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Review article

Future MRI tools in multiple sclerosis ☆

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ABSTRACT

Magnetic resonance imaging (MRI) is extremely sensitive in detecting multiple sclerosis (MS)-related abnormalities. As a consequence, it has become an established tool to diagnose the disease and to monitor its evolution. In patients at presentation with clinically isolated syndromes suggestive of MS, MRI has been formally included in the diagnostic work up and *ad hoc* criteria have been proposed and are updated on a regular basis. However, in patients with definite MS, the strength of the relationship between conventional MRI findings and subsequent clinical manifestations of the disease remains modest. This is likely due to the relatively lack of specificity of conventional MRI to the heterogeneous pathological substrates of the disease and its inability to provide accurate estimates of such a damage outside focal lesions as well as to define the mechanisms through which the central nervous system recovers after tissue injury has occurred. Non-conventional MRI techniques offer new biomarkers more closely linked to the pathological features of the disease, which are likely to contribute to overcome, at least partially, these limitations.

This review summarizes how MRI has improved our ability to diagnose MS and to predict its course, as well as how it is changing our understanding of the factors associated with the accumulation of irreversible disability in this condition.

Contents

1. Introduction

Due to its exquisite sensitivity in detecting multiple sclerosis (MS) related abnormalities, magnetic resonance imaging (MRI) has become an established tool to diagnose this disease and to monitor its evolution. MRI has been formally included in the diagnostic work up of patients at presentation with clinically isolated syndromes (CIS) suggestive of MS, and *ad hoc* criteria have been proposed and are updated on a regular basis. On the contrary, in patients with established MS, the ability of MR measures in explaining patients' clinical status and progression of disability is still suboptimal. This has prompted the development and extensive application of modern MR-based technologies to estimate overall MS burden in patients at different stages of the disease. This review discusses the main achievements obtained with the application of MR-based techniques at the initial stage of the disease, when an early identification of individuals who will develop definite MS is central for the optimization of treatment decisions. The role of these techniques in improving our

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understanding of the mechanisms associated to the accumulation of irreversible disability in patients with established MS is also discussed.

2. Patients with CIS

Several studies have been performed to identify early MRI predictors of conversion from CIS to definite MS. Fisniku et al. [1] followed a cohort of 107 CIS patients for 20 years to define the longitudinal relationships between T2 lesion extent and clinical course. T2 lesion volume and its change during the first five years of the study predicted the development of definite MS and correlated with disability 20 years later. Definite MS developed in 63% of patients after 20 years: 82% had an abnormal baseline MRI and 21% had normal baseline MRI. The rate of lesion growth during the follow-up was three times higher in patients who developed secondary progressive (SP) (2.89 cm^3/year) than in those who remained relapsing remitting (RR) MS (0.80 cm^3/year).

In a 8.7 year follow-up study, Minneboo et al. [2] found that the presence of at least two infratentorial lesions was the best predictor of long-term disability (hazard ratio = 6.3) in 42 CIS patients. In a 7-year study of CIS patients [3], baseline T1 hypointense lesion number and volume predicted the severity of executive deficits, and new T2 lesions at the three-month follow-up predicted a slowed information processing.

Recently, the application of double-inversion recovery (DIR) sequences [4] has contributed to imaging cortical lesions (CLs). These lesions have been detected in all the main disease clinical phenotypes, including patients with CIS [5]. The sensitivity of CL detection in the context of MS diagnosis has been recently assessed [6], and a model for disease dissemination in space (DIS) proposed, which includes the presence of at least one intracortical lesion, in addition to the presence of at least one infratentorial and one spinal cord or gadolinium (Gd)-enhancing lesion. This new DIS MRI criterion proved to have a higher specificity (93%) and accuracy (86%) than the available sets of criteria while maintaining a relatively high sensitivity (77%).

Several authors have evaluated whether the severity of damage to the so-called "normal-appearing white matter" (NAWM) contributes to the identification of CIS patients with a high risk of evolution to definite MS. While a seminal magnetization transfer (MT) MRI study suggested that the extent of NAWM abnormalities is an independent predictor of subsequent disease evolution [7], other studies did not [8–10]. A proton magnetic resonance spectroscopy (^{1}H-MRS) study [11] found that metabolic abnormalities are more pronounced in CIS patients who evolve to definite MS over a relatively short period of time.

Measures of irreversible tissue loss, in terms of atrophy, have also been evaluated. A significantly greater ventricular enlargement occurs in CIS patients who develop MS compared to those who do not [12,13]. Dalton et al.[14] showed a significant gray matter (GM) loss (but not WM loss) in patients at presentation with CIS who developed definite MS over the subsequent three years. A multivariate analysis study identified atrophy of the superior frontal gyrus, thalamus and cerebellum as an independent predictor of conversion to MS in CIS patients [15].

Using functional MRI (fMRI), an abnormal pattern of movement-associated cortical activations has been detected in CIS patients within three months of disease onset [16,17]. In a one-year follow-up of the same cohort [18], those patients who developed definite MS had a different motor fMRI response at first presentation when compared with those who did not. This suggests that the extent of early cortical reorganization following tissue injury might influence subsequent disease progression.

3. Patients with definite MS

In patients with definite MS, the strength of the association between conventional MRI findings and disability accumulation remains modest, at best. This is likely due to the relative lack of specificity of conventional MRI to the heterogeneous pathological substrates of the disease, its inability to provide accurate estimates of damage outside focal lesions, and the fact that it cannot identify the mechanisms through which the central nervous system recovers after tissue injury has occurred. Non-conventional structural and functional MR techniques have provided new markers, which are more closely linked to the pathological features of the disease, and may, at least in part, overcome the aforementioned limitations of conventional MRI.

3.1. Heterogeneity of the WM lesions

Variable degrees of MT ratio (MTR) reduction have been reported in acute and chronic MS lesions, with the most prominent changes found in T1-hypointense lesions [19]. A 3-year MT MRI study has shown that new enhancing lesions of SPMS patients have a more severe MTR decline than those of RRMS patients [20].

More recently, to monitor different aspects of the MS inflammatory process, MRI contrast agents composed of iron particles, known as ultrasmall particles of iron oxide (USPIO) or super-paramagnetic iron particles of oxide (SPIO), have been used. These particles are taken by cells of the monocyte/macrophage system. In RRMS patients, it has been shown that some lesions may enhance only with Gd, others only with USPIO, and others with both contrast media [21]. In addition, the same lesions can change their enhancing pattern over time [21]. These findings indicate that new contrasts might provide pieces of information, complementary to those offered by Gd-enhancing MRI scans, with the potential to depict the pluriformity of the MS inflammatory process.

High-field (3.0-4.0 Tesla) and ultra-high field (7.0 Tesla and higher) MRI scanners are becoming progressively available and contribute to detect a greater number and a larger volume of T2 and enhancing brain lesions. More in particularly, these MR scanners also provide a better definition of lesions in terms of location in the WM and GM, morphology and association with vasculature [22–24], at a resolution which resembles that of pathological assessment.

3.2. NAWM damage

Several MRI studies have evaluated the contribution of NAWM damage to locomotor disability and cognitive impairment in patients with MS [25,26]. A voxelwise assessment of the regional distribution of abnormalities of diffusion tensor (DT) MR indexes has been shown to be a rewarding strategy for understanding the heterogeneity of MS clinical phenotypes. In a recent study, this method has been applied to 172 MS patients with different clinical phenotypes [27] and it has been found that compared with healthy controls, CIS patients had significantly increased mean diffusivity, axial diffusivity, and radial diffusivity in the majority of WM tracts of the brain. Compared to controls, patients with primary progressive (PP) MS also showed a diffuse fractional anisotropy (FA) decrease involving the majority of WM tracts. No relevant difference in diffusivity measures was found between CIS and RRMS patients. Compared with benign (B) MS patients, those with RRMS had reduced FA values in all WM tracts and a decreased axial diffusivity in the majority of the tracts. SPMS had a pronounced damage to the majority of tracts and, compared with BMS, a pronounced FA alteration of the tracts relevant for motor impairment.

3.3. CLs

Using DIR sequence, CLs have been demonstrated to be more frequent in patients with SPMS than in those with CIS or RRMS [5]. Longitudinal studies have shown that new CLs continue to form in patients with early RRMS and in those with the progressive disease phenotypes over one to three year periods of follow-up [28–31]. An association has been found between CL burden and progression of disability over the