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The Relevance of Neuroimaging Findings to Physical Disability in Multiple Sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system and one of the leading causes of disability in young adults. While some patients with MS have a benign course in which they develop limited disability even after many years, other patients have a rapidly progressive course resulting in severe disability. However, the progression of the disease, particularly disability, is currently a predictable course with neuroimaging features to some extend. Magnetic resonance imaging (MRI) is not only the main diagnostic tool but also used to monitor response to therapies, thanks to its high sensitivity and ability to identify clinically silent lesions. This report presents a literature review which examines in detail the relationship between MRI findings and disability.

Keywords: Multiple sclerosis, magnetic resonance imaging, disability, predictors

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INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating, and neurodegenerative disease of the central nervous system (CNS) and the second most common cause of disability after trauma in young adults. Relapses, generally, are thought to reflect acute inflammation, whereas progressive disability results from diffuse neurodegeneration and successive relapses lead to accumulation of disability (1). The main goal of MS management is to reduce the long-term disability progression (2).

The established Expanded Disability Status Scale (EDSS) is the most widely used method for quantifying the clinical severity and functional deficits in MS. Higher scores on the EDSS imply high clinical disease severity.

While some patients with MS have a benign course in which they develop limited disability even after many years, other patients have a rapidly progressive course with a severe disability even in the early phase of the MS (3). Regarding its high sensitivity and ability in detecting clinically silent lesions, magnetic resonance imaging (MRI) has become the main imaging tool for both diagnosis and monitoring the treatment response. Therefore, there have been reported many studies in the literature focusing on the relationship between neuroimaging findings and MS disability.

Radiologically Isolated Syndrome

Radiologically isolated syndrome (RIS) is defined by incidental MRI findings suggestive of MS in clinically silent or asymptomatic patients. While radiological progression occurs in approximately two-thirds of individuals with RIS, one-third of individuals develop the first clinical event during a mean follow-up of five years (4, 5). Interestingly, approximately 10% of subjects with RIS progress directly into primary progressive MS (6, 7).

The recent studies have focused on identifying clinical and imaging predictors of developing the clinically isolated syndrome (CIS) or MS in RIS. High T2 lesion load, the presence of infratentorial lesions or spinal cord lesions and Gadolinium-enhancing lesions were identified as MRI predictors of conversion to clinical disease (8–10). Among these imaging findings, the spinal cord lesions seem to have the strongest impact on clinical conversion (7, 9). Recently, a large multicenter, multinational study including 451 subjects, has been performed by the RIS Consortium (7). In this study, asymptomatic cervical and thoracic spinal cord lesions were found to be the strongest predictor for the subsequent clinical events, whereas Gadolinium-enhancing lesions and infratentorial lesions did not predict clinical event development. Additionally, there were spinal cord lesions in all patients who progress to primary progressive MS, compared to 64% of those who converted to CIS. Conversely, another study involving 70 subjects showed that Gadolinium-enhancing on follow-up neuroimaging had a predictive value for conversion to clinical MS (10).

The influence of atrophy on clinical conversion is another investigated imaging predictor. The subjects with RIS who have also thalamic atrophy have increased risk for conversion. This result implies that RIS might reveal early features of CNS neurodegeneration, even before the first clinical event (11).

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Clinically Isolated Syndrome

Clinically isolated syndrome is a term widely used in neurological practice that describes a single clinical episode with features suggestive of a demyelinating inflammatory disorder of CNS. It usually affects optic nerves, brain stem, spinal cord, or rarely cerebral hemisphere. CIS is always isolated in time and space (monophasic and monofocal). It may be the first manifestation of MS with new symptoms or demyelinating lesions that fulfills MS diagnostic criteria, or it may remain a single demyelinating episode.

The risk of developing clinically definite MS from CIS has been estimated to be 42–82%, based on the duration of the follow-up period and the study cohort (12). Many risk factors for the conversion of CIS to MS have been investigated. The different conversion rates have been reported in the literature. In patients with optic neuritis, the rate of conversion to clinically definite MS has been reported between 10% and 85% (13, 14). The proportion of patients with spinal cord CIS who develop MS varies between 41% and 61% (14–16) whereas this rate remains around 53–60% in brainstem CIS (14, 15).

Presence of clinically silent T2 lesions carry the strongest risk of future clinical events leading to a diagnosis of clinically definite MS. Approximately 50–70% of patients with CIS have multiple T2 hyperintense white matter brain lesions, suggestive of demyelination on MRI (17). The patients with CIS, who have brain T2 lesions at baseline, have a 60–80% risk of conversion to MS within 10 years, while those without brain T2 lesions have only 20% risk for conversion (18–20). These T2 lesions should be suggestive of demyelination and need to be differentiated from small-vessel cerebrovascular disease lesions and migraine lesions. Some imaging features are in favor of MS: helpful for this differentiation: periventricular lesions, callosal lesions, juxtacortical, particularly U-fiber, lesions (typically spared in small-vessel lesions), central vein sign, infratentorial, especially peripheral brainstem and middle cerebellar peduncle, lesions (small vessel lesion usually involve central pons), spinal cord lesions.

Several studies have showed that the rates of conversion to MS have significantly increased in patients with T2 lesion more than with a normal baseline MRI (13, 14, 21). The risk of MS conversion after seven years was 30% in patients with less T2 lesions number compared with 70% in patients with more T2 lesion number at baseline neuroimaging (22). However, in another study with a follow up of 20 years (14) 82% of subjects with less T2 lesion number and 81% subjects with more T2 lesion number at baseline imaging converted to clinically definite MS (23). These results suggest that any T2 lesion at baseline carries a similar risk of conversion to MS in the long term while patients with a heavy T2 lesion burden tend to convert to MS at an earlier time.

In addition to the presence of T2 lesions, the location of T2 lesions also has a vital role in predicting CIS conversion. Patients who have infratentorial lesions have increased risk of conversion (15). Furthermore, this risk is slightly higher in those with brainstem lesions compared to the subjects with cerebellar lesion (15). About one-third of patients with CIS have asymptomatic spinal cord lesions (24). However, in a large multicenter study of 468 subjects with CIS, infratentorial lesions were not found to be associated with increased risk of conversion to MS (25). ON behaves differently from the other topographies of CISs such as spinal cord or brainstem for lower conversion to MS., (26). Nevertheless, the prognosis of the patients with optic neuritis has an abnormal baseline brain MRI does not differ from that of other different CIS (26). The presence of Gadolinium-enhancing lesions in baseline MRI independently predicts conversion to clinically-definite MS (21, 25, 27, 28). The patients who have a whole-brain or regional atrophy at the onset of CIS or during follow up have increased the risk of conversion (29–31).

T2 lesions

Although T2 hyperintense lesions accrual is the radiological hallmarks of disease activity in MS, a weak correlation was found between T2 lesions disability (32, 33). This weak correlation suggests that silent T2 lesions occur commonly in MS and this describes the clinico-radiological paradox (34). The possible explanations for this may be as follows: *Firstly*, the MRI lesions in MS occurs commonly "non-eloquent" areas of the brain. *Secondly,* histopathological correlates of the lesions are not so severe as to cause symptoms, for instance, mild inflammation. *Thirdly*, histopathologic changes in the normal-appearing white matter (NAWM) on conventional MRI contribute to clinical symptoms. And *finally*, all compartments of CNS such as spinal cord are not imaged. Many studies have shown that locations of T2 lesions have a more decisive influence on disability than overall lesion load in relapsing-remitting MS (RRMS) (18, 35). Although the correlation between T2 lesion load and disability is weak in the more advanced stage of the disease, T2 lesion load has a prognostic value in the onset of MS (Figure 1). Higher T2 lesion load has been associated with an increased risk of subsequent conversion to definite MS and long-term disability in patients with CIS (18, 35). However, this paradox relatively disappears regarding the topographic distribution of T2 lesions. For instance, infratentorial spinal cord lesions have more determinative value predicting the disability.

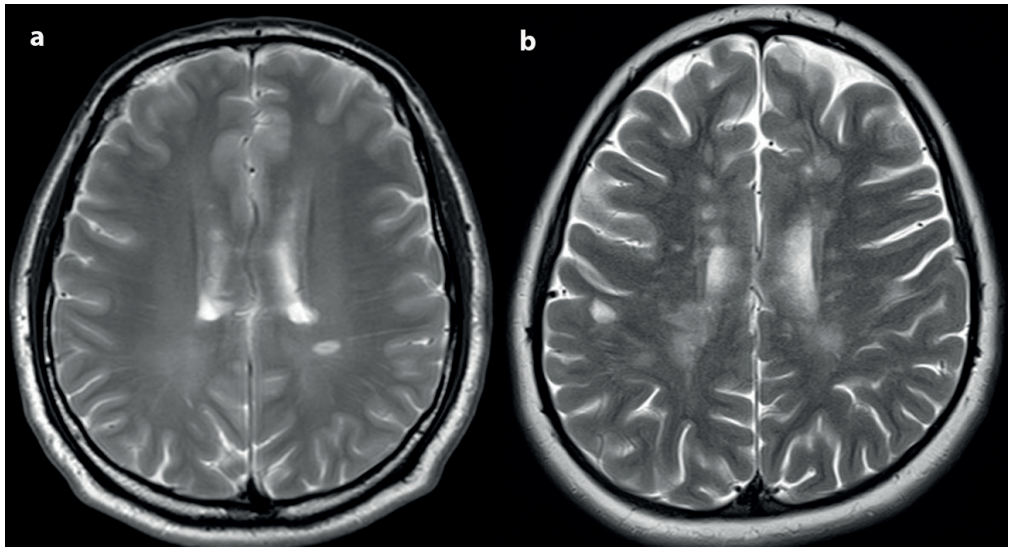

Figure 1. a, b. Axial T2-weighted MR images (a, b) show example of different T2 lesion burdens in two different patients with multiple sclerosis which have a same EDDS=5.

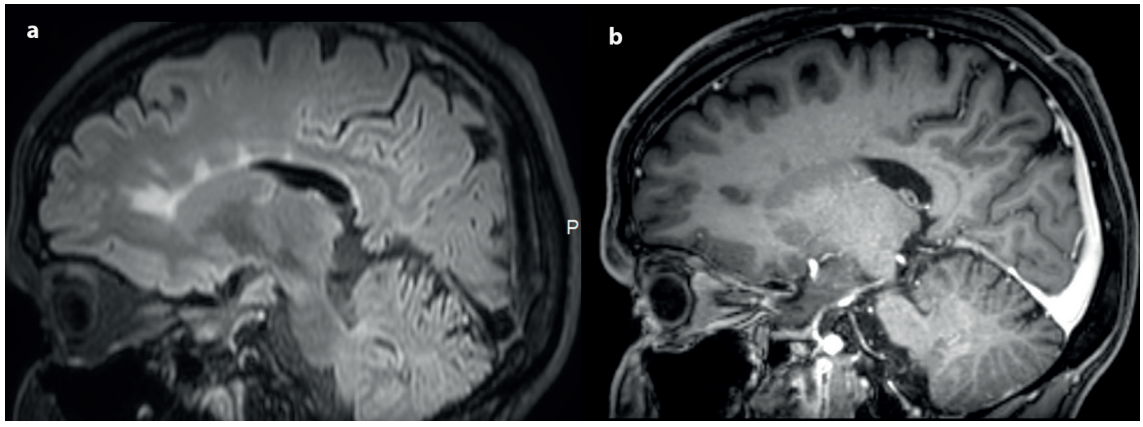

Figure 2. a, b. Sagittal FLAIR (a) and T1-weighted (b) images from the same plane in 28-year-old man with multiple sclerosis. Note that some T2 lesions does not correspond to the black hole lesions on T1-weighted image ('only T2 lesions').

Additionally, in their ten-year study, Wybreth et al. found that accumulation of brain T2 lesions mostly has an impact on cognition rather than physical performances (36).

Topographic Distribution of T2 Lesions

The importance of infratentorial lesions (including brainstem and cerebellum) was recently reemphasized in the MAGNIMS (MRI in MS) consensus guidelines in 2015 (15). Brain stem lesions are associated with an increased risk of disability. These lesions have a remarkable contribution to future disability because they are likely to affect the clinically eloquent areas (37). A large number of studies have consistently shown that spinal cord lesions have a clear role in predicting the accumulation of clinical disability (38–40) (Figure 3).

In a longitudinal study involving more than 300 MS cases, the gray matter (GM) atrophy and high cortical lesion load were found associated with physical disability progression (41). It is also shown that there was a strong correlation between a high number of cortical lesions and clinical disability (42). Many studies have suggested that thalamic volume were predictive of an increase in EDSS (43–45).

T1 Hypointense Lesions (Black Holes)

T1-black holes refer to the T1 hypointense lesion which persists for six months or longer beyond the acute stage. These lesions have been shown as a marker of axonal damage and significant demyelination in the studies of MRI-pathologic correlation (46, 47). Contrarily to T2 lesions, most studies have revealed a strong correlation between T1 black hole lesions and disability (48–50). 20–45% of "only T2 lesions" (i. e., not with T1-hypointensity) are associated with demyelination on histopathological examination whereas; this ratio increases up to 80% in T2 lesion with persistent T1 hypointensity; (51, 52) (Figure 2). A radiologic-pathologic correlation study was found that as the hypointensity of the T1 lesions increases, the axonal density decreases. It means that the darkest lesion has the lowest axonal density (47).

MR Imaging Volumetrics

Although atrophy of grey and white matter is not included in MS diagnostic criteria, it can be seen in early RRMS (53). Hence, brain atrophy, which may not be clinically relevant in the early stages of the disease, is considered a surrogate marker for neurodegeneration in MS. In the current practice, numerous automated or semi-automated software package is available for MR imaging volumetrics. The grey matter, white matter, cerebrospinal fluid, and global brain volume can be evaluated more precisely using automatic segmentation algorithms and voxel-wise methods.

The correlation between whole brain atrophy and EDSS is stronger than the correlation between T2 lesion burden and EDSS (34, 54, 55). Atrophy of the supratentorial brain has more strong correlations with a clinical disability than T2 lesion load (54, 56). Many studies revealed a strong relationship between GM atrophy and subsequent disability progression (57, 58). Furthermore, several studies with longer follow-up or MS Functional Composite disability scale suggested that GM atrophy reflected disability progression to a greater extent than WM atrophy or T2 lesions (56, 58, 59).

A large, multicenter, long-term study has identified that early brain atrophy rates were related to subsequent disability at ten-year (60). Jaspers et al. reported that central atrophy was associated with impairment in ambulatory function whereas both central and peripheral atrophy were related to impairment in neurologically more complicated tasks (61). Another relatively small cohort study suggested that larger maximal lifetime brain growth was associated with lower risk for disability progression over five years in patients with MS (62).

Unconventional/Quantitative MRI

Correspondence between the extent of visible damage on conventional MRI and clinical disability in MS has been modest and variable labeling "the clinic-radiological paradox." However, unconventional and quantitative MRI techniques including magnetization transfer imaging, diffusion tensor imaging (DTI) and proton MR spectroscopy (MRS) may be more sensitive to detect abnormalities in normal-appearing brain tissue that are not visible on standard T_1 or T_2-weighted images. To achieve more accurate analyses for elucidating relationships between disability and pathologic tissue change in MS, both unconventional and quantitative MRI techniques are required. Unfortunately, many of them have not yet been used in routine imaging diagnostics.

Diffusion Tensor Imaging is a multi-directional diffusion technique, which provides information about the microstructure of the brain. Previous reports showed that increased mean diffusivity values In T2 lesions were significantly related to disability, and low fractional anisotropy values in NAWM were associated with worse hand function. Gratsia et al. reported a correlation between ADC (apparent diffusion coefficient) in NAWM and EDSS (63). Another novel DTI technique so-called restriction spectrum imaging enables more specific estimation of tissue microarchitecture in detail. This method also allows measurement of microstructural features, such as white matter neurite density, that are undetectable by conventional diffusion imaging techniques. There were a significant correlation with EDSS and neurite density obtained in NAWM (64).

Magnetic Resonance Spectroscopy; N-acetylaspartate (NAA) is one of the major metabolites of CNS. The levels of NAA in various parts of the brain are directly correlated with neuronal health or integrity while decreased

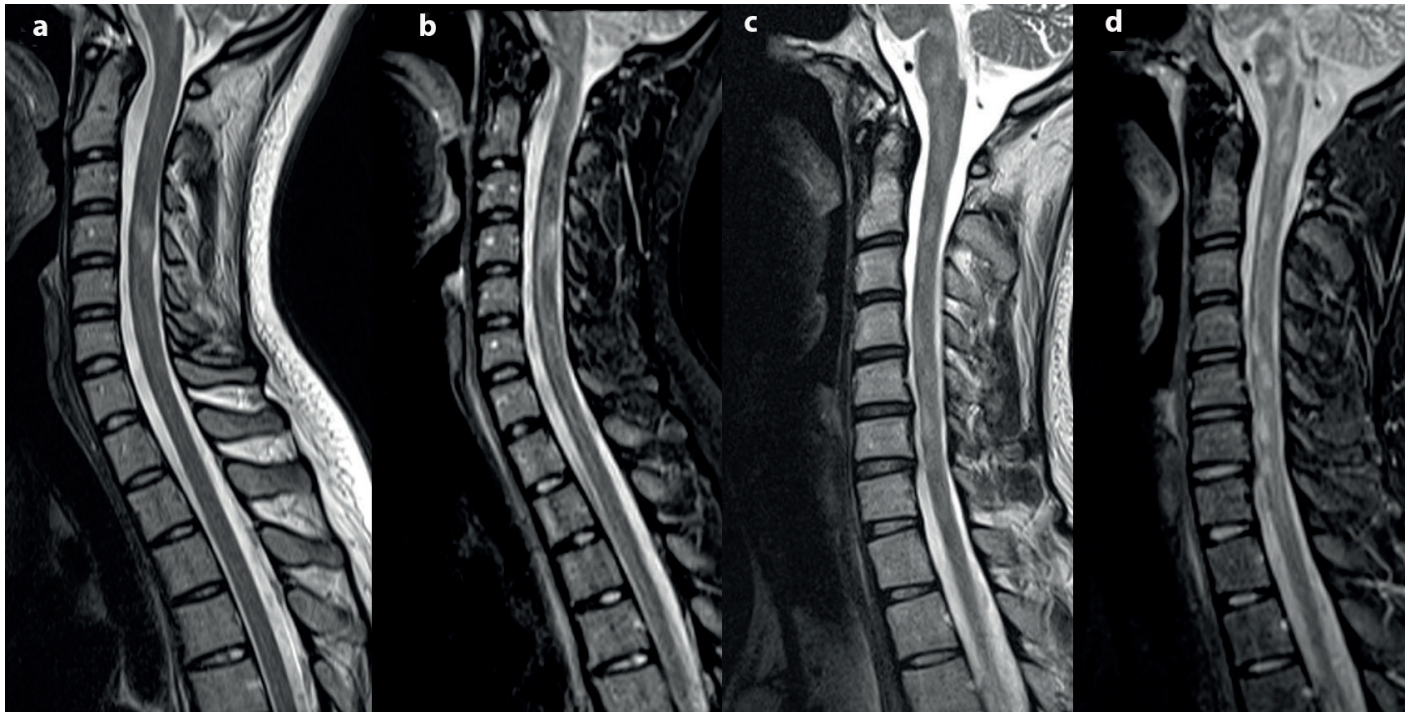

Figure 3. a–d. Sagittal FLAIR (a) and T1-weighted (b) images from the same plane in 28-year-old man and 33-year-old woman with relapsing-remitting multiple sclerosis, shows a few plaques in the cervical spinal cord. In another MS patient MR images shows higher T2 lesion burden in the spinal cord. Note that STIR image (d) is more sensitive in detection of MS plaques than T2-weighted image (c). Spinal cord lesions have a clear role in predicting the accumulation of clinical disability.

levels of NAA detected by MR spectroscopy indicate a neuronal/axonal loss. A decrease in brain NAA/creatinine ratio (NAA/Cr) was shown as an indicative of irreversible axonal dysfunction and reduced cerebral volume (65). Several reports have shown an annual decline between 4% and 6% in NAA/Cr ratio in MS patients, and a correlation between clinical disability and brain NAA/Cr ratio in RRMS (65).

Brain Iron Quantification; Quantitative Susceptibility Mapping (QSM) is a relatively novel quantitative MRI technique. QSM allows the determination of magnetic susceptibility distribution in the brain tissue. Iron and calcium are dominant susceptibility sources in the brain. Zivadinov et al. reported that in patients with reduced thalamic susceptibility in RRMS and secondary progressive MS (66). Authors suggested that the reduction of susceptibility in the thalamus could be related to lower iron content, which was found correlated with clinical disability, independent of tissue atrophy. In contrast to thalamus, the basal ganglia showed higher susceptibility in MS patients.

Emerging MRI Techniques

MRI findings may represent inflammation, demyelination, remyelination, axonal loss or scar tissue in MS. However, conventional MRI is unable to depict the underlying cause or composition of these MS lesions. Multi-compartment T2 relaxometry is an MR imaging technique which allows quantifying the relative contribution of the myelin water with respect to total water, termed the myelin water fraction (MWF). MWF has been shown to correlate strongly with gold-standard histopathological measurements of myelin content (67). Kolind et al. have also found a correlation between the more specific mental and sensory functional system scores and reduced MWF (68). Another study suggested that MWF was related to cortical thinning in RRMS and secondary progressive MS (69).

CONCLUSION

MRI not only plays a key role in the diagnosis of but also it is a helpful tool for predicting disease progression. A number of conventional and quantitative neuroimaging markers which are associated with disability progression have been identified.

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