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Beginning with the earliest MR studies of multiple sclerosis (MS), it was clear that the extent of disease activity seen on MR images was considerably greater than that seen clinically. Because monitoring disease activity with clinical measures has been notoriously difficult, this decade started with a sense that MR measures of disease activity would replace clinical measures and allow more precise monitoring of MS staging. The existence of a reliable surrogate measure of disease activity that could be easily quantified would improve both general patient care and the performance of clinical trials of new therapies. As the decade comes to a close, however, the most problematic issue relating to the use of MR imaging for study of MS is the generally poor relationship between MR measures of disease and clinical presentation. How does disease activity depicted on MR images correlate with that seen clinically and why is the relationship so poor?

As background, three principle clinical courses of MS are recognized today: are relapsing-remitting, secondary-progressive, and primary-progressive MS (1). In most cases, the illness begins as a relapsing-remitting disease but, over time, changes in disability occur independent of episodes of acute worsening. The presence of progression between exacerbations is the hallmark of the secondary-progressive phase. In a small number of cases, the illness begins as a progressive disease and, in about 10% of MS cases, the disease shows a progressive course without exacerbations. This course is known as the primary-progressive form of MS. Various studies have looked at the relationship between disease depicted on MR images and clinical presentation in each of these stages of MS (2). Efforts to identify a relationship between clinical and MR measures of disease have generally used two approaches. The first has been to look at the correlation between some MR measure and some measure of clinical disability in a population of patients at one point in time (a cross-sectional study). Other studies have, more appropriately, explored how predictive the extent of disease shown on some MR images is of what will happen clinically at some future point. It is the predictive value of MR imaging that will allow it to be useful as a surrogate measure of disease activity. What have the results of these studies been?

In cross-sectional studies, standard MR measures of disease, such as disease burden on T2-weighted images, have shown very limited correlations with level of disability. In general, these studies have yielded correlation coefficients of about 0.2 or 0.3, meaning that only a small part of the clinical disability is explained by the level of disease seen using the MR measure. Why have the correlations been so poor? Several explanations have been put forward. First, in almost all studies, disability has been measured using what is known as the expanded disability status scale (EDSS). The EDSS is heavily weighted, especially in its upper ranges toward ambulation and, thus, may not be a good measure of overall disease activity. The reports in the current issue point to improved correlations between juxtacortical lesions and cognitive dysfunction or cerebral lesion load and cognitive dysfunction. These studies support the notion that lesions in the cerebrum will be less likely to produce changes impacting standard neurologic evaluation, especially the EDSS, and will be more likely to produce cognitive changes not generally measured as a component of disability (Fulton [page 1951], Moriarity [page 1956]). In general, measures of disease burden fail to correlate with disease location.

Second, it has been postulated that lack of pathologic specificity of increased signal seen on T2-weighted images accounts for the limited correlations with disability. The pathologic processes that will probably be most closely related to disability, such as irreversible demyelination and axonal damage, represent only a portion of disease accounting for increased signal on T2-weighted images Acute inflammatory lesions and those lesions with partial remyelination will be indistinguishable on T2-weighted images. Thus, imaging techniques with greater pathologic specificity, such as magnetization-transfer imaging and spectroscopy, that can measure myelin and axonal damage, respectively, may provide better radiologic-pathologic correlations. Further, techniques such as lesion load, as measured by T1 hypointensities or atrophy, may provide better reflection of tissue loss and, thus, disability. Preliminary data, although not studied nearly as extensively as disease burden on T2-weighted images, such as that presented in the article by Patel et al in this issue (page 1946), suggest that while correlations are better with these newer and possibly pathologically more specific imaging techniques, the correlations are still far from optimal.

Studies examining the predictive values of MR measures of disease have been somewhat more encouraging and have also provided insights in explaining the above-noted poor correlations. In probably the most important study, investigators at Queen's Square initiated research of patients presenting with clinical symptoms or signs consistent with the first attack of MS such as optic neuritis (termed clinically isolated syndromes) (3). The investigators performed standard T2-weighted imag-

ing and careful neurologic evaluations and then brought the patients back 5 and 10 years later for re-evaluation and repeat MR examination. The results have shown that those patients with significant disease burden at the time of presentation had a substantially greater risk of developing clinically definite MS at 5 or 10 years. Further, there was a reasonable correlation between the level of disease burden seen initially and future disability. Thus, these findings indicate that the level of disease seen on MR images early in the course of disease does relate to the future course. Consistent with these results are the studies correlating the frequency of exacerbation with contrast-enhancing lesions. When examined longitudinally using a time-series analysis, it could be shown that exacerbations were more likely during periods when the frequency of contrast-enhancing lesions was increased (4). Similarly, longitudinal studies have shown that the number of contrast-enhancing lesions seen on an initial examination is a relatively good predictor of exacerbation rate over the next year (5). Finally, natural history studies of MS indicate that some correlation exists between exacerbation rate early in the disease and future disability (Weinshenker, 1994 #5578). Together, these findings indicate that MR measures of disease activity early in the disease provide insight into its future course. These same measures, however, seem to have very little relationship to future course when measured later in the disease. This suggests that the disease process may not be linear or unifactorial. Instead, it suggests that while disease activity early in the course provides a true reflection of the extent of acute inflammatory processes normally thought to be the hallmark of the disease, progression at later stages of the disease may involve different processes. For example, the frequency of acute inflammatory lesions early in the course will set the stage of future levels of clinical disease. Once these lesions are established, however, progression may involve pathologic processes that are independent of the acute inflammatory changes and may be more closely related to loss of axons and degenerative processes that are not easily measured by standard MR techniques. To resolve these very important questions, it will be necessary to apply newly evolving imaging techniques to define patient populations carefully and to place more emphasis on studies that look at the predictive value of MR measures of disease in patients with established MS, especially those with progressive MS. Despite the limited correlations between standard MR measures of disease activity and clinical disability, MR imaging has provided critical new insights into the natural history of MS and provides a powerful tool for studying the disease.

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References

1. Lublin F, Reingold S. **Defining the clinical course of multiple sclerosis: results of an international survey.** *Neurology* 1996; 48:901–911
2. Miller DH, Grossman RI, Reingold SC, McFarland HF. **The role of magnetic resonance techniques in understanding and managing multiple sclerosis.** *Brain* 1998;121:3–24
3. O'Riordan J, et al. **The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up.** *Brain* 1998;121:495–503
4. Smith ME, Stone LA, Albert PS, et al. **Clinical worsening in multiple sclerosis is associated with increased frequency and area of gadopentetate dimeglumine-enhancing magnetic resonance imaging lesions.** *Ann Neurol* 1993;33:480–489
5. Molyneux PD, Filippi M, Barkhof F, et al. **Correlations between monthly enhanced MRI lesion rate and changes in T2 lesion volume in multiple sclerosis.** *Ann Neurol* 1998;43:332–339