Toward understanding cortical lesions in multiple sclerosis

Jeroen J.G. Geurts, PhD
Hugo Vrenken, PhD

Address correspondence and reprint requests to Dr. Jeroen J.G. Geurts, VU University Medical Center, Departments of Pathology & Radiology, Room PK-1X 104, De Boelelaan 1118, 1081 HV Amsterdam, the Netherlands
j.geurts@vumc.nl

Neurology® 2010;75:1224–1225

Multiple sclerosis (MS) is insidious, with a complex pathology and unknown pathogenesis. MS researchers have realized that the condition is not a typical "white matter disease," but that damage to the cerebral gray matter (GM), both cortical and in deep gray nuclei, may be as extensive, or more so, as WM pathology.[1] Histopathology[2] and MRI studies[3,4] show that GM damage becomes increasingly prominent with progression of disease. In the chronic disease phase, total brain atrophy as measured with MRI is determined predominantly by GM atrophy.[3] While cortical demyelinated MS lesions were investigated and classified histopathologically,[5,6] their in vivo visualization remains challenging.[7] On conventional imaging techniques such as T2-weighted MRI, cortical lesions are missed in up to 95% of the cases,[7] and a need for advanced MRI techniques that could fill this gap became apparent.

One of these newly developed MRI techniques, double inversion recovery (DIR), uses 2 inversion pulses to suppress signals from WM and from CSF, leaving only the cerebral GM visible,[8] though also slightly suppressed. The resulting GM signal, with better contrast between normal-appearing GM and GM lesions, endows DIR with a 5-fold increase in detection of MS cortical lesions.[9] The downside of suppressing so much magnetic resonance signal is that the resulting DIR image has a poorer signal-to-noise ratio, making lesion identification more difficult and less reproducible. To translate DIR results reliably from single centers to a broader setting, formal consensus among raters from different centers is needed, as is postmortem verification that DIR signal hyperintensities truly represent cortical lesions.

Nevertheless, single center results have been important in showing that cortical hyperintensities on DIR are not only common and widespread in patients with MS, but can explain physical and cognitive impairment. Calabrese et al.[10] showed that cortical lesions appear early in relapse-onset MS and increase in number and size with progression of disease; further, they showed that these lesions are related to physical and cognitive impairment,[11] and are associated with other MRI indicators of damage such as T2 lesion load and WM and GM atrophy.[12] They also showed that cortical lesions are sparse in benign forms of the disease,[13] perhaps (partly) explaining a more favorable clinical course, and that cortical lesion development may be responsive to new treatments such as natalizumab. In this issue of *Neurology*®, the same authors[14] add to this work by showing for the first time that lesion probability mapping can be used to assess frequency and distribution of cortical lesions in a large group of patients with relapsing-remitting (RR) and primary progressive (PP) MS.

Overall, 68% of their patients with RRMS and 85% of the patients with PPMS had cortical lesions, but the number of lesions per patient (on average 5–6 lesions) was similar between groups. The distribution of cortical lesions was also similar between patients with RRMS and PPMS. The most anatomically specific analyses (voxel-wise statistics) did not yield any significant results, but quantification by brain anatomic region showed potentially interesting patterns of distribution of cortical MS lesions. Cortical lesions on DIR were most often found in frontal areas, but also in the temporal cortex. Anterior cingulate and motor areas seemed to be predilection sites, whereas cuneal, calcarine, and lateral occipital gyrus were relatively spared. This topographic distribution of focal cortical damage certainly warrants more investigation. Why would some areas of the MS cortex be more prone to pathology than others? In Alzheimer disease, pathology initially targets those areas that are most constitutively activated (default areas),[15] which suggests that neurons that are used more are lost faster. This is, as the authors indicate, an equally interesting hypothesis for the MS setting. With progressing pathology throughout WM and GM in MS, and functional reorganization of the brain occurring to maintain function, one may expect

See page 1234

e-Pub ahead of print on August 25, 2010, at www.neurology.org.

From the Departments of Radiology (J.J.G.G., H.V.), Pathology (J.J.G.G.), and Physics & Medical Technology (H.V.), VU University Medical Center, Amsterdam, the Netherlands.

Disclosure: Author disclosures are provided at the end of the editorial.

complex changes of brain network dynamics. Whether this results in selective vulnerability of certain neuronal networks or of so-called hubs (highly connected areas within brain networks), and whether these changes then contribute to cortical demyelination that can be visualized with DIR, are all highly intriguing questions.

Studies like the one by Calabrese and colleagues illustrate that much progress has been made in visualizing and analyzing GM abnormalities in MS, which now gives way to new and exciting ideas about the development and ontology of cortical pathology. Future studies should confirm the topographic pattern suggested by this study, but should also investigate the precise relations between demyelination and degeneration, e.g., by studying cortical lesion probability maps in relation to regional cortical atrophy measurements. Moreover, this framework should be used to study the combined effects of cortical MS lesions and cortical atrophy on clinical, especially cognitive, impairment. It is intriguing that this study shows more similarities than differences in number, volume, frequency, and distribution of cortical lesions between 2 groups of patients with MS, which are otherwise defined by discrepancies in clinical, radiologic, and pathologic features. This is yet another indication that there is more to MS than lesions only, and we await further developments within this field with enthusiasm.

DISCLOSURE

Dr. Geurts serves on scientific advisory boards for the Dutch MS Research Foundation and Merck Serono; serves on the editorial board of MS International; and has received research support from the Dutch MS Research Foundation and Biogen Idec. Dr. Vrenken receives research support from Merck Serono, Novartis, and the Dutch MS Research Foundation.

REFERENCES

1. Geurts JJ, Barkhof F. Grey matter pathology in multiple sclerosis. Lancet Neurol 2008;7:841–851.
2. Kutzelnigg A, Lucchinetti CF, Stadelmann C, et al. Cortical demyelination and diffuse white matter injury in multiple sclerosis. Brain 2005;128:2705–2712.
3. Fisher E, Lee JC, Nakamura K, Rudick RA. Gray matter atrophy in multiple sclerosis: a longitudinal study. Ann Neurol 2008;64:255–265.
4. Fisniku LK, Chard DT, Jackson JS, et al. Gray matter atrophy is related to long-term disability in multiple sclerosis. Ann Neurol 2008;64:247–254.
5. Bo L, Vedeler CA, Nyland HI, Trapp BD, Mork SJ. Subpial demyelination in the cerebral cortex of multiple sclerosis patients. J Neuropathol Exp Neurol 2003;62:723–732.
6. 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.
7. Geurts JJ, Bo L, Pouwels PJ, et al. Cortical lesions in multiple sclerosis: combined postmortem MR imaging and histopathology. AJNR Am J Neuroradiol 2005;26:572–577.
8. Pouwels PJ, Kuijer JP, Mugler JP III, Guttmann CR, Barkhof F. Human gray matter: feasibility of single-slab 3D double inversion-recovery high-spatial-resolution MR imaging. Radiology 2006;241:873–879.
9. Geurts JJ, Pouwels PJ, Uitdehaag BM, et al. Intracortical lesions in multiple sclerosis: improved detection with 3D double inversion-recovery MR imaging. Radiology 2005;236:254–260.
10. Calabrese M, Rocca MA, Atzori M, et al. A 3-year magnetic resonance imaging study of cortical lesions in relapse-onset multiple sclerosis. Ann Neurol 2010;67:376–383.
11. Calabrese M, Agosta F, Rinaldi F, et al. Cortical lesions and atrophy associated with cognitive impairment in relapsing-remitting multiple sclerosis. Arch Neurol 2009;66:1144–1150.
12. Calabrese M, Rocca MA, Atzori M, et al. Cortical lesions in primary progressive multiple sclerosis: a 2-year longitudinal MR study. Neurology 2009;72:1330–1336.
13. Calabrese M, Filippi M, Rovaris M, et al. Evidence for relative cortical sparing in benign multiple sclerosis: a longitudinal magnetic resonance imaging study. Mult Scler 2009;15:36–41.
14. Calabrese M, Battaglini M, Giorgio A, et al. Imaging distribution and frequency of cortical lesions in patients with multiple sclerosis. Neurology 2010;75:1234–1240.
15. Buckner RL, Snyder AZ, Shannon BJ, et al. Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. J Neurosci 2005;25:7709–7717.

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Neurology 2010;75;1224-1225 Published Online before print August 25, 2010
DOI 10.1212/WNL.0b013e3181f5d4f1