

Diagnostic Value of Double Inversion Recovery MRI in the Evaluation of Brain Lesions in Multiple Sclerosis

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Abstract:

Background: Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease of the central nervous system characterized by focal demyelinated plaques, inflammation, gliosis, neurodegeneration, and diffuse injury in normal-appearing tissue. Conventional magnetic resonance imaging (MRI) is central to diagnosis and monitoring but has limited sensitivity for cortical and grey matter lesions.

Objective: To review the pathological and clinical basis of MS imaging and the role, technical principles, clinical applications, advantages, and limitations of double inversion recovery (DIR) in the evaluation of MS brain lesions.

Conclusion: DIR provides valuable complementary information in MS brain imaging, particularly for cortical and juxtacortical lesions. It should complement rather than replace conventional T2-weighted and FLAIR sequences because lesion conspicuity remains dependent on anatomical location and sequence characteristics.

Keywords: Multiple Sclerosis; Double Inversion Recovery; Cortical Lesions; Grey Matter; FLAIR

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease of the central nervous system (CNS) that affects the brain, spinal cord, and optic nerves. It is characterized pathologically by focal demyelinated plaques accompanied by inflammation, gliosis, and neurodegeneration. MRI has revolutionized the diagnosis and monitoring of MS by allowing in vivo visualization of these lesions and is a cornerstone of the McDonald diagnostic criteria for demonstrating dissemination in space and time ⁽¹⁾.

Conventional MRI sequences sensitively detect white matter abnormalities, even when patients are asymptomatic; however, clinical disability does not always correlate directly with lesion burden. This discrepancy, commonly described as the clinico-radiological paradox, partly reflects the limited ability of conventional techniques to demonstrate cortical grey matter involvement and diffuse microscopic damage in normal-appearing tissue ⁽²⁾.

Cortical and deep grey matter involvement are clinically meaningful features of MS. Cortical lesions can occur early and increase in size and number over time, particularly in progressive disease. Nevertheless, only a small proportion of cortical lesions are visible in living patients even with high-resolution imaging, and subpial lesions remain especially difficult to detect ⁽³⁾.

Double inversion recovery (DIR) was developed to improve tissue contrast by suppressing signals from two tissues simultaneously. In brain imaging, the suppression of cerebrospinal fluid (CSF) and white matter signals provides clear delineation of the cerebral cortex and improves detection of subtle cortical and juxtacortical lesions. This review discusses the pathological and clinical context of MS imaging and the role of DIR in evaluating MS brain lesions.

Pathological Basis of Multiple Sclerosis

Neuropathology and Immunopathology

The pathological hallmark of MS consists of sharply defined areas of primary demyelination with astrocytic gliosis and chronic inflammation. These lesions occur not only in white matter but also in cortical grey matter, deep brainstem nuclei, and the spinal cord. Although axons are relatively preserved during primary demyelination, axonal and neuronal injury remains substantial and becomes a major pathological predictor of permanent disability when it exceeds the compensatory capacity of the CNS ⁽⁴⁾.

Remyelination may be complete or partial, but the extent of repair varies widely among patients. Beyond focal plaques, subtle and diffuse degeneration occurs in tissue that appears normal, contributing to brain and spinal cord atrophy. The relative contributions of focal demyelination, axonal injury, remyelination, and diffuse degeneration vary according to disease phenotype, stage, and individual course ⁽⁵⁾.

Inflammation and White Matter Lesions

MS is a chronic inflammatory condition of the CNS characterized by perivascular clusters of T and B lymphocytes that extend into the surrounding tissue. Inflammation is usually most intense early in the disease and tends to decline with age and disease duration, although it may remain prominent in progressive MS. Microglial activation and macrophage accumulation occur at sites of demyelination and axonal injury and may also affect normal-appearing white and grey matter ^(6,7).

White matter lesions include active lesions with severe blood-brain barrier disruption, slowly expanding chronic active lesions, inactive lesions, and partially remyelinated shadow plaques. Active lesions are more common during the early relapsing phase, whereas slowly expanding lesions represent a substantial proportion of plaques in progressive MS and may require long-term high-resolution MRI follow-up for detection ⁽⁸⁾.

Grey Matter Demyelination and Diffuse Injury

Cortical lesions involving the forebrain, cerebellum, and hippocampus are now recognized as a major component of MS pathology. Subpial lesions are the most frequent cortical lesion type but often remain undetected in vivo. Cortical lesions may appear early and increase with disease duration, particularly in progressive MS ⁽³⁾.

Subpial demyelination is associated with meningeal inflammation and commonly begins at the cortical surface before extending inward. Activated microglia contribute to cortical injury, while severe neuronal loss may occur in both lesional and normal-appearing cortex. Deep grey matter structures, including the thalamus, hypothalamus, and basal ganglia, may also contain demyelinated plaques and show progressive neuronal injury ^(9,10).

Diffuse injury in normal-appearing tissue includes low-grade inflammation, axonal damage, microglial activation, and gliosis. Some diffuse damage may arise independently of visible lesions, while Wallerian degeneration following earlier axonal or neuronal injury also contributes. These abnormalities become more prominent with age and disease progression and are incompletely demonstrated by conventional MRI ^(11,12).

Clinical Course and Multiple Sclerosis Phenotypes

MS is heterogeneous and multifactorial, with diverse symptoms and variable clinical trajectories. In most patients, the early course consists of episodes of neurological dysfunction that develop over days to weeks and are followed by partial or complete recovery. The early clinical spectrum includes clinically isolated syndrome (CIS) and relapsing-remitting MS (RRMS). Some patients later develop sustained progression, termed secondary progressive MS (SPMS), while a smaller group demonstrates progression from onset, termed primary progressive MS (PPMS) ^(13,14).

CIS is the first focal or multifocal inflammatory demyelinating event suggestive of MS. It develops acutely or subacutely, lasts at least 24 hours, and occurs without fever or infection. Typical manifestations

include optic neuritis, internuclear ophthalmoplegia, brainstem or cerebellar syndromes, and partial transverse myelitis ⁽¹⁵⁾.

RRMS is the predominant phenotype at onset and is characterized by clearly defined attacks followed by full or partial recovery. Disease activity is identified by clinical relapses or new inflammatory MRI changes. Over time, some patients accumulate disability and transition to SPMS, which is defined by gradual sustained worsening after an initial relapsing-remitting course ^(16,17).

PPMS is characterized by increasing disability from onset, with possible plateaus, temporary improvement, or occasional acute relapses. It often presents as a gradually worsening spinal cord syndrome and has no unique imaging feature that independently distinguishes it from RRMS in an individual patient ^(18,19).

Diagnosis of Multiple Sclerosis

MS diagnosis is based on clinical findings supported by brain and spinal cord MRI and, when required, cerebrospinal fluid examination and other ancillary tests. The clinical attack should be compatible with central nervous system inflammatory demyelination, and no better explanation should account for the presentation ⁽¹⁶⁾.

The 2017 McDonald criteria established MRI as a surrogate for demonstrating dissemination in space and dissemination in time. Imaging demonstrates lesions in different characteristic CNS regions and documents the appearance or accumulation of lesions over time. In patients with a typical CIS, simultaneous enhancing and non-enhancing lesions, a new T2 or enhancing lesion on follow-up, or CSF-specific oligoclonal bands may establish dissemination in time ⁽²⁰⁾.

MRI is the first-line imaging examination in suspected MS. Brain and spinal cord MRI with and without contrast is recommended unless contraindicated. Typical MRI findings should always be interpreted with the clinical history and examination because the McDonald criteria are intended to confirm MS once clinically suspected, not to distinguish MS from all alternative neurological diseases.

Ancillary investigations include CSF-specific oligoclonal bands, evoked potentials, optical coherence tomography, and targeted autoantibody testing. Aquaporin-4 and myelin oligodendrocyte glycoprotein antibodies are particularly important when the presentation or imaging features are atypical for MS and raise concern for neuromyelitis optica spectrum disorder or MOG antibody-associated disease ^(21,22).

Conventional MRI in Multiple Sclerosis

MRI provides positive findings in approximately 95% of patients with clinically definite MS and is superior to computed tomography for visualizing small lesions. Conventional protocols include T1-weighted, contrast-enhanced T1-weighted, T2-weighted, and FLAIR sequences, each demonstrating different components of lesion pathology ⁽²³⁾.

T1-Weighted Imaging and Black Holes

A T1 black hole is an abnormal hypointense area relative to normal-appearing white matter that corresponds to a hyperintense lesion on T2-weighted imaging. Acute black holes may coincide with contrast enhancement, whereas chronic or persistent black holes remain hypointense without enhancement. Persistent T1 hypointensity reflects expansion of the extracellular space and loss of structural components and is associated with severe demyelination and axonal loss ⁽²⁴⁾.

Contrast-enhanced T1-weighted imaging detects active inflammatory lesions. Gadolinium enhancement indicates blood-brain barrier disruption and usually persists for two to six weeks. Enhancement may be nodular or ring-like, and the open-ring sign can support the diagnosis of a tumefactive demyelinating lesion when differentiated from tumors or infection ^(23,25).

T2-Weighted Imaging

MS plaques are typically hyperintense on T2-weighted imaging, with round or ovoid, well-circumscribed lesions. T2 hyperintensity is sensitive but not pathologically specific because inflammation, demyelination,

edema, and gliosis can produce similar signal changes. Most lesions are discrete, although confluent and poorly defined dirty-appearing white matter may occur around the lateral ventricles ^(23,26).

T2 lesion number and volume are used as surrogate markers in clinical trials and longitudinal monitoring. Serial assessment requires standardized imaging protocols to ensure reproducibility and accurate comparison ⁽²⁷⁾.

Fluid-Attenuated Inversion Recovery

FLAIR produces heavily T2-weighted images while suppressing the CSF signal. This improves the contrast of periventricular lesions and supports detection of juxtacortical and cortical lesions. MS lesions commonly appear as bilateral asymmetric hyperintense foci and may show the characteristic Dawson's-finger configuration ^(24,28).

FLAIR has historically demonstrated lower sensitivity in the posterior fossa. Three-dimensional FLAIR provides more homogeneous CSF suppression and better depiction of small lesions than two-dimensional FLAIR but may require longer acquisition and be more susceptible to motion. Although 3D FLAIR improves lesion detection in several regions, DIR may remain superior for purely cortical lesions ^(29,30).

Limitations of Conventional MRI

Despite its essential role, conventional MRI has limited sensitivity for grey matter involvement and diffuse microscopic white matter injury. Conventional lesion burden also correlates only weakly with clinical disability. These limitations have encouraged both refined analysis of conventional data and the development of non-conventional MRI techniques ⁽²⁾.

Non-Conventional MRI Techniques

Magnetic Resonance Spectroscopy

Proton magnetic resonance spectroscopy provides metabolic information from lesions and normal-appearing tissue. Changes in N-acetylaspartate, choline, creatine, myo-inositol, and glutamate may reflect axonal injury, membrane turnover, gliosis, and inflammatory activity.

Magnetization Transfer Imaging

Magnetization transfer imaging is sensitive to macromolecular tissue integrity and may demonstrate abnormalities in lesions and normal-appearing white matter. Reduced magnetization transfer ratio has been associated with myelin loss and tissue destruction.

Diffusion MRI

Diffusion-weighted and diffusion tensor imaging characterize water mobility and tissue organization. Apparent diffusion coefficient and fractional anisotropy measurements may reveal structural damage within plaques and normal-appearing tissue that is not visible on conventional imaging.

Functional and Perfusion MRI

Functional MRI demonstrates altered activation and recruitment within visual, motor, and cognitive networks, supporting a role for cortical plasticity in maintaining function despite structural injury ⁽³¹⁾. Perfusion MRI measures cerebral blood flow, cerebral blood volume, and mean transit time and may identify inflammatory or vascular abnormalities that precede conventional MRI changes ^(2,32).

Susceptibility-Weighted Imaging

Susceptibility-weighted imaging is sensitive to iron and deoxygenated hemoglobin and can demonstrate venous structures, iron deposition, and lesion heterogeneity. It may identify lesions missed using conventional techniques and contributes to assessment of the central vein sign and paramagnetic tissue changes ⁽³³⁾.

Double Inversion Recovery

Technical Principles

Inversion-recovery sequences use an inversion pulse and a selected inversion time to suppress the signal of a specific tissue. FLAIR applies this principle to suppress CSF. DIR extends the method by applying two successive inversion pulses with appropriately selected inversion times, allowing simultaneous suppression of two tissues ⁽³⁴⁾.

In brain grey matter DIR imaging, the first inversion interval allows brain tissue magnetization to recover while CSF remains close to zero because of its longer T1 relaxation time. The second inversion interval is selected to null white matter magnetization. At this point, grey matter remains negatively magnetized and produces measurable signal, while CSF and white matter signals are suppressed.

The resulting high contrast between grey matter and surrounding CSF and white matter provides excellent cortical visualization. DIR can therefore delineate cortical and deep grey matter structures, demonstrate regional grey matter signal differences, and support segmentation-based assessment of cortical thickness and morphology ^(35,36).

Role in Cortical and Juxtacortical Lesion Detection

The ability to detect cortical lesions is clinically important because a substantial proportion of MS pathology involves the cerebral cortex or the cortico-subcortical junction. Extensive subpial demyelination may involve broad areas of cortical grey matter, while conventional MRI remains suboptimal because of limited contrast between grey and white matter ⁽³⁷⁾.

FLAIR improves cortical and subcortical lesion detection compared with conventional T2-weighted imaging, but the exact boundary between cortex and subcortical white matter may remain difficult to define. This complicates classification of juxtacortical, mixed white matter-grey matter, and purely intracortical lesions. DIR improves contrast at this interface and enhances the in vivo detection and classification of intracortical and leukocortical lesions ^(35,38).

DIR also reduces the partial-volume limitation created when multiple tissue types contribute to a single voxel. Its selective signal suppression provides direct tissue differentiation rather than relying exclusively on post-processing classification, although performance remains dependent on the efficiency of suppression pulses ⁽³⁶⁾.

Clinical Applications Beyond Multiple Sclerosis

The principal clinical applications of DIR include black-blood imaging and neuroanatomic brain imaging. Selective grey matter visualization may support assessment of cortical atrophy, local cortical thickness, and structural abnormalities in neurological and psychiatric disorders ⁽³⁹⁾.

DIR has been used to demonstrate cortical tubers, focal cortical dysplasia, heterotopias, and other cortical malformations that may be missed using conventional sequences. In subcortical band heterotopia, it can delineate the cortex, outer white matter, heterotopic grey matter band, and inner white matter as distinct structural layers ⁽³⁹⁾.

Advantages and Limitations

The major advantage of DIR in MS is improved conspicuity of cortical, intracortical, and juxtacortical lesions through simultaneous suppression of CSF and white matter. This supports more accurate lesion localization and classification and may improve assessment of cortical disease burden.

Nevertheless, DIR does not demonstrate the complete histopathological cortical lesion burden, particularly for subpial lesions. Sequence performance may also be affected by low signal-to-noise ratio, prolonged acquisition time, flow and pulsation artifacts, incomplete tissue suppression, and differences between

two-dimensional and three-dimensional acquisition. Accordingly, DIR should be interpreted together with conventional T2-weighted and FLAIR sequences rather than as a stand-alone replacement.

Future Perspectives

Three-dimensional DIR, higher magnetic field strengths, optimized inversion times, improved motion correction, and standardized acquisition protocols may enhance lesion conspicuity and reproducibility. Combining DIR with other advanced techniques, including phase-sensitive inversion recovery, susceptibility imaging, diffusion imaging, and quantitative cortical assessment, may provide a more comprehensive evaluation of cortical and diffuse MS pathology.

Future work should also clarify the relationship between DIR-detected cortical lesions, cognitive impairment, physical disability, and disease progression. Standardized lesion definitions and multi-reader validation remain necessary before cortical DIR measures can be used consistently as diagnostic, prognostic, or treatment-monitoring biomarkers.

Conclusion

DIR is a valuable advanced MRI sequence for evaluating MS brain lesions, particularly cortical, intracortical, and juxtacortical abnormalities that may be poorly visualized using conventional imaging. By suppressing CSF and white matter signals simultaneously, DIR improves cortical contrast and supports more accurate lesion localization and classification. However, conventional T2-weighted and FLAIR sequences remain essential because no single sequence demonstrates all components of MS pathology. DIR is therefore best incorporated as a complementary component of a comprehensive MS imaging protocol.

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