AJNR

MR Studies of the Spinal Cord in Patients with Multiple Sclerosis: What Should We Do?

David B. Hackney

AJNR Am J Neuroradiol 1999, 20 (9) 1581-1583
http://www.ajnr.org/content/20/9/1581

MR Studies of the Spinal Cord in Patients with Multiple Sclerosis: What Should We Do?

In this issue of the *AJNR*, Rocca et al (page 1710) report a comparison of three imaging techniques for detection of plaques in patients with definite multiple sclerosis (MS). They find that a fast short tau inversion recovery (fast STIR) technique was superior to a fast spin-echo (FSE) and a magnetization transfer–prepared gradient-echo (MT-GE) approach. The fast STIR images showed the largest number of lesions, and lesions that were visible with FSE or MT-GE were almost always apparent with fast STIR. This confirms the findings of an earlier investigation by Hittmair and colleagues (1) that reported fast STIR to be a highly sensitive technique, but contradicts Thorpe's results (2) citing similar performance for fast STIR and FSE. As the authors of the current article note, there have been many studies of sensitivity of pulse sequences for detection of MS plaques, with MT-GE, FSE, fluid-attenuated inversion recovery (FLAIR), and conventional spin-echo (SE) yielding inconsistent results (3–5). These earlier works, and the results reported by Rocca and colleagues, raise the question of which imaging approach should be used for evaluation of patients with suspected or known MS. In order to answer this question, we must decide what we are seeking. If the goal is to detect the largest number of candidate lesions, then the methods employed by Rocca et al, and by others who have conducted similar studies, are appropriate. The sequence that reveals the largest number of possible lesions will be considered best. This ''more is better'' approach is appropriate only if one can assume that detecting the largest number of lesions is useful and, by implication, that most or all abnormalities found on these images truly represent MS plaques. There are, however, reasons to suspect that the highest lesion count may not be the best measure of imaging performance in evaluation of MS, and that at least some of the lesions detected may represent false-positive results.

Why Perform MR Studies of the Spinal Cord in Patients with MS?

Similar to the case in the brain (6), MR studies will increase the overall sensitivity of clinical evaluation of MS. It is well known that some patients present only with spinal symptoms, and that a smaller number of patients present at a time when there are no detectable lesions in their brains. Adding a spinal cord survey will permit us to recognize evidence of MS earlier in the clinical course and, perhaps, institute aggressive therapy before further deterioration takes place. Spinal imaging also may increase the specificity of diagnosis if it is assumed that all apparent abnormalities truly are real, that there are no benign causes of high-intensity regions (ie, nothing analogous to the UBOs of the brain), and that detection of plaques in the cord may guide the diagnosis to MS when there is a larger differential diagnosis before the imaging study. In patients with known demyelinating disease, spinal cord imaging may be helpful in characterizing the severity of current involvement and in predicting future progression of the disease. For example, it has been reported that the expanded disability status scale (EDSS) has particularly strong associations with spinal disease (7, 8). Thus, the severity of spinal cord lesions may come to be a predictor of the need for early and aggressive therapy. MR assessment of spinal cord involvement may also become a method for following the response to therapy.

What Parameters Should Be Measured?

All of the indications discussed above rest upon availability of suitable MR parameters to be measured and followed. In some studies of cord involvement, there has been an assumption that the technique that reveals the greatest number of lesions is optimal (1, 3, 9). From the purely imaging point of view, diagnostic accuracy would appear to be the most important criterion. Thus, one would ask to what extent the MR findings matched the actual number and distribution of cord lesions, as might be assessed at postmortem examination. Such studies, however, are almost impossible to perform, because one will rarely be in the position of being able to confirm that lesions seen on MR images were correctly diagnosed as to their presence and etiology. For this reason, authors have focused on the ''sensitivity'' of the sequence for detection of lesions. This is the easiest parameter to measure, requiring only identification of abnormalities in at least some of the cords imaged. Of course, what is being measured is not sensitivity by the formal definition of TP/(TP + FN) where TP = true positive and FN = false negative. This cannot be calculated because there is no objective proof of the presence or absence of each lesion identified on the images. Instead, the authors have reported the ratio (number of lesions detected by the technique to be tested)/(number of lesions presumed to have been present by a reference criterion). Often, as in this case, the reference criterion is the consensus interpretation of all available data, including the test technique. The assumption is that the technique that depicts the largest number of lesions is the best. Implicit is the assumption that false-positive findings are rare, inconsequential, or both. This latter assumption probably is a reason-

able conclusion to draw when the patient population consists exclusively of those who are highly likely to have real lesions in their cords (for example, patients with definite MS). Nevertheless, when the full range of patients undergoing MR imaging is considered, the ''no false positives'' assumption is more difficult to accept. In the absence of supporting evidence, the possibility of false-positive examinations and false-positive lesions within an examination will remain real and will be more likely as the number of apparent lesions increases.

Does This Retrospective Analysis Add to the Information Available from Prospective Interpretation?

The finding that fast STIR was the best performing sequence in retrospective analysis is difficult to interpret. In the retrospective analysis, the authors reviewed all images from a patient simultaneously and used this evaluation to reclassify some lesions seen previously as ''false positive'' on the initial reading and others seen only on retrospective analysis as ''false negative'' on the initial reading. The only criterion for deciding whether a lesion was truly present was the overall interpretation of all images together. Because it is not known whether the overall interpretation was more accurate than the interpretation of any imaging sequence in isolation, conclusions about lesion presence on the retrospective review do not necessarily reflect a higher standard of truth. If the authors were most frequently swayed by the findings on one particular sequence, then that sequence would have the best figures for false-positive and false-negative interpretations, although it would not necessarily be more accurate. The retrospective review is a summary of how persuasive the images were found to be, without confirmation that these impressions of accuracy were correct. Although the authors have proved that more apparent abnormalities will be detected with the fast STIR technique than with the FSE or MT-GE sequences they employed, neither the prospective nor the retrospective arms of their study confirm that the reporting of cervical cord abnormalities will be more reliable or that diagnostic certainty will be increased. With no data on intra- or interobserver variability, these results do not tell us whether fast STIR results will be more reproducible than those of other pulse sequences. The authors found that they were far more likely to detect ''false negatives'' than ''false positives'' on retrospective review. Accordingly, the number of lesions detected increased from stage 1 to stage 2 for each pulse sequence. This implies a greater willingness to accept a lesion as present when the interpretations of different images conflict than to conclude that the positive finding was incorrect. There were 38 ''false negatives'' and only two ''false positives'' in the study. Because the fast STIR sequence revealed the most stage 1 lesions, and the authors rarely concluded that a stage 1 lesion was a false-positive finding (only one such lesion was reported for fast STIR), stage 2 simply indicated that the fast STIR images were believed to be the most persuasive. It is likely that in many cases the findings were similar to those illustrated in figure 2 (page 1713). Here both MT-GE and FSE appear to confirm the presence of one of the lesions that was identifiable with fast STIR, but only fast STIR demonstrated both abnormalities. The decision that both lesions were real and that fast STIR was the superior technique is appealing in this case, but these results cannot ensure diagnostic accuracy.

What Other Criteria Might Be Employed for Analyzing Spinal Cord MR Studies of MS Patients?

In a study comparing 2D FSE with 3D FSE, Stevenson et al (5) identified far more lesions with the 3D technique. They did not attempt to correlate the number of lesions found with the patients' clinical status or disease progression. With similar methods, Keiper et al (3) found a smaller number of lesions by using FLAIR than by using spin-echo techniques. Again, there was no information about the relationship between lesion count and clinical findings. Fukutake et al (10) found that the presence of lesions on sagittal images correlated well with somatosensory evoked responses in MS patients. Trop et al (11) found cord lesions in 96% of MS patients who were selected for inclusion based on signs and symptoms of myelopathy. They reported weak but significant correlations between lesion load (a combination of number of and size of lesions), sensory function, and EDSS. Follow-up of these patients, however, revealed that 30% of cases of clinical improvement or stability were associated with progression of imaging findings, and that in most patients who deteriorated clinically, the imaging findings were stable or improved. Trop and colleagues recorded not only the number of lesions, but their size and enhancement properties. Nijeholt et al (7) characterized MS lesions as focal, diffuse, or both. Eighty-three percent of patients had focal or focal-plus-diffuse lesions. More interesting were their correlations of lesion type with clinical status. Diffuse abnormalities were more strongly associated with progressive MS than with relapsing-remitting disease. Diffuse abnormalities alone, without focal lesions, were never seen in patients with relapsing-remitting MS. Focal lesion load (defined as a combination of lesion count and longitudinal extent of cord plaques) was not significantly related to EDSS score. Nevertheless, the presence of diffuse lesions, with or without focal plaques, was significantly associated with poorer EDSS scores. There was a significant association of EDSS with spinal cord cross-sectional area. Filippi et al (12, 13) and Losseff et al (8) also have reported significant associations between cord area or diameter and the clinical status of these patients. The change in EDSS has been found to be related to changes in cord atrophy (12). In a study of a variety of imaging criteria, cord cross-sectional area was

found to be the best predictor of EDSS in primary progressive MS (14). In a comprehensive review of the role of imaging in MS, Miller et al (15) concluded that, although the presence of plaques on T2-weighted images at initial presentation is a highly significant finding in patients with suspected MS, ''the correlations between T2 abnormalities and disability are modest'' in established MS. They attributed this dichotomy to the low pathologic specificity of the T2 changes seen on routine images and argue that newer methods that may indicate demyelination or axonal degeneration should be more valuable for predicting outcome in MS patients. In a pilot study, Silver et al (16) reported the feasibility of obtaining MT studies of the spinal cord in MS patients, creating the hope that the success of this approach in the brain (6, 17) may be replicated in the spine.

This brief editorial suggests that a simple enumeration of lesions may not be the ideal method for characterizing MS of the spinal cord. Therefore, although it is useful to know that fast STIR will reveal more lesions than other techniques, it is not clear this is the most important criterion. Unfortunately, we are lacking studies that compare diagnostic and predictive values of lesion count, lesion load (11), lesion type (7), cross-sectional dimensions (4, 8, 12, 13), MT measures (16), or other parameters across acquisition techniques. Are all of these measures valuable? Is there a best subset of parameters that captures all the information to be obtained from a spinal MR study of these patients? What is the optimal method for acquiring each set of images? As radiologists, we need to know not only how best to generate the data, but also what measurements are the most useful for our clinical colleagues.

Although it appears at the moment unlikely that counting spinal MS lesions is the best way to analyze MR studies, it is important that we know the performance of candidate pulse sequences for detecting abnormalities. Potential confusion due to false-positive findings is a constant fact of life in radiologic practice. Once a potential abnormality has been recognized, radiologists consider a variety of factors such as location and size of the lesion, signal characteristics, and clinical setting to decide whether an apparent lesion is real. A technique that consistently reveals more candidate lesions will be useful provided that the false-positive rate is not unacceptably high. Rocca et al have told us that radiologists seeking to detect the largest possible number of lesions would do better to employ fast STIR than FSE or this MT-GE sequence. Because the fast STIR technique is ''low-tech'' and readily implemented on many instruments, this strong performance in lesion detection will be available to a large number of sites.

Application to Other Diseases

The finding of high sensitivity for fast STIR should be applicable to diseases other than MS. Thus, detection of cord lesions of all etiologies may be improved by adding fast STIR to the protocol, perhaps substituting it for other T2-weighted sequences. As is the case for MS, the questions of whether the detected lesion actually exists, and the contribution of its detection to patient management, will remain for further study in the academic arena and confirmation with other patient information in the clinical realm.

DAVID B. HACKNEY
Member, Editorial Board

References:

1. Hittmair K, Mallek R, Prayer D, Schindler EG, Kollegger H. **Spinal cord lesions in patients with multiple sclerosis: comparison of MR pulse sequences.** *AJNR Am J Neuroradiol* 1996;17:1555–1565
2. Thorpe JW, Kidd D, Moseley IF, et al. **Spinal MRI in patients with suspected multiple sclerosis and negative brain MRI.** *Brain* 1996;119:709–714
3. Keiper MD, Grossman RI, Brunson JC and Schnall MD. **The low sensitivity of fluid-attenuated inversion-recovery MR in the detection of multiple sclerosis of the spinal cord.** *AJNR Am J Neuroradiol* 1997;18:1035–1039
4. Lycklamaa Nijeholt GJ, Castelijns JA, Weerts J, et al. **Sagittal MR of multiple sclerosis in the spinal cord: fast versus conventional spin-echo imaging.** *AJNR: Am J Neuroradiol* 1998;19:355–360
5. Stevenson VL, Moseley IF, Phatouros CC, MacManus D, Thompson AJ, Miller DH. **Improved imaging of the spinal cord in multiple sclerosis using three-dimensional fast spin echo.** *Neuroradiology* 1998;40:416–419
6. Grossman RI, McGowan J. **Perspectives on Multiple Sclerosis.** *AJNR Am J Neuroradiol* 1998;19:1251–1265
7. Lycklamaa Nijeholt GJ, Barkhof F, Scheltens P, et al. **MR of the spinal cord in multiple sclerosis: relation to clinical subtype and disability.** *AJNR Am J Neuroradiol* 1997;18:1041–1048
8. Losseff NA, Webb SL, O'Riordan JI, et al. **Spinal cord atrophy and disability in multiple sclerosis. A new reproducible and sensitive MRI method with potential to monitor disease progression.** *Brain* 1996;119:701–708
9. Moseley IF, Miller DH, Gass A. **The contribution of magnetic resonance imaging to the assessment of optic nerve and spinal cord involvement in multiple sclerosis.** *J Neurol Neurosurgery Psych* 1998;64:S15–S20
10. Fukutake T, Kuwabara S, Kaneko M, Kojima S, Hattori T. **Sensory impairments in spinal multiple sclerosis: a combined clinical, magnetic resonance imaging and somatosensory evoked potential study.** *Clin Neurol Neurosurgery* 1998;100:199–204
11. Trop I, Bourgouin PM, Lapierre Y, et al. **Multiple sclerosis of the spinal cord: diagnosis and follow-up with contrast-enhanced MR and correlation with clinical activity.** *AJNR Am J Neuroradiol* 1998;19:1025–33
12. Filippi M, Colombo B, Rovaris M, Pereira C, Martinelli V, Comi G. **A longitudinal magnetic resonance imaging study of the cervical cord in multiple sclerosis.** *J Neuroimaging* 1997;7:78–80
13. Filippi M, Campi A, Colombo B, et al. **A spinal cord MRI study of benign and secondary progressive multiple sclerosis.** *J Neurol* 1996;243:502–505
14. Lycklamaa Nijeholt GJ, van Walderveen MA, Castelijns JA, et al. **Brain and spinal cord abnormalities in multiple sclerosis. Correlation between MRI parameters, clinical subtypes and symptoms.** *Brain* 1998;121:687–697
15. Miller DH, Grossman RI, Reingold SC and McFarland HF. **The role of magnetic resonance techniques in understanding and managing multiple sclerosis.** *Brain* 1998;121:3–24
16. Silver NC, Barker GJ, Losseff NA, et al. **Magnetisation transfer ratio measurement in the cervical spinal cord: a preliminary study in multiple sclerosis.** *Neuroradiology* 1997;39:441–445
17. McGowan JC, Filippi M, Campi A and Grossman RI. **Magnetization Transfer Imaging: Theory and application to multiple sclerosis.** *JNNP* 1998;64(Suppl):S66–S69