Neuroimaging Biomarkers in Multiple Sclerosis (MS)

State-of-the-art MR imaging in MS patients: conventional MRI, quantitative neuroimaging biomarkers, and advanced brain imaging techniques.

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About Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease affecting the central nervous system (Compston and Coles, 2008). The disease usually affects young adults, who suffer from a variety of neurological symptoms, with periods of relapse and remission (relapsing-remitting MS), or progressively leading to irreversible disabilities (primary or secondary progressive MS).

The pathophysiology of the disease is complex, and not perfectly understood at this time. An immune-mediated inflammation process is associated with demyelination and subsequent axonal damage. Although multiple sclerosis is primarily a white matter disease, gray matter is also affected. Some studies suggest that gray matter atrophy could be linked with an independent degenerative process of the disease (Steenwijk et al., 2014), in addition to the well-known demyelinating one.

Magnetic resonance imaging (MRI) is useful:

- at the diagnostic step, in patients with a clinically isolated syndrome (CIS), or MS. A variant of the CIS is the radiologically isolated syndrome (RIS), in which the discovery of lesions suggestive of MS is an incidental finding in a routine MRI examination (Granberg et al. 2013).
- at the follow-up step, in patients with established MS.
- in clinical trials, in order to assess the therapeutic effect of a new drug.
- to monitor the potential adverse effects of MS-targeted drugs and, especially, to exclude the rare onset of progressive multifocal leukoencephalopathy (PML) in patients treated with Natalizumab (Yousry et al., 2012).

At the diagnostic step, MR imaging is included in the diagnostic work-up, alongside clinical assessment, analysis of the cerebrospinal fluid (CSF), and evoked potentials. The MR-based diagnosis relies on the demonstration of lesion dissemination in space and time, as defined by consensus criteria, such as the revised McDonald criteria (Polman et al., 2011). MRI is also useful for the differential diagnosis with other brain diseases.

In the brain, different MRI sequences can reflect different aspects of the disease’s complex pathophysiology (Filippi and Rocca, 2011):

- Fluid-attenuated inversion-recovery (FLAIR) images, in which the white matter lesions appear as bright spots, reflecting different levels of myelin loss, inflammatory activity, and gliosis (figure 1). The sensitivity of the sequence is high but its specificity is low, as other lesions (e.g., vascular lesions) can mimic MS plaques.
- Dual-echo T2- and proton density-weighted images, in which the white matter lesions appear hyperintense, such as on FLAIR images. They can be particularly useful in the posterior fossa, where FLAIR images have limited sensitivity, and are more prone to artifacts.

FIGURE 1: FLAIR images of a patient with multiple sclerosis, loaded in BrainMagix’s longitudinal follow-up module. An increased lesion load, and a large atrophy of the brain can be observed, 20 years after the onset of the disease.
• 3D high-resolution T1-weighted images, useful for brain volumetry and for detecting the black holes, i.e. persistently dark lesions, associated with severe tissue damage (i.e., both demyelination and axonal loss).
• Post-contrast T1-weighted images, acquired after the injection of a gadolinium-based contrast agent. Active lesions, corresponding to areas of ongoing inflammation, show a signal enhancement on these images, as a result of an increased blood-brain-barrier permeability.
• Double inversion recovery (DIR) images, in which two inversion pulses are used, in order to suppress both the signal of white matter and the one of the CSF. The sequence is useful for depicting cortical gray matter lesions, which are usually not well visible on the other series. However, the sensitivity of the sequence remains limited (Sethi et al., 2012).
• Phase-sensitive inversion recovery (PSIR) images, only available at 3 Tesla, which may be more sensitive than DIR images for the detection of cortical gray matter lesions (Sethi et al., 2012).

Imaging of the spinal cord and of the optic nerve, which are also affected by multiple sclerosis, is outside the scope of this review. Readers interested in this topic can refer to (Filippi and Rocca, 2011).

Quantitative Imaging in MS Patients

Longitudinal MRI follow-up in MS patients can be optimized by the use of dedicated tools, such as BrainMagix’s follow-up module (figure 1), in order to compare the examinations and follow the disease’s progression. Although standardized slice positioning, parallel to the sub-callosal plane, improves the repeatability of the examinations, images registration is necessary, in most of the cases, in order to improve the matching. A transparent fusion tool, within (intra-) or between (inter-) the time points, is useful for the characterization (on multiple image weighting) and the follow-up of each lesion. Image subtraction techniques can also be used in order to quickly identify new or growing lesions (Moraal et al., 2009).

The counting and volume of the T2 (white matter) lesions, and their progression, are useful biomarkers. These are usually measured on FLAIR images. However, the sensitivity of this contrast is poor in the posterior fossa (Stevenson et al., 1997), and may require the segmentation of the T2 images in this region. Total lesion volume increases by approx. 5%–10% per year in untreated patients (Filippi and Rocca, 2011).

There is a substantial body of histopathological evidence that supports chronic black holes (i.e. white matter lesions with a persistently hypointense appearance relative to normal-appearing white matter (NAWM) on a T1-weighted MRI) as being indicative of irreversible demyelination and axonal damage. As a result, the progression of black holes is considered as a promising imaging surrogate endpoint in MS (Tam et al., 2012).

Contrast-enhancing lesions can also be quantified, as a marker of the disease’s inflammatory activity. At this stage, the quantification of cortical lesions, as measured in DIR or PSIR sequence, is still challenging because of their limited sensitivity and of the lack of standardization between centers (Filippi and Rocca, 2011). Automated MS lesion segmentation algorithms have been widely published in the literature (García-Lorenzo et al., 2013). However, their use on a variety of patients, centers, MRI scanners, and sequences is still challenging. Therefore, BrainMagix’s longitudinal follow-up module implements a semi-automated algorithm that, while reducing the user’s interaction time, still requires his/her validation.

Technical parameters, such as slice thickness, can also affect the measurement and its reproducibility. The reduction of the slice thickness from 5 to 3 mm makes it possible to detect smaller lesions, leading to an increase of the measured lesion volume by approximately 8% (Molyneux et al., 1998) and a decrease of the intra- and inter-observer variability (Filippi et al., 1998).
The brain volume can be measured based on the segmentation of a high resolution 3D T1-weighted image (figure 2). In MS patients, this volume decreases by approx. 0.7%–1% per year, on average (Filippi and Rocca, 2011). The brain parenchymal fraction (BPF), i.e. the ratio of brain parenchymal volume to the total volume within the brain surface contour (Rudick et al., 1999; Vågberg et al., 2013), is also often used as an indicator of atrophy in MS patients. In addition, some brain structures seem to be more affected by the atrophy than others, depending on the phase of the disease. Therefore, brain morphometry, implemented in BrainMagix’s SurferMagix module, is a useful biomarker.

There is a poor correlation between lesion load and symptoms (Messina and Patti, 2014). Brain atrophy seems to be better correlated with disability progression (Sormani et al., 2014) and especially with cognitive impairment (Messina and Patti, 2014), in line with the presence of a neurodegenerative process in the disease (Steenwijk et al., 2014).

**Advanced MRI in Multiple Sclerosis**

Diffusion tensor imaging is useful in assessing the integrity and myelination of white matter tracts (figure 3). Increased apparent diffusion coefficient (ADC) and decreased fractional anisotropy (FA) can be observed in T2 lesions, and even in normal appearing white matter (NAWM). Globally, abnormal mean diffusivity and FA generally correlate with the progression of the disease, and with cognitive impairment (Hulst et al., 2013). Locally, white matter abnormalities can, in some cases, be correlated with clinical disabilities, e.g., mean diffusivity of the cortico-spinal tract with motor impairment (Filippi and Rocca, 2011).

Magnetization transfer MR imaging, which uses an off-resonance pulse in order to saturate the protons bound to the brain tissue matrix, can be used to measure their capacity to exchange magnetization with the surrounding free water, i.e. the magnetization transfer ratio (MTR). This ratio is reduced in MS lesions, correlated with the degree of myelin loss and axonal damage (Schmierer et al., 2004), and its reduction in NAWM and gray matter can even be predictive of the development of new lesions (Filippi and Agosta, 2007) and of the future clinical disability (Agosta et al., 2006).

Perfusion studies have identified both diffuse and focal perfusion abnormalities in MS patients. Functional MRI (fMRI) has been used to show functional reorganization in the brain of MS patients. Dynamic changes of metabolites concentrations can be observed, even preceding the lesion formation, with MR spectroscopy. However, none of these three modalities is currently included in routine MS protocols, due to the difficulties in interpreting the results and their meaning at the individual level (Filippi and Rocca, 2011).

**MS Imaging for Treatment Monitoring and in Clinical Trials**

The quantitative parameters described hereinabove, and especially the number and volume of new and enlarged lesions, can be used to monitor treatment, alongside clinical assessment. Studies have shown that these measurements are valid surrogate markers of clinical activity (Sormani et al., 2009). These may become increasingly useful in clinical practice, especially for monitoring the new drugs, such as Natalizumab, which targets a complete stabilization of the disease (zero tolerance).

At the individual level, the prediction of the efficacy of a treatment would be a major step toward precision medicine. Although some studies have shown that MR-based measurement could be used as early predictors of treatment response, there is still no consensus on the optimal criteria, and MR imaging is not recommended as the sole predictor of treatment response at this stage (Filippi and Rocca, 2011).

These neuroimaging biomarkers are also used in the framework of clinical trials, testing new drugs. Follow-up of the lesion load is mainly linked with the inflammatory aspect of the disease. In addition, specific biomarkers, such as the measurement of brain atrophy, of T1-hypointense black holes, and of the magnetization transfer ratio, can be used to monitor the neurodegenerative aspect of the disease (Barkhof et al., 2009), especially when testing drugs with a neuroprotective effect. However, standardization and validation of the biomarkers, across clinical trials and centers, is still missing and should be promoted by consensus meetings.
References


About the Author

After graduating as an electrical engineer and doctor of medical sciences, Laurent Hermoye founded Imagilys. He endeavors to bring the most advanced brain imaging techniques from bench to bedside. His efforts have resulted in multiple publications in medical journals and at international conferences, but also in a neuroimaging software, BrainMagix, which has been used on thousands of patients. Through continuing medical education at Harvard Medical School, he is continually at the leading edge of the newest techniques.

About Imagilys

Imagilys develops and sells a neuroimaging software, BrainMagix. We help our customers, throughout the world, to diagnose and to treat patients with severe neurological, neurosurgical, and psychiatric diseases. We help pharmaceutical companies and CROs to use neuroimaging biomarkers for the discovery of promising drugs. Finally, we train doctors on advanced neuroimaging techniques, in the framework of our Advanced Clinical Neuroimaging Courses.