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Longitudinal Persistence of Meningeal Enhancement on Post-Contrast 7 Tesla 3D FLAIR MRI in Multiple Sclerosis

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Abstract

Background and Purpose: Preliminary research has demonstrated that post-gadolinium 3D FLAIR MRI at 7T may be a valuable tool for detecting abnormal meningeal enhancement and inflammation in MS; however, researchers have not systematically investigated its longitudinal persistence. We hypothesize that persistence of meningeal enhancement in MS varies based on pattern of enhancement as well as demographic and clinical factors such as treatment status, disease phenotype, and disability score.

Materials and Methods: Thirty-one subjects with MS were prospectively scanned before and after intravenous contrast administration at 2 time points, approximately 1 year apart. Fifteen subjects in the cohort were scanned another time approximately 1 year later. Foci of enhancement were categorized into four subtypes: subarachnoid spread/fill, subarachnoid nodular, vessel wall, and dural foci. We reviewed follow-up scans to determine whether foci changed between time points and then compared persistence to demographic and clinical variables.

Results: Persistence ranged from 71–100% at 1 year, and 73–100% at 2 years depending on enhancement pattern. Subarachnoid spread/fill and subarachnoid nodular subtypes persisted less often than vessel wall and dural foci. Persistence was not significantly different between those on/off treatment and those with progressive/non-progressive diseases phenotypes. Number of persisting foci was significantly different in subjects with/without increasing Expanded Disability Status Scale scores (median 12 v 7.5, p=0.04).

Conclusion: Longitudinal persistence of meningeal enhancement on 3D FLAIR at 7T in MS varies by pattern of enhancement and correlates with worsening disability; however, it is not significantly different in those on/off treatment or those with progressive/non-progressive disease phenotypes.

Introduction

MS is a chronic inflammatory demyelinating disorder classically affecting white matter within the brain and spinal cord. In the last few decades an additional pathophysiologic

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mechanism—meningeal inflammation—has been elucidated in MS, which is now believed to directly contribute to cortical demyelination, cortical neuroaxonal loss, microglial activation, and oligodendrocyte dysfunction.[1–6] Visualization of meningeal inflammation on MRI has become an active, and somewhat controversial, area of recent investigation.[7] Landmark studies have demonstrated that gadolinium-enhanced 3D FLAIR sequences, which have long been useful for identifying meningeal infection and carcinomatosis, can also be used to image meningeal disease in the MS population. At a magnetic field strength of 3T, Absinta et al. found that approximately

25% of MS patients demonstrate leptomeningeal enhancement on gadolinium-enhanced FLAIR.[7] Protocols for imaging meningeal enhancement were improved by Zivadinov, et al[8] who showed the benefit of acquiring both pre- and post-contrast acquisitions and generating subtraction images when assessing meningeal enhancement, as these techniques decrease false positives and reduce interpretation time. Recent preliminary research also has suggested that 7 Tesla (7T)

MRI may be more sensitive than 3T for detecting meningeal enhancement. Although no direct 3T versus 7T comparisons have been made in the same study population, up to 90% of MS patients undergoing contrast-enhanced brain MRI at 7T demonstrated at least one enhancing focus.[9] This result closely approximates the 89% of MS patients reported to show some element of leptomeningeal inflammation at autopsy.[10,11] Given this radiologic-pathologic concordance, it is conceivable that 7T 3D FLAIR may soon provide a non-invasive *in-vivo* method of detecting and accurately quantifying the extent of meningeal inflammation in patients with MS. Meningeal enhancement was noted to be a persistent phenomenon in prior 3T studies;[7] however, at 7T where sensitivity for meningeal enhancement in MS appears to be significantly higher, it remains unknown whether smaller, more subtle foci of enhancement wax and wane in a predictable pattern over time or whether they remain longitudinally stable. Also unknown is the degree to which enhancement persistence over time is associated with previously described enhancement shape and morphology, including subarachnoid spread/fill and subarachnoid nodular patterns.[7,9] As prior studies have shown that the *prevalence* of meningeal enhancement varies with enhancement morphology,[7,9] in this study we hypothesized that *persistence* of meningeal enhancement in MS would vary based on morphology of enhancement as well as demographic and clinical factors such as treatment status, disease phenotype, and disability scores. Greater understanding of the imaging and clinical characteristics of meningeal enhancement is necessary if these features are to aid in the diagnosis of and prognosis for MS patients.

Methods

Standard protocol approval and informed consent

The institutional review boards at the authors' institutions approved this HIPAAcompliant, prospective study. Written, informed consent was obtained from all participants.

Participants

Thirty-one volunteers, aged 26–61, with diagnoses of relapsing-remitting MS, secondary progressive MS, or primary progressive MS according to the 2010 revised McDonald Criteria were recruited.[12] Exclusion criteria included contraindication to contrast-enhanced MRI.

MRI protocol

Study participants were prospectively scanned at two time points, approximately 1 year apart on a 7T Philips Achieva scanner with a volume-transmit/32-channel head coil (Nova Medical, Wilmington, MA). Fifteen patients in the cohort were scanned at an additional third visit approximately 1 year later. Scans were performed between September 9, 2014 and August 21, 2017. Dielectric padding was used for improved image homogeneity.[13] Scanning parameters are listed in Table 1. Images were acquired prior to the administration of contrast and again after the intravenous administration of 0.1 mmol/kg gadoteridol (ProHance, Bracco Imaging, Milan, Italy). MP2RAGE images were initiated approximately 3 minutes after contrast administration and magnetization prepared FLAIR images were initiated approximately 20 minutes after contrast administration.

Image Processing and Analysis

MP2RAGE images were processed to create a T1-weighted image and a T1 map.[14] Images were then manipulated using MIPAV (version 7.2, http://mipav.cit.nih.gov/). Magnetization prepared FLAIR images underwent N4 inhomogeneity correction prior to analysis.[15] Pre- and post-contrast magnetization prepared FLAIR images were registered to the pre-contrast T1 map. A magnetization prepared FLAIR subtraction image was created by direct subtraction of the registered pre- and post-contrast images.

The magnetization prepared FLAIR subtraction image, alongside the pre- and postcontrast magnetization prepared FLAIR images, were reviewed by two independent raters (PGY4 radiology resident and an academic MS neurologist), who were blinded to subject identity, disease state, and treatment regimen. Hyperintensities noted on the subtraction image were located on anatomic images and demarcated if present in the meningeal space on post-contrast images only. All foci were localized in three orthogonal planes prior to notation. When needed, co-registered MP2RAGE T1-weighted images were used for confirmation of anatomic locations. The pattern of enhancement was categorized based on location and morphology, and stratified into one of four sub-types. Subarachnoid spread/fill foci were characterized by the presence of contrast in the subarachnoid space distributed in an amorphous manner (Figure 1a). Subarachnoid nodular foci were characterized by small, round areas of contrast, usually 1–2 voxels (0.7–1.4mm) in size, and were adherent to the pial surface (Figure 1b). Vessel wall enhancement was characterized by contrast outlining the outer margin of a large meningeal vessel with signal void in the lumen of the vessel, often resulting in a characteristic tram-track appearance (Figure 1c). Dural foci were characterized by discrete regions of enhancement clearly situated along the dural surface without extension into the subarachnoid space (Figure 1d). Following both independent reviews, a consensus review was performed under the supervision of an expert 3rd rater (academic neuroradiologist with 12 years of experience). After consensus review, follow-up

images underwent linear registration (with 9 degrees of freedom) to baseline images. Consensus regions of contrast enhancement on baseline images were reviewed for their presence or absence on follow up scans. The total number of foci per subject that persisted between scans was compared among different morphologies of meningeal enhancement and correlated with demographic and clinical data. Additionally, the proportion of baseline foci per subject that persisted to follow-up scans was also compared to morphologic, demographic, and clinical factors.

Disability measures

The Kurtzke Expanded Disability Status Scale (EDSS) was used to characterize disability.[16] EDSS progression was defined as an increase of EDSS score at follow-up of greater than or equal to 1.0 if baseline EDSS < 5.0 or an increase of greater than or equal to 0.5 if baseline EDSS was 5.0 or higher. The Modified Fatigue Impact Scale was used to assess MSrelated fatigue.[17,18] The Symbol Digits Modalities Test was used to assess cognitive functioning.[19] These tests were administered at each study visit.

Statistical analysis

Statistical analysis was performed in Stata 10.1 IC (StataCorp, College Station, TX). Nonparametric testing was used due to non-normal distribution of data. We performed group comparisons for demographic and clinical variables using the Wilcoxon rank-sum statistic. We computed Spearman's rank correlation for correlation testing. All statistical tests were performed with a significance threshold of $p < 0.05$. Due to the small sample size and exploratory nature of this study, adjustment for multiple comparisons was not performed.

Results

We recruited 31 patients with MS; most had the relapsing remitting MS phenotype (n=21, 68%), although 7 subjects had secondary progressive MS (23%) and 3 subjects had primary progressive MS (10%) (Table 2). No subject had a comorbid neuroinflammatory disorder. Most subjects were on disease-modifying therapy (n=25, 81%). This was a relatively stable and moderately disabled patient population with a median of 0 (0–3) relapses in the year prior to enrollment and a median Expanded Disability Status Scale score of 3 (1–6.5). Enhancing white matter lesions were seen in 3 subjects on review of T1-weighted images, with 2 subjects having 1 enhancing lesion and 1 subject having 2 enhancing lesions.

At baseline a total of 284 enhancing foci were identified across all 31 subjects. Table 3 lists the anatomic distribution of these foci within the brain. It is notable that the vast majority (>98%) of the observed foci were located supratentorially. Figure 2 shows the percentage of enhancing meningeal foci identified at baseline that were persistent at later time points. Figures 3 and 4 provide examples of persisting and resolving enhancing meningeal foci from each group. Table 4 and supplemental tables 1–3 compare the persistence of meningeal enhancement to demographic and clinical variables. We found no significant difference in the total number or proportion of longitudinally persistent enhancing meningeal foci between those on or off treatment, or between those with progressive phenotypes (primary progressive MS and secondary progressive MS) versus a relapsing phenotype (relapsing

remitting MS). However, we did find significantly more (p = 0.04) persistent foci in Expanded Disability Status Scale progressors (median 12, range 1–15) compared to those who were not (7.5, 1–24). We also observed a non-significant trend towards a negative association (Rho = −0.31, p = 0.09) between the proportion of persisting foci overall and the interval change in Symbol Digits Modalities Test scores at 1 year (supplemental table 3). Surprisingly and counterintuitively, we observed a positive correlation (Rho = 0.45, p = 0.01) between the proportion of enhancing meningeal foci that persisted at 1 year and baseline Symbol Digits Modalities Test scores (supplemental table 3). This association was driven by the correlation (Rho = 0.48, p = 0.01) between the proportion of subarachnoid spread/fill subtype that persisted at 1 year and baseline Symbol Digits Modalities Test scores. We also observed 15 foci of meningeal enhancement that developed in the interval between baseline and follow-up scans. The morphologies of these 15 foci were as follows: 6 subarachnoid spread/fill, 4 subarachnoid nodular, 2 vessel wall, and 3 dural foci.

Discussion

In this study, we catalogued two enhancement patterns described in prior analysis (subarachnoid nodular and subarachnoid spread/fill)[7,9] in addition to describing two new patterns of meningeal enhancement for the first time: vessel wall enhancement and dural foci. Previous studies without pre-contrast comparison sequences excluded from consideration regions of postcontrast hyperintensity in/near dural sinuses, large subarachnoid veins, and the basal meninges in order to reduce false positives, because these structures often manifest pre-contrast T1 or FLAIR hyperintensity.[7,9] Using similar technique to the recent investigation by Zivadinov et al[8], we coregistered and subtracted pre- and post-contrast MP-FLAIR sequences in all cases. Given this protocol, we did not have to exclude any structures a priori, and we were confident in our ability to differentiate true vessel wall and dural foci enhancement from intrinsically increased signal. Which anatomic/pathologic substrates are represented by vessel wall and dural foci is unknown, but interestingly, both closely match what was recently described for visualization of meningeal lymphatics by FLAIR MRI.[20–22] Thus, it is possible that these findings may represent gadolinium absorption by lymphatic structures after leakage into the cerebrospinal fluid. The accumulation of gadolinium signal alongside the outer wall of vessels in the vessel wall pattern is also very reminiscent of the expected location and direction of drainage of solutes from brain parenchyma along the recently described glymphatic system.[23] Alternatively, it is also possible that vessel wall and dural foci could represent the reaccumulation, under hydrostatic pressure, of cerebrospinal fluid-leaked gadolinium back into the venous system. They could also feasibly represent the actual sites of blood-brain and blood-cerebrospinal fluid barrier disturbance secondary to ongoing inflammation.[24] As age and gender matched healthy controls were not utilized in this study, the specificity of dural and vessel wall enhancements to MS is unknown. Future work is needed to determine if such findings are specific to MS, neuroinflammatory disease in general, or are seen in all-comers.

We found no significant difference in the total number or proportion of persisting meningeal enhancement per subject between those on treatment and those off treatment. Lack of a significant difference between subjects on/off treatment may in part be explained by the low statistical power of our study, as a relatively small number of untreated subjects were

included. However, the lack of difference is not surprising, as prior studies have also failed to show differences in meningeal enhancement between those who are and are not taking diseasemodifying medications.[7] Our data reinforces the notion that current immunomodulatory medications may not adequately control meningeal inflammation. Of note, none of our subjects received a course of corticosteroids during the course of the study. However, it is notable that 10 out of 31 subjects in this cohort switched between disease modifying therapies from baseline to follow-up scans, including 2 subjects who changed to rituximab and 1 subject who switched to alemtuzumab – both monoclonal antibodies that impact B-cell function. Despite such changes, the vast majority of foci remained stable. Given the sample size of this report, we would not want to comment on the persistence (or lack thereof) of foci with individual therapy changes, as conclusions from 1 or 2 examples would not be generalizable. Future comparative studies are needed to determine if changes in any specific disease modifying therapies or monoclonal regimens alter the longitudinal persistence of meningeal enhancement.

Surprisingly, we did not detect a significant difference in persistence of meningeal enhancement between MS subjects with progressive phenotypes (primary progressive MS and secondary progressive MS) and those with relapsing remitting MS. This finding runs counter to the previously proposed theory that meningeal enhancement may be a substrate specific to progressive MS, with the associated cortical demyelination and volume loss representing a distinctly late marker of disease.[1,7] Indeed, previous studies have shown that the presence of leptomeningeal enhancement at 3T was 1.7 fold higher in progressive MS compared to relapsing remitting MS, and autopsy findings of meningeal inflammation were more profound in those with secondary progressive MS.[1,7] However, our 7T data show no difference in the frequency of longitudinal persistence of meningeal enhancement between MS patients with progressive and relapsing phenotypes.

Although the persistence of enhancing foci was not related to clinical phenotype, we did detect a significant relationship between the persistence of foci (especially subarachnoid spread/fill foci) at 1 year with disability progression (by Expanded Disability Status Scale) over the same time period. If post-contrast meningeal enhancement on MP-FLAIR is indeed representative of meningeal inflammation, this finding may indicate that persistent, rather than transient meningeal inflammation is required to affect prognosis in MS patients. This notion is supported by autopsy data showing that the development of structures that support ongoing inflammation, such as ectopic lymphoid follicular tissue, in the meninges of MS patients is associated with earlier onset of disease, shorter diagnosis-death interval, and more severe cortical pathology.[1,25] If this relationship can be confirmed in larger studies, perhaps the elimination of persistently enhancing meningeal foci can become a target outcome for MS patients.

While we found a significant relationship between changes in Expanded Disability Status Scale and the persistence of enhancement, we were unable to detect any similar association between imaging findings and MS-related fatigue or cognitive deficits (supplemental tables). This difference may be due to our study’s small sample size, or short follow-up duration. Still to be investigated is the rate at which foci of meningeal enhancement develop over time, whether the rate of development is associated with enhancement morphology, and whether

the rate of development is associated with demographic and clinical parameters. It is important to note that this study focused on subjects with MS only; future work is needed to elucidate the rate of longitudinal persistence of meningeal enhancement in other neuro-inflammatory diseases.[26] Finally, our study is limited by possible false discovery, as we did not perform multiplecomparison correction, given the exploratory nature of this investigation. Therefore, our results will require replication before widespread acceptance of these conclusions. Despite these limitations, these preliminary results provide important new insight into the longitudinal activity of meningeal enhancement in MS.

Conclusion

Here we describe the results of a prospective, systematic investigation into the longitudinal persistence of meningeal enhancement in MS using 7T 3D FLAIR. Given our pre- and post-contrast technique, we are able to include for the first time vessel wall and dural foci subtypes, which persist most frequently and their appearance very closely matches recent descriptions of meningeal lymphatics or the glial lymphatics system.[19–22] Longitudinal persistence of meningeal enhancement is not significantly different between those on or off immunomodulatory treatment; nor is there a significant difference in rates of longitudinal persistence between those with progressive clinical phenotypes (primary progressive MS and secondary progressive MS) and those without a progressive clinical phenotype (relapsing remitting MS). However, there is a significantly increased number of persistent foci in subjects that have worsening Expanded Disability Status Scale scores at 1 year compared to those that do not, suggesting that persistently enhancing meningeal foci may be an *in-vivo* imaging marker for ongoing meningeal inflammation causative of clinical progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Magliozzi R, Howell O, Vora A, et al. Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. Brain J Neurol 2007 4;130(Pt 4):1089–104
2. Lucchinetti CF, Popescu BFG, Bunyan RF, et al. Inflammatory cortical demyelination in early multiple sclerosis. N Engl J Med 2011 12 8;365(23):2188–97 [PubMed: 22150037]
3. Choi SR, Howell OW, Carassiti D, et al. Meningeal inflammation plays a role in the pathology of primary progressive multiple sclerosis. Brain J Neurol 2012 10;135(Pt 10):2925–37
4. Serafini B, Rosicarelli B, Magliozzi R, et al. Detection of ectopic B-cell follicles with germinal centers in the meninges of patients with secondary progressive multiple sclerosis. Brain Pathol 2004 4;14(2):164–74 [PubMed: 15193029]
5. Kowarik MC, Cepok S, Sellner J, et al. CXCL13 is the major determinant for B cell recruitment to the CSF during neuroinflammation. J Neuroinflammation 2012 5 16;9:93 [PubMed: 22591862]

6. Nielsen AS, Kinkel RP, Tinelli E, et al. Focal cortical lesion detection in multiple sclerosis: 3 Tesla DIR versus 7 Tesla. J Magn Reson Imaging 2012 3;35(3):537–42 [PubMed: 22045554]
7. Absinta M, Vuolo L, Rao A, et al. Gadolinium-based MRI characterization of leptomeningeal inflammation in multiple sclerosis. Neurology 2015 7 7;85(1):18–28 [PubMed: 25888557]
8. Zivadinov R, Ramasamy DP, Hagemeier J, et al. Evaluation of Leptomeningeal Contrast Enhancement Using Pre-and Postcontrast Subtraction 3D-FLAIR Imaging in Multiple Sclerosis. Am J Neuroradiol 2018 4;39(4):642–7. Epub 2018 Feb 8 [PubMed: 29439125]
9. Harrison DM, Wang KY, Fiol J, et al. Leptomeningeal Enhancement at 7T in Multiple Sclerosis: Frequency, Morphology, and Relationship to Cortical Volume. J Neuroimaging 2017 9;27(5):461–8 [PubMed: 28464368]
10. Howell OW, Reeves CA, Nicholas R, et al. Meningeal inflammation is widespread and linked to cortical pathology in multiple sclerosis. Brain J Neurol 2011 9;134(Pt 9):2755–71
11. Howell OW, Schulz-Trieglaff EK, Carassiti D, et al. Extensive grey matter pathology in the cerebellum in multiple sclerosis is linked to inflammation in the subarachnoid space. Neuropathol Appl Neurobiol 2015 10;41(6):798–813 [PubMed: 25421634]
12. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011 2;69(2):292–302 [PubMed: 21387374]
13. Haines K, Smith NB, Webb AG. New high dielectric constant materials for tailoring the B1+ distribution at high magnetic fields. J Magn Reson 2010 4;203(2):323–7 [PubMed: 20122862]
14. Marques JP, Kober T, Krueger G, et al. MP2RAGE, a self bias-field corrected sequence for improved segmentation and T1-mapping at high field. NeuroImage 2010 1 15;49(2):1271–81 [PubMed: 19819338]
15. Tustison NJ, Avants BB, Cook PA, et al. N4ITK: improved N3 bias correction. IEEE Trans Med Imaging 2010 6;29(6):1310–20 [PubMed: 20378467]
16. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983 11;33(11):1444–52 [PubMed: 6685237]
17. Multiple Sclerosis Council for Clinical Practice Guidelines. Fatigue and multiple sclerosis: evidence-based management strategies for fatigue in multiple sclerosis. Paralyzed Veterans of America 1998, p 1–33.
18. Flachenecker P, Kumpfel T, Kallmann B, et al. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. Mult Scler 2002 12;8(6):523–6 [PubMed: 12474995]
19. Smith A Symbol digit modalities test: Manual. Los Angeles: Western Psychological Services; 1973.
20. Aspelund A, Antila S, Proulx ST, et al. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. J Exp Med 2015 6 29;212(7):991–9 [PubMed: 26077718]
21. Raper D, Louveau A, Kipnis J. How Do Meningeal Lymphatic Vessels Drain the CNS? Trends Neurosci 2016 9;39(9):581–6 [PubMed: 27460561]
22. Absinta M, Ha S-K, Nair G, et al. Human and nonhuman primate meninges harbor lymphatic vessels that can be visualized noninvasively by MRI. eLife 2017 10 3;6
23. Plog BA, Nedergaard M. The Glymphatic System in Central Nervous System Health and Disease: Past, Present, and Future. Annu Rev Pathol 2018 1 24;13:379–94 [PubMed: 29195051]
24. Ortiz GG, Pacheco-Moises FP, Macias-Islas MA, et al. Role of the blood-brain barrier in multiple sclerosis. Arch Med Res 2014 11;45(8):687–97 [PubMed: 25431839]
25. Zivadinov R, Ramasamy DP, Vaneckova M, et al. Leptomeningeal contrast enhancement is associated with progression of cortical atrophy in MS: A retrospective, pilot, observational longitudinal study. Mult Scler 2017 9;23(10):1336–45 [PubMed: 27811339]
26. Absinta M, Cortese ICM, Vuolo L, et al. Leptomeningeal gadolinium enhancement across the spectrum of chronic neuroinflammatory diseases. Neurology 2017 4 11;88(15):1439–44 [PubMed: 28283598]

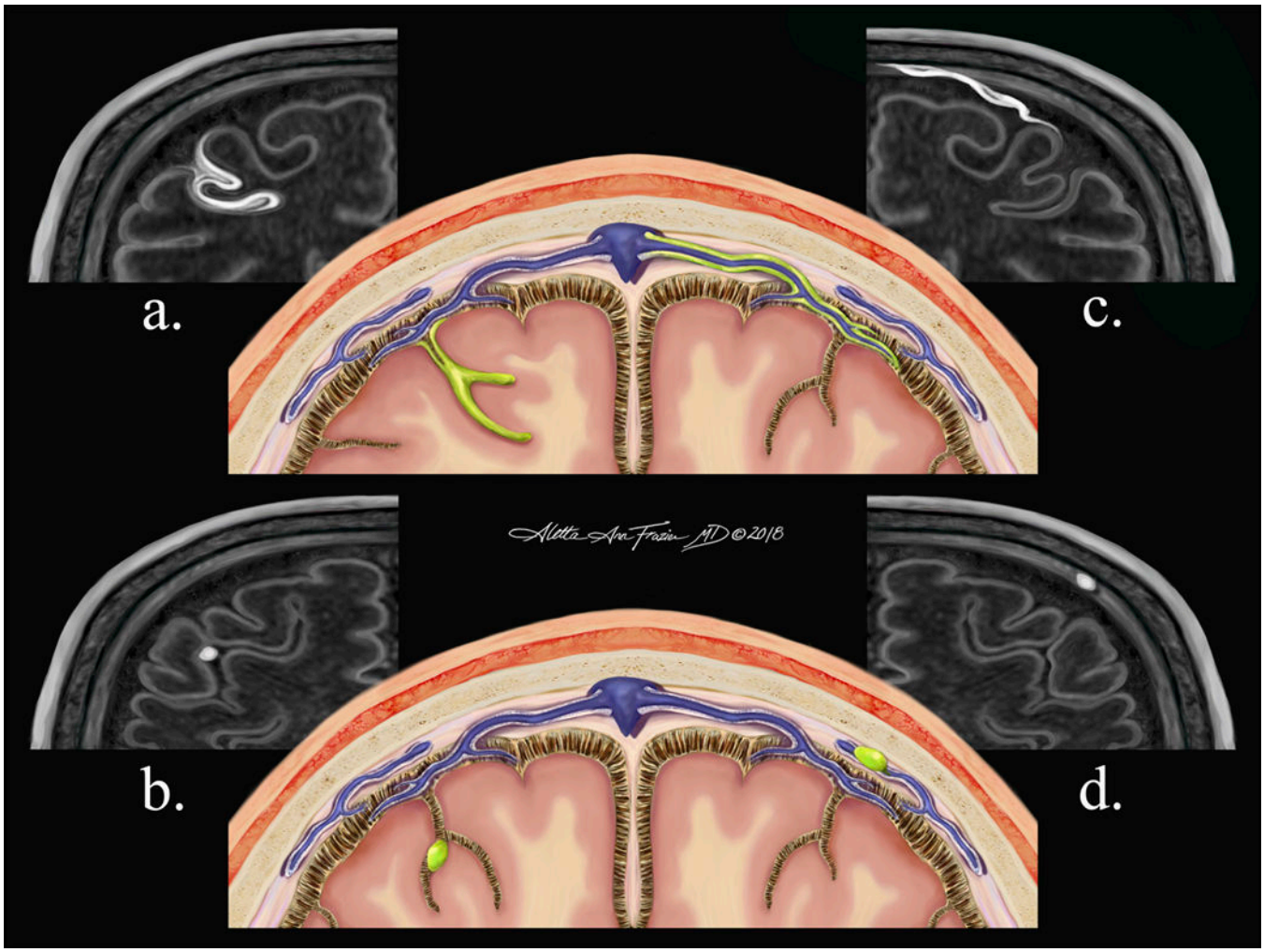

Figure 1:
Original illustration depicting the four morphologies of meningeal enhancement seen in this analysis. Subarachnoid spread/fill pattern (represented by green coloring in a) is an amorphous and ill-defined collection of contrast pooling within cerebral sulci. Subarachnoid nodular pattern (b) is defined as a punctate, discrete site of meningeal enhancement located within cerebral sulci abutting the pial surface. Venous rim pattern (c) is characterized by extension of contrast along the outer margin of large meningeal vessels with preserved internal flow void creating a characteristic tram-track appearance. Dural nodular pattern (d) is a circumscribed, rounded focus of contrast situated along the dural margin without extension into the subarachnoid space. The perivascular, tubular white structures (seen in schematics a,b,&d) represent the recently discovered meningeal lymphatic system. Reaccumulation of leaked contrast from the cerebrospinal fluid into these meningeal lymph channels is a potential mechanism for the venous rim pattern (c).

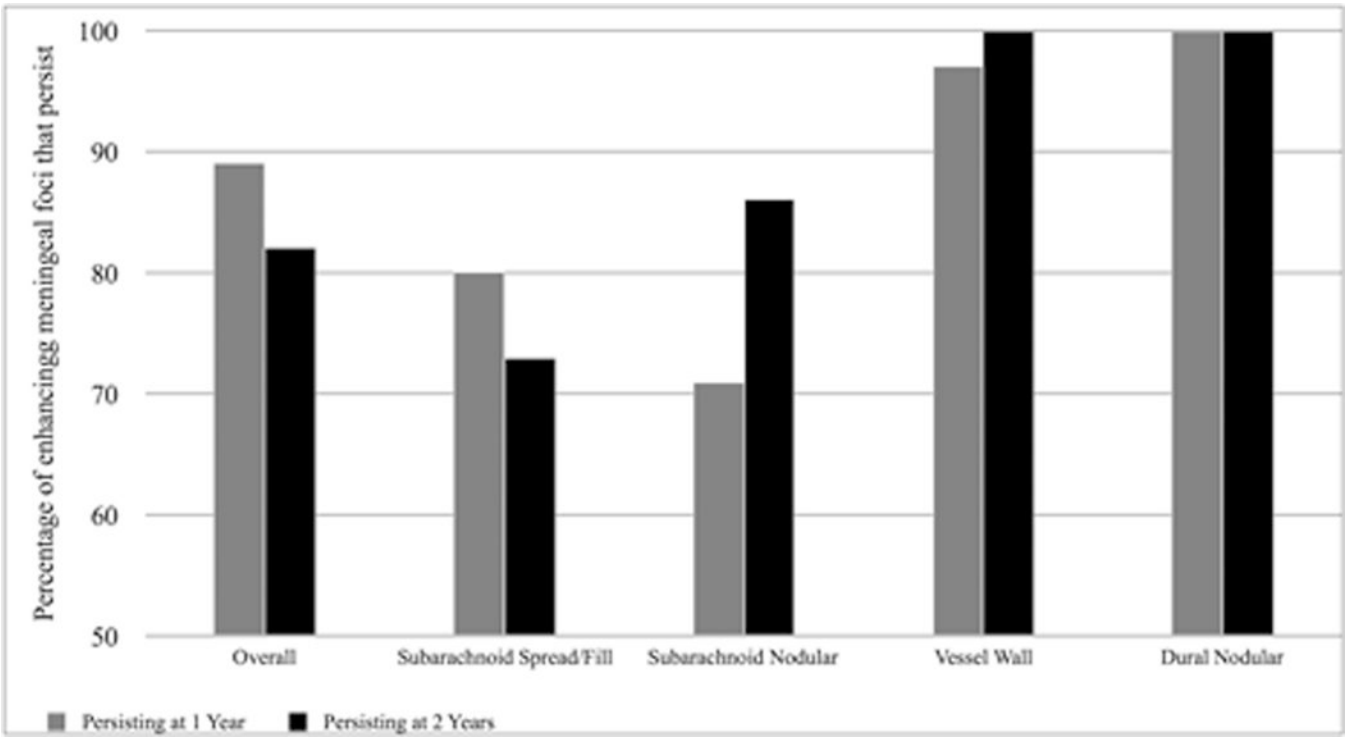

Figure 2:

Graph displaying the percentages of baseline enhancing meningeal foci that persist 1 year later (gray bars) and 2 years later (black bars). All 31 participants were scanned at baseline and at 1 year, but 2-year data is limited to 15 participants. At 1 year, persistence was noted in 253/284 (89%) overall foci, 91/114 (80%) subarachnoid spread/fill foci, 10/14 (71%) subarachnoid nodular foci, 104/107 (97%) vessel wall foci, and 46/46 (100%) dural nodular foci. At 2 years, persistence was noted in 132/161 (82%) overall foci, 45/62 (73%) subarachnoid spread/fill foci, 6/7 (83%) subarachnoid nodular foci, 55/55 (100%) vessel wall foci, and 34/34 (100%) dural foci.

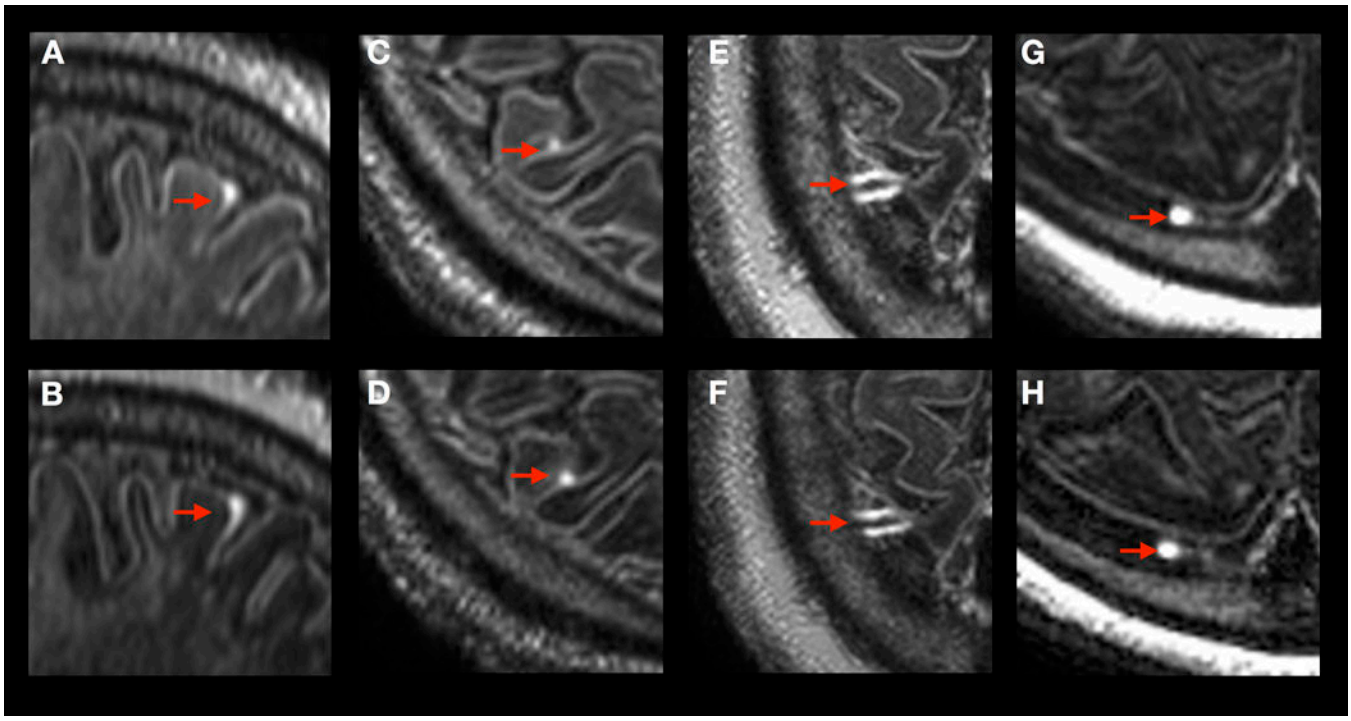

Figure 3:

Examples of persisting foci of meningeal enhancement on delayed post-contrast FLAIR at 7T. Sagittal reformatted images show subarachnoid spread/fill enhancement that persists from December 15, 2015 (A) to March 3, 2017 (B) in a 58 year-old woman with relapsing-remitting MS. Axial images show subarachnoid nodular enhancement that persists from October 8, 2014 (C) to March 3, 2017 (D) in a 49 year-old man with relapsing remitting MS. Axial images show vessel wall enhancement that persists from March 14, 2016 (E) to April 4, 2017 (F) in a 57 year-old man with primary progressive MS. Axial images show dural enhancement that persists from May 9, 2016 (G) to May 31, 2017 (H) in a 44 year-old woman with secondary progressive MS. Note that no intrinsic signal was observed in these locations on pre-contrast acquisitions (not shown).

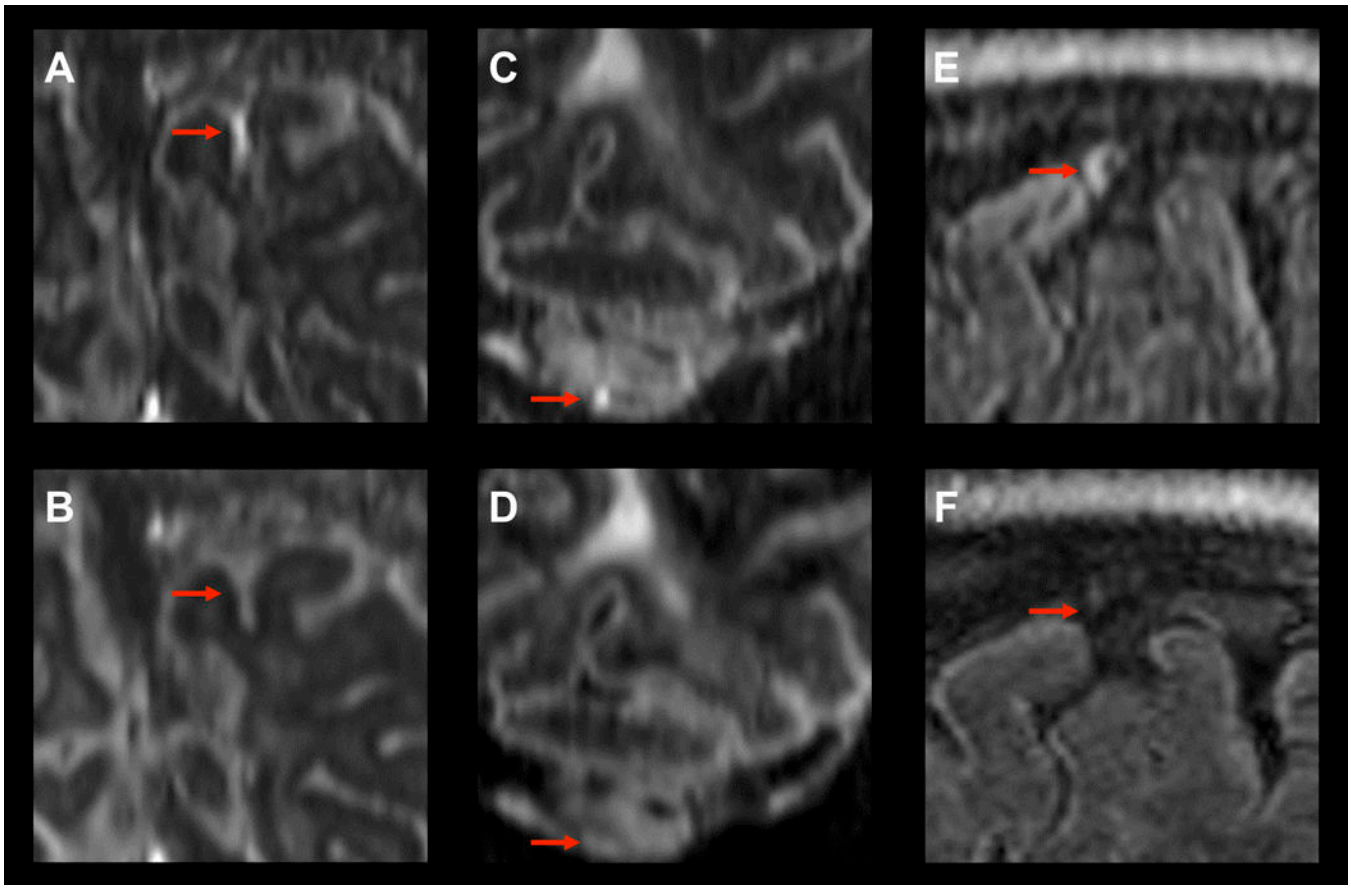

Figure 4:

Examples of resolving foci of meningeal enhancement on delayed post-contrast FLAIR at 7T. Coronal reformatted images show subarachnoid spread/fill enhancement that resolves between October 23, 2014 (A) and February 26, 2016 (B) in a 49 year-old woman with relapsing-remitting MS. Coronal reformatted images show subarachnoid nodular enhancement within cerebellar folia that resolves between October 8, 2014 (C) and February 19, 2016 (D) in a 49 year-old man with relapsing remitting MS. Sagittal formatted images show vessel wall enhancement that resolves from May 9, 2016 (E) to May 31, 2017 (F) in a 44 year-old woman with secondary progressive MS. Note that no foci of meningeal enhancement classified as dural subtype resolved in this study.

Table 1:

MRI sequence parameters

Sequence	Resolution (in mm)	Repetition Time (TR)	Inversion Time (TI)	Echo Time (TE)	Parallel Imaging	Flip Angle (FA)	Time
MP2RAGE	0.7 × 0.7 × 0.7	TR_{volume} = 8.25s TR_{TFE} = 6.9ms	TI_1 = 1s TI_2 = 3.3s	1.97 ms	SENSE= 2×2	FA_1 = 7° FA_2 = 5°	9:46
MPFLAIR	0.7 × 0.7 × 0.7	8000ms	2077 ms	400 ms	SENSE= 2 ×3	90°	10:48

Table 2:

Cohort baseline characteristics

Age at Enrollment, Years	49 (26–61)
Sex	11/31 Males (35%), 20/31 Females (65%)
Disease Subtype at Enrollment	21/31 (68%) RR, 7/31 (23%) SP, 3/31 (10%) PP
Disease Duration at Enrollment, Months	109 (8–461)
Patients with New Relapses in Past 30 Days	1/31 (3%)
Number of Relapses in Past Year Per Subject	0 (0–3)
Modified Fatigue Impact Scale (MFIS) Score at Enrollment	43 (0–78)
Symbol Digits Modality Test (SDMT) at Enrollment	50 (35–81)
Expanded Disability Status Scale (EDSS) Score at Enrollment	3 (1–6.5)
Immunomodulatory Treatment Status at Baseline	25/31 (81%) On Treatment
	6/31 (19%) Not On Treatment
Treatment Type at Baseline	3/25 (12%) Interferon
	6/25 (24%) Glatiramer
	2/25 (8%) Natalizumab
	1/25 (4%) Teriflunomide
	4/25 (16%) Fingolimod
	9/25 (36%) Dimethyl Fumarate
# of subjects who switched between disease modifying therapies from baseline to follow-up scans	10/31

RR = Relapsing remitting MS

SP= Secondary progressive MS

PP = Primary progressive MS

Median values are shown with range of observed values in parentheses.

Table 3:

Anatomic distribution within the brain of enhancing meningeal foci at baseline

Region of the Brain	Number of Foci At Baseline	Percentage of Foci at Baseline
Right Frontal	60	21.1
Left Frontal	64	22.5
Right Parietal	44	15.5
Left Parietal	44	15.5
Right Occipital	20	7.0
Left Occipital	24	8.4
Right Temporal	16	5.6
Left Temporal	8	2.8
Right Cerebellum	2	0.7
Left Cerebellum	2	0.7

Table 4:

Wilcoxon rank-sum test for longitudinal persistence of meningeal enhancement versus demographic and clinical factors

	On Treatment (n=25)	Not on treatment (n=6)	Progressive MS (n=10)	Non-Progressive MS (n=21)	EDSS Progressor at 1 year[#] (n=7)	EDSS Non-Progressor at 1 year[#] (n=24)
Total Number of Overall Foci Persisting at 1 Year Per Subject	9 (1–24)	9 (1–15)	8 (1–24)	9 (1–15)	12 (1–15)	7.5 (1–24) [*]
Total Number of Subarachnoid Spread/Fill Foci Persisting at 1 Year Per Subject	2 (0–9)	2 (0–6)	2 (0–9)	2 (0–9)	5 (1–9)	2 (0–9)
Total Number of Subarachnoid Nodular Foci Persisting at 1 Year Per Subject	0 (0–2)	0 (0–1)	0 (0–0)	0 (0–2) [*]	0 (0–0)	0 (0–2)
Total Number of Vessel Wall Foci Persisting at 1 Year Per Subject	3 (0–11)	3.5 (1–6)	2 (0–6)	3 (0–11)	3 (0–11)	3 (0–7)
Total Number of Dural Foci Persisting at 1 Year Per Subject	1 (0–9)	1 (0–6)	1 (0–9)	1 (0–6)	1 (0–6)	1 (0–9)

[*] $p<0.05$

[#] Criteria for EDSS progressor status as listed in the Methods section

EDSS = Expanded Disability Status Scale

Median values listed with range of observed values in parentheses.