MULTIPLE SCLEROSIS IN 2015

Managing the complexity of multiple sclerosis

Olga Ciccarelli and Alan Thompson

The application of imaging biomarkers has provided new insights into the mechanisms of damage in multiple sclerosis (MS) and the risk of MS development and progression. The goal of eliminating all disease activity requires a timely escalation of treatment. This increasing complexity is compounded by the need to treat comorbidities.

Multiple sclerosis (MS) is an increasingly complex disease in terms of its pathogenesis, comorbidities, prognosis and treatment, and successful patient management requires knowledge of this complexity. In 2015, there have been advances in our understanding of the mechanisms of the disease, ways in which to formulate patient prognoses, how best to escalate treatment escalation, and the role of comorbidities. All of these aspects need to be incorporated into an effective management plan (Fig. 1).

The mechanisms that underlie the pathogenesis of MS are yet to be fully elucidated, but they are known to include a cascade of events that induce physical and cognitive deficits. A reduction in neuronal integrity and function that affects the grey matter compartment is thought to be the key pathological process that leads to cognitive impairment in MS. However, findings of a study published by Freeman *et al*.[1] in 2015 suggest that synaptic and/or dendritic damage occurs prior to quantifiable grey matter volume loss, and might reflect neuronal and axonal loss that contributes to clinical deficits.

In this study, Freeman *et al*.[1] used [^{11}C]flumazenil ([^{11}C]FMZ) PET, which quantifies $GABA_A$ receptor density *in vivo*, to identify grey matter damage beyond cortical lesions[2]. FMZ is an antagonist of the central benzodiazepine receptor, a component of the $GABA_A$ receptor complex that is present on axosomatic and axodendritic synapses throughout the cortical and subcortical grey matter. The number of [^{11}C]FMZ binding sites per grey matter region was lower in several cortical areas (the parietal, cingulate, and insular cortices and the left frontal cortex) and subcortical regions (the thalamus, hippocampus and amygdala) in patients with MS than in healthy controls. Greater amounts of neuronal damage were seen in patients with secondary-progressive MS than in patients with relapsing–remitting MS (RRMS), but the most striking result was that [^{11}C]FMZ binding was lower in patients with RRMS than in healthy controls, even in the absence of significant grey matter atrophy. A significant relationship was found between the level of cortical [^{11}C]FMZ binding and performance on several cognitive tests. A goal of future research is to provide neuroprotective and reparative therapies that could be applied at such early stages of MS to stop or at least slow down neurodegeneration and reduce cognitive impairment in progressive MS[3].

Clinically isolated syndromes (CIS) represent a patient's first neurological episode that is suggestive of MS. Most patients with CIS develop RRMS within 5 years of onset, and most patients with MS develop progressive MS 10–15 years after onset of MS. Although challenging, formulating a prognosis that accurately predicts the development of MS and the accumulation of neurological disability is crucial for designing successful treatment plans for individual patients. A key step towards such individualized treatment of patients with CIS is to "stratify" them into groups according to demographic, clinical, radiological and biological characteristics. Patients in different groups are likely to have a different risk of developing MS and long-term disability, so will benefit from different treatments at different time points. A study published by Tintore *et al*.[4] in 2015 illustrates the importance of this step.

Tintore and colleagues prospectively studied a single-centre cohort of 1,015 patients with CIS who were clinically and radiologically followed up for a mean of 6.8 years[4]. The results showed that ≥10 brain lesions visible with MRI at the onset of CIS was a "high-impact" prognostic factor that predicts the development of MS and disability. The presence of oligoclonal bands in the cerebrospinal fluid was a "medium-impact" prognostic factor that predicts the conversion from CIS to MS and the accumulation of disability. Presentation of CIS with optic neuritis and the use of a disease-modifying treatment had a (probably marginal) protective effect against the development of MS and disability. Other demographic factors, such as gender and age at onset, were "low-impact" prognostic factors. The study had some methodological limitations, such as the number of patients who dropped out during follow-up (unavoidable in this type of longitudinal study) and the fact that the latest 2010 McDonald diagnostic criteria were not used. Nevertheless, the results provide further clarity about the heterogeneous outcomes of patients with CIS and help to inform their prognosis.

The ability to predict disease course is particularly important now that we have a range of new treatments for RRMS; although there is now a consensus that early treatment is optimum, the nature and timing of escalation to second-line treatment remains a challenge. The ultimate goal of such escalation is to increase the chance that patients reach a persistent, long-term status of 'no evidence of disease activity (NEDA)'.[5]

A central question that surrounds second-line treatment is whether natalizumab is more effective than fingolimod once failure of first-line treatment has been established. A head-to-head comparison between these two drugs is unlikely to be conducted, but Kalincik *et al*.[6] in 2015 extracted data from the MSBase registry to compare the outcomes of treatment escalation to natalizumab or fingolimod in patients with MS who had experienced disease activity while receiving injectable disease modifying treatments. The relapse rate after switching to natalizumab was 50% lower than after switching to fingolimod, with a corresponding increase in the proportion of relapse-free patients on natalizumab. Importantly, however, 6-month sustained disability progression rates did not differ between the two treatments. This finding highlights the need to identify new treatments that can slow or stop

progression of MS, a major initiative being driven by the Progressive MS Alliance, who, in 2015, published an appraisal of current knowledge in this area and suggested future steps[3]. One other important consideration is that drug efficacy is only one factor that is considered by doctors and patients when discussing treatment escalation; treatment safety and tolerability, together with risk assessment[7], are additional, important elements, particularly from the patient's perspective.

In addition to specific treatment approaches, a holistic approach to management, including a focus on well-being, is paramount, and identifying and managing comorbidities is an important element of this approach. The impact of comorbidities on clinical symptoms and disability progression in MS is becoming clear, and knowledge of how physical and mental comorbidities affect MS will improve management of the complexity of the disease. In 2015, Marrie *et al*.[8] addressed the question of whether comorbidities are responsible for the reduced survival associated with MS. They used population-based administrative data to study 5,797 people with MS and 28,807 healthy controls who were matched for sex, year of birth and geographical region. Median survival from birth was 75.9 years in the MS population, and 83.4 years in the control population, which corresponded to a 2-fold unadjusted increase in the hazard of death in the MS population. Comorbidities (depression, diabetes and ischaemic heart disease) were associated with increased mortality in MS, but did not confer a greater risk of mortality in the MS population than in the control population. Mortality from infectious diseases and diseases of the respiratory system was higher in the MS population than in the control population. These findings extend the results of previous studies that reported an effect of comorbidity on the diagnosis of and disability in MS[9] , suggesting that treatment and prevention of comorbidities improves survival in MS. Future research will fill important gaps in our knowledge about the worldwide epidemiology of comorbidity in MS[10].

These recent advances in MS research and clinical trials will help clinicians to manage the complexity of MS in clinical practice and will inform future research in the field. We anticipate that 2016 will bring major advances in the treatment of progressive MS, which remains a substantial unmet need.[3]

Queen Square MS Centre, UCL Institute of Neurology & NIHR UCLH/UCL Biomedical Research Centre, Queen Square, BOX 9, WC1N 3BG, London, UK.
Correspondence to alan.thompson@ucl.ac.uk

References

1. Freeman L, et al. The neuronal component of gray matter damage in multiple sclerosis: A [(11) C]flumazenil positron emission tomography study. *Ann Neurol*. **78**, 554-67 (2015).
2. Louapre C, et al. Beyond focal cortical lesions in MS: An in vivo quantitative and spatial imaging study at 7T. *Neurology*. **85**, 1702-09 (2015).

3. Salvetti M, et al. Progressive MS: from pathophysiology to drug discovery. *Mult Scler*. **21**, 1376-84 (2015).
4. Tintore M, et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. *Brain.* **138**, 1863-1874 (2015).
5. De Stefano N, et al. Long-term assessment of no evidence of disease activity in relapsing-remitting MS. *Neurology*. 2015 Nov 10;85(19):1722-3.
6. Kalincik T, et al. Switch to natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis. MSBase Study Group. *Ann Neurol*. **77**, 425-35. (2015).
7. Clanet MC ,et al. Risk evaluation and monitoring in multiple sclerosis therapeutics. *Mult Scler*. **20**, 1306-11 (2014).
8. Marrie RA, et al. Effect of comorbidity on mortality in multiple sclerosis. *Neurology*. **85**, 240-247 (2015).
9. Marrie RA, et al. Comorbidity delays diagnosis and increases disability at diagnosis in MS. *Neurology.* **72**, 117-124 (2009).
10. Marrie RA, et al. A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: overview. *Mult Scler.* **21**, 263-281 (2015).

Acknowledgment
The NMR Unit and its staff are supported by the UK MS Society, NIHR UCLH/UCL BRC, EPSRC, and UCL internal funding schemes.

Competing interests
OC serves as a consultant for Biogen, GE Healthcare and Novartis, and payments are made to her institution; she receives an honorarium as Associate Editor of Neurology. AJT serves as a consultant for Biogen Idec, Novartis, Medday, Eisai and Genzyme; he has received speaking fees from Novartis, Teva, EXCEMED, Remedica, and an honorarium from Sage Publications (as Editor in Chief, Multiple Sclerosis Journal)

Figure 1. Towards successful management of the complexity of multiple sclerosis.

Key advances
- Synaptic and/or dendritic loss might be an early pathological abnormality in multiple sclerosis (MS) and precede MRI-detectable volume loss[1].
- In clinically isolated syndrome, oligoclonal bands and the lesions detected with brain MRI are medium-impact and high-impact prognostic factors, respectively, for the development of MS and early disability[4].
- The relapse rate was 50% lower when patients switched from injectable disease-modifying treatment to natalizumab than when they switched to fingolimod, but no difference was observed in disability progression[6].
- Although MS patients live longer than before, their life expectancy remains ~7 years shorter than that of a matched healthy population; treatment of comorbidities might improve survival[8].
- The Progressive MS alliance is driving an initiative to identify new treatments to slow or stop progression of MS[3].

Olga Ciccarelli studied Medicine and completed training in Neurology at the University of Rome “La Sapienza”, Italy. She was then awarded a PhD in Neurological Science at University College London (UCL), UK. She is now Professor of Neurology at the UCL Institute of Neurology. She runs multiple sclerosis specialist and diagnostic clinics at the National Hospital for Neurology and Neurosurgery, London, UK. Her research aims to understand the mechanisms of damage and recovery in the CNS using advanced imaging techniques. She is an Associate Editor of *Neurology*.

Alan Thompson is the Dean of the University College London (UCL) Faculty of Brain Sciences, Garfield Weston Professor of Clinical Neurology and Neurorehabilitation at the UCL Institute of Neurology, consultant neurologist at the National Hospital for Neurology and Neurosurgery and Chair of the Neuroscience Programme at the UCLP Academic Health Sciences Centre, all in London, UK. His main area of expertise is demyelinating disease, particularly the diagnosis, evaluation and management of multiple sclerosis (MS). He is Chair of the Scientific Committee of the International Progressive MS Alliance, Senior Investigator for the National Institute for Health Research, London, UK, Editor-in-Chief of *Multiple Sclerosis Journal,* and a Guarantor of *Brain.*