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**Tissue-Specific MR Imaging in Multiple Sclerosis**

À Rovira

EDITORIAL

# Tissue-Specific MR Imaging in Multiple Sclerosis

Conventional MR imaging techniques (cMRI), such as T2-weighted sequences and gadolinium-enhanced T1-weighted sequences, which are highly sensitive for detecting multiple sclerosis (MS) plaques, have become established as the most important paraclinical tool for diagnosing MS, as well as for understanding the natural history of the disease and monitoring the efficacy of experimental treatments. In fact, cMRI metrics have become common primary end points in phase II immunomodulatory drug therapy trials.[1] However, a possible role of cMRI metrics as surrogate end points in phase III trials has been disclaimed because of the poor correlation between cMRI metrics and the clinical disease course, particularly disability progression, which is driven by the neurodegenerative component of the disease.[2]

Explanations for this clinical-radiologic discrepancy include inappropriate clinical rating, neglect of spinal cord involvement, underestimation of damage to the normal-appearing brain tissue (both white and gray matter), and compensation by cortical adaptation.[3] However, one of the major contributors to this paradox is the lack of pathologic specificity of T2-weighted imaging, which provides only a dichotomous type of information, that is, it simply discriminates between MS focal lesions and normal-appearing white matter but not between the type and degree of the underlying pathologic substrates (edema, inflammation, demyelination, remyelination, reactive gliosis, and axonal loss)[4] that contribute differently to the development of permanent disability.

In the last 15 years, a huge effort has been made by the MR imaging research community to overcome the limited pathologic specificity of cMRI by developing new MR imaging techniques that selectively measure the more destructive aspects of MS pathology and monitor the reparative mechanisms, such as T1 hypointense lesions, quantitative analysis of global and regional brain volume, magnetization transfer MR imaging, diffusion-weighted MR imaging, and proton MR spectroscopy. These techniques appear to be more sensitive biomarkers for measuring the pathologic processes underlying the progression of clinical disability (demyelination and axonal loss).[5]

The first MR imaging−based measure proposed as a specific marker of focal MS lesions with severe tissue destruction was T1 hypointense lesions.[6] However, these so-called T1 "black holes" may have a different pathologic substrate depending, in part, on the lesion age. Hypointensity is present in ≤80% of recently formed lesions and likely represents marked edema, with or without myelin destruction or axonal loss. In most cases, acute ("wet") black holes become isointense or slightly hypointense within a few months, as inflammatory activity abates, edema resolves, and reparative mechanisms such as remyelination become active, resulting in partial axonal preservation. Less than 40% evolve into persisting or chronic black holes,[7,8] which correlate pathologically with permanent demyelination and severe axonal loss. Several immunomodulatory drugs (glatiramer acetate, interferon beta, and natalizumab) reduce the progression of acute gadolinium-enhancing lesions into persistent or chronic black holes, supporting a certain neuroprotective effect of these treatments by disrupting the advancement of tissue destruction.[9-11]

However this MR imaging−based measure has some important drawbacks that limit its use as a true marker of severe irreversible tissue damage. One of the most important limitations is the fact that the definition of what constitutes a black hole is arbitrary, highly dependent on the MR imaging technique used, and based on visual inspection. Therefore, it remains a challenge to accurately discriminate between slightly/moderately and strongly hypointense T1 lesions, which reflect different degrees of remyelination and axonal loss. This pathologic heterogeneity has been demonstrated by postmortem studies[12] and by in vivo MR spectroscopy and magnetization transfer imaging studies, which have shown that tissue damage is extremely variable in individual black holes.[13,14] Consequently, patients with similar black hole lesion volume may have different degrees of disability depending on the nature of the histopathologic substrate.

For this reason, new ways of measuring black holes have been recently developed, such as the T1 hypointensity ratio[15] and the one proposed in this issue of *American Journal of Neuroradiology* by Riva et al.[16] These authors assessed the ability of a new MR imaging technique, which they call "tissue-specific imaging" to selectively identify black holes with the longest T1 values, which likely reflect lesions with severe demyelination and axonal loss. The results of this study are promising and provide data indicating that this technique could be a sensitive method for detecting and quantifying hypointense T1 lesions with more advanced tissue destruction. Nevertheless, additional studies are required before new MR imaging−based measures can be considered markers of disease severity and progression in MS or surrogate markers of remyelination and neuronal protection in clinical trials. These additional studies should demonstrate their reproducibility, sensitivity to disease evolution and treatment changes, and their value in reflecting and predicting the accumulation of irreversible disability.[17]

All these necessary efforts are especially important nowadays, when there is a growing interest in developing neuroprotective agents in MS, which consequently demands new imaging strategies for achieving and monitoring myelin repair and axonal loss.[18]

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À. Rovira
*Magnetic Resonance Unit (I.D.I.)*
*Department of Radiology*
*Hospital Universitari Vall d'Hebron*
*Barcelona, Spain*