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LEADING TOPIC

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Multiple sclerosis and related disorders: where do we stand in 2022?

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Multiple sclerosis (MS), one of the leading causes of neurological disability in young adults [1], is a highly heterogenic condition, varying from single clinically (or even radiologically) isolated episodes to progressive phenotypes [2]. With no one specific biomarker for MS at our disposal [3], the diagnosis is based on clinical judgement guided by detailed diagnostic criteria that have evolved over the years to incorporate magnetic resonance imaging (MRI) and laboratory data (the presence of cerebrospinal fluid-specific oligoclonal bands) [4]. With the introduction of subsequent versions of the McDonald criteria, time to MS diagnosis has gradually shortened [5, 6]. Therefore, the careful exclusion of other disorders that can mimic MS is crucial to avoid the dramatic consequences of misdiagnosis, including the application of highly effective MS-specific disease-modifying treatments to patients with non-specific symptoms and non-localising atypical MRI findings, migraine or one of the many other MS mimics [7, 8].

Despite revolutions in the diagnostic and therapeutic fields, MS remains a challenge, especially in atypical cases. In this issue of PJNNS, we have brought together a series of manuscripts which add interesting observations and fresh perspectives on MS and related disorders (Tab. 1).

Firstly, in this issue, Jurynczyk et al. discuss the increasing role of imaging in differentiating MS from other disorders [9]. They point out that the classical approach of proving an MS diagnosis by fulfilling dissemination in time and space criteria may be misleading, since conditions that have recently been re-classified as non-MS, such as neuromyelitis spectrum disorders (NMOsd) or myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) may have overlapping clinical and radiological features. In seronegative NMOsd cases, where anti-aquaporin 4 antibodies (AQP4-IgG) are absent, a careful imaging based on strict protocols [10, 11] remains the best available tool to distinguish these cases from MS.

The gold standard in the differentiation of atypical central nervous system inflammatory demyelinating diseases (CNS-IDDs) would be pathology, as discussed by another paper featured in the current issue [12], although it is not always available. In this paper, together with colleagues from the Mayo Clinic, we discuss how to analyse the neuropathological material to reliably distinguish MS from other CNS-IDDs, highlighting the pathological hallmarks of MS, acute disseminated encephalomyelitis (ADEM), NMOsd and MOGAD, and providing representative pathology illustrations.

Although considered as the gold standard, even pathology is not in every case definitive, and the paper also presents potential pitfalls, yet again emphasising the role of clinical judgement in borderline cases, such as in our previously published case of a rheumatoid arthritis patient treated with infliximab who developed CNS demyelination highly atypical for MS clinically and radiologically, but pathologically indistinguishable from MS [13]. From a broader perspective, as discussed in the current paper [12], it is crucial to document detailed data on cases with available pathology, such as in the Multiple Sclerosis Lesion Project, which was an innovative international collaborative effort to study the clinical-radiological-pathological correlates of the MS lesion [14, 15], resulting in better understanding of the dynamic nature of an MS plaque [16–19].

A lot of pathological data for MS comes from cases of tumefactive demyelination where biopsy is performed so as to exclude a neoplastic nature of the lesion. However, as Juryńczyk et al. discuss [9], several clinical scenarios should be considered in cases of tumefactive demyelinating lesions (TDLs). In this issue, Topkan et al. present a case of a seronegative NMOsd patient who developed a tumefactive demyelinating lesion while on rituximab treatment [20]. Although seronegative for AQP-4 IgG, the patient did fulfill the 2015 NMOsd

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Table 1. Leding Topic papers: Multiple sclerosis; PJNNS 3/2022

Title	Authors
INVITED REVIEW ARTICLES	
Update on the Pathology of the Central Nervous System Inflammatory Demyelinating Diseases	Kalinowska-Łyszczarz A., Guo Y., Lucchinetti C.F.
Increasing role of imaging in differentiating MS from non-MS and defining indeterminate borderline cases	Juryńczyk M., Jakuszyk P., Kurkowska-Jastrzębska I., Palace J.
Immunosenescence and multiple sclerosis	Adamczyk-Sowa M., Nowak-Kiczmer M., Jaroszewicz J., Berger T.
Clinical trials in multiple sclerosis: past, present, and future	Manouchehri N., Shirani A., Salinas V.H., Tardo L., Hussain R.Z., Pitt D., Stuve O.
RESEARCH PAPERS	
Anti-EBNA1 IgG titre is not associated with fatigue in multiple sclerosis patients	Fleischer M., Schuh h., Bickmann N.M., Hagenacker T., Krüger K., Skripuletz T., Fiedler M., Kleinschnitz C., Pul R., Skuljec J.
Different blood-brain-barrier disruption profiles in multiple sclerosis, neuromyelitis optica spectrum disorders, and neuropsychiatric systemic lupus erythematosus	Jasiak-Zatońska M., Pietrzak A., Wyciszkiewicz A., Więsik-Szewczyk E., Pawlak-Buś K., Leszczyński P., Kozubski W., Michalak S., Kalinowska-Łyszczarz A.
Highly active disease and access to disease-modifying treatments in patients with relapsing-remitting multiple sclerosis in Poland	Brola W., Adamczyk-Sowa M., Kułakowska A., Głażewska J., Smaga A., Bartosik-Psujek H.
LETTER TO THE EDITORS	
Tumefactive demyelinating lesion in patient with neuromyelitis optica spectrum disorder	Topkan T.A., Sokmen O., Kocer B., Karabudak R., Gocun P.U.

revised consensus criteria [21], with longitudinally extensive transverse myelitis as his first disease manifestation, and a symptomatic cerebral syndrome as the other core clinical syndrome. The pathology revealed macrophage infiltration with active myelin degradation. Unfortunately, AQP-4 and complement stains were lacking, which would be crucial to confirm NMOsd pathology.

This highlights the need for a standardised protocol for tissue sampling, preservation procedures and stains, that should be performed in patients with atypical demyelinating syndromes [22].

Another paper in the current issue discusses the differentiation of MS, NMOsd and neuropsychiatric systemic lupus erythematosus (NP-SLE) from a biomarker perspective [23]. Indeed, SLE is another MS mimic to be considered, with a significant clinical and biological overlap between the two [24, 25]. Jasiak-Zatońska et al. analysed the serum profile of blood-brain-barrier (BBB) disruption markers in the three study groups and found the levels of sPECAM-1, sICAM-1 and S100B were the lowest in NMOsd. The highest levels of sPECAM-1 were observed in NPSLE, and the highest levels of sICAM-1 were found in NPSLE and MS. These findings suggest that there is indeed a different profile of BBB disruption reflected by cell adhesion molecules shedding into serum compartment. The authors conclude that these molecules could become new add-on biomarkers used in CNS-IDD differential diagnosis. Such an approach, using a combination of biomarkers that yields the highest specificity and sensitivity for a specific disorder, may signal the future of diagnostic work-up in atypical/borderline cases of CNS demyelination.

Over the last three decades, our therapeutic power in MS has dramatically increased, with nearly 20 therapies approved for use in MS [26, 27]. Such progress has mainly been applicable to the relapsing forms of MS, and much less so to the progressive phenotypes [28] Carefully planned clinical trials and sophisticated statistical analysis tools shape and guide the therapeutic landscape in MS, which has become extensive and diverse. In our leading topic issue on MS and related disorders, Manouchehri et al. discuss milestones in the evolution of clinical trials in MS [29]. They point out how the evolution of MS diagnostic criteria and definitions alongside the latest achievements in imaging techniques has translated into the improvement of pharmacotherapy trial design. Importantly, they critically assess the evolution of clinical trials in MS. This paper helps readers to appreciate trial design importance for interpreting the data and translating it into clinical practice. Also, the authors discuss how future trials will need to adjust to the current disease modifying therapies (DMT) landscape. This is an important and very valuable paper for researchers and practicing neurologists alike.

Another manuscript featured in this issue discusses the DMT approach for patients with highly active MS in Poland [30]. The original paper by Brola et al. is of special importance in the context of the Polish MS population, as it provides evidence that the country's current reimbursement criteria for highly effective MS therapies are too strict. This needs to be discussed in the context of the growing body of evidence that high-efficacy DMTs should be used early in the disease course to provide the maximum benefit in long-term disability progression [31–33]. We must bear in mind that even a rapid escalation approach may not be enough to prevent disability

accumulation in MS patients with ongoing disease activity. Importantly, if we decide to use high-efficacy DMTs, we should use them sooner rather than later, also given the perspective of the natural ageing of the immune system. This phenomenon, known as immunosenescence, is discussed in the current issue in a comprehensive review by Adamczyk-Sowa et al. [34]. Today, as the population of DMT-using MS patients is growing older, this issue is increasingly important. With age-related decrease of MS activity, the potential benefit of DMTs declines but the risks increase. Adamczyk-Sowa et al. sum up the available information on how the immune system in MS patients changes with age and provide information on how it could potentially be affected by DMT use in this population, with special regards to infection and carcinogenesis risks. They point out that some features of immunosenescence, such as accelerated telomere shortening, are observed in MS patients at a younger age than in healthy subjects.

How the immune system in MS patients differs from that of healthy individuals has been subject to a multitude of research directions. Just recently, the MS world has yet again been directed towards Epstein-Barr virus (EBV) and its potential role in MS pathogenesis. This was prompted by a paper published in 'Science' by Bjornevik et al. who showed in a largest-to-date sample that EBV infection drastically increased the odds of MS development [35]. In line with this study, a complete EBV seropositivity was also present in the cohort of MS patients that Fleischer at al. analysed in the current issue of the PJNNS [36]. Fleischer et al. dived into the subject of EBV and its potential link to MS-related fatigue. Although they did not find any associations between serum levels of immunoglobulins specific for EBV antigens, namely EBNA1 and VCA, and the levels of fatigue, sleepiness, and depression among MS patients, they did observe that in the subgroups matched for disease duration over 10 years, patients with relapsing-remitting MS (RRMS) had higher EBNA1 titres than those with chronic progressive MS, suggesting that EBV might in fact contribute to MS clinical course. As prognostic markers for disease course transition from RR to the secondary progressive phase are still lacking, given the findings by Fleischer et al., EBNA1 levels could be considered in this regard, something which warrants further study.

With the ever-growing basic scientific understanding regarding MS and related disorders, and a growing body of clinical evidence, this topic remains a major research mine and continues to pose a fascinating clinical challenge.

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