was negative by polymerase chain reaction (PCR). The patient was started on the same scheme of ART plus corticosteroids, prednisone 60 mg in two divided doses per day with a rapid improvement. After two years of follow-up, the patient is still in a good clinical condition. His last CD4 T cell count was 352 cell/µL and the plasma viral load was undetectable. The last MRI scan of the brain showed a right sequela cortico-subcortical parieto-occipital image, hypointense in T1, hyperintense in T2 and hypointense in FLAIR, consistent with gliosis. This lesion is associated with a mild to moderate retraction of the brain ventricular system (Figures 4 and 5).

Discussion

Progressive multifocal leukoencephalopathy (PML) is a CNS infection caused by the polyomavirus JCV that compromises the oligodendrocytes and the myelin protein. Generally, this condition is strongly associated with HIV-1 infection and in rare cases with other conditions characterized by a compromised immune response. Most recently, PML has been described in association with the use of humanized monoclonal antibodies. PCR studies demonstrate JCV-DNA in the brains of patients without PML, especially in oligodendrocytes and astrocytes. The frequency of PML in HIV-1 infected patients varies from 0.7% to 9.8%, but a neuropathological autopsy series of Thurhner et al. reported the highest prevalence highest (11%).

The most common clinical manifestations of PML include weakness (80%), neuro-ophthalmological alterations such as disturbances of visual field (50%) and cognitive deterioration.

Neuropathology examination reveals multiple areas of demyelization varying in size and grade. All CNS regions can be involved, but the lesions are predominant in the parieto-occipital lobes. Cerebellar, brainstem and spinal cord involvement is less frequent. In the classic form of the disease, PML might develop in HIV+ patients shortly after the initiation of ART as a form of IRIS. In a retrospective analysis of 39 patients with PML, five (13%) presented an inflammatory form of the disease. Specific cytotoxic T lymphocytes for JCV were detectable in four patients and the outcome was favorable in three of them.

PML might develop in HIV+ patients shortly after the initiation of ART as a form of IRIS. In HIV-1 infected patients without ART, the sensitivity ranged from 72% to 92% and the specificity from 92% to 100%. In the appropriate clinical context a positive result confirms the diagnosis. When the detection of JCV-DNA in CSF is negative or when the neuroimaging findings contraindicate lumbar puncture as in our patient, stereotactic brain biopsy is needed to establish the diagnosis.

Relevant histopathological findings include the presence of large oligodendrocytes with typical virus-bearing nuclear inclusions and atypical giant astrocytes. Necrotic areas can also be found in the central foci.

The definitive diagnosis of PML includes clinical and MRI findings and the study of CSF with evidence of JCV DNA. In atypical cases, the definitive diagnosis should be confirmed only by the biopsy smears, as in our patient.
Cinque et al. proposed a classification for HIV-1-associated PML based on the presence of inflammatory features. As a result, patients can be classified in the classic or non-inflammatory form of the disease and inflammatory PML. In the classic form there is no indication for corticosteroids, whereas in the inflammatory group, the initiation of corticosteroids should be considered with ART. We think that our patient should be included in the second form or inflammatory PML.

In a recent review of 12 patients treated with steroids, early and prolonged treatment was associated with a better outcome. Published data indicate that inflammatory responses in PML are not infrequent and they are generally associated with a favorable prognosis, as in our patient.

In conclusion, the knowledge of typical and atypical images of PML is important to differentiate this entity from other opportunistic infections and tumors that can involve the brain of HIV seropositive patients. Hence, infectologists, neurologists, radiologists and clinicians should not rule out the diagnosis of PML in the presence of atypical neuroradiological findings.

References


Brain Microbleeds: Distribution and Influence on Hematoma and Perihematomal Edema in Patients with Primary Intracerebral Hemorrhage

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Key words: intracerebral hemorrhage, brain microbleeds, perihematomal edema, stroke

SUMMARY – Brain microbleed is a marker of small vessel microhemorrhagic or microaneurysmal lesions, which may induce intracerebral hemorrhage (ICH). This study to prospectively evaluated the association between microbleeds, hematoma and perihematomal edema volume, and various clinical data, as well as patient outcome. Thirty-one patients with ICH and 31 healthy age-matched subjects were enrolled in our study. They were divided into two groups according to the presence or absence of microbleeds detected by MRI. Serial clinical and laboratory data were recorded. Modified Rankin Scale and Barthel Index were estimated three months after hemorrhage. The major location of microbleeds among patients with ICH was the basal ganglia. The volume of perihematomal edema was correlated with the initial hematoma volume on the first, fifth and seventh days after hemorrhage in patients with microbleeds. For patients without microbleeds, this correlation was also significant on the seventh day. Cerebral microbleeds in patients with ICH, especially in the basal ganglia region, represent micro-angiopathy, and are associated with leakage of blood and formation of perihemorrhage edema. Brain microbleeds found in patients with ICH warrant further investigation for evaluation of stroke risk.

Introduction

Primary intracerebral hemorrhage (ICH) is estimated to affect more than one million people worldwide each year, most of whom either die or are left seriously disabled. One of the reasons for the relatively poor outcomes for ICH is the elevation of intracranial pressure due to the mass effect from the hematoma and perihematomal edema. The elevated intracranial pressure may eventually result in decreased cerebral perfusion or tissue shifts and herniation syndromes. Moreover, the coagulation cascade is activated after ICH, and atypical neurotoxins from breakdown of hemoglobin and the inflammatory process are also responsible for neurological deterioration when the patient has suffered an ICH. However, the clinical diagnosis of ICH does not always accurately reflect the underlying etiology which may include cerebral amyloid angiopathy or hypertensive vasculopathy, which may have begun several years before the acute ICH.

Brain microbleeds (BMBs) were first described in the mid-1990s. A microbleed is defined as a rounded focus <5 mm in diameter that is hypointense on T2*-weighted, gradient-echo sequences or DWI, which are highly
sensitive to paramagnetic substances such as deoxyhemoglobin, a product of blood degradation, or ferritin, a non-heme iron. A microbleed is distinguishable from other intracerebral hematomas, but is indistinct from flow voids, leptomeningeal hemosiderosis, and non-hemorrhagic subcortical mineralization. In such cases, reduction in the MRI signal is usually caused by hemosiderin deposits. Although BMBs are generally considered clinically silent, growing literature evidence supports the idea that BMBs are a marker of small vessel microhemorrhagic or microaneurysmal lesions, which may be of particular interest in elucidating the causes of macroscopic ICH. However, few studies have investigated the prevalence and spatial distribution of BMBs in relation to the factors associated with outcome after ICH.

This study undertook a prospective MRI evaluation of BMB prevalence in ICH patients to elucidate the associations between BMBs, various clinical data, imaging findings, and patient outcome.

Material and Methods

Patients

Thirty-one patients admitted to our institution within 24 hours after onset of symptoms due to acute ICH were enrolled in this study. Patients were enrolled after ICH was confirmed by initial CT scan. Exclusion criteria were: large hematomas requiring emergency surgery, history or CT findings of old ICH, or other neurological insult, and evidence of intraventricular hemorrhage on initial CT scan. Thirty-one healthy age- and gender-matched subjects were also enrolled. Patients were divided into two groups according to whether they had BMBs detected by MRI. All subjects or their family informants were prospectively interviewed for clinical data including history of diabetes mellitus (DM), coronary artery disease (CAD), hypertension (HTN), or any other neurological deficits.

Laboratory studies including serum glucose, alanine transaminase (ALT), blood urea nitrogen (BUN), creatinine (Cr), triglycerides (TG), cholesterol (Chol), white blood cell count (WBC), hemoglobin (Hgb), platelet count (PLT), low density lipoprotein (LDL), glycated hemoglobin (HbA1c) were recorded as the first levels drawn. Time of symptom onset was defined as the last time the patient was known to be symptom-free. NIHSS and Glasgow Coma Scale (GCS) were estimated by two experienced neurosurgeons (T-Y.Y and M-H.L) within 24 hours after ICH. Modified Ranking Scale (mRS) and Barthel Index (BI) were estimated by the same neurosurgeons at three months after ICH. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, and all patients gave written informed consent.

MRI

Magnetic resonance imaging scans were obtained with a 1.5T human MRI scanner (Gyroscan Intera; Philips Medical Systems. Best, The Netherlands) at baseline (within 24 hours) and at five and seven days after onset of symptoms. Standard sequences for depiction of anatomy, hematoma, and extent of edema as well as microbleeders included axial T2*-weighted gradient echo images for location and volume of the hematoma as well as presentation of BMBs (repetition time [TR]/echo time [TE] = 355/13. 81 ms, excitations = 1, flip angle = 18º, section thickness = 6. 5 mm with a gap = 1. 5 mm and matrix = 512 x 256) and axial fluid-attenuated inversion recovery (FLAIR) images for extension of perihematomal edema ([TR]/[TE] = 6000/120 ms, excitations = 2, flip angle = 90º, same section thickness and matrix).

Statistical Analysis

To validate the reliability of T2*-weighted gradient echo images for detection of BMBs number and location, and to learn which can give the same result on different occasions (intra-observer reliability) or between different neuroradiologists (inter-observer reliability), the contribution of estimated number and locations of BMBs were estimated by one radiologist (W-M.L) on different occasions and by two radiologists (W-M.L and Y-H.T) with intra-class correlation coefficients (ICC). A one-way ICC with absolute agreement was used to assess intra-observer reliability, and a two-way ICC with absolute agreement was used to examine inter-observer reliability. The numeric variables are presented as means with standard deviation or corresponding 95% CIs, and were compared by performing the unpaired t test. Categorical or ordinal variables were compared by means of the Fisher’s exact test as appropriate. Performance characteristics of each variable, including sensitivity and specificity,
The most prevalent location of BMBs among ICH patients was the basal ganglia, whether assessed on the first, fifth or seventh day \( (P = 0.0151, 0.0026, \text{and } 0.0054 \text{ on the first, fifth and seventh days, respectively}; \text{Table } 2) \). Table 3 shows the correlation between the total volume of the lesion, including edema and hematoma (V), the volume of hematoma (H), and the volume of perihematomal edema (PE). The total volume of lesion and the volume of hematoma on day 1 are related to volumes of perihematomal edema in patients with BMBs on the first, fifth and seventh days after ICH. In patients without BMBs, the volume of perihematomal edema was associated only with the total lesion volume on the seventh day.

### Discussion

Brain microbleeds have been increasingly recognized since the advent of modern MRI imaging techniques. However, in clinical prac-
or T2*-weighted MRI sequences. Silent BMBs occur in 3%-6% of otherwise healthy elderly subjects, and the prevalence gradually increases with age from 6.5% in the age category 45 to 50 years old to 35.7% among subjects.

Figure 1 Illustrative fluid-attenuated inversion recovery (FLAIR) and axial T2*-weighted gradient echo (GRE) images in two cases. A,B) An 80-year-old man with weakness of the left limbs. FLAIR (A) showed right parietal hematoma (arrow) with perihematomal edema (arrowhead). GRE (B) showed numerous lobar microbleeds (arrows). C,D) A 77-year-old woman with weakness of the left limbs. FLAIR (C) showed right thalamic hematoma (arrow) with perihematomal edema (arrowhead). GRE (D) showed a single microbleed in the pons (arrow).
80 years of age. In the United States, BMBs were found in 20% of patients with ischemic stroke, and in 54%-71% of patients with acute spontaneous ICH. The clinical history of male gender, cigarette smoking, and white matter disease are also recognized as factors associated with BMBs. In addition, BMBs are found in a greater overall proportion of Asian stroke patients, as described by Jeerakathil et al.\(^7\). In this study, the incidence of BMBs in ICH patient was 71%, which is higher than noted in previous publications. This is probably due to the older age of our patients (mean: 67.6 years of age). There was no significant association between BMBs and age, gender, hypertension, or diabetes mellitus. This observation is in accord with that of a previous report\(^8\). The results of laboratory studies, including factors associated with coagulopathy such as BUN, Cr, ALT, and platelet count; those associated with risk of CAD such as TG, cholesterol, and LDL; studies associated with inflammation and edema such as WBC; and clinical assessments such as GCS, NIHSS on day 1 and after three months, MRS, and BI, all lacked a significant association with BMBs.

The location of BMBs is believed to be associated with underlying vascular pathology. BMBs found in deep or infratentorial regions are associated with known risk factors for hypertensive vasculopathy whereas cortical-subcortical BMBs represent underlying cerebral amyloid angiopathy\(^9\). For ICH patients, 39% of BMBs were found to be in cortical-subcortical regions, and 38% in the basal ganglia or thalamus\(^6\). Deep and subcortical BMBs are found to be a risk factor for the development of non-hypertensive deep ICH\(^9\), and posterior fossa hemorrhage is a predictor of poor outcome in adult patients\(^10\). In this study, BMBs were preferentially seen in the basal ganglion area (\(P\) value<0.001) compared with lobar hemi-

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### Table 2 Locations of BMBs in ICH patients.

<table>
<thead>
<tr>
<th>Locations of BMBs</th>
<th>Day 1</th>
<th>Day 5</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>chi-square</td>
<td>P value</td>
<td>chi-square</td>
</tr>
<tr>
<td>Frontal</td>
<td>3.044</td>
<td>0.2183</td>
<td>1.879</td>
</tr>
<tr>
<td>Parietal</td>
<td>2.439</td>
<td>0.2954</td>
<td>3.699</td>
</tr>
<tr>
<td>Temporal</td>
<td>4.411</td>
<td>0.1102</td>
<td>3.699</td>
</tr>
<tr>
<td>Occipital</td>
<td>3.044</td>
<td>0.2183</td>
<td>3.699</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>10.444*</td>
<td>0.0151*</td>
<td>11.889*</td>
</tr>
<tr>
<td>Thalamus</td>
<td>2.439</td>
<td>0.2954</td>
<td>2.439</td>
</tr>
<tr>
<td>Infra-tentorial</td>
<td>0.423</td>
<td>0.5156</td>
<td>0.875</td>
</tr>
<tr>
<td>Brainstem</td>
<td>1.879</td>
<td>0.1705</td>
<td>2.439</td>
</tr>
</tbody>
</table>

\*\(P\) value<0.05.

### Table 3 Correlation of BMBs-associated parameters in ICH patients.

<table>
<thead>
<tr>
<th>Parameters 1</th>
<th>Parameters 2</th>
<th>with BMBs (n=22)</th>
<th>without BMBs (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Spearman’s (\rho)</td>
<td>(P) value</td>
</tr>
<tr>
<td>Day 1 Edema</td>
<td>Day 1 V</td>
<td>0.9447</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Day 1 Edema</td>
<td>Day 1 H</td>
<td>0.8058</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Day 5 Edema</td>
<td>Day 1 V</td>
<td>0.8159</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Day 5 Edema</td>
<td>Day 1 H</td>
<td>0.6364</td>
<td>0.0015*</td>
</tr>
<tr>
<td>Day 7 Edema</td>
<td>Day 1 V</td>
<td>0.8137</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Day 7 Edema</td>
<td>Day 1 H</td>
<td>0.6307</td>
<td>0.0016*</td>
</tr>
</tbody>
</table>

\(V\): total volume of lesion, including hematoma and edema; \(H\): volume of hematoma; \(Edema\): volume of perihematomal edema; \(D1\): first day after ICH

\*\(P\) value<0.05
spheres. This result is similar to that of Lee et al. who claim that brain BMBs are regionally associated with intracerebral hemorrhage 11.

Perihematomal edema plays an important role in secondary brain injury after ICH 12. PE develops within three hours of onset of symptoms in most patients, and reaches its maximum between ten and 20 days after ICH and is directly related to hematoma volume. However, the association between BMBs and PE has not been clearly defined. In our study, the volume of PE on the first, fifth and seventh days was significantly related to the total volume of hematoma and hemorrhage after the onset of ICH in patients with co-existing BMBs ($P<0.05$). In patients without BMBs, edema volume was associated only with the total volume of the lesion on the seventh day. We propose that BMBs might be an important predictor of increase in edema and total lesion volumes at an early stage.

Multiple mechanisms are involved in the development of brain edema after ICH. These include a very early phase (first few hours) involving hydrostatic pressure and clot retraction, a second phase (first two days) involving activation of the coagulation cascade and thrombin production, and a third phase (after three days) involving RBC lysis and hemoglobin-induced neuronal toxicity 1. The products of hemoglobin degradation can release iron, and can contribute to brain edema formation 13. A recent study found a significant positive correlation between serum ferritin and the relative volume of perihematoma edema on days 3 and 4 in patients with spontaneous ICH 14. Another study revealed that deferoxamine, an iron chelator, can reduce hematoma- and hemoglobin-induced edema, suggesting that iron plays an important role in edema formation after ICH 15. Degradation of hemoglobin contained in erythrocytes results in the formation of hemosiderin, which is paramagnetic and is the key compound underlying magnetic susceptibility effects that allow BMBs to be detected by MRI. Based on these reports and our results, we hypothesize that the BMBs are marker of small vessel pathology that can represent a tendency for RBC lysis and hemoglobin leakage following ICH, and thus is associated with lesion extension and with damage caused by PE.

There are several limitations to this study. First, our results were derived from a small sample size, and further group analysis could not be carried out. Second, because PE peaks between ten and 20 days after ICH in humans, an additional MRI scan at this time point may have provided more information.

Conclusion

The role of the BMBs in ICH patients is still under investigation. In the current study, the most common location of BMBs in ICH patients was the basal ganglia. Cerebral microbleeds in patients with intracerebral hemorrhage may represent micro-angiopathy, and are associated with leakage of blood, and the formation of perihemorrhage edema. When MRI reveals BMBs in the evaluation of a patient with ICH, this finding warrants further investigation for evaluation of stroke risk.
References


Vacuum Epidural Cyst with Acute Neurological Presentation
A Case Report

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Key words: degenerative cysts, synovial cysts, vacuum cysts, intraspinal gas

SUMMARY – The widespread use of MRI in the assessment of low back pain has led to increased detection of degenerative cysts of the spine, which was essentially a surgical diagnosis earlier. The awareness of degenerative cysts, the significance of their role in the etiology of radicular and back pain and their effective management is evolving. We describe a case of bilateral, gas-filled lumbar facet synovial/ ganglion cysts causing focal arachnoid inflammation and lateral lumbar canal stenosis.

Introduction
Degenerative cysts of the spine include herniated disc cysts, facet joint cysts, ligamentum flavum cysts and cysts of the posterior longitudinal ligament. Generally, these degenerative cysts are fluid-filled, so it is vital to differentiate them from more ominous conditions like neoplasms and infections. Cysts associated with degenerative facet joints are categorized as either synovial cysts or ganglion cysts. Synovial cysts, as the name indicates, are lined by synovium, whereas ganglion cysts are lined by non-synovial tissue. It is generally not possible to make a distinction between the two by imaging, unless the cyst is far removed from the facet joint, which would then make it more likely to be a ganglion cyst.

Vacuum phenomenon and gas collections are well-documented radiological findings in the spine. They commonly occur in discs, Schmorl’s nodes and facet joints. They are also known to occur in the spinal canal (extra- or intra-dural) and in vertebral bodies (intravertebral cleft phenomenon). Rarely, they can be seen in synovial cysts and ganglion cysts. Fick was the first to describe the vacuum phenomenon in 1910 while he was studying joints under traction. In 1937, Magnusson reported the same phenomenon in intervertebral discs and postulated that the creation of spaces, subsequently filled by gas, required a reduction of barometric pressure within the joint. In 1942, Knuttson correlated vacuum phenomenon with disc degeneration. Ford, in 1977, analysed intradiscal gas which was later confirmed by Yoshida et al. in 1997 to comprise predominantly of nitrogen (90-92%) combined with oxygen, carbon dioxide, and traces of other gases.

Case Report
A 51-year-old woman with increasing low back pain, bilateral radicular pain and neurogenic claudication which had progressively worsened over the previous three months was referred to MRI of the lumbosacral (LS) spine. The patient’s radicular pain extended into the posterior aspect of the thigh and leg, exacerbated by walking and attenuated by lying down. There was also numbness over the dorsum of the feet and big toe. Her clinical history was otherwise unremarkable. Clinical examination revealed limited straight leg raising test on 40°, bilaterally. There was some weakness of feet dorsiflexion and the extensor hallucis longus muscles, with diminished knee reflexes and hypoesthesia was detected over the right L4 and L5 dermatomes.
MRI of the LS spine showed a small, well-defined, oval-shaped T1 and T2 signal void lesion in the right lateral epidural space at L4/5 level (Figure 1A) in close association with the adjacent facet joint and ligamentum flavum, it was compressing and displacing the thecal sac and causing clumping of the cauda equina (Figure 1B). There was marginal enhancement of the cyst wall and adjacent thecal sac (Figure 1C). Additionally, bilateral facet joint arthropathy at the same level with no significant disc bulge was also noted. To further characterize the intraspinal signal void, limited CT scan of the lumbar spine at L4-L5 level (Figures 2A,B) was done immediately after completing the MRI scan. It showed bilateral epidural gas-filled cysts. The larger one was in the right lateral space corresponding to the signal void noted in the MRI images. The other lesion in the left lateral epidural space was retrospectively located in the MRI scan (Figure 2A). Adjacent bilateral L4-L5 facet joints showed degenerative changes including intra-articular gas (vacuum) (Figure 2A).
Vacuum Epidural Cyst with Acute Neurological Presentation

A.H. El Beltagi

Synovial cysts from adjacent apophyseal joints into the epidural space or neural foramen. Ganglion cysts develop in situ secondary to mucoid degeneration of the mesenchymal connective tissue or haemorrhage in the posterior longitudinal ligament or ligamentum flava. Disc cysts are often located in the ventrolateral space, and are believed to arise secondary to fluid production within a softened degenerated disc which leaks out and in time develops a pseudomembrane. Alternatively, the herniated disc can irritate the adjacent internal epidural venous plexus, causing it to rupture; the resulting haematoma evolves into a cyst. Posterior longitudinal ligament ganglion cyst, which is more common in young men, is also located in the ventrolateral space.

Facet joint synovial cysts are by far the commonest degenerative cysts of the spine. Most of these are located in the lumbar spine at L4-L5 and L5-S1 levels adjacent to and communicating with the apophyseal joints. There is a definite predilection for females over the age of 50 years. They are believed to arise secondary to trauma or osteoarthritis of the facet joints, more commonly in patients with hypermobile

Discussion

Degenerative cysts of the spine can be incidental or symptomatic, mimicking herniated discs or canal stenosis. These cystic lesions are being encountered more frequently as MRI has become the imaging modality of choice in evaluating low back pain. A vast majority of these lesions are epidural, but they can also be intradural, present within the neural foramen or located peri-spinally. These cysts contain serous or protein-rich fluid and are sometimes complicated by intracystic haemorrhage.

The nomenclature of these cysts is variable and has not yet been standardized. The two commonly used systems to classify degenerative cysts are based on their pathology or the structures from which they originate. Based on the structure of origin, they are named disc herniation cysts, facet joint cysts, ligamentum flavum cysts and posterior longitudinal ligament cysts. Pathologically, these cysts are either synovial cysts or ganglion cysts. Alternatively, they can also be classified based on their location within the spinal canal as ventrolateral, lateral and posteromedian.

Synovial cysts extend from adjacent apophyseal joints into the epidural space or neural foramen. Ganglion cysts develop in situ secondary to mucoid degeneration of the mesenchymal connective tissue or haemorrhage in the posterior longitudinal ligament or ligamentum flava. Disc cysts are often located in the ventrolateral space, and are believed to arise secondary to fluid production within a softened degenerated disc which leaks out and in time develops a pseudomembrane. Alternatively, the herniated disc can irritate the adjacent internal epidural venous plexus, causing it to rupture; the resulting haematoma evolves into a cyst. Posterior longitudinal ligament ganglion cyst, which is more common in young men, is also located in the ventrolateral space.

Facet joint synovial cysts are by far the commonest degenerative cysts of the spine. Most of these are located in the lumbar spine at L4-L5 and L5-S1 levels adjacent to and communicating with the apophyseal joints. There is a definite predilection for females over the age of 50 years. They are believed to arise secondary to trauma or osteoarthritis of the facet joints, more commonly in patients with hypermobile
facet joints. Generally, cyst contents follow the signal intensity of CSF, but may contain protein-rich contents or haemorrhage. The cyst sac may have a hypointense rim due to calcification, fibrosis or haemosiderin deposition. Because these cysts communicate with the facet joints, the facet joint gas secondary to the vacuum phenomenon can potentially extend into these cysts, detected as signal void on all sequences as demonstrated in our case.1,6

It may not always be possible to differentiate a ganglion cyst from a synovial cyst by MRI. If communication with a facet joint is established, synovial facet joint cyst can be diagnosed. Cysts distant from the joints are more likely to be ganglion cysts. Cysts in the ventrolateral epidural space can be either a herniated disc cyst or posterior longitudinal ligament cyst. The lateral cysts can be synovial facet joint cysts or ligamentum flavum cysts. Cysts in the posterior median epidural space can arise secondary to intraspinal extension of interspinous bursae which occurs in Bastrup’s disease.8,9

The term vacuum phenomenon used in radiological reporting describes any gas-like density in joints and spine. A real vacuum phenomenon is a dynamic process created by rapid expansion of a joint space resulting in negative pressure, whereas true gas collection occurs in degenerating discs and joints following sustained vacuum phenomenon. It has been hypothesized that the transition from true vacuum to gas and/or fluid and back to vacuum in joints and discs is a complex cyclical dynamic process, although experimental evidence is lacking. The vacuum phenomenon is triggered by distraction of the joint which occurs in the spine during extension and in the supine position. The gas is from dissolved nitrogen in tissues which escapes in a gaseous state when sufficient negative pressure is generated.2,4

Gas collection depends on the permeability of surrounding tissues, vascularity, mobility and the attitude of the joints involved.4,5

Intraspinal gas collections are rare. In our patient, the facet joint synovial cysts were in a state of either being entirely gas-filled or collapsed with no fluid or gas content. The cyst in the right lateral epidural space showed rim and adjacent thecal sac enhancement, with aggregated nerve roots in the cauda equina. These findings may denote associated oedema and inflammatory changes with possible adherence of the cyst to the thecal sac, which has likely worsened our patient’s symptoms. Kumar et al. (2) reported a gas and fluid-containing herniated disc, which was found to be adherent to the nerve root and thecal sac intraoperatively. Demonstration of gas by CT was helpful in confirming the cause of the intraspinal epidural low signal on MRI as well as excluding calcified pseudoneoplasm of the neural axis (CAPNON).10

Management of intraspinal epidural gas cyst ranges from conservative to minimally invasive to surgical resection. Different authors have published cases where surgical needle puncture of intraspinal lumbar cysts relieved radicular symptoms.11 This highlights the importance of surgical management in symptomatic cysts. However, it has also been suggested they can spontaneously regress.1,4 Our patient was reluctant to opt for the surgical management, she had temporary symptomatic relief by medical treatment and her subsequent course is unknown at present. It would have been ideal to reimage the patient after her symptoms subsided to further assess the dynamics of gas translocation (within the facet joints and adjacent synovial cysts), as well as the possible regression of adjacent dural enhancement. However, the patient was lost to follow-up.

In conclusion, the presence of intraspinal, extradural signal void associated with an adjacent degenerative facet joint in MRI suggests a vacuum synovial or ganglion cyst. CT imaging is recommended to differentiate calcification from air. The dynamic nature of these vacuum cysts, reflected by their change in size (as demonstrated in our patient in her CT images acquired immediately after MRI) can explain the intermittent exacerbation and relief of radicular symptoms related to posture. We suggest adjacent nerve root crowding and dural enhancement are indicators of associated oedema or acute inflammation which may indicate aspiration or surgical intervention for symptomatic relief rather than conservative management.
References


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