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Multiple Sclerosis : the upward trajectory continues

The rate and range of publications in multiple sclerosis (MS) continues apace reflecting the on-going developments in the field with new treatments, not only for relapsing remitting, but more recently positive phase III trials in both primary and secondary progressive MS. Selecting only five papers from the last year that improve our understanding, provide new insights, or raise awareness is thus a major challenge.

The concept of clinically isolated syndrome is now very well established and the MS community is grappling with appropriate characterisation of patients with no clinical symptoms, but who are found to have abnormalities on MRI that are consistent with those seen in MS - so called radiologically-isolated syndromes (RIS). An elegantly written paper by Kantarci and colleagues followed a large RIS cohort of 453 subjects studied in 22 clinical sites. During a 15-year follow-up, 128 evolved to symptomatic MS, 15 of whom developed primary progressive MS[1] (PPMS), with a median time to conversion of 3.5 years, demonstrating that subjects with RIS evolve to PPMS in the same frequency as would be expected in general MS populations. The strongest predictors of evolution of PPMS included male sex, a more advanced age, and the presence of initially asymptomatic spinal cord lesions. Such observations suggest that RIS can be considered as pre-symptomatic MS and drive the need to place more weight not only on brain, but also spinal cord MRI findings, even when presenting in isolation and will doubtless be considered carefully in the International Diagnostic meeting in Philadelphia.

One of the key questions in relation to the pathology of MS is how new lesions form and whether they can be prevented. In an intriguing paper, Smith and his colleagues, guided by the hypothesis that demyelination can occur in the relative absence of lymphocytes, and with distinctive characteristics suggestive of a tissue energy deficit, explored the potential for inspired oxygen in lipopolysaccharide-induced lesions (which are described as pattern III lesions, essentially linked to primary oligodendrocyte injury) in the rat spinal cord[2]. Their serial evaluation showed that lesions occurred at the white matter- grey matter border (in the vascular watershed

area) and were associated with hypoxia, superoxide and nitric oxide formation. Furthermore, inspired oxygen reduced demyelination. Whilst these findings, together with the safety of oxygenation, including the reversal of ongoing hypoxia, need to be verified, they suggest a key role for hypoxia in the pattern III lesions.

The application of pathologically specific imaging biomarkers is another strategy to increase our understanding of underlying disease mechanisms in MS and while MRI has proven very valuable in diagnostics and clinical trials, Positron Emission Tomography (PET) provides additional scope as has been very beautifully demonstrated in Bodini's study of demyelination and remyelination[3]. They carried out a longitudinal study in 20 MS patients and 8 healthy controls combining PET with a specific tracer to explore myelin dynamics - Pittsburgh compound B ([^{11}C]PiB) and MRI. They described the dynamics of both demyelination and remyelination and computed an index of remyelination, which may reflect the individual remyelination potential and inversely correlated with clinical disability. This should encourage further application of high-resolution PiB-PET to assess the efficacy of remyelinating therapies.

The acceleration of new treatments for progressive MS, as articulated by the Progressive MS Alliance, took a major hit when the important and well- designed, trial of fingolimod in primary progressive MS turned out to be negative[4]. Nonetheless, this trial has the potential to tell us much about the mechanisms underlying progression and bringing this data together with other trials of primary progressive MS will be extremely valuable. Of more promise is the positive trial of phenytoin in optic neuritis[5]. This phase II trial of patients with acute optic neuritis, presenting within 2 weeks from onset, was based on the premise that phenytoin is neuroprotective through its inhibition of voltage-gated sodium channels. There was a positive finding of a 30% reduction in the extent of retinal nerve fibre layer loss in the treatment arm. This encouraged the authors to postulate that they may well be demonstrating a neuroprotective effect an important therapeutic approach in progressive MS.

Finally, and under the banner of raising the profile of an important but neglected area is the series of papers on MS co-morbidities, emanating from a workshop led by Ruth Anne Marrie in Toronto in March 2015. A supplement containing six papers was produced in Multiple Sclerosis Journal (MSJ) which described the landscape prior to the workshop. The meeting resulted in two major outputs which aim to clarify the prevalence of key co-morbidities in MS[6] and, importantly, determine how they should be incorporated into clinical trials both in terms of safety and efficacy of the intervention under study[7].

There is a clear sense of advancement in both our understanding and treatment of this complex condition, with further developments in progressive MS eagerly awaited.

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