Advances in Multiple Sclerosis and its Variants

Conventional and Newer Imaging Techniques

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KEYWORDS

• Multiple sclerosis • Conventional MR imaging • Diffusion tensor imaging • MR spectroscopy • Myelin free water component

KEY POINTS

- Multiple sclerosis (MS) and its variants are inflammatory and neurodegenerative central nervous system (CNS) diseases characterized by white matter plaques, atrophy, and diffuse abnormalities in surrounding gray and white matter.
- Conventional magnetic resonance (MR) imaging is sensitive for focal white matter lesions and atrophy in MS, but correlates poorly with clinical measures of disease.
- Improvements in technology have increased the sensitivity of conventional MR in evaluating MS, and automated techniques have improved accuracy and allowed the quantification of disease.
- Nonconventional MR imaging techniques detect the diffuse CNS changes present outside white matter plaques in MS and may correlate more closely with patients' symptoms.
- Imaging of the spinal cord and optic nerves in MS provides another method for evaluating disease severity and progression, with improved correlations with clinical disease.

INTRODUCTION

Multiple sclerosis (MS) and its variants such as neuromyelitis optica are inflammatory as well as neurodegenerative diseases of the central nervous system (CNS) characterized by demyelination, inflammation, gliosis, and neuronal loss.[1–3] Although MS has traditionally been thought of as a primarily autoimmune disease of white matter with focal demyelinating plaques, diffuse abnormalities are now known to be present throughout the CNS.[3,4] Extensive changes in the normal-appearing white matter (NAWM) have been shown in all MS subtypes and clinically isolated syndromes, with postmortem histopathologic studies showing glial hyperplasia, edema, inflammatory infiltrates, and thinning of myelin.[5,6] In addition, gray matter is not spared by the disease, with focal

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lesions as well as diffuse abnormalities presenting early in cortical and subcortical structures.[5,7,8]

Conventional magnetic resonance (MR) imaging plays an important paraclinical role in the diagnosis of MS by showing dissemination of disease in both space and time.[9] MR imaging also aids in monitoring disease progression, evaluating the efficacy of novel treatments, and providing important prognostic information in patients presenting with clinically isolated syndromes such as transverse myelitis.[2,4,10,11] In transverse myelitis, the demonstration of white matter lesions in the CNS on MR imaging significantly increases the likelihood of the patient subsequently developing clinically definite MS.[11] In addition, in patients with established MS, conventional MR findings such as cerebral atrophy also carry important prognostic implications for the subsequent course of the disease.[1,4]

Although conventional MR remains the mainstay for imaging of MS and variants, several nonconventional MR techniques have been developed that can detect and quantify the full breadth of abnormalities present in the surrounding white and gray matter.[2,12] This article begins by reviewing current conventional MR imaging of MS, highlighting some of the strengths and limitations of the technique. Several recent advances in conventional MR imaging of MS are discussed. The article then explores several of the most promising nonconventional MR methods currently being developed to better characterize inflammatory and neurodegenerative diseases such as MS. In addition, optic nerve imaging is briefly reviewed.

CONVENTIONAL MR IMAGING OF FOCAL WHITE MATTER LESIONS

Conventional MR techniques in MS imaging are based on the delineation of demyelinating white matter plaques in the brain and spinal cord.[4,12] Multiple conventional MR pulse sequences are used in this evaluation, including T2-weighted, proton density–weighted, and fluid-attenuated inversion recovery (FLAIR)–weighted sequences, as well as T1-weighted imaging before and after the administration of gadolinium contrast (**Box 1**).[4,13] These pulse sequences provide a sensitive method for detecting and quantifying focal white matter disease as well as more acute inflammatory activity in patients with MS (**Fig. 1**).[14] However, white matter MS lesions shown on conventional MR are not specific to a particular underlying pathologic mechanism, and can reflect various processes including edema, gliosis, inflammation, demyelination, and axonal loss.[12,15]

Box 1
Conventional MR sequences used in the evaluation of MS and its variants

- Fast spin echo T2-weighted or proton density (PD)-weighted imaging
  - White matter lesion detection, improved visualization in posterior fossa with PD-weighted imaging
- FLAIR, axial and sagittal planes
  - Suppression of cerebrospinal fluid (CSF) with improved detection of periventricular white matter lesions
- Noncontrast T1-weighted imaging
  - Demonstration of white matter lesion hypointensity associated with axonal loss in more chronic plaques
- Diffusion-weighted imaging
  - Diffusion restriction associated with white matter lesions indicating acute inflammation
- Contrast-enhanced T1-weighted imaging
  - White matter lesion enhancement suggesting breakdown of blood-brain barrier and acute inflammation

Certain imaging features of white matter lesions (**Box 2**) increase the specificity of conventional MR findings for underlying pathologic mechanisms.[14] For example, lesion hypointensity on T1-weighted imaging is correlated with axonal loss, and is found most often in chronic lesions.[4,13,15] Enhancement of white matter lesions on postcontrast T1-weighted imaging is more often associated with acute to subacute inflammation and breakdown of the blood-brain barrier.[4,13,15] Although most of these enhancing MS plaques become permanent T2-hyperintense lesions, only approximately half go on to T1 hypointensity and associated neuronal loss, highlighting the brain's reparative capacity.[15] Restricted diffusion also suggests a more acute process. In addition, hypointensity on T2-weighted imaging in cortical and deep gray matter structures such as the thalamus and basal ganglia is likely caused by excessive iron deposition in patients with MS and may correlate with other imaging findings and patientsymptoms.[16–18]

Despite the sensitivity of conventional MR findings for focal white matter disease in MS, as well as the relative pathologic specificity of some imaging features, there remains a discrepancy between the burden of white matter disease as measured