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ARTICLE

Improving acute demyelinating lesion detection: which T1-weighted magnetic resonance acquisition is more sensitive to gadolinium enhancement?

Aumento da detecção das placas desmielinizantes agudas: qual aquisição de ressonância magnética ponderada em T1 é a mais sensível em demonstrar impregnação pelo gadolínio?

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ABSTRACT

Because of the need for a standardized and accurate method for detecting multiple sclerosis (MS) inflammatory activity, different magnetic resonance (MR) acquisitions should be compared in order to choose the most sensitive sequence for clinical routine. **Objective:** To compare the sensitivity of a T1-weighted image to a single dose of gadolinium (Gd) administration both with and without magnetization transfer to detect contrast enhancement in active demyelinating focal lesions. **Methods:** A sample of relapsing-remitting MS patients were prospectively examined separately by two neuroradiologists using a 1.5 Tesla scanner. The outcome parameters were focused on Gd-enhancement detection attributed to acute demyelination. All MR examinations with at least one Gd-enhancing lesion were considered positive (MR+) and each lesion was analyzed according to its size and contrast ratio. **Results:** Thirty-six MR examinations were analyzed with a high inter-observer agreement for MR+ detection (κ coefficient > 0.8), which was excellent for the number of Gd-enhancing lesions (0.91 T1 spin-echo (SE), 0.88 T1 magnetization transfer contrast (MTC) sequence and 0.99 magnetization-prepared rapid acquisition with gradient-echo (MPRAGE). Significantly more MR+ were reported on the T1 MTC scans, followed by the T1 SE, and MPRAGE scans. Confidently, the T1 MTC sequence demonstrated higher accuracy in the detection of Gd-enhancing lesions, followed by the T1 SE and MPRAGE sequences. Further comparisons showed that there was a statistically significant increase in the contrast ratio and area of Gd-enhancement on the T1 MTC images when compared with both the SE and MPRAGE images. **Conclusion:** Single-dose Gd T1 MTC sequence was confirmed to be the most sensitive acquisition for predicting inflammatory active lesions using a 1.5 T magnet in this sample of MS patients.

Keywords: Multiple sclerosis; gadolinium; magnetic resonance imaging.

RESUMO

No que se refere à necessidade de um método preciso e padronizado para a detecção de atividade inflamatória em esclerose múltipla (EM), diferentes aquisições de RM devem ser comparadas com objetivo de escolher a sequência mais sensível para a rotina clínica. **Objetivo:** Comparar a sensibilidade das sequências ponderadas em T1 após a administração endovenosa de uma única dose de gadolínio, com e sem a adição da transferência de magnetização, para detectar a impregnação das lesões desmielinizantes focais agudas. **Métodos:** Uma amostra de pacientes com EM-RR foi prospectivamente avaliada separadamente por dois neurorradiologistas em um equipamento de RM de 1,5 Tesla. Os parâmetros de desfecho foram direcionados para a avaliação da detecção de impregnação pelo Gd atribuída à desmielinização aguda. Todos os exames de RM que demonstraram ao menos uma lesão com impregnação pelo Gd foram considerados positivos (RM+) e cada lesão foi analisada de acordo com suas dimensões e contraste. **Resultados:** Trinta e seis exames de RM foram analisados. Os avaliadores demonstraram elevada concordância para a detecção de RM+ (coeficiente> 0,8), sendo excelente quanto ao número de lesões com impregnação pelo Gd (0,91 SE, 0,88 T1 MTC e 0,99 MPRAGE). A sequência T1 MTC apresentou número significativamente maior de RM+, seguida pelas sequências T1 SE e MPRAGE. De forma análoga, a sequência T1 MTC demonstrou maior acurácia na detecção de lesões com impregnação pelo Gd, seguida pelas sequências T1 SE e MPRAGE. As demais comparações demonstraram aumento estatisticamente significativo na relação de contraste e na área de impregnação pelo Gd nas imagens T1 MTC quando comparadas às imagens SE e MPRAGE. **Conclusão:** A sequência T1 MTC com uma única dose de Gd confirmou ser a sequência mais sensível em demonstrar lesões inflamatórias agudas em equipamento de 1,5 T nessa coorte de pacientes com EM.

Palavras-chave: Esclerose múltipla; Gadolínio; imagem por ressonância magnética.

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Magnetic resonance imaging (MRI) has been widely used to study multiple sclerosis (MS), and it has become an established tool not only for early diagnosis (first examination) but also for disease monitoring[1]. In 1988, Miller et al.[2] demonstrated that intravenous administration of gadolinium (Gd) was useful in the detection of biologically-active lesions in MS patients. Currently, it is assumed that detecting a single Gd-enhancing lesion after the first clinical event suggestive of either brain or spinal cord demyelination (clinically isolated syndrome) can argue for "dissemination in time", a fundamental imaging requirement to fulfill the current diagnostic criteria of MS[3], which, in turn, could both accelerate early therapy and potentially interfere in the outcome[4]. At later stages, focal Gd-enhancing detection can also provide a strong argument for optimizing therapy by identifying persistent, active inflammation in a probable aggressive course of disease or a suboptimal treatment response at follow-up[5].

Selection of the most appropriate T1-weighted image (T1WI) acquisition after intravenous contrast administration remains a matter of debate. Recent literature has defined some alternatives for increasing the sensitivity of contrast enhancement on MRI acquisitions by either increasing the concentration of Gd in the tissues through increasing the injected dose or by using a delayed T1WI acquisition[6,7,8,9]. However, all these alternatives increase both costs and/or timing, in addition to the risks of using an exogenous substance such as Gd[10].

A promising alternative method for improving the enhancement of lesion conspicuity relies on decreasing the signal of the surrounding brain parenchyma by pre-applying an additional radiofrequency pulse, thus, generating the so-called magnetization transfer (MT) effect[11]. This technique provides additional information as a pathological marker, including tissue composition analysis and remyelination detection, allowing MR to assess the structural changes that occur in normal-appearing white matter, not provided by conventional sequences[12]. A magnetization transfer contrast (MTC) sequence helps to detect the demyelinating substrate on a pre-contrast MR acquisition, distinguishing demyelination from other focal brain lesions.

An MTC is the result of selectively observing the interaction of bulk water protons with the protons contained in various macromolecules, such as cell proteins and cell membranes[13], that has been used in MS patients since 1992[14]. The restricted-motion protons bound within the "macromolecular matrix" have a very broad resonance peak, and there is rapid exchange of energy between the protons in this matrix. When this broad peak of the macromolecular matrix has been saturated, there is an exchange with the protons of the bulk water component, so that there will be some signal loss in the resulting image. The larger the macromolecular matrix, the larger the energy transfer is to the free water protons and the greater the signal loss is on the "saturated" image relative to the "unsaturated image". This is accomplished by combining a saturation transfer technique with standard MRI procedures[15]. The extent of saturation can be quantified using the magnetization transfer ratio (MTR), which has proven to be a sensitive marker of tissue damage not only in the white matter (WM) but also in the gray matter (GM), and both are associated with clinical outcomes, although GM is more strongly associated than normal-appearing WM is[16]. It is worth noting that there are some differences between MTC and MTR acquisitions because while one image with an MT sequence is required to obtain the T1 MTC sequence, on the other hand, to measure MTR, two volumes are needed, one with MT and other without this pulse.

Regarding the need for a standardized and accurate method for detecting MS inflammatory activity, different T1WI acquisitions should be compared in order to choose the most sensitive sequence for institutional routine, considering both the timing and costs of the MR examinations.

METHODS

Standard protocol approvals

The protocol was reviewed and approved by the institutional review board and the local ethics committee and all participants gave written informed consent.

Study design and subjects

A prospective study was conducted from February to December of 2016. To be included in the trial, a patient had to have imaging findings indicative of MS according to the 2016 Magnetic Resonance Imaging in MS consensus guidelines[1] and revisions of the McDonald Criteria, 2017[3]. Studies of patients that did not fulfill the correct imaging protocol, had poor quality images that limited interpretation or a clinical contra-indication that precluded Gd-administration and patients undergoing either corticotherapy or immunosuppression in the month prior were excluded from this study.

Data acquisition

All data were acquired on a 1.5 T system (*Achieva, Philips Medical System*) using a 16-channel SENSE neurovascular coil. In line with the recent guidelines statements[1,3], we acquired a 3D sagittal volumetric fluid-attenuated inversion recovery (FLAIR) and sagittal volumetric T2WI just after intravenous contrast administration in order to postpone the acquisition of T1 sequences. The 3D FLAIR images were acquired for brain lesion detection (slice thickness 0.7 mm; field of view [FOV] 220 x 220 x 180 mm^3; matrix 184 x 184; repetition time/echo time [TR/TE]/inversion time, 7.000/263/2.300 ms; and acquisition time 8.31 min). The 3D T2WI was obtained using the following parameters: slice thickness 0.5 mm; FOV 230 x 230 x 165 mm^3; matrix 208 x 209; TR/TE 1800/231 ms; and acquisition time 4.46 min.

The 2D T1 spin-echo (SE) acquisition was obtained using the following parameters: 25 slices; slice thickness 5 mm; FOV 220 x 189 x 126 mm^3; matrix 244 x 168; TR/TE 614/15 ms; and acquisition time 1.45 minutes. Comparative T1 SE with an additional MTC on-resonance pulse (T1 MTC) (25 slices; slice thickness 5 mm; gap 0.5 mm; FOV 220 x 200 x 137 mm^3; matrix 212 x 134; TR/TE 600/12 ms; and acquisition time 5.26 min), and three-dimension magnetization-prepared rapid gradient-echo (3D-MPRAGE) (140 slices; isotropic resolution 1 x 1 x 1.1 mm^3; TR/TE 7.7/3.8 ms; flip angle 8°; and acquisition time 5.42 min) sequences were also obtained before and after Gd intravenous administration (0.1 mmol/kg Gd – Gadovist [gadobutrol], Schering). The MTC subtracted images were generated through automatic post-processing immediately after MR acquisition with no extra time for processing.

This study was designed in three steps in order to prevent the influence of time on the MR acquisition after intravenous Gd injection. Initially T1 SE, T1 MTC, and 3D-MPRAGE was the sequence order acquired; then T1 MTC, 3D-MPRAGE, and T1 SE sequences were acquired in the second step; and finally, 3D-MPRAGE, T1 MTC, and T1 SE were acquired in the third step.

Imaging analysis

All images were independently assessed by two neuroradiologists (D.C.F and L.L.F.d.A.) with five and 25 years of neuroimaging experience, who were blinded to the patient identity, clinical data, as well as to the order of post-contrast image acquisition to avoid any recall bias, in the MS workup. Strict criteria were applied to the designation of a Gd-enhancing lesion: all 'definite' enhancing lesions were included, whereas areas of bright signal that were indistinguishable from flow artifact or Gd-diethylenetriamine penta-acetic acid contrast within vessels, without comparable high signal on T2/FLAIR, were excluded. All Gd-enhancing lesions observed in the T1 MTC sequence were confirmed by subtraction post-processing to exclude subjective misinterpreted lesions that appeared as a high-signal on the pre-Gd administration sequence (Figure 1).

The readers were asked to separate the MR scans into positive (MR+) when there was any focal Gd-enhancing lesion, and negative (MR-) when no lesion was detected. Each sequence from the same patient was separately analyzed and the observers were not aware of the order of sequence acquisition.

They also counted in consensus the Gd-enhancing lesions in each MR examination to measure their maximal transverse diameter and to compute relative contrast (Figure 2) defined as $(Signal_{lesion} - Signal_{WM}) / (Signal_{lesion} + Signal_{WM})$[17]. The pre-contrast FLAIR sequence was always available during the interpretation to confirm whether a specific enhancing lesion was detectable (Figure 1A).

Statistical analyses

The level of agreement between the two neuroradiologist readers as to the number of Gd-enhancing lesions and active MR examinations was expressed by *Kendall* and κ coefficients.

Discrepancies in the number or size of the Gd-enhancing lesions, as well as the contrast relative ratio, were resolved by consensus. Fisher's exact test was used to compare the number of MR+ scans detected by the neuroradiologists. The Wilcoxon signed rank test was used to compare the number of Gd-enhancing lesions, the contrast relative ratios and the maximal diameter (size) of the greatest contrast

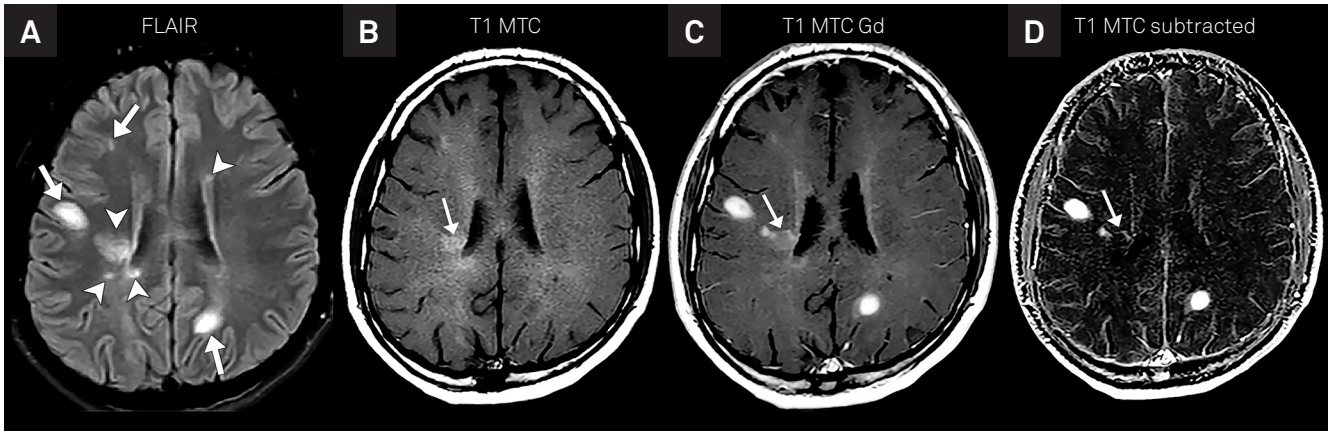

Figure 1. Multiple sclerosis in a 26-year-old female. An axial fluid-attenuated inversion recovery image (A) depicts periventricular white matter (arrowheads) and juxtacortical (arrows) demyelinating lesions at the level of the uppermost aspect of the lateral ventricles. An axial pre-contrast T1 magnetization transfer contrast (MTC) sequence (B) demonstrates spontaneously high signal in normal-appearing white matter and in some demyelinating lesions, making it difficult to determine the presence of inflammatory activity on the T1 MTC post-contrast sequence (C). Thus, it is imperative to obtain the subtracted image (D) to avoid misinterpretation, as the larger lesion in the right periventricular white matter shows a high signal in the pre-contrast and also post-contrast sequences, but the subtracted image demonstrated only faint gadolinium enhancement (*thin arrows*).

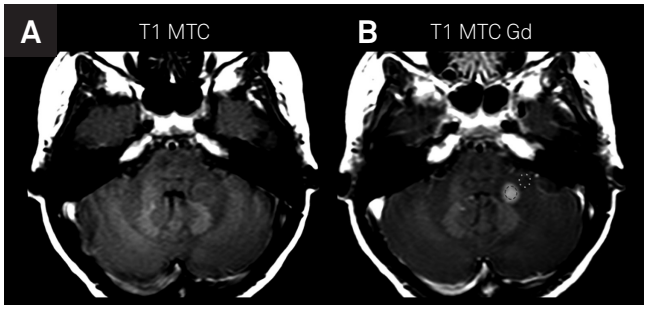

Figure 2. Multiple sclerosis in a nine-year-old female. An axial pre-contrast T1 magnetization transfer contrast (MTC) (A) and T1 MTC post-contrast (B) sequences demonstrate an ovoid acute demyelinating lesion (avid enhancement) in the left middle cerebellar peduncle. Contrast ratio analysis was performed in consensus by positioning the region of interest on the larger lesion with enhancement and another region of interest on the adjacent background (white matter), as shown by red and light blue dashed circles, respectively. Afterwards, contrast ratio was measured according to the equation $(Signal_{lesion} - Signal_{white\ matter}) / (Signal_{lesion} + Signal_{white\ matter})$. The spontaneous selective hyperintensity on the dentate nuclei are attributed to Gd deposition after multiple MR acquisitions.

enhancing lesion between the prescribed post-contrast MR acquisitions. Statistical analyses were performed using the Statistical Package for the Social Sciences, version 21 (SPSS, Chicago, Ill). A corrected p-value of.05 was considered statistically significant.

RESULTS

Five patients were excluded from the sample, three of whom had been misdiagnosed as MS and two additional patients for inadequate protocols. According to the defined criteria, 35 participants with clinically definite MS were enrolled (23 women and 12 men; mean age 36 years; range 9–61 years), and 36 different MR examinations were evaluated during the period of this study.

The number of Gd-enhancing lesions and both active MR examinations (MR+) per reader, and after reaching consensus, are given in Table 1.

Table 1. Active MR examination and number of lesions.

Variable	No. MR+ / No. of lesions		
	SE	MTC	3D-MPRAGE
Neuroradiologist 1	12 /30	12/37	09 /16
Neuroradiologist 2	12 /32	13 / 46	09 /17
Consensus	12 /32	13 / 46	09 /17

MR+: Magnetic resonance scan showing positive lesion; SE: spin-echo; MTC: magnetization transfer contrast; 3-D: three-dimensional; MPRAGE: magnetization-prepared rapid acquisition with gradient-echo. The number of MR+ of both T1 SE and T1 MTC demonstrated statistically significant differences compared with 3D-MPRAGE ($p < 0.05$; Fisher's). Contrary to this, the scores of MR+ between T1 SE and T1 MTC did not reach significance. All comparisons related to the number of lesions demonstrated statistically significance differences, except for the number of lesions between T1 SE and T1 MTC ($p = 0.096$, Wilcoxon).

The inter-observer agreement was excellent (κ coefficient > 0.8), with only a single discordant sequence between the neuroradiologists out of a total of 108 sequences from the 36 examinations analyzed. Kendall's coefficient of concordance for agreement on the number of Gd-enhancing lesions between readers was 0.91 for T1 SE, 0.88 for T1 MTC and 0.99 for T1 3D-MPRAGE (Table 2). The T1 MTC sequence showed the highest MR+ score, as well as the best performance in the detection of more active demyelination (Figure 3). Despite the inter-observer agreement, the T1 MTC sequence showed the greatest discrepancy between the neuroradiologists: 37 (observer 1) *versus* 46 (observer 2) lesions.

The mean diameter and contrast relative ratio of the Gd-enhancing lesions were significantly higher on the T1 MTC than on both the T1 SE ($p = 0.016$ and 0.002, Wilcoxon) and T1 3D-MPRAGE sequences ($p = 0.011$ and 0.008, Wilcoxon). These same parameters were significantly higher on the T1 SE than on the T1 3D-MPRAGE sequence ($p = 0.013$ and 0.008, Wilcoxon) (Table 3; Figure 4).

Table 2. Inter-observer agreement of active MR examinations and number of lesions.

Variable	MR+ / No. Lesions					
	SE		MTC		3D-MPRAGE	
Agreement	1	0.91	0.93	0.88	1	0.99

SE: spin-echo; MTC: magnetization transfer contrast; 3-D: three-dimensional; MPRAGE: magnetization-prepared rapid acquisition with gradient-echo.

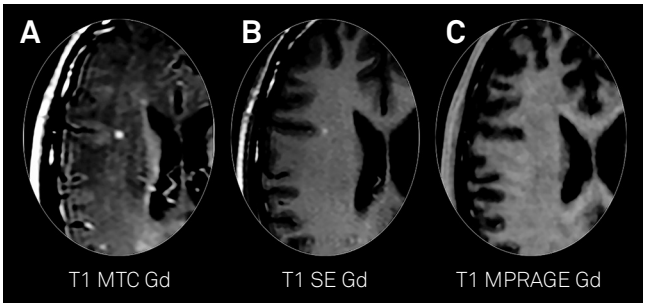

Figure 3. Multiple sclerosis in a 27-year-old male. Three axial T1-weighted post-contrast MR images after administration of the paramagnetic contrast agent reveal greater conspicuity (greater size and contrast) of the T1 magnetization transfer contrast (A) compared to the T1 spin-echo sequence (B). Conversely, the T1 3D-MPRAGE sequence (C) fails to demonstrate the breakdown of the blood-brain barrier.

Table 3. Mean number of Gd-enhancing lesions, areas of enhancement and contrast ratios.

Variable	SE	MTC	3D-MPRAGE
No. of lesions	2.5 (1–7)	3.1 (1–9)	1.7 (1–3)
Mean diameter of enhancement (mm^2)	73.9	83.9	76.2
Mean contrast ratio	103.2	212.2	41

All comparisons showed statistical significance ($p < 0.05$; Wilcoxon), except for the number of lesions between SE and MTC ($p = 0.096$). SE: spin-echo; MTC: magnetization transfer contrast; 3-D: three-dimensional; MPRAGE: magnetization-prepared rapid acquisition with gradient-echo

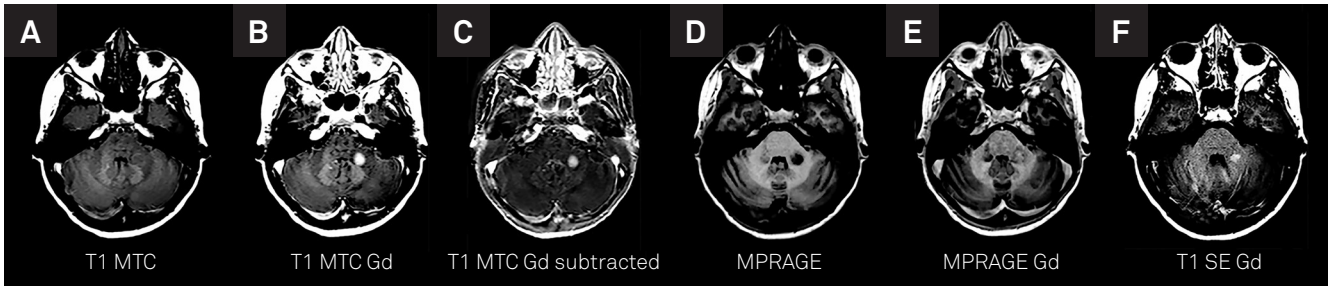

Figure 4. Multiple sclerosis in a 33-year-old female. An axial pre-contrast T1 magnetization transfer contrast (MTC) image (A) shows an ill-defined lesion in the left middle cerebellar peduncle with marked enhancement after intravenous gadolinium administration (B), confirmed by the post-processed subtraction image (C). An axial pre-contrast (D) T1 3D-MPRAGE image better demonstrates the lesion in the pre-contrast study. However, only faint enhancement was demonstrated on the post-contrast 3D-MPRAGE sequence (E). A post-contrast T1 spin-echo (SE) image (F) clearly shows the lesion, although it has more flow-related artifacts.

DISCUSSION

MRI has been playing a fundamental role in the evaluation of MS since its introduction in clinical practice in the mid-1980s. Unfortunately, all current MRI techniques remain insensitive to the complete underlying disease processes that give rise to all the pathophysiologic alterations in this disease. Nevertheless, it is well known that the elimination of the progression of inflammation and neurodegeneration in an early stage of the disease is a determining factor for a better prognosis of MS[18]. Consequently, a complete understanding of the cascade of events involved in the etiology and pathogenesis of MS is crucial to achieve both earlier diagnoses and more efficient treatments, with optimal and individualized therapy for patients with MS.

Theoretically, the diagnosis of MS can be confirmed only on a clinical basis. However, a clinical-radiological paradox has been demonstrated and imaging findings can replace certain clinical criteria in a substantial proportion of patients[1], as MRI has provided direct insights into several pathophysiological aspects of the brain, becoming a critical tool for this purpose.

The current diagnostic criteria for MS are based on the demonstration of dissemination in space and in time in the absence of no better explanation or an alternative diagnosis[3]. In this setting, Gd administration in the first MR examination of patients with clinically-suspected MS was used to confirm, in a single examination, dissemination in time by the coexistence of lesions with and without enhancement[19]. Alternatively, the main purpose of MRI in follow-up examinations is to verify the stability of lesions with the absence of active inflammation, defined as new or enlarging T2-hyperintense lesions, Gd-enhancing lesions, or a combination of both[1]. These findings are evaluated regardless of whether they are associated with symptoms, given that these measures of inflammatory activity are in the order of ten times the frequency of clinical relapses[20]. These relapses tend to provide only gross information of the disease process per se, because only symptoms related to eloquent areas are correlated with the appearance and resolution of Gd enhancement.

A cascade of pathophysiological events, ranging from focal lymphocytic infiltration, microglial activation, demyelination, and axonal degeneration, characterizes the pathogenesis of MS. In this scenario, disruption of the blood-brain barrier is a complex event triggered mainly by inflammatory infiltrates, comprising T lymphocytes, B lymphocytes, plasma cells, activated microglia, and dysfunctional astrocytes[21], which most likely takes place in an early stage of the disease[18]. Beyond that, some researchers have suggested that disruption of the blood-brain barrier in normal-appearing brain tissue begins before the onset of demyelination and infiltration of leukocytes in MS lesions[22], a disruption that is associated with a leak of paramagnetic Gd-containing chelates[23], adding new insights to our understanding of the pathogenesis of MS.

The close association of enhancement with acute inflammatory activity makes this an attractive MRI measure to use to test the effectiveness of a therapeutic agent on new inflammatory disease. It is assumed that Gd enhancement represents areas of blood-brain barrier breakdown associated with inflammatory changes[24], and it has been adopted as a very sensitive marker of disease activity in MS[19], providing important information in regard to its therapeutic efficacy[25]. Although these have become widely-used outcome measures for monitoring disease activity in clinical trials and clinical practice, their use as surrogates or biomarkers of disability and relapses, which are key clinical outcome measures, have found either no correlation[26] or a weak correlation[27].

The increased understanding of MS pathogenesis, as well as the introduction of disease-modifying therapies, added the need for a correct diagnosis at an early stage and for monitoring the efficacy of these therapies. The presence of new activity on MRI, demonstrated by both changes in the amount and size of T2-hyperintense and contrast-enhanced T1 lesions, is an important marker for the clinical setting that can be interpreted as a suboptimal treatment response, and a change of treatment should be considered on a case-by-case basis. This approach, together with the absence of

relapses and disability and the brain atrophy stability, has been defined as disease stability or 'no evidence of disease activity' (NEDA 4)[28], which has been used to assess a positive treatment response in patients with relapsing-remitting MS after two years. More specifically, three or more new T2-hyperintense lesions or a new enhanced lesion within the first two years predicted worse disease progression[29].

In this scenario, several strategies have been made to improve the sensitivity of acute inflammation detectability in MS patients. Among these, greater contrast material[6,8] and delayed scanning[7] increase the demonstration of faint blood-brain barrier disruption with consequent Gd enhancement.

The use of Gd-based contrast agents is a mainstay in the MRI diagnosis and follow-up of many central nervous system disorders. The International Society of Magnetic Resonance in Medicine Safety Committee reported that there has been some evidence of Gd deposition within the human brain after multiple Gd contrast administration, especially in the dentate nucleus and globus pallidus, particularly when linear compounds were used[10]. Thus, the National Institutes of Health recommends that the necessity of Gd administration in specific clinical indications should be carefully re-evaluated given the uncertain long-term public health impact of the deposition of Gd within the brain[30], though the precise causal role, if any, that repeated Gd injections play in MS pathogenesis remains unknown. Despite the fact that Waesberghe et al.[8] had concluded that triple-dose Gd demonstrated greater effectiveness than single-dose Gd in combination with an MT pulse sequence in detecting enhancing MS lesions, it seems to us that currently this protocol is less appropriate based on the uncertainties about costs and the Gd deposition.

Despite the different techniques that have been reported for identifying more enhancing lesions in brain MR images of MS patients, an adequate MR protocol may increase imaging sensitivity and specificity without additional costs or time. The sensitivity of a delayed post-contrast T1 sequence acquisition has been reported to be higher than that of early acquisition[7]. We performed a routine intravenous contrast injection before the acquisition of T2 and FLAIR sequences, which added approximately ten minutes for the T1WI post-contrast acquisition without an appreciable loss of T2 signal characteristics. This approach is a practical and cost-effective way to achieve increased sensitivity and had been included in the Magnetic Resonance Imaging in MS's statements[1].

Substantial contrast is achieved when an MT pulse is added to a T1WI post-contrast acquisition, allowing for the detection of more pathologic tissues with blood-brain barrier dysfunction in which Gd has been taken up, while the signal remains decreased in normal tissues (background)[31], as MT does not affect the proton relaxation induced by Gd chelates (paramagnetic agents). Our results reinforce previous reports that have proposed making intracranial lesions more visible by adding an MT pulse to a T1WI acquisition to detect Gd enhancement[6], thus, improving blood-brain barrier disruption detectability and the conspicuity of T1WI after Gd administration.

We found that, after administration of a single dose of Gd in patients with MS, the T1 MTC sequence at 1.5 T detected more enhancing lesions and, especially, more patients (MR active examination) with enhancing lesions than the T1 3D-MPRAGE, as well as more than the T1 SE sequences, a finding that was in agreement with previous studies[9,32]. Optimized MR protocols that preserve single-dose Gd without time-consuming or additional monetary costs are relevant to reducing intravenous Gd administration, thereby avoiding brain deposition of this agent[10]. This step could assist clinicians in tailoring early individual therapeutic interventions that may eliminate disease progression.

However, although the T1 MTC sequence showed considerable improvement in terms of the conspicuity and detectability of the intracranial lesions[33], this sequence should always be obtained before and after administration of contrast material. This procedure is required to avoid overestimation of disease activity due to the use of an off-resonance MT pulse that increases the signal intensity of non-enhancing lesions because of their lower MT ratio. Additionally, it is of fundamental importance to carry out the post-processing of the pre- and post-contrast magnetization T1 SE sequences to obtain the subtracted image, thus avoiding misinterpretation[32]. The increase in the lesion's conspicuity of the MTC sequence over the other studied sequences could be explained by either a greater mean diameter or contrast ratio. From a clinical point of view, MR activity analysis in MS is of paramount importance, as it has been demonstrated that a suboptimal treatment interferes with the clinical course.

A recent study conducted by Crombé et al.[34] showed higher detection rates at 3.0 T for Gd-enhancing lesions (especially smaller ones) using a 3D-MPRAGE sequence than using standard 2D gradient-echo sequences, with better suppression of artifacts related to vascular pulsation[34] and the additional advantage of the ability of the generated dataset to be subsequently reformatted to obtain high-quality images in any plane. However, we found that this finding was not confirmed on 1.5 T scanners, as observed by other authors[35-37].

We demonstrated that the T1 3D-MPRAGE volumetric sequence showed both fewer lesions and positive examinations when compared with spin-echo T1 sequences, with and without an additional MT pulse, with inherent repercussions for the diagnosis and therapeutic efficacy. In addition, the 3D-MPRAGE sequence also had the disadvantage of showing all T1 lesions as "black holes", making it difficult to recognize the substrate of the lesion (edematous x chronic), whereas the pre-contrast T1 MTC sequence showed the demyelinating lesion as a high signal, adding to the differential recognition.

Contrast administration remains important in the detection of blood-brain barrier disruption, as well as being the

gold standard MR technique to detect active inflammation in MS patients. Potential sequences that also require Gd-based contrast, recently been reported in the literature, are the double inversion recovery[38] and post-contrast susceptibility weighted imaging[39]. A new era of MRI research has also been developed for depicting the functionality of specific cells in the central nervous system through new contrast agents that have offered insight into the pathogenesis of MS *in vivo*; however, they are not yet available for routine clinical use[40].

This report has several limitations because it was a single-center prospective study with a relatively small number of patients without pathologic correlation. Also, worthy of note is the fact that the T1 MTC sequence shows some differences both in terms of scanners, as well as among services. In this sense, further standardized multicentric studies with bigger datasets and with different scanners should be performed in order to better demonstrate and validate our results.

The MR Imaging in MS 2016 guideline[1] suggests a protocol standardization for both baseline and follow-up examinations that included 2D or 3D T1 post-contrast sequences without the need for pre-contrast acquisition. As the pre-contrast T1 MTC sequence is required to certify Gd enhancement, there is an increase in the final scan time, which could be accepted by the increase in the inflammatory activity evaluation with their potential repercussions on the clinical management as discussed.

It seems feasible to adopt the T1 MTC sequence into clinical routine using 1.5 T equipment, which remains the most available MR scanner in the world.

In conclusion, the current study supports the use of a T1WI sequence with an MT pulse to study MS patients in clinical routine, with a single dose of intravenous Gd administration. This procedure showed increased sensitivity in the detection of more active demyelinating lesions, mainly in comparison with the T1 3D-MPRAGE sequence, as well as with the conventional axial T1 SE, using a 1.5 T magnet. We argue that a T1WI sequence with an additional MT pulse is the best option to predict inflammatory active lesions in MS, with a potential impact on the initiation, monitoring, and optimization of therapy.

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