Hot Topics in Neuro-Therapy: Veno-occlusion in Multiple Sclerosis

MS IMAGING UPDATE
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Introduction
Because of its sensitivity in revealing focal white matter (WM) abnormalities, MRI has become a valuable tool for the assessment of patients with multiple sclerosis (MS). This is the case in the diagnostic work-up of MS, but it also plays a major role in elucidating the mechanisms underlying disease progression and in monitoring the accumulation of pathology underpinning disability. Considerable effort has been devoted to developing imaging strategies capable of providing an accurate estimate of the extent of disease-related damage. There are established guidelines for integrating MR findings into the diagnosis of patients who present with clinically isolated syndromes (CIS) suggestive of MS, and specific acquisition protocols have been suggested for longitudinally monitoring change in patients with established disease. However, in MS research, conventional MRI has been substantially augmented by quantitative MR techniques, which have shown greater sensitivity and specificity for assessing the heterogeneous pathological substrates of the disease not only in focal T2-visible lesions, but also in the normal-appearing white matter (NAWM) and gray matter (GM). More recently, new imaging methods, capable of measuring pathological processes related to the disease that have been neglected in the past (such as iron deposition and perfusion abnormalities) and the advent of high- and ultra-high field magnets have provided further insight into MS pathobiology.

MRI and MS pathophysiology
In patients with definite MS, the strength of the association of conventional MRI findings with the subsequent clinical manifestations of the disease remains modest, at best. This is likely due to the relative lack of specificity of conventional MRI in the evaluation of the heterogeneous pathological substrates of the disease, its inability to provide accurate estimates of damage outside focal lesions, and the fact that it cannot be used to identify the mechanisms through which the central nervous system recovers after tissue injury has occurred. Structural, metabolic and functional MR techniques have provided new markers, more closely linked to the pathological features of the disease, which may in part overcome the aforementioned limitations of conventional MRI. These are the main findings derived from these studies:

a) Heterogeneity of WM lesions. Variable degrees of magnetization transfer ratio (MTR) reduction have been reported in acute and chronic MS lesions, with the most prominent changes found in T1-hypointense lesions. Recently, 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 introduced to monitor different aspects of the MS inflammatory process. These particles are taken by cells of the monocyte/macrophage system. As a consequence, USPIO-enhancement reflects cellular infiltration and may complement Gd-enhancement.

b) Cortical lesions. The introduction of DIR sequences, that use two inversion times to suppress the signal from both WM and CSF, has markedly improved the sensitivity of MRI to detect CLs in vivo. CLs are more frequently seen in patients with SPMS than in those with CIS or RRMS, whereas in patients with benign (B) MS they are fewer than in those with early RRMS. An association has been found between CL burden and progression of disability over the subsequent two and three years in patients with different disease phenotypes, as well as between CL burden and the severity of cognitive impairment in patients with relapse-onset MS.
c) Atrophy. The rate of whole brain atrophy in MS is only 0.5-1% per year and, therefore, the techniques used to measure atrophy must be highly reproducible and sensitive to small changes. Brain atrophy begins at the earliest stage of MS and progresses through the whole disease course, probably at a constant rate. It tends to correlate better with disability and cognitive impairment than other conventional MRI measures, in both cross-sectional and longitudinal studies. In comparison to WM, GM atrophy is more strongly associated with disease progression. Atrophy in deep GM structures begins very early in the disease and cortical thinning is detectable soon thereafter. Focal and diffuse damage measured in the WM predict subsequent GM atrophy in RRMS, but predictors of GM atrophy are lacking in SPMS, when GM atrophy may accelerate.

d) Diffuse NAWM damage. Outside T2 lesions, quantitative MRI discloses the presence of abnormalities in the NAWM of patients with MS. Several studies with serial MR investigations have shown that, at least in some cases, subtle WM changes can be seen in areas which days to weeks later develop into classical enhancing lesions. These changes consist of a reduction of MTR, increase in mean diffusivity (MD), and mild to moderate reduction of N-acetylaspartate (NAA). NAWM MTR histogram-derived measures evolve at different rates in the major MS clinical phenotypes. NAWM MTR reduction has also been shown to predict the accumulation of clinical disability over the subsequent five years in patients with definite MS. In patients with pediatric MS, the absence or mildness of MT and DT MRI abnormalities in the NAWM and GM has been advocated to explain their favorable short-term clinical evolution.

e) Diffuse GM damage. Reduced MTR values have been demonstrated in the brain GM from patients with different MS phenotypes. Such MTR abnormalities were found to be more pronounced in patients with PPMS or SPMS than in those with RRMS. GM MTR changes correlate with clinical disability and cognitive impairment. In patients with RRMS, GM MTR was found to be an independent predictor of the accumulation of disability over the subsequent eight years. Longitudinal studies of GM volume and DT MRI studies have demonstrated a worsening of GM damage over time in patients with RRMS, SPMS and PPMS.

f) Quantification of regional damage in the NAWM and GM. Improvements in methods of analysis have allowed assessing the distribution of damage in the NAWM and GM at a regional level. Overall, these studies have shown that the regional distribution of damage in the NAWM and GM differs among the major disease clinical phenotypes and that such an assessment contributes to ameliorate the correlations between MRI quantities and clinical and neuropsychological evaluations in these patients.

g) Quantification of cervical cord damage. Conventional and DT MRI of the cervical cord was obtained from relapse-onset MS patients at baseline and after a mean follow up of 2.4 years: baseline cord cross-sectional area and FA correlated with an increased disability at follow up. Using a MT-weighted approach, signal abnormalities in the dorsal and lateral columns of the spinal cord were correlated with vibration sensation and strength, respectively. Compared to controls, MS patients with a cervical cord relapse have reduced NAA levels and a lower structural connectivity in the lateral CST and posterior tracts. Such abnormalities were correlated with disability.

h) Cortical reorganization. Studies with functional MRI (fMRI) of the visual, cognitive and motor systems have consistently demonstrated functional cortical changes in all MS phenotypes, with altered activation of regions normally devoted to the performance of a given task and/or the recruitment of additional areas in comparison to healthy subjects. Similar results have been seen with fMRI in the cervical spinal cord. fMRI abnormalities in MS patients occur relatively early in the course of the disease, even in patients with CIS and pediatric MS, and tend to vary over the course of the disease, not only after an acute relapse, but also in clinically stable patients. Functional and structural MRI abnormalities in MS patients are strictly correlated, suggesting that increased recruitment of “critical” cortical networks helps to limit the functional impact of MS-related damage. However, increased cortical recruitment cannot continue indefinitely, and a lack of, or exhaustion of, the “classical” adaptive mechanisms has been considered as a possible factor responsible for unfavorable clinical evolution or for accelerated cognitive decline.
MRI and Chronic Cerebrospinal Venous Insufficiency in MS

In MS patients, Zamboni and coworkers described anomalies of venous outflow at color-doppler high-resolution examination and multiple severe extracranial stenosis at venography, affecting the internal jugular, the vertebral, and the azygous veins. The authors focused their evaluation on 5 anomalous parameters of cerebral venous drainage and defined as abnormal the presence in a single subject of at least two of these parameters. This picture was termed chronic cerebrospinal venous insufficiency (CCSVI) and was found in all MS patients studied and none of the controls. Several studies have been and are currently being performed to scrutinize the CCSVI theory. The following is the contribution provided by MRI techniques to shed light on the value of the CCSVI theory in MS.

a) Neuroimaging studies directly assessing the CCSVI theory. The use of phase contrast MR sequences, which allow noninvasive evaluation of the flow direction, velocity and volume of extra-and intracranial blood and CSF, showed no difference between MS patients and healthy controls regarding internal jugular venous outflow, aqueductal CSF flow or the presence of internal jugular blood reflux, whereas internal jugular vein stenoses were documented in three MS patients. Abnormalities of blood flow patterns due to CCSVI have been proposed to cause increased iron deposition in the brain, a finding which is indeed frequently observed in MS patients. Iron deposition in the human brain occurs also with normal aging and in the course of many neurodegenerative diseases, which reportedly have not been associated with CCSVI.

Among other techniques, susceptibility-weighted imaging (SWI) has been applied to assess iron deposition and cerebral venous oxygen level changes in MS patients. These studies have shown an increased iron concentration in the deep GM nuclei in MS patients compared to healthy controls. In a pilot study of 16 RRMS patients, such an increased iron concentration was related to the number of abnormal venous ultrasound criteria fulfilled. However, a SWI study at 3.0 T demonstrated a significantly reduced visibility of the venous vasculature in the periventricular WM of RRMS patients. In line with previous positron emission tomography studies, which showed a reduction of oxygen utilization and extensive hypometabolism in the GM and NAWM of MS patients, this reduced visibility and volume of the cerebral venous system, reflecting a decreased venous blood deoxyhemoglobin concentration, can be interpreted as a result of a decreased oxygen extraction in the diseased MS tissue. On the contrary, occlusion of the venous vasculature should lead to an intracranial venous engorgement (increased visibility and volume) and enhancement of susceptibility effects, due to increased oxygen extraction.

b) MS and brain vasculature. Using susceptibility weighted MR venography based on SWI, which is sensitive to deoxygenated blood, Tan et al. identified a central vein in 94/95 lesions from 17 patients with MS. The typical ovoid shape and orientation of the long axis of MS lesions correlated well with the course of the veins. A few studies performed at 7.0 Tesla showed the ability of MRI to define the morphological characteristics of MS lesions in the WM and GM at a resolution which resembles that of the pathological assessment. Remarkably, some of these studies also allowed a better definition of the relationship between demyelinating lesions and the deep venous system to be achieved, and confirmed that the majority of MS plaques are centered around the microvasculature. While such a perivascular distribution of MS plaques fits with the notion of the inflammatory and immunological nature of the disease, it does not support the CCSVI theory. Indeed, venous occlusion should result in venous hypertension, which in turn should cause abnormalities such as edematous swelling, and hemorrhagic and ischemic infarctions, findings which are not seen in demyelinating plaques of MS patients.

Abnormalities of regional cerebral hemodynamics in MS have been investigated using perfusion MRI. These studies have for the most part demonstrated widespread hypoperfusion in focal lesions, NAWM and the cortical and deep GM of MS patients with the main disease clinical phenotypes. This is consistent with earlier histopathological studies reporting vascular occlusive changes in MS, characterized by thrombosis of small veins and capillaries, vein wall hyalinization and intravascular fibrin deposits. To assess whether NAWM hypoperfusion in MS may be related

to a primary vascular etiology or rather be secondary to hypometabolism, a study correlated diffusivity measures with perfusion findings in the corpus callosum of patients with RRMS. These authors reported a correlation between decreased perfusion and decreased MD, a finding more consistent with what would be expected in primary ischemia than in secondary hypoperfusion. The notion that ischemia may play a role in the pathogenesis of a subset of MS lesions is also supported by the in vivo descriptions of reductions in the apparent diffusion coefficients in new focal lesions of MS patients, and by pathological observations showing that, in some MS patients, lesions share similarities with tissue alterations seen in the early stages of ischemia. Remarkably, a longitudinal study showed that abnormalities of cerebral perfusion may precede overt change of blood-brain barrier permeability during the development of focal MS lesions, suggesting the presence of inflammation-related vasodilatation in the acute stage of lesion formation.

Conclusions

Conventional and modern MR-based techniques have markedly improved our ability to diagnose MS, to predict its course, and to understand its pathophysiology. Considering the CCSVI theory in MS, the available neuroimaging findings do not support but rather point to a concomitant disturbance of the brain microcirculation in patients with MS, which deserve further investigation, but can be well explained by secondary vascular inflammatory changes known to occur with this disease. As recently reviewed by D’Haeseleer et al., a vascular dysfunction is likely to play a role in the complex pathogenesis of MS. However, available data to support their presence and importance are still scanty and at any rate insufficient to draw definitive conclusions. Clearly, improving the knowledge of these aspects is important, since it might modify the way we treat patients and reshape the armamentarium needed to monitor the evolution of MS.

References


