

Imaging Biomarkers in multiple sclerosis

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MS is a disease characterized by focal, inflammatory, demyelination, as well as neurodegeneration involving myelin and axons. Although traditionally considered a white matter disease, the pathology, in fact, involves both white matter and gray matter. MRI can provide markers of the different aspects of MS pathobiology.

WHITE MATTER LESIONS

Acute focal WM inflammation is generally considered to be driven by entry of peripheral immune cells into the CNS across the blood-brain barrier (BBB). MRI can report on this by means focal Gadolinium (Gd)-enhancement and new lesion formation in the white matter. The effect of disease modifying therapies on Gd-enhancement provides reliable trial-level surrogacy for the effect of these same drugs on relapses. The tight relationship between Gd-enhancement and clinical symptoms that is necessary for surrogacy at the individual patient level is not found. This is likely due to a combination of factors including the fact that the usual clinical readouts tend to be insensitive to pathology in most regions of the brain, the MRI readouts tend to be unspecific for the nature and severity of tissue injury, and the brain is able to re-organize its function to adapt to injury.

The accumulated burden of focal inflammatory disease in white matter can be assessed by the T2w and T1w lesion volume. T2w lesions tend to be sensitive to, but not specific for, destructive pathology. T1w lesions are less sensitive but more specific for destructive pathology. Thus, the proportion of Gd-enhancing lesions that evolve to chronic T1 hypointense lesions (chronic Black Holes) has been used a marker of lesion destructiveness.

Demyelination and remyelination in focal inflammatory lesions can be quantified with greater pathological specificity by using magnetisation transfer ratio imaging (MTR). This has been done by quantifying the average MTR in newly formed *lesions* as these lesions evolve over time. This approach averages heterogeneous pathology which can be better quantified by determining the proportion of initially Gd-enhancing *voxels* that show significant decreases or increases in MTR consistent with demyelination and remyelination.

GRAY MATTER LESIONS

Focal demyelination also occurs in GM. These occur in deep GM and cortical GM (cGM). The demyelinating lesions in cGM are very difficult to detect. Some types of cGM lesions can be seen on MRI, but the vast majority are “MRI invisible”, probably due to combination of their small size and a lack of T2 or T1w “contrast”.

NEURODEGENERATION

It is important to appreciate that the pathology of MS is not restricted to the MRI-visible lesions. Although the pathology in normal-appearing WM (NAWM) and normal-appearing GM (NAGM) is much more subtle than in the WM lesions, normal-appearing brain tissue (NABT) makes up more than 90% of the CNS, and so, when pathology in NABT becomes sufficiently severe, it can have effects that are more important than those of the focal lesions.

The most straightforward way to assess the degenerative component of MS is to measure changes in whole brain volume (atrophy). This is best done using a technique that is precise and capable of resolving subvoxel changes. Regional pathology can also be assessed. For example, pathology in NAWM or NAGM can be quantified by measuring changes in their volume. However, the software generally used to perform WM and, particularly, GM segmentation is often not reliable, particularly if it does not have a separate class for lesions. More pathologically specific markers of degeneration can be derived from non-conventional MRI acquisition methods, such as MTR, MRS, and possibly DTI.

Additional reading

Filippi M, Falini A, Arnold DL et al. Magnetic resonance techniques for the in vivo assessment of multiple sclerosis pathology: consensus report of the white matter study group. *J Magn Reson Imaging*. 2005;21:669-675