

## Imaging multiple sclerosis outside the brain

Multiple sclerosis (MS) is a pathologically and clinically complex and chronic disease of the central nervous system. It usually presents in young adults and although it follows a highly variable course within and between individual sufferers, it results in serious long-term neurological disabilities in a majority of patients. Disease-modifying treatments have emerged in the last 15 years that – to a greater or lesser extent – ameliorate the early relapsing-remitting phase of the disease, which is characterized pathologically by recurrent, multifocal inflammatory demyelinating white matter lesions in the brain, spinal cord and optic nerves. The later progressive phase of the disease is as yet untreatable, and is characterized by a more widespread pathological process that involves both gray and white matter, brain and spinal cord, and exhibits limited or low-grade inflammation but prominent neurodegeneration.

Most demyelinating brain lesions are clinically silent. It is therefore not surprising that brain MRI is extremely valuable in detecting these characteristic lesions and in assisting an early diagnosis. Serial brain MRI also detects new and active lesions and has become an indispensable tool in proof-of-concept trials in helping to identify effective new disease-modifying treatments for relapsing-remitting MS. It is also increasingly used to monitor individual patients who are receiving a disease-modifying treatment. In progressive MS, the sensitive measurement of brain atrophy using registration-based methods has emerged as a useful tool for evaluating potential neuroprotective treatments in proof-of-concept trials. Many other more advanced structural, metabolic and functional imaging techniques – including MR spectroscopy, diffusion, magnetization transfer, perfusion, functional MRI and positron emission tomography – have been used to study the brain in MS and, in this way, have provided valuable insights into the pathogenesis and pathophysiology of the disease.

Notwithstanding these developments in brain imaging, there has been a high and continuing interest in imaging of the spinal cord and the optic nerves because both of these structures are of major clinical importance in MS. The first presentation of MS in about 25% of patients is with an attack of clinically isolated optic neuritis, and most patients with relapsing-remitting MS will experience optic neuritis at some stage. Although good or partial recovery of vision is the rule, 10-20% are left with substantial visual impairment following the attack. The spinal cord is also a very common site of relapses with effects on mobility, sensation (including pain) and sphincter function. Even more importantly, spinal cord pathology is the most common cause of progressive disability in MS, with increasing spasticity, upper motor neuron weakness and sphincter disturbance being seen in the majority of patients with primary (from onset) and secondary (after a relapsing-remitting phase) progressive MS.

Detection of focal spinal cord lesions on conventional MRI is very helpful in certain diagnostic contexts, for example when brain MRI is normal or in older subjects where brain white matter lesions are less specific. MRI measures of spinal cord atrophy have consistently shown some of the most robust correlations that have been seen between an imaging measure and clinical measures of locomotor disability. This is not surprising given that neurodegeneration in the cord underlies so much of the physical disability seen in MS. Recent technical progress – including serial high resolution and high cord-CSF contrast imaging combined with automated cord segmentation and voxel-based image analysis of cord volume changes (Valsasina et al., 2013; Kearney et al., 2013) – holds the promise of new and sensitive methods for monitoring clinically relevant neuroprotection in progressive MS trials. In spite of the technical challenges, the quality of more advanced MR applications in the cord, including diffusion tensor and functional imaging, is improving all the time, assisted by the better signal-to-noise ratio achievable on higher field scanners; these developments can be expected to generate valuable new insights into pathophysiological mechanisms of progressive myelopathy in MS.

The anterior visual pathway is an especially attractive site for the study of disease mechanisms in MS, given the availability of precise and quantitative measures of visual function, in addition to the visual evoked potential (VEP) that assesses nerve conduction and is especially sensitive to the effects of demyelination. Furthermore, optical coherence tomography (OCT) provides a sensitive quantitative measure of axonal loss following optic neuritis and a close correlation between retinal nerve fiber thickness and residual visual function has been identified (Trip et al., 2005). OCT-measured retinal nerve fiber layer thickness is now being used to evaluate putative neuroprotective

agents in optic neuritis treatment trials. MR imaging of the optic nerve lesion *per se* provides a unique opportunity to *directly* determine the associations of quantitative MRI abnormalities in a clinically eloquent inflammatory demyelinating lesion with both function (quantitative measures of vision and VEPs) and axonal loss (OCT) – and by analogy to infer the probable effects on neural function and axonal integrity of similar “quantitative MR-affected” lesions that occur elsewhere in the central nervous system. The study reported by Samson et al. in the present issue of *Functional Neurology* describes quantitative diffusion tensor imaging of the optic nerves at 3 Tesla (Samson et al., 2013). Although not without technical challenges, this study clearly identifies measurable diffusion abnormalities in clinically affected optic nerves and should provide a stimulus for future research in this important area.

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