Title: MRI as a biomarker
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Syllabus contribution

Multiple sclerosis (MS) is a chronic, persistent inflammatory-demyelinating disease of the central nervous system that typically presents as an acute clinically isolated syndrome attributable to a monofocal or multifocal demyelinating lesion, which usually affects the optic nerve, spinal cord, or brainstem and cerebellum.

Conventional MRI techniques (cMRI), such as T2-weighted (T2W) sequences and gadolinium-enhanced T1-weighted sequences, which are highly sensitive for detecting 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 endpoints in phase II immunomodulatory drug therapy trials. However, a possible role of cMRI metrics as surrogate endpoints 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.

Explanations for this clinical-radiological 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. However, one of the major contributors to this paradox is the lack of pathological specificity of T2W 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 substrate (edema,

inflammation, demyelination, remyelination, reactive gliosis, and axonal loss), which contribute differently to the development of permanent disability.

In the last 15 years, a huge effort has been made by the MRI research community to overcome the limited pathological specificity of cMRI, by developing new MRI 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 have increased our understanding of the pathogenesis of the disease, and appear to be more sensitive biomarkers for measuring the pathologic processes underlying the progression of clinical disability (demyelination and axonal loss). Therefore, MRI can serve as a true biological marker of the severity of this disease, a role which is 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.

REFERENCES

- Bakshi R, Minagar A, Jaisani Z, Wolinsky JS. Imaging of multiple sclerosis: role in neurotherapeutics. NeuroRx. 2005;2:277-303.
- Barkhof F. The clinico-radiological paradox in multiple sclerosis revisited. Curr Opin Neurol 2002; 15:239 –245.
- Giacomini PS, Arnold DL. Non-conventional MRI techniques for measuring neuroprotection, repair and plasticity in multiple sclerosis Current Opinion in Neurology 2008, 21:272–277
- Goodin DS. Magnetic resonance imaging as a surrogate outcome measure of disability in multiple sclerosis: have we been overly harsh in our assessment? Ann Neurol 2006; 59:597–605.
- Miller DH. Biomarkers and Surrogate Outcomes in Neurodegenerative disease: Lessons from Multiple Sclerosis. NeuroRx 2004; 1:284-294
- Rovira A, León A. MR in the diagnosis and monitoring of multiple sclerosis: an overview. Eur J Radiol. 2008;67:409-14
- Rovira A. Tissue-specific MR imaging in multiple sclerosis. AJNR Am J Neuroradiol. 2009 Aug;30:1277-8
- Simon JH. Brain atrophy in multiple sclerosis: what we know and would like to know Mult Scler. 2006; 12:679-687
- Sormani MP, Bonzano L, Roccatagliata L, et al. Magnetic resonance imaging as a potential surrogate for relapse in multiple sclerosis: a meta-analytic approach. Ann Neurol 2009; 65: 270–277.
- Zivadinov R. Can imaging techniques measure neuroprotection and remyelination in multiple sclerosis? Neurology 2007; 68 (Suppl 3):S72–S82