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Clinical 3-tesla FLAIR* MRI improves diagnostic accuracy in multiple sclerosis

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Abstract

Objective—To evaluate clinical FLAIR* 3T MRI, which is sensitive to perivenular inflammatory demyelinating lesions, in diagnosing multiple sclerosis (MS).

Background—Central veins may be a distinguishing feature of MS lesions. FLAIR*, a combined contrast derived from clinical MRI scans, has not been studied as a clinical tool for diagnosing MS.

Methods—Two experienced MS neurologists evaluated 87 scan pairs (FLAIR/FLAIR*), separately and side-by-side, from 68 MS cases, 8 healthy volunteers, and 11 individuals with other neurological diseases. Raters judged cases based on experience, published criteria, and a visual assessment of the “40% rule,” whereby MS is favored if >40% of lesions demonstrate a central vein. Diagnostic accuracy was determined with area-under-the-receiver-operating-characteristic curve (AUC), and inter-rater reliability was assessed with Cohen’s kappa (κ).

Results—Diagnostic accuracy was high: rater 1, AUC 0.94(95% confidence interval: 0.89,0.97) for FLAIR, 0.95(0.92,0.98) for FLAIR*; rater 2, 0.94(0.90,0.98) and 0.90(0.85,0.95). AUC improved when images were considered together: rater 1, 0.99(0.98,1.00); rater 2, 0.98(0.96,0.99). Inter-rater agreement was substantial for FLAIR(κ =0.68) and FLAIR*(κ =0.74), despite low agreement on the 40% rule(κ =0.47) ($p < 0.001$ in all cases).

Conclusions—Joint clinical evaluation of FLAIR and FLAIR* images modestly improves diagnostic accuracy for MS and does not require counting lesions with central veins.

Keywords

MRI; Central veins; Multiple sclerosis; Diagnosis

Introduction

MRI is a long-standing essential tool in the diagnosis of multiple sclerosis (MS). White matter changes – hyperintensities seen on T2-weighted MRI – are the basis for diagnosing MS (1), and the presence of contrast-enhancing lesions guides management decisions in the clinical setting. The brain's vasculature plays a significant but not fully elucidated role in the pathophysiology of MS lesions; this relationship has been known since Charcot (2) and was first demonstrated on MRI a decade-and-a-half ago (3). Magnetic susceptibility-weighted (or T₂*-weighted) MRI, which can visualize cerebral veins due to the presence of deoxyhemoglobin, has provided further insight into the relationship between disease activity and the vasculature, especially in demonstrating that a preponderance of MS lesions possess a central vein (4–12). Additionally, a few studies have demonstrated the utility of the central vein in diagnosing MS versus other diseases that feature white matter T2 hyperintensities on MRI (13–16). However, these findings have generally relied on counting lesions in images acquired at 7 tesla (T), a magnetic field strength that is currently neither widely available nor approved for clinical use. At 3T, obtaining sufficiently sensitive T₂*-weighted images is challenging due to poorer susceptibility contrast, which makes smaller veins less visible. In addition, the conventional gradient-echo sequence routinely used for T₂* weighting requires long scan times for whole brain coverage. We developed a sequence, termed FLAIR*, that combines a 3D T₂-FLAIR with a T₂*-weighted scan and can be obtained on a 3T scanner in a time frame feasible for clinical use (17).

In prior work applying FLAIR* to MS patients of all subtypes (18), we found that a majority of MS lesions clearly associate with a central vein, as expected based on the pathology. Therefore, in the current study, we asked whether the availability of FLAIR*, as an adjunct to conventional T₂-FLAIR, can improve diagnostic accuracy in the MRI assessment of MS in a setting that approximates typical radiological practice. In addition, investigating the relevance of the central vein has been reported to require the clinically unfeasible process of counting perivenular and non-perivenular lesions (13). As such, we sought a simpler alternative whereby the previously proposed “40% rule” (i.e., do >40% of lesions appear to be associated with a central vein?) (13) is assessed qualitatively rather than quantitatively. Overall, our goal in this study was to evaluate whether FLAIR*, in conjunction with traditional MRI sequences, can be used in a clinical setting to increase diagnostic accuracy of MS.

Methods

Participant selection and scanning

All subjects were enrolled in our Institutional Review Board-approved natural history protocol following written informed consent. Participants were required to be between 18–70 years old and able to receive an MRI scan with gadolinium. MS was diagnosed by experienced clinicians based on 2010 Criteria (1) and with corroborating evidence from lumbar punctures in some cases.

In this natural history protocol, scans may be obtained on several different MRI scanners. The dataset described in this paper comprises those scans that were collected on a 3T whole-

body MR system (Philips Healthcare, Best, The Netherlands) with a manufacturer-provided 8-channel receive-only head coil and the body coil for transmission. The MRI protocol included T₁-weighted magnetization-prepared rapid acquisition of gradient echoes (T₁-MPRAGE), T₂-weighted FLAIR, and T₂*-weighted segmented echo-planar imaging (T₂*-segEPI). These 3D sequences covered the entire brain and were acquired in the sagittal plane within a clinically feasible time frame (10 minutes total) (17). Further sequence details are available in Table 1. During scanning, a single dose (0.1 mmol/kg) of the contrast agent gadobutrol (Gadavist; Bayer Healthcare, Leverkusen, Germany) was injected using a power injector (MEDRAD, Warrendale, PA). T₁-MPRAGE was acquired before contrast agent injection, T₂*-segEPI during injection, and T₂-FLAIR approximately 4 minutes after injection.

Image post-processing

As detailed previously (18), three post-processing steps are required to generate FLAIR* images: (a) coregistration between T₂-FLAIR and T₂*-segEPI; (b) interpolation of the registered T₂-FLAIR to match the higher resolution of T₂*-segEPI; and (c) multiplication of the coregistered, interpolated T₂-FLAIR to T₂*-segEPI. An additional skull-stripping step was included using MIPAV (Medical Image Processing, Analysis & Visualization, NIH) and JIST (Java Image Science Toolkit, Johns Hopkins/Vanderbilt) (19,20) to facilitate the image registration necessary in our in-house processing pipeline; this step is not strictly required to generate FLAIR* images. All images were reformatted into 448 axial sections without further interpolation.

Image evaluation

Two experienced MS neurologists (MA and IC, with 9 and 16 years of experience) separately and blindly evaluated all 87 3T scan pairs (T₂-FLAIR/FLAIR*), first viewing each scan alone and, approximately 1 year after the single-scan evaluation, the two scans side-by-side. Images were loaded into the MIPAV environment, and the reviewers were free to study the images in any single plane or all 3 planes simultaneously.

The complete image set included two volumes per subject (T₂-FLAIR and FLAIR*), which were presented in random order with all identifiers stripped; one author (ICG) was responsible for this process and was therefore unblinded. For the separate analysis, the image set included volumes from the consecutive follow-up visit for 9 participants, and 12 randomly selected volumes (6 FLAIR*, 6 T₂-FLAIR) appeared twice in order to evaluate intra-rater and inter-rater reliability. The repeated and duplicated scan sets were the same for the two reviewers. For the paired analysis, the follow-up scans were interspersed with the other scan pairs, but scans were not duplicated in the paired analysis.

In evaluating the separate images, two authors were asked to complete a survey (Appendix) for each image. The two evaluators were asked to identify the type of image (T₂-FLAIR or FLAIR*), whether lesions were present in specific locations (brainstem, cerebellum, deep gray matter, periventricular white matter, subcortical white matter, juxtacortical white matter), and their diagnosis of MS or not MS based on integration of their own clinical experience with published criteria. A visual analog scale, later translated into a 100-point

scale, was used to assess both image quality and certainty of the positive or negative diagnosis of MS. Reviewers were also asked to evaluate whether the findings met 2010 McDonald criteria for dissemination in space (1) and whether the percentage of lesions with perceived central veins was >40% (13). For the paired analysis, raters were only asked to provide their diagnosis and associated certainty (on the same visual analog scale).

Statistical analysis

For each rater, the accuracy of an MS diagnosis and self-assessed diagnostic confidence were assessed by the area under the receiver operating characteristic (ROC) curve (AUC). Separate AUC values were calculated for each rater's 3 assessments (FLAIR, FLAIR*, and combined FLAIR/FLAIR*). The sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were reported for each rater's 3 assessments. Inter-rater reproducibility was assessed with the Cohen's kappa coefficient (κ). Fisher's exact test was used to assess the difference in misdiagnosis rate between the two image types. A t-test was used to compare group means for image quality and rater confidence. We fit a generalized linear mixed-effects model with logistic link, with fixed-effects for rater and MRI contrast, and random intercept for MRI study, to assess the effect of image contrast and rater on the probability of a correct diagnosis.

Results

Results are reported for scan pairs (T₂-FLAIR and FLAIR*) from 68 (78%) MS cases and 19 (22%) controls (Table 2). Seven of the control cases were healthy volunteers with no known neurological illness or risk factors. Five control cases had human T-cell lymphotropic virus-1 (HTLV-1)-associated myelitis/tropical spastic paraparesis (HAM/TSP) and one had asymptomatic HTLV-1 infection. No final diagnosis was reached for the remaining 6, but after workup the disease was thought to be non-inflammatory in 4.

Sample scan pairs are shown in Figures 1–3. In MS cases, FLAIR* scans showed that discrete plaques were centered on small veins (Figure 1A). This was seen in some control cases but was much more rare (Figure 1B). In some cases (e.g., Figure 2A), FLAIR* images more clearly demonstrated both plaques and their central veins, aiding one or both raters in arriving at the correct diagnosis. In other cases, foci of signal abnormality that had typical appearance of MS plaques (e.g., the juxtacortical focus in Figure 2B) had no evident central veins, swaying raters away from the MS diagnosis. However, FLAIR* was not always helpful, as demonstrated in Figure 3 for a HAM/TSP case with multiple perivenular lesions (Figure 3A), an MS case where central veins were present in retrospect but not appreciated by either rater at the time of evaluation (Figure 3B), and a healthy volunteer with a perivenular focus of signal abnormality in a location atypical for MS (Figure 3C).

Across all scan pairs, the two raters distinguished T₂-FLAIR and FLAIR* images with 100% accuracy, consistent with the clear difference in appearance of the two contrasts. Figure 4 shows that despite inter-rater differences in absolute image-quality ratings consistent with the subjective nature of this analysis, the two reviewers considered image quality to be higher for T₂-FLAIR than FLAIR* ($p < 0.0002$ for both raters, Wilcoxon rank-sum test).

Across both raters and all images reviewed, the diagnostic error rate was 11% (10% for MS cases, 12% for non-MS cases). For T₂-FLAIR, the overall error rate was 9%; for FLAIR*, 11% ($p=0.7$ for difference between T₂-FLAIR and FLAIR*, Fisher's exact test); and for the combined T₂-FLAIR and FLAIR*, 7%. In the mixed-effects model, neither image contrast (T₂-FLAIR vs. FLAIR*) nor rater identity was associated with the probability of a correct response. The mixed-effect model parameter estimates and p-values are provided in Table 3. In the single analysis, diagnostic certainty, rated on a visual analog scale later translated into a percentile, was higher (mean $\pm$ standard deviation: 86% $\pm$ 16%) for correctly diagnosed cases than for those incorrectly diagnosed (67% $\pm$ 18%; t-test, $p<0.0001$). Similar results were obtained in the paired analysis (93% $\pm$ 10% vs. 65% $\pm$ 14%; $p<0.0001$).

Consistent with these results, the ROC analysis showed that diagnostic accuracy was high for both raters and both scan types. For rater 1, the AUC was 0.94 (95% confidence interval: 0.89,0.97) for T₂-FLAIR and 0.95 (0.92,0.98) for FLAIR*; for rater 2, 0.94 (0.90,0.98) and 0.90 (0.85,0.95), respectively. The AUC improved when images were considered together: rater 1, 0.99 (0.98,1.00); rater 2, 0.98 (0.96,0.99). The ROC curves are shown in Fig. 2. The sensitivity, specificity, NPV, and PPV for each rater's 3 assessments are provided in Table 4.

For the repeated T₂-FLAIR cases ($n=6$), the number of cases with discordant diagnoses and identification of lesion-containing regions was 0 for one rater and 1 for the other, indicating that both diagnostic certainty and accuracy, as well as localization of lesions in brain regions, was high for this contrast. For FLAIR*, most survey responses had a similar degree of discordance. However, there were 3 cases with discordant responses for the presence of lesions in the deep gray matter. When asked whether the percentage of lesions with central veins was more than 40%, one rater was fully concordant over time, whereas the other logged 3 discordant responses. Inter-rater agreement on diagnosis was substantial for T₂-FLAIR ($\kappa=0.76$) and FLAIR* ($\kappa=0.74$), despite low agreement for whether the percentage of lesions with central veins was $>40\%$ ($\kappa=0.49$) ($p<0.001$ in all cases). For the presence of lesions in individual brain regions, κ was as low as 0.18 (FLAIR*, deep gray matter; $p=0.06$), but typical values for other brain regions were in the 0.5 to 0.8 range and were highest for T₂-FLAIR in the brainstem ($\kappa=0.78$, $p<0.001$).

Discussion

The “central vein sign” has been proposed to be a useful and potentially specific marker of brain lesions caused by the inflammatory demyelinating process of MS. The specificity of this sign has not been definitively established, and there are furthermore no consensus criteria to evaluate its value in either the research or the clinical setting; additionally, it has been evaluated primarily through 7T research MRI. Although guidelines have been proposed, such as the “40% rule” (whereby cases in which $>40\%$ of lesions have a central vein) (13), these have not been validated in a multicenter setting. It is important to recognize that in order to be useful, any set of criteria would need to be cognizant of the fact that in a busy clinical practice, the application of complicated, time-consuming research rules to diagnostic scans, particularly rules that require lesion counting, would be challenging. With this in mind, we set out to investigate whether the addition of FLAIR* images to conventional T₂-FLAIR might improve diagnostic accuracy for MS when evaluated in a

clinical setting, based on the presumption that nearly half of lesions in MS possess a central vein.

To accomplish this goal, our raters separately analyzed T₂-FLAIR and FLAIR* scan volumes individually and as linked pairs, integrating published MS diagnostic criteria with their own experience – much as a neuroradiologist might do in clinical practice. The major results of the study are the following: (a) T₂-FLAIR alone led to accurate diagnosis in ~90% of cases; (b) the addition of FLAIR*, when evaluated alongside T₂-FLAIR, added meaningfully to diagnostic certainty, despite the lower image quality of FLAIR* that is attributable mostly to susceptibility artifacts; and (c) visual assessment of the “40% rule,” without dedicated and time-consuming lesion counting, is not sufficiently reproducible to be useful in clinical practice.

Taken together, these results indicate that it is possible to overcome the intrinsic technical limitations of 3T MRI for detection of the “central vein sign,” and indeed that FLAIR* would be useful in the clinical setting to help diagnose MS when evaluated alongside conventional MRI scans. This further suggests that although the “40% rule” may not be the most clinically applicable cut off, evaluating for the increased presence of central veins modestly increases diagnostic certainty. We believe that the diagnostic specificity of central vein assessment in MS still requires broader investigation, considering that other conditions might also present a venocentric pattern of lesion development (for example, the HAM/TSP case in Figure 3). Nonetheless, the results of our study suggest several difficult clinical situations that might particularly benefit from central vein assessment using FLAIR*: (1) atypical clinical presentations or unclear symptoms with radiological findings suggestive for MS; (2) cases where the pattern of lesion distribution is not fully typical of MS; and (3) heterogeneous white matter lesion accrual in MS patients with comorbidities such as microvascular ischemic disease.

To further test whether FLAIR* can help differentiate MS from its mimics, and might therefore be useful as part of future diagnostic imaging criteria and recommendations (24), the next logical step would be to prospectively evaluate cases of radiologically isolated syndrome (RIS) and clinically isolated syndrome (CIS) to determine the prognostic value of assessing central veins. More broadly, while there are now multiple studies suggesting that the central vein sign is reproducible and has merit as part of a diagnostic toolkit in diagnosing MS, this finding has not yet been validated through a multi-center study, and more rigorous use as a diagnostic sign will require consensus criteria that are straightforward to apply objectively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Representative FLAIR (top row) and FLAIR* (bottom row) images from (A) a 52-year-old man with multiple sclerosis of 24 years' duration and Expanded Disability Status Scale score of 2, indicating minimal disability in one functional system, and (B) a 50-year-old female healthy volunteer. In (A), focal white matter lesions are typical of multiple sclerosis and all demonstrate central linear or nodular hypointensity compatible with a central vein (two examples are highlighted with boxes). In (B), deep white matter lesions in the frontal lobes have no central veins (boxes). In these cases, the two raters made the proper diagnosis with high confidence.

Figure 2.

FLAIR (top row) and FLAIR* (bottom row) images from (A) a 45-year-old woman with multiple sclerosis of 7 years' duration and Expanded Disability Status Scale score of 5, indicating limited ambulation and disability-related impairment of daily activities, and (B) a 37-year-old male healthy volunteer. In (A), focal white matter lesions are ambiguous on the FLAIR, but the FLAIR* scan shows that several have clear central veins. This led one of the two raters to diagnose the case properly on the FLAIR*, whereas neither made the correct diagnosis on FLAIR alone; both raters made the correct diagnosis when the two images were presented simultaneously. In (B), a juxtacortical lesion that might otherwise be considered typical of multiple sclerosis lacks a central vein on FLAIR*. This led one rater to

an incorrect diagnosis of multiple sclerosis on FLAIR but a correct diagnosis of “not multiple sclerosis” on FLAIR*. In the simultaneous presentation, one rater misdiagnosed multiple sclerosis with low confidence (54%), and the other rater properly diagnosed “not multiple sclerosis” with 100% confidence.

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Figure 3.

FLAIR (top row) and FLAIR* (right column) images from (A) a 43-year-old woman with human T-cell lymphotropic virus-associated myelopathy/tropical spastic paraparesis of 7 years' duration; (B) a 24-year-old woman with multiple sclerosis of 2 years' duration and Expanded Disability Status Scale score of 1, indicating no disability and minimal signs in one functional system; and (C) a 45-year-old male healthy volunteer. In (A), subcortical and deep white matter lesions have a nonspecific appearance, but some appear perivenular (boxes), which led one reviewer to reduce confidence in the diagnosis of "not multiple sclerosis" from 81% to 37% on the FLAIR*. In (B) and (C), both raters made the proper diagnosis on FLAIR but the wrong diagnosis on FLAIR*, indicating that in some cases the perivenular configuration of multiple sclerosis lesions can be subtle (boxes in B) and that incidental lesions in non-multiple sclerosis cases can have central veins (box in C).

Figure 4.

(A) Violin plots of image quality scores for the two raters, where the center dot shows the median, the thick black line the interquartile range, the thin black line the 95% confidence interval, and the width of the “violin” the probability density. Image quality was rated subjectively on a scale of 0–100. Rater 1 had consistently higher image quality scores, but both raters felt that susceptibility artifacts in the FLAIR* images lowered their overall quality ($p < 0.0002$). (B, C) Receiver operating characteristic (ROC) curves for diagnostic accuracy for rater 1 (B) and rater 2 (C), showing that combining T₂-FLAIR and FLAIR* is superior to evaluating either alone, as judged by the area under the curve (AUC).

Table 1

MRI parameters

Parameter	T ₁ -MPRAGE	T ₂ -FLAIR	T ₂ *-segEPI
repetition time [msec]	7	4800	53
echo time [msec]	3	372	29
inversion time [msec]	900	1600	–
flip angle [deg]	9	90	10
number of echoes	240	178	15
field of view [mm ³]	240 × 240 × 180	240 × 240 × 180	240 × 240 × 180
voxel resolution [mm ³]	1 × 1 × 1	1 × 1 × 1	0.55 × 0.55 × 0.55
parallel imaging factor	2 × 1 (RL × AP)	2 × 2.6 (RL × AP)	2 × 2 (RL × AP)
number of averages	1	2	2
acquisition time [min:sec]	5:17	6:00	3:50

Abbreviations: MPRAGE, magnetization-prepared rapid acquisition of gradient echoes; FLAIR, fluid-attenuated inversion recovery; segEPI, segmented echo-planar imaging; RL, right-left; AP, anterior-posterior.

Table 2

Demographics

	MS cases	control cases	p-value
# cases	68	19	
age (years), mean $\pm$ SD	46 $\pm$ 12	49 $\pm$ 11	0.35 *
sex, # (%) female	32 (47%)	13 (68%)	0.12 §
meeting McDonald 2010 criteria for dissemination in space, # (%)	64 (94%)	6 (32%)	<0.001 §
MS disease duration (years), mean $\pm$ SD	11.6 $\pm$ 10.1		
EDSS, median (min, max)	1 (0,7)		

* Student's t-test;

§ Fisher's exact test.

Abbreviations: MS, multiple sclerosis; SD, standard deviation; EDSS, Expanded Disability Status Scale.

Table 3

Mixed-effects model parameters and p-values

	Estimate	Standard Error	z value	p-value
Intercept	7.73	1.34	5.77	<.01
Rater 2	−0.38	0.50	−0.75	0.45
Flair*	−0.51	0.51	−0.99	0.32

Table 4

Positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity for each rater and both raters combined

Rater	Imaging Modality	PPV	NPV	Sensitivity	Specificity
Rater 1	FLAIR	.97	.66	.89	.90
	FLAIR*	.97	.75	.93	.90
	FLAIR + FLAIR*	.97	.95	.98	.90
Rater 2	FLAIR	.96	.77	.94	.85
	FLAIR*	.96	.61	.86	.85
	FLAIR + FLAIR*	.89	.85	.97	.57
Combined	FLAIR	.96	.71	.91	.88
	FLAIR*	.97	.67	.90	.87
	FLAIR + FLAIR*	.93	.90	.98	.73