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Cerebral lesions of multiple sclerosis: is gadolinium always irreplaceable in assessing lesion activity?

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PURPOSE
We aimed to identify imaging characteristics on conventional magnetic resonance imaging that could predict multiple sclerosis (MS) brain lesion activity without contrast media administration.

MATERIALS AND METHODS
Magnetic resonance data sets of forty-two patients with relapsing-remitting MS who presented symptoms or signs suggestive of new disease activity were retrospectively reviewed. We classified the MS lesions into three types according to different patterns present on T2-weighted images and evaluated their relationship with the contrast uptake. Evolving aspects of each type of lesion were observed in 18 patients during a follow-up period ranging from nine to 36 months.

RESULTS
On T2-weighted images, only the pattern consisting of a thin border of decreased intensity compared with the lesion's center and perifocal edema (Type II) reached diagnostic accuracy in terms of its relationship with gadolinium enhancement ($P = 0.006$). The sensitivity was 0.461, and the specificity was 0.698. In contrast, enhancement was not significantly related to the pattern consisting of a lesion center that was homogeneously brighter than its periphery (Type I) or less-hyperintense T2 focal lesions with either homogeneous or inhomogeneous center (Type III) ($P > 0.05$ for both).

CONCLUSION
The assessment of MS lesion activity should include a careful evaluation of T2-weighted images in addition to contrast enhancement assessment. The presence of an accompanying peripheral thin rim of hypointensity on T2-weighted images related best with contrast enhancement and subsequent lesion activity and may represent an additional pattern for disease activity assessment when gadolinium examination is contraindicated or influenced by prior therapy.

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Multiple sclerosis (MS) is a chronic inflammatory disease characterized by demyelination and widespread tissue damage in the white and grey matter in the central nervous system (CNS) and spinal cord (1). MS has a very heterogeneous neurological presentation. In diagnosing MS, magnetic resonance imaging (MRI) studies with and without gadolinium contrast are required, according to McDonald 2005 (2) and the modified McDonald criteria 2010 (3), to provide information about the CNS involvement of demyelinating lesions. A decreased incidence of clinical relapse in MS is commonly used as a measure of therapeutic intervention efficacy. Despite their generalized use in clinical trials of relapsing-remitting and progressive multiple sclerosis, the current MRI measures add little if anything to the clinically relevant relapse and disability outcomes when used independently (4). At the present time, there is limited association between the lesions detected with conventional MRI and clinical status (5), with a low reported sensitivity to diffuse grey-matter and white matter disease (6, 7). Therefore, there is a sustained need for research to find better MRI markers of disease activity.

It is generally believed that because acute MS lesions are associated with a transient breakdown of the blood-brain barrier (BBB), gadolinium contrast agents would produce enhancement of these lesions on T1-weighted images. Beginning with the earliest magnetic resonance studies of MS, it became clear that the correlation between enhanced lesions and clinical disease activity is modest at best (8). Nevertheless, contrast enhancement remains a sensitive method for detecting active MS lesions, with all the implications derived from its presence (from diagnosis to treatment trial monitoring). However, there are conditions under which the administration of gadolinium-based agents is prohibited (9). Additionally, contrast administration cannot help document disease activity following steroid treatment when variable degrees of enhancing lesions suppression occurs (10).

Still, is the information offered by the administration of contrast really irreplaceable? Certainly, a less invasive and more cost-effective method is needed in clinical practice to assess MS lesion activity. Ideally, this assessment method would also work for patients in whom gadolinium agents cannot be used or are influenced by medication. Furthermore, the confidence intervals for correlations between contrast-enhanced lesions and MS relapses exclude the possibility that contrast enhanced lesions can be a good surrogate outcome for the occurrence MS relapses (11). Furthermore, when studies centered their analysis on the morphological characteristics of the conventional MRI lesions of MS (rim lesions and ring enhancement) and the patients' clinical characteristics (12),

only ring-enhancing lesions seemed to be associated with a worse prognosis.

Therefore, the present study aimed to identify imaging characteristics that could predict lesion activity without the administration of contrast media by analyzing the morphology and signal patterns of brain MS lesions on T2-weighted images that are present in all routine MRI protocols for MS surveillance and correlating these results with the findings obtained from contrast-enhanced T1-weighted images.

Materials and methods

This study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki and its later amendments. Our hospital institutional review board approved this study and waived the need for informed consent because of the retrospective nature of the research.

Patients

We reviewed the data sets and MRI evidence of brain MS lesions in 67 patients with relapsing-remitting MS who had symptoms or signs on neurologic examination suggestive of new disease activity. All the patients were diagnosed with relapsing-remitting MS type according to the revised McDonald criteria (2). From this group, we selected only the MR images of patients who had a disease onset of less than 10 years, presented supratentorial focal lesions and did not receive any steroid treatment within 30 days prior to their MRI studies. Forty-two patients (10 males and 32 females) aged 19 to 54 years (mean age, 33 years) fulfilled the study inclusion criteria. The mean disease duration was 3.4 years (range, 1–8 years). Follow-up MR images were also available for 18 patients and were conducted in intervals varying from two weeks to six months. The follow-up period ranged from nine to 36 months.

MRI protocol

The MRI examinations were performed between January 2004 and March 2012 at 1.0 and 1.5 Tesla (T) (General Electric Medical Systems, Milwaukee, Wisconsin, USA). The scanning protocol included axial slices through the brain with a 192×256 or 256×256 pixel matrix and T2-weighted images fast spin-echo (90–120/2500–3500/1 [repetition time/echo time/excitations]) and T1-weighted images spin-echo (10–20/600–650/2) before and after an intravenous injection of 0.1 mmol/kg gadolinium contrast (gadolinium-DTPA, Magnevist, Schering, Berlin, Germany or gadolinium-DTPA, Magnegita, Biokanol Pharma GmbH, Rastatt, Germany). The postinjection delay was at least 5 min as is stated on our routine MRI post-contrast studies. The slice thickness was 3 or 5 mm (1.25 or 1.50 mm gap). All available follow-up examinations (18 patients) were performed on the same MRI unit for each individual patient.

Image evaluation

The four radiologists working on this study were divided into two teams of two radiologists each. To reduce the interobserver variability, the radiologists within each team worked together. Consensus was reached by agreement. From the T2-weighted images, focal supratentorial ovoid lesions were selected for visual assessment by the first team of radiologists (D.M.P., I.P.S.), who were blinded to the study purpose (at the time of selection). A total of 300 lesions were chosen. The other team of radiologists (C.A.T., M.M.B.) evaluated the intensity of the lesions compared with the surrounding normal white matter and with each other, the internal homogeneity of lesions, and the presence or absence of accompanying peripheral rim hypointensity, as defined by previous studies (12, 13). The patterns of lesions on T2-weighted images were then classified into three types according to their morphology and signal intensity. Type I and II lesions were defined as having the highest signal intensity core on T2-weighted images when compared with all other MS lesions. Type II lesions had also a hypointense thin rim (either complete or incomplete) that delineated the core periphery. Both types of lesions are surrounded in most cases by a hyperintense area of edema. Type II lesions overlap with the patterns previously described by Schwartz et al. (13) and Llufriu et al. (12). The Type III pattern exhibits a less hyperintense pattern on T2-weighted images and is well defined and either homogeneous or inhomogeneous (small hypointense ring, arc or dot) in the center. Each lesion was then analyzed on precontrast and postcontrast T1-weighted images to evaluate the presence of contrast uptake and its pattern.

Statistical analysis

Fisher's exact test was used to explore whether the different T2 types of lesions were related to lesion enhancement on T1-weighted images. A P value less than 0.05 was considered statistically significant. The sensitivity and specificity of predicting gadolinium enhancement was also calculated. All statistical tests were performed using GraphPad Prism, Version 6.0. (GraphPad Software Inc, La Jolla, California, USA). Linear unidimensional measurement of the longest diameter of lesions was also performed.

Results

Of the 300 focal MS lesions selected, 154 lesions (51.3%) showed contrast enhancement on postcontrast T1-weighted images. Contrast-enhanced lesions were absent in two patients.

Table 1 describes the number and frequency of lesions belonging to Types I to III upon T2-weighted-image assessment and the number and frequency of contrast-enhanced lesions associated with each type of lesion. Type III lesions coexisted with Type I or II lesions or with both Type I and Type II in all

Table 1. The overall number of lesions and the number of contrast-enhanced lesions by type

Lesion type	Number of lesions	Contrast-enhanced lesions
Type I	54 (18%)	24 (15.6%)
Type II	115 (38%)	71 (46.1%)
Type III	131 (44%)	59 (38.3%)

Table 2. Contingency table to test associations between Type II lesions and contrast enhancement

Type of lesion	Gd+	Gd-
Type II lesion (n)	71	44
All other types of lesions (n)	83	102
Sensitivity (95% CI)	0.461 (0.380–0.543)	
Specificity (95% CI)	0.698 (0.617–0.771)	

CI, confidence interval; Gd+, contrast-enhanced lesions; Gd-, unenhanced lesions.

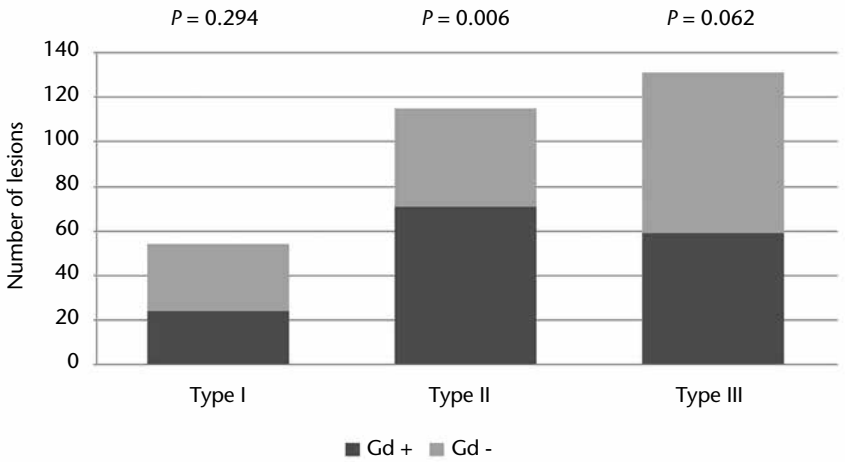

Figure 1. Relationship between lesion type on T2-weighted images and contrast enhancement on T1-weighted images of demyelinating lesions in patients with multiple sclerosis. No statistically significant relationship was observed between Type I or Type III lesions and enhancement. In contrast, Type II lesions were statistically significantly related to contrast enhancement. *P* values, Fisher's exact test; Gd+, contrast enhanced lesions; Gd-, unenhanced lesions.

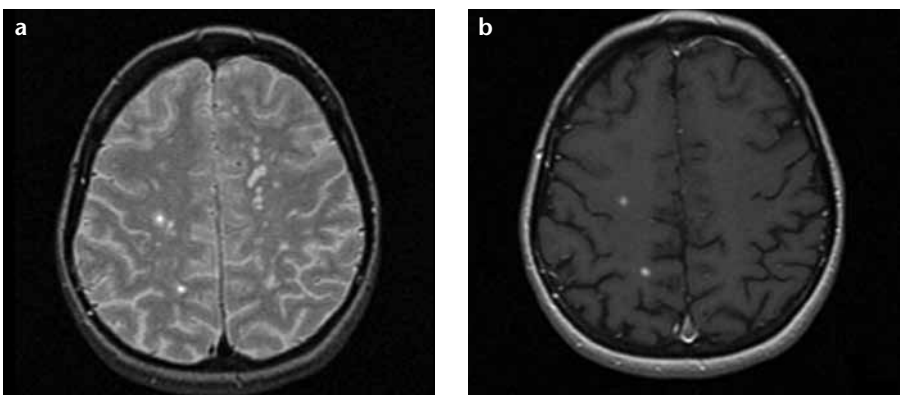

Figure 2. a, b. Two Type I lesions in the right corona radiata with their center homogenously brighter than their periphery on T2-weighted images **(a)**. Less hyperintense Type III white matter lesions are also present bilaterally. The corresponding contrast enhancement was nodular and visible only in Type I lesions **(b)**.

patients. Type I lesions coexisted with Type II lesions in eight patients. Eight patients presented all types of lesions.

There was a statistically significant relationship (P = 0.006) between the Type II lesions on T2-weighted images and the presence of contrast enhancement (Fig. 1). The sensitivity and specificity is shown in Table 2. The coexistence of Type II lesions with and without enhancement was observed in 14 patients. Neither Type I nor Type III lesions was found to be statistically significant related with contrast enhancement (Fig. 1). The P values were 0.294 and 0.062, respectively.

The corresponding contrast enhancement pattern among Type I lesions was predominantly (79%) nodular (Fig. 2) and appeared in small, 4.9±1.5 mm lesions. The ring-like enhancement (21%) in Type I lesions was linked to larger lesions of 8.8±0.5 mm. The enhancement pattern associated with Type II lesions was mostly (87.32%) ring-like and either complete or incomplete (Fig. 3) in lesions measuring 12.2±5.9 mm. The nodular enhancement of Type II lesions appears only in 12.7% of Type II enhanced lesions with dimensions of 7.5±1.4 mm. The enhancement pattern related to Type III lesions was nodular (69%), ring-like (21%) and other (arcs, open-ring or one small point in the center of the ring) in 10% of lesions; the size of the enhanced Type III lesions was 8.2±3.2 mm.

For the five patients with enhanced Type I lesions who had follow-up MRIs within less than a month, we observed three persistent enhancing lesions with conversion from a nodular to ring-like enhancement pattern as the lesion progressively expanded from 5.1±0.8 to 7.0±0.3 mm. Conversion from a ring-like pattern to nodular pattern was not observed. Six ring-like enhanced Type II lesions had a follow-up within one month or less and showed an increase in size from 9.8±2.3 to 13.2±3.5 mm in four lesions, while two lesions remained unchanged. Twenty-two ring-like enhanced Type II lesions demonstrated a reduction in size and intensity associated with a progressive decrease and shift of the T2 hypointense rim toward the lesion's center (Fig. 4) on follow-up scans performed three and nine months later. The dimensional change was from 12.6±5.1 to 5.1±2.4 mm nine months later. The hypointense rim on T2 changed to a central hypointense dot in 12 lesions from the 13 patients with follow-up MRIs (median, 12 months; range, 1–36 months). Fourteen contrast-enhanced Type III lesions also showed a decrease in size from 8.9±2.6 to 4.7±1.3 mm 12 months later.

Discussion

In our retrospective study, we focused on extracting possible predictive MRI features of active MS lesions from the

T2-weighted images and analyzed their sensitivity and specificity when compared with patients' postcontrast images.

To date, previous studies (14–16) modeling the development of MS lesions found a positive relationship between the peak intensity of the lesion center on T-weighted images and contrast enhancement. One important parameter in our classification of the lesions was the signal intensity of the MS lesions on T2-weighted images. On this basis, a subclassification of three distinct MS lesion types (I, II, and III) was made. The lesions classified as belonging to Type I and Type II had a similar high-intensity core, but only Type II lesions were statistically significantly related with the presence of contrast enhancement.

Studies by Tievsky et al. (17) and Llufriu et al. (12) demonstrated in ring-enhancement lesions with colocalized rim hypointensity that there was a relationship between the T2 hyperintensity core and a high apparent diffusion coefficient, with reduced anisotropy compared with the rim, normal-appearing white matter and chronic lesions. Llufriu et al. (12) assumed that this most likely represents the presence of vasogenic edema in the extracellular space superimposed on a decrease in diffusivity caused by cytotoxic edema from massive cell infiltration; alternatively, it may be caused

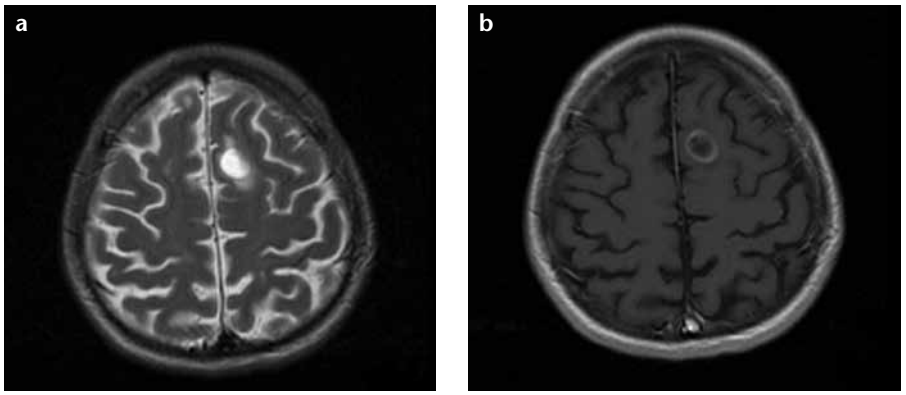

Figure 3. a, b. Frontal left white matter lesion (Type II) with marked hyperintensity centrally, surrounded by a slightly lower signal intensity rim and then by a second zone of somewhat less intense T2 prolongation **(a)**. Ring-like enhancement was associated with this lesion **(b)**.

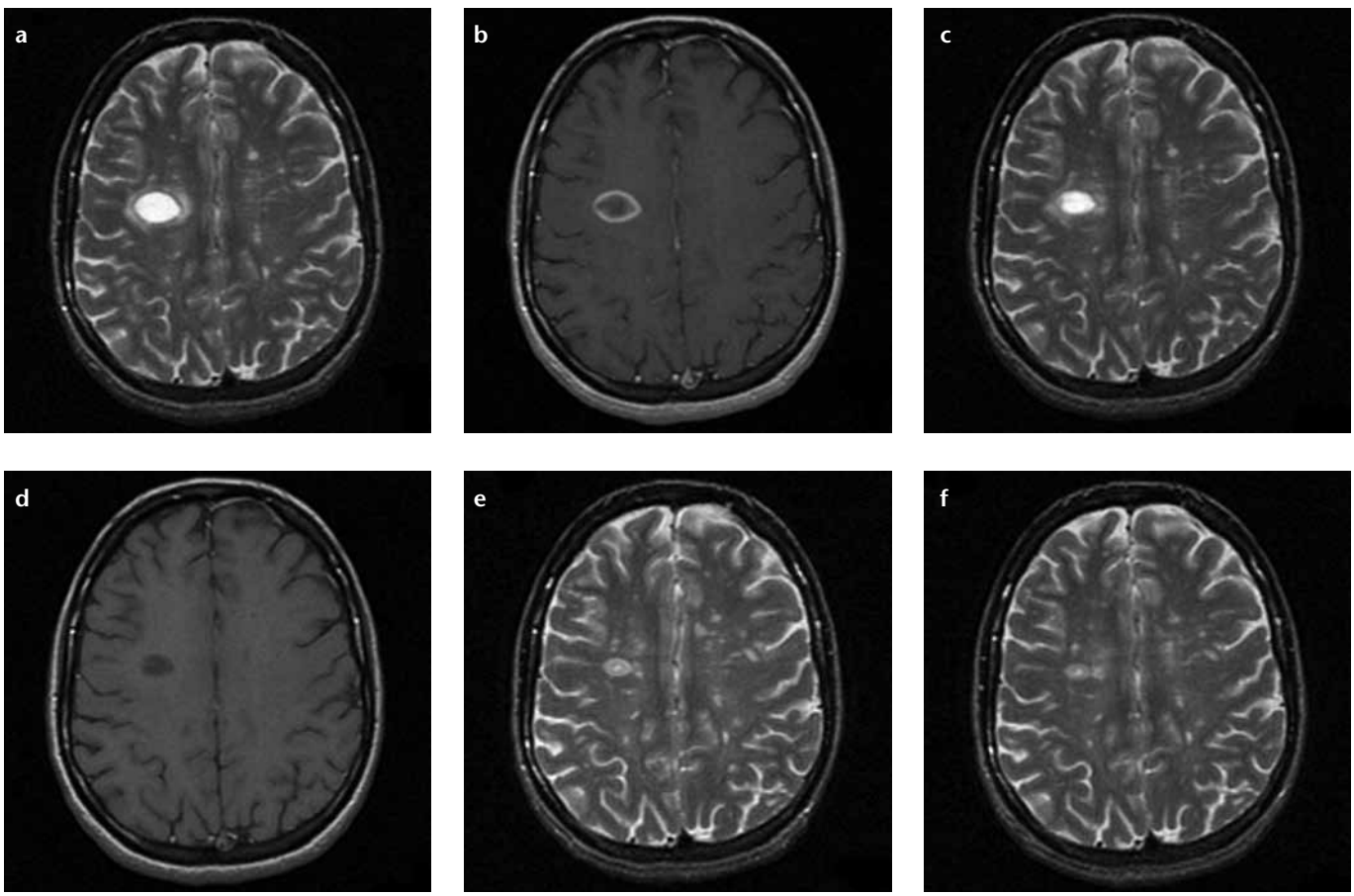

Figure 4. a–f. An axial T2-weighted image **(a)** with an ovoid Type II lesion in the right corona radiata associated with other Type III punctate shows less hyperintense lesions in the white matter. The postgadolinium axial T1-weighted image **(b)** has a fairly regular rim of contrast enhancement around the periphery of the right-sided Type II lesion. After three weeks, the T2 aspect persisted **(c)**, even when the contrast enhancement had disappeared **(d)**. As the lesions decreased in size and core intensity, a progressive decrease and shift of the hypointense rim toward the lesion center was observed three **(e)** and nine **(f)** months later, respectively.

by the cell infiltration by itself. In our study, diffusion-weighted images were not available either because the local routine MRI protocol for MS did not include this acquisition or because the 1T scanner did not include this facility.

It is well known that gadolinium enhancement is a consequence of blood brain barier disruption and leakage, which appear in the acute inflammatory phase of the lesion (18). Although inflammation is considered one of the earliest changes observed in MS lesions, neuropathological and immunocytochemical studies revealed that blood brain barier leakage may be found to variable degrees in every MS lesion (19). Quantitative contrast-enhanced MRI also showed that subtle blood brain barier leakage was a consistent feature in nonenhancing lesions (20). Those observations suggest that enhancement cannot detect all the inflammatory changes, particularly when the level of inflammation is low. He et al. (21) noted that lesion activity should not be equated with enhancement; more activity is taking place that is not necessarily defined by enhancement alone. Another explanation might be linked to the fact that poorly enhanced lesions could have escaped detection, as shown in previous reports using the magnetization transfer and image subtraction techniques (22–24).

When enhanced Type I lesions showed a nodular (predominant) or ring-like pattern, the ring-like pattern was linked to larger lesions. Additionally, in patients with Type I lesions who had follow-up MRIs within less than a month, we observed in the group with persistent enhancing lesions a conversion from a nodular to a ring-like pattern as the lesions expanded progressively, but not from a ring-like to a nodular pattern. This observation seems to support the assumption that the initial enhancing pattern must have been nodular, as previously reported (21). In their 1997 study, Brück et al. (25) found no clear histopathologic differences between ring-like and nodular enhanced lesions. We can also suppose that distinct enhancement patterns may solely be a consequence of the timing of image acquisition after gadolinium administration (26) because of the increased dimensions of the lesions.

Type II lesions differ from Type I by the presence of a low signal rim that delineates the core periphery. Previous pathological studies revealed the morphological correlate of this pattern, which is represented by a rim of activated macrophages in the zone of myelin destruction at the lesion's border (25). The macrophages' ferritin or hemosiderin content could explain the rim of T2 shortening. In our study, such hypointense T2 rims largely corresponded with an area of ring enhancement on T1 postcontrast MR images. The nodular enhancement appeared in few lesions and was linked to a small lesion dimension. Statistically, only this type of lesion was significantly related to enhancement. Nevertheless, the sensitivity and specificity of Type II lesions in predicting lesion activity was rather low. However, as we have already mentioned, we considered gadolinium contrast enhancement the gold standard for evaluating lesion activity, even it might not be sufficiently sensitive for this purpose. Llufriu et al. (12) reported that rim lesions colocalized with ring enhancement in only 40% of lesions, while in our cases, 54% of Type II lesions showed this correspondence. The difference may arise from the fact that we selected only patients with clinical signs of a relapse. In any case, the relationship between the rim lesions and nodular enhancement was fairly close in both studies at 12.5% (12) and 12.7% of lesions, respectively. Another similarity with the Llufriu et al. (12) study was the coexistence of rim lesions with and without enhancement in the same patient (three patients vs. 14 in our study).

In the Type II lesions, we also observed that as the lesions decreased in size and intensity, there was a progressive decrease and shift of the hypointense rim toward the lesion's center. This finding could be superimposed upon the previously demonstrated change in enhancement dynamics in MS lesions from centrifugal to centripetal (27). Only two Type II lesions increased in size on follow-up scans, an aspect possibly related to a shorter interval between examinations (less than a month). However, not all Type II lesions enhanced in our patients, and follow-up scans (when available) did not show a subsequently enhancement of those lesions. This aspect might have been linked to a decrease in the level of inflammation that may have been too low to be revealed by contrast enhancement alone.

The Type III lesions had a less hyperintense signal on T2-weighted images, no peripheral edema and either a homogeneous or an inhomogeneous center. While not significantly related with contrast load, the enhancement of these lesions could embrace almost any pattern described: nodular, ring-like, arcs, open-ring, or one small point in the center of the ring.

Despite the different patterns displayed by MS focal lesions both on T2-weighted images and postcontrast scans, we believe that in fact all of these represent patterns evolving from Type I toward III. The coexistence that was detected between Type III lesions and Type I or II lesions in all cases and between all types of lesions in eight patients might sustain this hypothesis. Additionally, this finding is consistent with the prior observation that the initial heterogeneity (28) of demyelinating lesions in the earliest phase of MS lesion formation may disappear over time as different pathways converge into one general mechanism of demyelination (29).

In follow-up scans, we observed a reduction in the size and intensity of Type II lesions associated with a progressive decrease and shift of the T2 hypointense rim toward the lesion's center. Additionally, when the follow-up period available was more extensive, the hypointense rim on T2 changed to a central hypointense dot in 12 lesions, which at that stage looked similar to the Type III lesions. Llufriu and al. (12) reported a persistence of the hypointense border on T2 in 12% of lesions at 3.5 and 13 months and a change to a homogeneous T2-weighted hyperintensity in 88% lesions. It is possible that the pattern with a central hypointense dot on T2-weighted images evolves towards a homogeneous T2 pattern, and the fact that we did not observe such evolution may have been linked to the different follow-up periods of the studies (median, 12 months; range, 1–52 months in Llufriu et al. [12]; and median, 12 months; range, 1–36 months in ours).

Nevertheless, despite our results, further longitudinal, preferably prospective studies with a larger patient population are needed to improve the accuracy of lesion activity detection. It will be interesting to see whether future long-term studies using a larger sample size can reproduce these data.

This study has some limitations. First, the retrospective design of this study precluded the standardization of techniques and the similarity of the follow-up intervals. In addition, the fact that the examinations were performed on different units (1 and 1.5 T) with different parameters of pulse sequences (even though follow-up examinations for individual patients were performed on the same MRI unit) decreased the uniformity of the study. Second, infratentorial lesions were neither counted nor appreciated in this study. Third, we used contrast enhancement as the standard for determining the active lesions even if the use of this single criterion might have been insufficient for lesion activity detection. Diffusion-weighted images, which might have improved activity detection, were not acquired in our patients. Contrast enhancement also depends on many factors, including both the dose of contrast material and the time from injection to imaging. Late-phase imaging and triple dosing may improve the conspicuity of acute lesions (30). Additionally, we could not appreciate in all cases whether the active lesions were in fact new or older and had been reactivated because the selected MR images were the first images recorded for those patients. Subsequently, we could not formulate any conclusions regarding this aspect. Fourth, we did not perform a quantitative measurement of the region of interest, which is more objective than visual assessment and could improve the accuracy of assessing the patterns of MS lesions. However, in the current daily practice, visual assessment remains a more realistic approach.

In conclusion, we believe that information about the activity of MS brain lesions in patients who had symptoms or signs on neurologic examination that suggested new disease activity, may be extracted from both contrast-enhanced and unenhanced MR images. Our results suggest that evaluation of MS lesion activity should include a careful evaluation of T2-weighted image aspects in addition to contrast-enhancement assessment. The lesion pattern in T2-weighted images consisted of a thin rim of decreased intensity compared with the lesion's center, and the perifocal edema related best with contrast-enhancement and subsequent lesion activity. Perhaps future, larger clinical studies will conclude that MS lesions should be evaluated in terms of patterns on noncontrast imaging, at least in the small subset of MS patients with gadolinium restrictions and steroid treatment, possibly even in other patients with MS in a subset of their examinations.

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Conflict of interest disclosure

The authors declared no conflicts of interest.

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