MR Imaging in Monitoring and Predicting Treatment Response in Multiple Sclerosis

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KEYWORDS

• Multiple sclerosis • MR imaging • Interferon • Patient assessment
• Relapsing-remitting multiple sclerosis • Scoring system • Treatment response

KEY POINTS

- Conventional MR imaging measures have been established as a promising tool for predicting and monitoring treatment response, mainly if combined with clinical measures (relapses and disability progression).
- Baseline brain MR imaging scans are required in any patient starting a disease-modifying treatment. Timing of this reference scan should consider the precise onset of treatment and the mechanism of action of the drug that is being evaluated.
- There is a need for additional and alternative MR imaging markers for disease and treatment monitoring leading to an individualized therapeutic approach, including new targets of immune modulation/suppression, neuroprotection, and remyelination.
- MR imaging studies should be performed with at least 1.5-T field strength magnets, using a standardized protocol, and following the technical recommendations suggested in recently published guidelines.
- The data currently available are not sufficient to support the use of volume measures of brain or spinal cord to monitor treatment response.

INTRODUCTION

Multiple sclerosis (MS) is a chronic disorder of the central nervous system in which autoreactive immune cell activation causes a focal and diffuse inflammation, demyelination, and axonal loss.

MR imaging is the most sensitive tool for the identification of lesions that characterize MS, as detected in more than 97% of patients with clinically definite MS. As a result of this high sensitivity, MR imaging has become an essential technique not only in the diagnosis of MS but also as a prognostic marker in the initial phase of the disease, both in relation to the prediction of clinical relapses and the severity of future disability, and contributing to the understanding of its natural history.[1]

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With the approval of a new generation of disease modifying drugs (DMD) for MS, MR imaging is acquiring an important role in monitoring and predicting the efficacy of these treatments, as well as in the detection of opportunistic infections and paradoxic reactions.

MR IMAGING MEASURES

Conventional Techniques

In the study of MS, T2-weighted sequences (T2 conventional, fast T2, T2-fluid-attenuated inversion recovery [FLAIR]), and contrast-enhanced T1-weighted sequences, are considered conventional MR imaging techniques. Despite its limited specificity in determining the pathologic substrate of focal MS lesions, T2-weighted sequences are useful in the study of the natural history of MS. Thus, longitudinal studies have revealed that new lesions appear 5 to 10 times more frequently than clinical relapses, indicating that MS is a dynamic disease even in phases of clinical remission (**Fig. 1**).[2] This progression can be quantified from the number of new or enlarged T2 lesions, or by calculating their volume (lesion load) using semiautomated or fully automated segmentation techniques. These measures commonly are used as a surrogate marker in assessing the effectiveness of new treatments in phase III clinical trials. The increase of this lesion volume ranges from 5% to 10% annually. DMD have shown a significant and sustained reduction in the degree of this increase[3,4] (**Table 1**).

Natural history studies of MS using contrast-enhanced T1-weighted sequences also show that the activity and progression of the disease still exist in phases of clinical stability. Active lesions that enhance gadolinium are more frequent than clinical relapses.[2] A significant decrease in the number of lesions with inflammatory activity has also been observed in clinical trials in patients receiving DMD,[3] and nowadays this measure is used in the monitoring of inflammatory activity in patients receiving these treatments[5] (see **Table 1**).

Brain Atrophy

From all MR imaging techniques that have been used to measure the neurodegenerative component of MS, cerebral volume as an atrophy marker has been proved to be the most robust and feasible for use in clinical studies.[6]

Interest in using brain volume as a marker of neurodegeneration has increased in recent years with the development of new treatments with a potential neuroprotective effect. Brain volume measures are used routinely as surrogate markers of efficacy in clinical trials, in order to analyze the potential protective effect of treatments on the progression of brain atrophy.[7] Brain atrophy, which is detectable even in the early stages of disease, correlates not only with the irreversible disability but also with fatigue and cognitive impairment.[8,9] Global or regional brain atrophy is currently considered a clinically relevant measure in relation to the progression of the disease.[10] In addition, brain volumetric measures have proved to be robust and sensitive to longitudinal changes, and are also good predictors of patients who develop significant disability progression. The progressive decline in brain volume occurs in patients with MS more rapidly than in healthy persons (**Fig. 2**). It has been reported that the annual rate of decline in brain volume is approximately 0.5% to 1.3% in patients with MS, which is higher than in young adults (18–50 years old), which ranges from 0.1% to 0.3%.[11]

Different studies have shown that the degree of progression of brain atrophy in short periods of time (1–2 years) is a good predictor of the degree of disability in the medium term (8–10 years).[12] In addition, brain atrophy occurs in the earliest stages of the disease. It has been reported that during the first 9 months after a clinically isolated syndrome (CIS) a significant decrease in brain volume occurs in patients who experienced a second clinical episode and thus converted to clinically definite MS (CDMS).[8] In contrast, other reports showed that the progression of brain atrophy

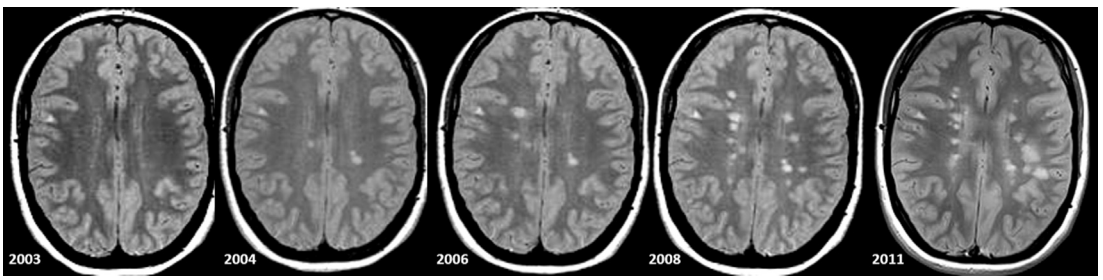

Fig. 1. Proton density-weighted sequences. Serial study for 8 years in a patient with MS showing the progression in the number and volume of focal demyelinating lesions affecting the white matter of the cerebral hemispheres.