Meningeal inflammation in multiple sclerosis

The key to the origin of cortical lesions?

Caterina Mainero, MD, PhD
Celine Louapre, MD, PhD

Correspondence to Dr. Mainero: caterina@nmr.mgh.harvard.edu

Neurology® 2015;85:12–13

Cortical demyelinating lesions are a common pathologic feature of multiple sclerosis (MS), an immune-mediated inflammatory and degenerative disorder of the CNS. Most knowledge on cortical demyelinating lesions in MS derives from neuropathology, which demonstrated that cortical lesions, though more commonly observed in progressive MS, may occur from the earliest stages of the disease, seemingly independent of lesions in white matter (WM).[1–4]

Histopathologic examinations of MS brains described a wide spectrum of cortical lesions in MS, based on their location relative to the venous supply of the cerebral cortex,[5] and within the cortical laminae.[4] Subpial lesions, which involve the outer layers of the cortex without extending to WM, represent the most common type of cortical plaques in MS, particularly in the progressive stages of the disease.

At present, we are unsure of the causes of subpial demyelination and neurodegeneration in MS. Some pathologic studies reported that cortical lesions in progressive MS showed only modest lymphocytic and macrophagic inflammatory infiltrates and blood–brain barrier (BBB) breakdown,[4] which are typical of WM lesions. However, in some cases subpial lesions appeared topographically associated with meningeal inflammatory infiltrates organized in follicular-like structures.[2,3] These observations have led to the hypothesis that subpial lesions in MS may be induced by soluble factors, which diffuse from the meninges into the cortex and trigger demyelination directly or indirectly through activation of microglia.[2] Examinations using brain biopsies obtained early in MS demonstrated the presence of cortical inflammatory demyelinating lesions,[1] topographically associated with areas of meningeal inflammation. In some cases cortical and BBB damage preceded the appearance of classic WM lesions, supporting the existence of an early pathologic process that primarily targets the cortex, independently from WM, and possibly linked to meningeal inflammation.

In this issue of *Neurology*®, Absinta et al.[6] report the use of postcontrast T2-weighted fluid-attenuated inversion recovery (FLAIR) brain MRI as a tool for imaging in vivo meningeal inflammation, using the surrogate measure of BBB leakage in leptomeningeal vessels in a cohort of 299 MS cases. Overall, 25% of patients with MS exhibited at least one focal area of leptomeningeal contrast enhancement. Persons with progressive MS were more likely to display leptomeningeal contrast enhancement (33% of secondary and primary progressive patients) than those with relapsing-remitting MS (19% of patients). Interestingly, MS cases positive for focal leptomeningeal contrast enhancement had higher disability scores and greater brain and cortical atrophy than negative leptomeningeal enhancement MS cases. Pathology in 2 MS progressive cases that later came to autopsy disclosed perivascular lymphocytic and mononuclear infiltration in 3 areas of leptomeningeal contrast enhancement, in association with subpial cortical demyelination. Histopathologic characterization of a control area in a sulcus that had no evidence of leptomeningeal enhancement in vivo showed absence of perivascular clusters of inflammatory cells, despite the presence of subpial demyelination.

Leptomeningeal contrast enhancement remained substantially stable over time in a subset of patients with MS who underwent follow-up scanning 1–5 years after the baseline MRI, suggesting persistent inflammatory infiltration of the meningeal vessels of interest. Such findings also suggest that BBB leakage in the meningeal compartment might be different than that known to occur in WM vessels, where it usually resolves more rapidly after lesion formation.

The exciting results from the work of Absinta et al., if reproduced in other MS cohorts, indicate that postcontrast FLAIR MRI is a promising tool for assessing leptomeningeal vascular leakage linked to meningeal inflammation in MS. A study by Eisele et al.[7] using a similar MRI protocol based on FLAIR postcontrast scans, however, was not able to detect BBB dysfunction of leptomeningeal vessels in a heterogeneous cohort of 112 patients with MS. The study also included fewer patients with progressive MS. Standardization of acquisition protocols and

See page 18

From the A.A. Martinos Center for Biomedical Imaging (C.M., C.L.), Massachusetts General Hospital, Charlestown; and Harvard Medical School (C.M., C.L.), Boston, MA.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

consensus recommendations for scans assessment would be needed for comparisons of data across centers and MS cohorts.

The strengths of the present study include the large cohort and confirmation by pathologic examination. There are further aspects that require investigation. Although challenging, these would include future assessments of sensitivity of the method by conducting a more comprehensive and systematic pathologic sampling, as previously performed in histopathologic-MRI correlations of cortical MS lesions.[8,9] Given that leptomeningeal postcontrast FLAIR enhancement relies on disrupted integrity of leptomeningeal vasculature BBB, it may not be sensitive to areas of meningeal inflammation in which vascular abnormalities are more subtle, or occur and resolve rapidly. It would also be interesting to know whether focal leptomeningeal enhancement occurs in disorders other than MS, and the underlying mechanisms that make leptomeningeal enhancement in MS stable over time and fixed in space.

Knowledge remains elusive on the association between meningeal inflammation and cortical demyelination, particularly the subpial type, and on the temporal dynamics of such association in vivo. The combination of postcontrast FLAIR MRI with quantitative protocols at 7T, as well as longitudinal observations, could help to clarify these aspects. Recent work from our group used 7T magnetic resonance quantitative T2* imaging to map in vivo cortical integrity throughout the cortical width in a cohort of participants at different stages of MS.[10] A gradient of cortical pathology occurred throughout stages of MS, with changes being mostly localized in the outer cortical layers and cortical sulci in the earliest disease stages (≤3 years disease duration), and involving deeper cortical laminae, sulci, and gyri in later MS. We interpreted these findings as expression of a cortical pathologic process driven from the pial surface. This pattern of localization of cortical pathology could be related to meningeal inflammation, favored by the topographic distribution of the cortical vascular supply or by regions of low CSF flow.

Current and future developments in molecular imaging of B- and T-lymphocytes, and microglia, could add important information for understanding the nature and extent of meningeal inflammation in MS in vivo and its link to cortical demyelination, helping to answer the question whether cortical demyelination is primarily associated with inflammation.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES

1. Lucchinetti CF, Popescu BF, Bunyan RF, et al. Inflammatory cortical demyelination in early multiple sclerosis. N Engl J Med 2011;365:2188–2197.
2. 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 2007;130:1089–1104.
3. Magliozzi R, Howell OW, Reeves C, et al. A gradient of neuronal loss and meningeal inflammation in multiple sclerosis. Ann Neurol 2010;68:477–493.
4. Peterson JW, Bo L, Mork S, Chang A, Trapp BD. Transected neurites, apoptotic neurons, and reduced inflammation in cortical multiple sclerosis lesions. Ann Neurol 2001;50:389–400.
5. Kidd D, Barkhof F, McConnell R, Algra PR, Allen IV, Revesz T. Cortical lesions in multiple sclerosis. Brain 1999;122:17–26.
6. Absinta M, Vuolo L, Rao A, et al. Gadolinium-based MRI characterization of leptomeningeal inflammation in multiple sclerosis. Neurology 2015;84:18–28.
7. Eisele P, Griebe M, Szabo K, et al. Investigation of leptomeningeal enhancement in MS: a postcontrast FLAIR MRI study. Neurology 2015;84:770–775.
8. Pitt D, Boster A, Pei W, et al. Imaging cortical lesions in multiple sclerosis with ultra-high-field magnetic resonance imaging. Arch Neurol 2010;67:812–818.
9. Schmierer K, Parkes HG, So PW, et al. High field (9.4 Tesla) magnetic resonance imaging of cortical grey matter lesions in multiple sclerosis. Brain 2010;133:858–867.
10. Mainero C, Louapre C, Govindarajan ST, et al. A gradient in cortical pathology in multiple sclerosis by in vivo quantitative 7 Tesla imaging. Brain 2015;138:932–945.