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Review Article

Insights into the Course of Illness of MS: Clinical and Radiological Aspects

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Abstract: Patients with MS manifest a high degree of variability in their disease course and at first glance the disease outcome may seem unpredictable. Here we present a framework for clinicians challenged by the management of MS patients and by highlighting important aspects of the disease to be taken into account, we review the complex relationship between inflammation and neuronal degeneration. Details of illustrative cases are here described with the goal to emphasize the involvement of the spinal cord as a key element leading to progressive phases of the disease and to underscore the utility of recent paraclinical tools including quantified MRI volumetrics. We provide insights that allow understanding the variability of disease courses of MS, assessing the rate by which the disease generates clinical and radiological burdens for individual patients, and how currently available treatments have a predictable impact on outcomes. In line with latest views on the therapeutic approach for MS, instituting an immune therapy capable of arresting the inflammatory process before the cascade of degenerative phenomena takes place is portrayed as a strategy to prevent progressive stages of the disease, increasing the chance to induce a state of permanent remission when the treatment could be discontinued.

Keywords: MS Course of Illness, Neuronal Degeneration, Disease Progression, MRI for MS, Treatment Strategies

1. Introduction

A central challenge in the clinical management of multiple sclerosis (MS) is the unpredictable nature of the disease. This variability has been demonstrated by several natural history studies of mostly untreated patients, who experienced a wide range of long-term outcomes. These studies revealed clinical and demographic characteristics that provided the first prognostic insight into long term outcomes [1-6]. With the goal to unveil the genetic predisposition to MS, extensive investigations led to the understanding that MS is a multifactorial disorder due to both genetic and environmental factors [7-10]. Consistently, the histocompatibility complex and many other immune regulating genes have been implicated [11, 12]. Genetic contributions however, are neither necessary nor sufficient to cause the disease. This view of heterogeneity was explored decades ago at the histological level by Lucchinetti *et al.* and both inflammatory and degenerative phenomena appeared to be part of the disease processes [13, 14].

The misconception that most MS patients with relapsing remitting disease manifest a gradually progressive accumulation of disability has been revised in a recent classification of MS [15]. In line with concepts of heterogeneity, many patients may enter a phase of complete remission with prolonged clinical and radiological stability. This supports consideration to discontinue therapy in certain cases [16]. Conversely, other patients experience a relentless accumulation of neurological deficits consistent with a neurodegeneration that is likely multifactorial. Mitochondrial dysfunction and oxidative stress related phenomena are only part of the pathophysiology. The discovery of lymphoid-like structures in the meninges of some patients with progressive forms of MS has brought attention to the possible intrathecal

release of soluble inflammatory factors contributing to neuronal degeneration [17, 18]. The recurrent theme is that the variability among patients is due to different mechanisms in different subjects with the common end point of neuronal demise in the progressive disease course.

MRI remains the most useful and widely-validated biomarker of MS disease activity. Multiple studies have demonstrated that both the number and location of MS T2-hyperintense lesions are predictive of long-term outcomes of MS [19-22]. The burden of disease in the early stages correlates with long term disability. However, the accuracy of such prediction is unsatisfactory, especially when faced with individualized clinical decision-making. For instance, in one twenty year longitudinal study of MS patients, 65% of those with more than 10 discrete lesions on MRI brain at the time of first presentation, developed greater than mild disability and 45% accrued moderate-to-severe functional impairment [23]. The discrepancy of MRI lesion burden compared to clinical disability has been referred to as Clinical-MRI paradox [24]. This suggests that for a subset of MS patients, tissue damage exists independent of the inflammatory activity [25]. Patients with relatively high T2-lesion burden but robust functional capacity highlight the challenges posed to clinicians to confidently prognosticate and counsel patients.

More recently, several companies have introduced FDA-approved, HIPAA-compliant software that enables clinicians to obtain a quantified volumetric analysis of the patients' brain MRI. The reports often include the T2-hyperintense and T1-hypointense lesion volumes, as well as the whole brain volume (normalized to a standard template) with comparison to age-matched healthy control normograms. If more than one MRI is acquired (using the same scanner and protocol), the software additionally performs longitudinal estimates of how these parameters change. The end product is an account that allows for a bedside-quantification of age-adjusted brain atrophy as well as brain atrophy rates over time, both being indirect but summative measures of the neurodegenerative phenomena afflicting many MS patients.

At a group level, these volumetric atrophy assessments have demonstrated clinical relevance in the prognostication of MS. Measurements of brain atrophy strongly predict the subsequent development of long-term disability or accelerated clinical disease, providing complementary information to the T2-hyperintense lesion load [26-30]. A recent study examining favorable versus unfavorable outcomes in patients with disease duration <20 years showed that it was whole brain and gray matter atrophy that separated out clinical disability trajectories, rather than T2 lesion volumes [31]. Moreover, in a notable investigation with 10-year follow-up of 372 early relapsing MS patients, baseline age-adjusted brain volume was a significant predictor of long-term disability progression. The number of clinical relapses or new T2-hyperintense lesions was less relevant, implying a neurodegenerative phenomenon. The authors refer to this finding as "silent progression" [32].

Finally, T1-hypointense "black holes" also remain clinically important, as a reflection of the severity of underlying tissue destruction in MS lesions. For example, Giorgio *et al.* observed that baseline T1-hypointense lesion volume together with growth of these T1 lesions was the strongest factor predicting 10-year disability progression in a multivariable model [33]. Another group later reported similar findings, that baseline T1-hypointense lesion volume was a strong predictor of 12-year disability, adjusting for many other factors including age and T2-lesion volume [34]. Slow expansion of T1-hypointense lesions was recently validated as a reliable measure reflecting chronic, smoldering inflammation in MS and disability progression [35].

Major caveats nonetheless remain when incorporating these metrics into bedside clinical practice. How precise, reliable and robust are these measurements? Highlighting this point is the lack of large-scale validation for these individual analysis pipelines, as well as the many technical variables which can introduce substantial noise into the measurement, especially if done longitudinally [27].

While correlations between cognitive functions and effects of the disease on gray matter are increasingly being recognized [36, 37], (Case 1 and Case 2), understanding the substrate of motor disability has been more straightforward. Involvement of the motor pathway causes restrictions of mobility and the direct relationship between anatomy and motor deficits was established in studies where demyelinating lesions affecting the pyramidal pathway were identified with the highest degree of correlation [3, 38]. Moreover, it has been observed that certain demyelinating lesions are more likely to lead to a relentless loss of function suggesting that the underlying process varies. Specific areas of the spinal cord are more susceptible to neuronal degeneration, emphasizing the high prognostic relevance of cord involvement [39].

The purpose of this article is to review important clinical questions related to heterogeneity in MS, as exemplified through a case series incorporating quantified MRI as contemporary paraclinical information. We aim to help the general neurologist identify "high risk" MS patients who would likely be at most urgent need for interventional therapy. We highlight high-impact clinical and MRI factors that can be used for prognosis. While acknowledging ongoing discussions regarding various valid approaches to treatment of the MS patient, we underscore a shift in evidence proposing beneficial early use of pharmacological agents with immune reconstitution properties for preventing long-term disability.

2. Clinical Cases

Case 1: Relapsing MS with accelerated brain atrophy [Figure 1].

At 25 years old, a female patient experienced numbness to the right extremities and as the disturbances resolved spontaneously, no medical testing was pursued. Eight years later, the patient experienced new sensory and motor symptoms to the left side, most significantly affecting the left leg, and MRI scans led to the diagnosis of MS. After about one year on therapy with high dose interferon, patient suffered from horizontal diplopia that persisted for about two months

before resolving completely. A few months later, the patient manifested left optic neuritis and the MS therapy was changed to ocrelizumab.

Although the patient has recovered from the motor deficits affecting the left leg, at 35 years of age she notices the decreased function of that limb and she complains of subjective cognitive impairments. Neuropsychology testing was not done and at her still young age, the residual brain reserve capacity allows employment and normal levels of functions (EDSS 2.0).

MRI scans demonstrate an advanced stage of MS that considering the relatively short duration represents an aggressive relapsing remitting form of the disease (Figure 1). The remarkable loss of brain volume to less than 1% of healthy control comparisons, and the overall high burden of the demyelinating lesions (32.7 mL) with substantial neuroaxonal loss represented by T1 hypointensity (26.0 mL volume) are summarized via automated software (Figure 1 F and G). Stability is documented in the two-year interval on therapy with a B-cell depleting agent.

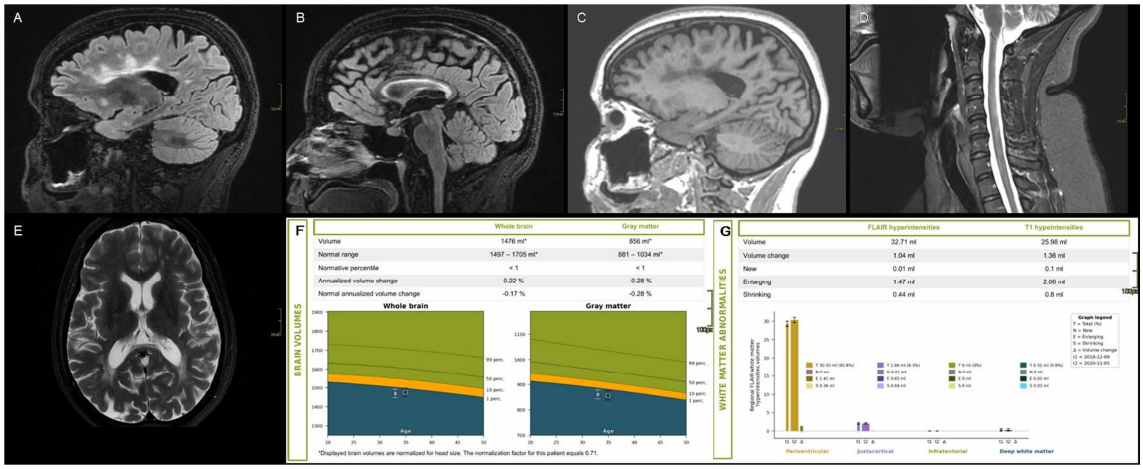

Figure 1. *Magnetic resonance imaging (MRI) sequences demonstrating the distribution of Multiple Sclerosis (MS) lesions seen in this patient. A, Sagittal Fluid Attenuated Inversion Recovery (FLAIR) sequence demonstrates the classic radial distribution of white matter lesions perpendicular to the body of the lateral ventricles. B, Sagittal FLAIR sequence demonstrates MS lesions along the callosal-septal margin. C, Sagittal T1 series demonstrates corresponding low T1 signal of many of the white matter lesions which has higher correlate to overall disability than FLAIR hyperintense lesions. D, Sagittal Short Tau Inversion Recovery (STIR) demonstrates multiple hyperintense MS lesions involving the cord. E, Axial T2 sequence demonstrates diffuse cerebral atrophy with abnormal prominence of the ventricles and sulci. F, Quantitative analysis utilizing ICOMETRIX software shows markedly advanced atrophy of the brain below 1% when matched for age, sex, and head size with normal controls at two points in time. G, Quantitative analysis utilizing ICOMETRIX software shows the volume and distribution of the MS lesions at the two time points as the brain volume measurements.*

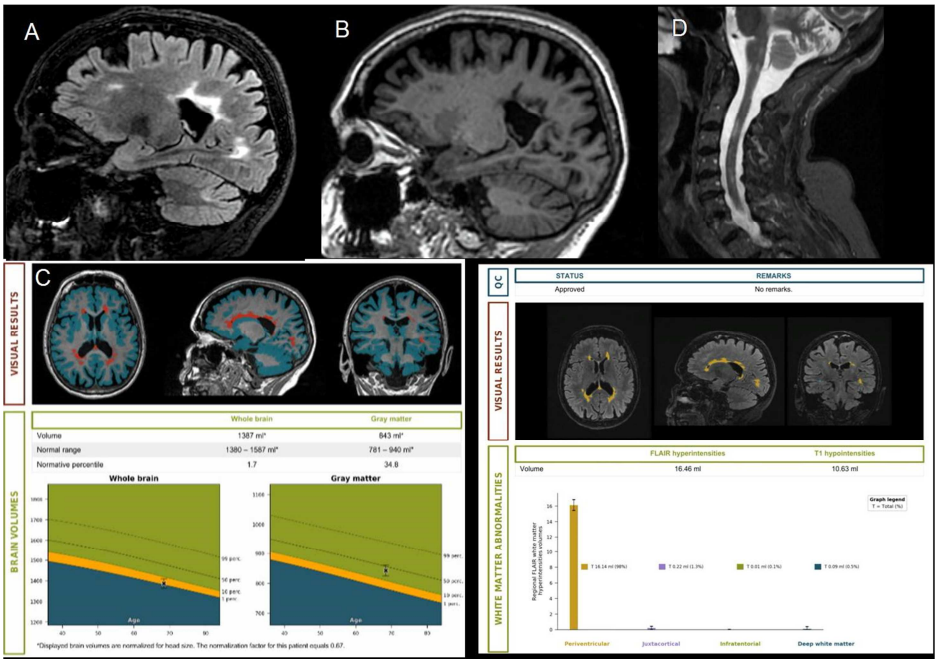

Figure 2. *Magnetic resonance imaging (MRI) sequences demonstrating the distribution of multiple sclerosis lesions seen in this patient. A, Sagittal Fluid Attenuated Inversion Recovery (FLAIR) sequences demonstrate white matter disease of the brain. B, Sagittal T1 series demonstrates low T1 signal of many of the white matter lesions. C, Quantitative analysis utilizing ICOMETRIX software shows advanced atrophy of the brain when matched for age and head size with normal controls. D, Sagittal Short Tau Inversion Recovery (STIR) sequence demonstrates typical MS lesions scattered throughout the cervical cord.*

Case 2: Patient with a long-standing stabilized MS course [Figure 2].

Patient is a 69-year-old woman who manifested MS with optic neuritis at 16 years of age. Over the years she experienced many clinical relapses of MS from which she had partial recoveries and she accumulated disability with neurological deficits including leg weakness, gait ataxia with spasticity, ophthalmoparesis, cognitive complaints, bladder dysfunction. Her ability to walk is restricted but she ambulates without assistance. The patient was not on MS therapies until 56 years of age when she was prescribed mycophenolate; she continued this medication for ten years before being changed to B-cell depleting agents for three years and finally discontinuing therapy at age 69.

Her ability to function has not changed since the start of the immune therapies. She is capable of regular physical exercise and she has maintained a stable clinical status. The hypothetical preservation of the energy machinery in the affected neural tissue could be viewed as the basis for the maintained neurological functions. (25 foot walk: 6.5 seconds; EDSS 5.0).

MRI scans of this patient demonstrate scattered white matter lesions in a typical pattern for MS involving the spinal cord, brainstem, and periventricular and deep white matter of the brain; there has been loss of whole brain volume as assessed via the automated quantification software (Figure 2C).

Case 3: Rapidly progressive MS course, refractory to treatment [Figure 3].

Patient is a 41-year-old female who was diagnosed with MS when she was in her early twenties after recurrent optic neuritis. She was on therapy with interferon for approximately four years. With two pregnancies the treatment was interrupted and not resumed until she was 34-year-old, about a ten-year gap. At that point, she manifested leg weakness and gait impairment. Despite attempts to treat her with natalizumab followed by ocrelizumab and superimposed courses of high doses of steroids, she progressively accumulated more motor deficits. Within three years, she went from ambulatory to wheelchair bound with tetraparesis (EDSS 8.5).

This case is illustrative of a form of rapidly progressive disease correlated to severe spinal cord involvement, refractory to treatment. MRI scans demonstrate relatively mild disease burden in the brain (Figure 3A-D) and extensive involvement of the spinal cord. Images of the spinal cord early in her treatment demonstrate multiple cervical cord lesions (Figure 3E) that increased and became confluent over a ten year interval (Figure 3F). Two years later, repeat imaging of the cord shows significant progression of the disease with atrophy of the upper cervical cord (Figure 3G) reflective of the deteriorating clinical course.

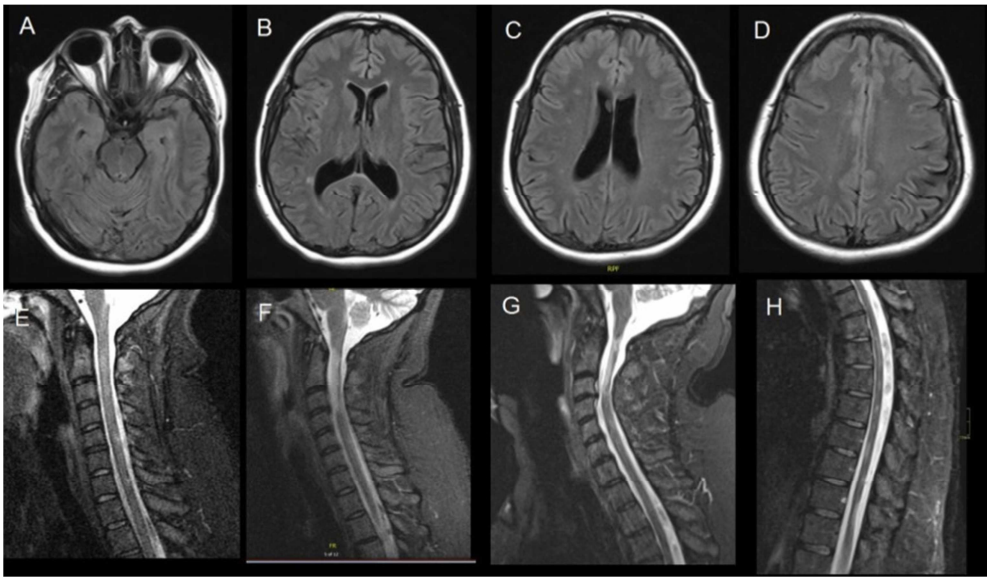

Figure 3. *Magnetic resonance imaging (MRI) sequences demonstrating the distribution of multiple sclerosis lesions seen in this patient. A-D, Axial Fluid Attenuated Inversion Recovery (FLAIR) sequences demonstrate mild white matter disease of the brain. E-F, Sagittal Short Tau Inversion Recovery (STIR) sequence demonstrates scattered MS lesions in the cervical cord, significantly progressed in a ten-year interval. G, Sagittal Short Tau Inversion Recovery (STIR) sequence demonstrates cervical cord atrophy intervening in subsequent two years. H, Multiple scattered lesions throughout the thoracic cord.*

Case 4: MS patient with a progressively disabling clinical course [Figure 4].

Patient is a 46-year-old female who manifested MS with leg weakness and spasticity when she was 32-year-old and her symptoms continued to progress despite the use of glatiramer acetate for about ten years and ocrelizumab for one year. Approximately six months after an autologous bone marrow transplant at age 44, the patient noticed increased problems with balance and worsening spasticity of the legs resulting in falls. Patient started to require a cane. Within one year, her walking became restricted to a few steps with bilateral support (EDSS 7.0). This case is interpreted as manifestations of a relentless demise of neurons, likely occurring independent of inflammatory activity.

The MRI scans illustrate the brain-spinal cord dissociation. There were no changes of the mild burden of

demyelinating lesions over time (Figure 4A-D); the MRI of the C-spine demonstrates extensive and confluent areas of signal abnormalities (Figure 4E-F), progressed in the most recent scan at three years with cord atrophy (Figure 4G-H). Cervical spondylosis worsened likely secondary to falls.

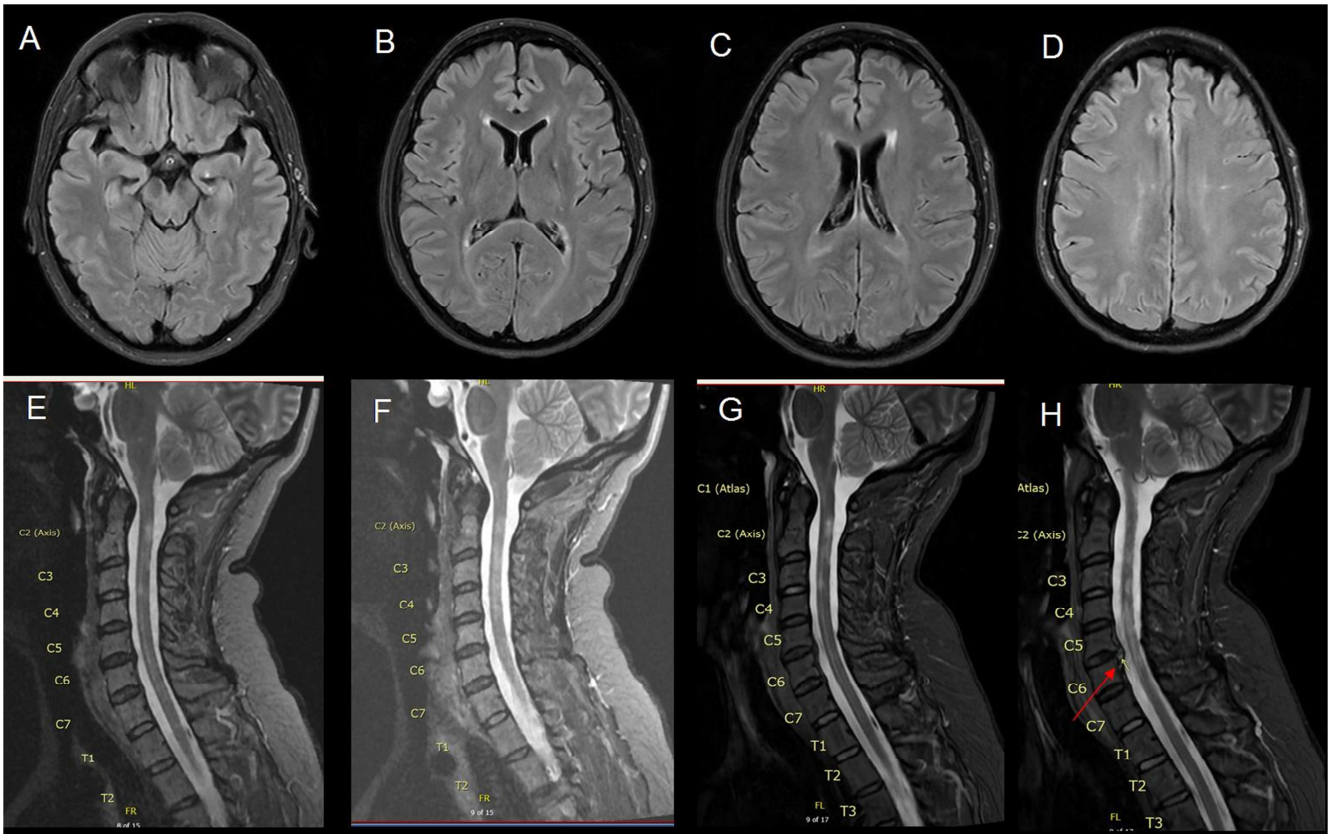

Figure 4. *Magnetic resonance imaging (MRI) sequences demonstrating the distribution of Multiple Sclerosis (MS) lesions seen in this patient. A-D, Axial Fluid Attenuated Inversion Recovery (FLAIR) sequences demonstrate a small amount of MS disease burden in the brain. E-H, Sagittal Short Tau Inversion Recovery (STIR) sequences demonstrate a few scattered lesions in the cervical cord (E-F) with significant progression of the disease on follow-up imaging 3 years later (G-H). Cervical spondylosis has progressed at the C5-C6 level likely secondary to falls (H, arrow).*

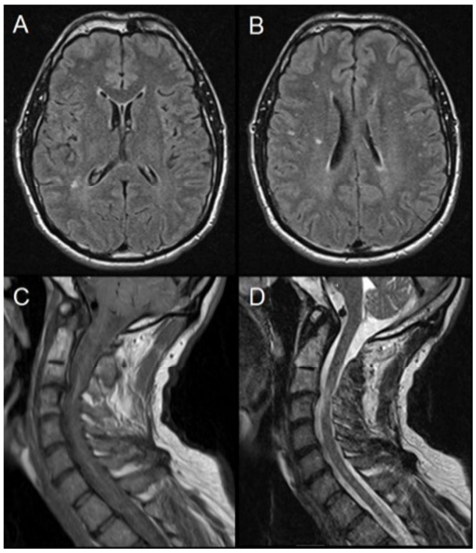

Figure 5. *Magnetic resonance imaging (MRI) sequences demonstrating the distribution of multiple sclerosis (MS) lesions seen in this patient. A-B, Axial Fluid Attenuated Inversion Recovery (FLAIR) sequences demonstrate a small amount of MS disease burden in the brain. C, Sagittal Proton Density (PD) sequence demonstrates an MS plaque at the C3-C4 level. D, Sagittal T2 sequence demonstrates cervical spondylosis adjacent to the MS plaque.*

Case 5: Patient with the challenging overlap between MS and cervical spondylosis, leading to progressive disability [Figure 5].

A 56-year-old male manifested MS at 30 years of age with optic neuritis. After a recurrent episode of optic neuritis one year later, the patient remained clinically asymptomatic until around age 50, when his right hemiparesis started to become noticeable; this weakness continued to unremittingly progress with features of lower extremity spasticity and lower motor neuron deficits to the right upper extremity (EDSS 6.5). Based on his initial presentation, one could have suspected this patient to be poised for a benign form of MS; the disability relates to the unfortunate affliction of the cervical cord for which a surgical intervention was not a considered an option.

The MRI brain, stable for over ten years, detects minimal areas of signal abnormalities (Figure 5A-B). MRI C-spine demonstrated cord signal abnormalities particularly at the C3-C4 level in correspondence with cervical spondylosis but without significant central spinal canal stenosis (Figure 5C-D).

Case 6: Patient with typical, stable relapsing remitting MS, acquiring disability from toxic/metabolic causes [Figure 6].

Patient is a 43-year-old female who manifested MS with

right optic neuritis at 19 years of age and she was treated with interferon for about four years before remaining off therapies for the following fourteen years during which she experienced clinical relapses of MS with good recovery from the events. She initiated B-cell depleting treatment at the age of 39 and the MRI scans documented stability of the burden of demyelinating lesions. However, in association with the initiation of high daily alcohol consumption, the patient's disability progressed, specifically for gait and cognitive impairments.

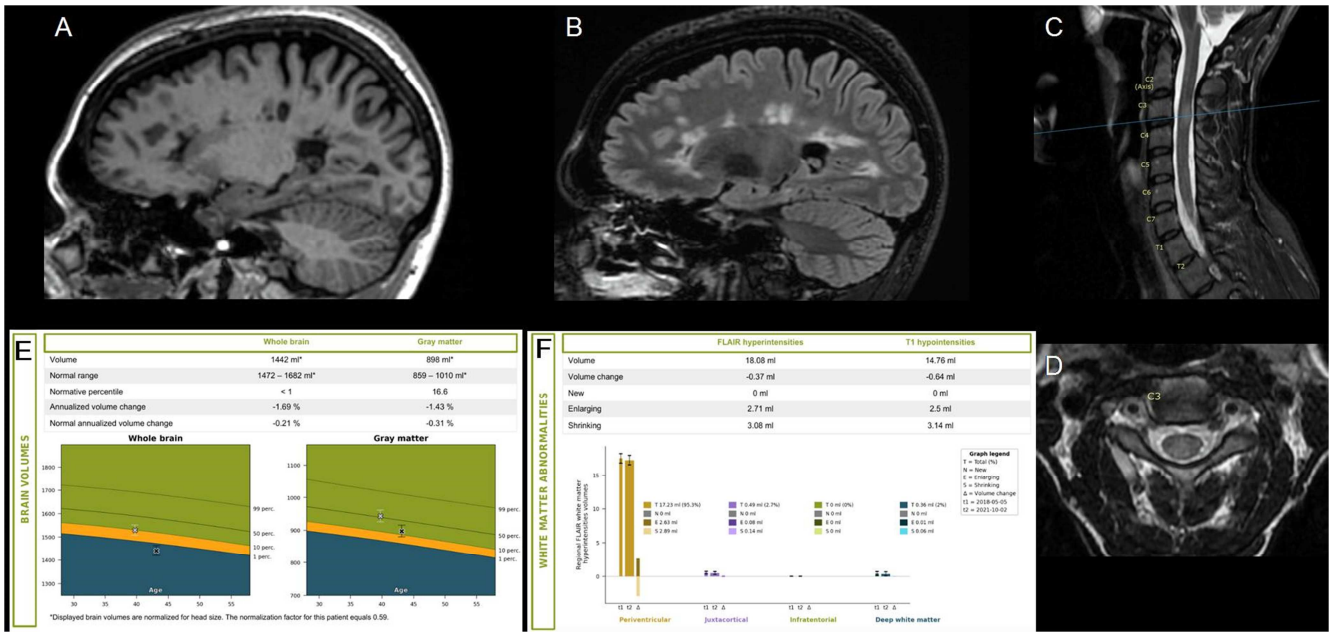

Figure 6. *Magnetic resonance imaging (MRI) sequences demonstrating the distribution of multiple sclerosis (MS) lesions seen in this patient. A, Sagittal T1-weighted and B, Fluid Attenuated Inversion Recovery (FLAIR) sequences demonstrate classic "Dawson's fingers" periventricular lesions. C, Sagittal Short Tau Inversion Recovery (STIR) and D, Axial T2-weighted sequences demonstrate an MS plaque at the C3-C4 level. E-F, Quantified MRI reports demonstrating rapid loss of brain volume of approximating 1.7% annually (E) and unchanged lesion burden (F) in the interval between the two time points.*

Table 1. *Disease modifying therapies for MS divided by effect on immune system.*

	Drug Name	Primary mechanism of action	Administration	Frequency
Continuously-administered therapies	Teriflunomide (Aubagio®)	Dihydroorotate dehydrogenase inhibition	Oral tablet	Daily
	Dymethyl fumarate (Tecfidera®)	Nuclear factor erythroid-derived 2 (Nrf2) pathway activation	Oral capsule	Twice daily
	Diroximel fumarate (Vumerity®)		Oral capsule	Twice daily
	Monomethyl fumarate (Bafiertam®)		Oral capsule	Twice daily
	Fingolimod (Gilenya®)	Sphingosine 1-phosphate (S1P) receptor modulation	Oral capsule	Daily
	Siponimod (Mayzent®)		Oral tablet	Daily
	Ozanimod (Zeposia®)		Oral capsule	Daily
	Ponesimod (Ponvory®)		Oral tablet	Daily
	Interferon beta-1b (Betaseron®)	Immune modulation through control of cytokine release and cell activation	Subcutaneous injection	Every other day
	Interferon beta-1b (Extavia®)		Subcutaneous injection	Every other day
	Interferon beta-1a (Avonex®)		Intramuscular injection	Weekly
	Interferon beta-1a (Rebif®)		Subcutaneous injection	Three times a week
	Peginterferon beta-1a (Plegridy®)		Subcutaneous or intramuscular injection	Every two weeks
	Glatiramer acetate (Copaxone®)	Multiple, including T-cell modulation	Subcutaneous injection	Daily or three times a week
	Natalizumab (Tysabri®)	Monoclonal antibody, non-cytolytic alpha4-integrin receptor binding	IV infusion	Monthly
	Alemtuzumab (Lemtrada®)	Monoclonal antibody, cytolytic anti-CD52 binding	IV infusion	Course 1: daily x 5 days Course 2: daily x 3 days
	Ocrelizumab (Ocrevus®)	Monoclonal antibody, cytolytic anti-CD20 binding	IV infusion	Every six months
Immune Reconstitution therapies	Ofatumumab (Kesimpta®)		Subcutaneous injection	Monthly
	Cladribine (Mavenclad®)	Purine antimetabolite	Oral tablet	Course 1: daily x 5 days Course 2: daily x 5 days
	Autologous bone marrow transplant	Reconstitution of mononuclear immune cells	IV infusions	Single treatment with multiple steps

The most recent MRI scans demonstrate the unchanged pattern and burden of demyelinating lesions in the brain parenchyma and spinal cord in the three-year interval between scans (Figure 6A-F). At the two time points, the dramatic loss of whole brain and grey matter volumes are assessed via the computerized measurements (Figure 6E-F). The impact of metabolic factors afflicting the overall health of brain as an organ is illustrated here [40].

3. Discussion

MS presents as a continuum of disease severity often punctuated with seemingly stochastic events of worsening or breakthrough disease. Based on those concepts of heterogeneity expressed above, the disease may seem to have an unpredictable course of illness and one would not expect that a single therapeutic agent would work for every patient. This notion is likely to apply unless (or until) an improbable underlying, unified pathogenesis for MS is discovered. The clinician and patient are meanwhile faced with the challenging task of selecting an immune-modifying therapy that offers the highest benefit-risk ratio for a given specific presentation.

The chronic nature of MS requires variable degrees of commitment to be kept under control depending on its severity, and treatments could be divided in two categories. One strategy requires the medication to be administered continuously in order to maintain its effects and that carries the two-fold drawback of possible difficulties with compliance and the chance of reactivation if the treatment is interrupted [41-43]. The other, conceived under the incentive of finding options for those more aggressive forms of the disease, relies on therapeutics that induce a dramatic and long-lasting modification of the immune system, thus requiring more infrequent administrations, simultaneously minimizing issues of compliance.

The early clinical trials with injection medications (interferons and glatiramer acetate) demonstrated that on average the occurrences of relapses could be reduced [44] but the total number of partial or complete non-responders was high. Secondary to the better understanding of the disease mechanisms of MS, more effective therapies have become available and the ever-growing armamentarium has attained higher rates of success at controlling the disease [45]. Newer medications have brought on improvements in the quality of life for patients. Contrary to the idea that more than one agent would be needed to treat most patients, B-cell depletion and other monoclonal antibody therapeutics demonstrated extraordinary levels of efficacy across the spectrum of MS patients, with the exception of non-inflammatory progressive forms of MS, discussed below.

Untreated, the disease decreases the life expectancy of the average MS patient [46, 47]; but not being considered deadly per se, the safety of the MS treatments is a priority. Nonetheless, there is an appeal to treatments that have a lasting impact, and the strong rationale of employing more effective therapies to achieve a full remission before irreversible neuronal damage takes place, has been proposed. This is supported by data collected from large repositories [48-50]. Patients who received medications classified as higher efficacy drugs early on, had lower risk of transitioning to progressive stages of the disease [49]. The prime time for autologous bone marrow stem cell transplant has been ushered in by refined protocols with drastically reduced complication rates [51]. In this regard, the quicker identification of patients with aggressive and/or subclinical disease activity is emphasized and we see a role for quantitative MRI in decision making (see Case 1 and Case 2).

However, even with a theoretical rebooting of the immune system, the problem of neurodegeneration remains foremost in the contemporary treatment of MS. A cure for MS will remain elusive until the pathophysiology of progressive MS (and the related concept of accelerated brain and spinal cord tissue loss) is defined and ameliorated (see Case 3 and 4). As illustrated in the clinical examples described here, it is not likely that one mechanism of neuronal degeneration takes place in every patient with progressive forms of MS. One could envision that the dynamic nature of the immune system could lead after years of inflammatory activity to a state of remission, either spontaneous or by virtue of the immunomodulatory therapies. In those clinical scenarios, as long as the reserve capacity of the nervous system has not been compromised, patients will experience lifelong stability of their condition (see Case 2) [16]. In the topographical model conceived by Krieger *et al*., the reserve capacity could be consequence of the severity of the inflammatory attack and the intrinsic resilience of the affected tissue, and conceptually the immune therapy could prevent progressive, degenerative phases of the disease [52]. On the contrary, a destructive inflammatory and/or metabolic process damaging the energy machinery of neurons could initiate the cascade of events causing the gradual demise of neurons as we suspect occurred in Cases 3, 4 and 6 [18]. Growing evidence has been accumulated on the role played by comorbidities such as cerebrovascular disease on the MS course [53-55]. Moreover, as we recognize the significance of spinal cord involvement on long term motor disability, concerns are raised for the possible effect of certain degrees of cervical spondylosis. The anatomical changes related to neck movements are not captured by routine static MRI scans and those could cause vascular congestion and microtrauma to the blood brain barrier, driving inflammation into the spinal cord. The possibility of spondylosis resulting in extrinsic compression of the spinal cord and contributing to the cascade of neurodegeneration is theorized (see Case 5) [56-58].

Such broader views of the disease mechanisms lend support to the understanding that different scenarios are contributed by different factors and consequently the solution must take those into account (see Case 6). Resolving the inflammatory activity, addressing comorbidities and eluding traumatic damage are of paramount importance. Promoting preservation of neuronal functions through stimulation and rehabilitation are all germane to prevent disability.

Endeavors aimed at neuroprotection and remyelination have encountered major challenges and those therapies have

not reached clinical practice [59]. On the other hand, the attention drawn by the role of microglia in regulating inflammation as well as recovery and maintenance after tissue injury has led to a new targeted therapeutic. The discovery that the activity of microglial cells with reparative properties could be modulated by specific inhibition of the Bruton tyrosine kinase, a molecule capable of penetrating the central nervous system was created and there is hope for improving progressive forms of MS [60]. Several clinical studies are in progress to address the ongoing quest for remyelination and stem cell therapies remains a prospect for a not-too distant future.

4. Conclusion

This review aims at bringing to the attention of clinicians an updated view mainly on three aspects of MS, 1) recognition and management of spinal cord involvement as substrate for motor disability, 2) utility and practical implications of MRI volumetric assessments via automated/computerized measurements, 3) effects on long term outcomes of interventions that radically impact the immune system.

Credit Author Statement

Bomprezzi R. conceptualization of the study, data collection and manuscript drafting.

Chen AP. data collection, critical review and manuscript revision for intellectual content.

Hemond CC. data collection, critical review and manuscript revision for intellectual content.

References

[1] Weinshenker BG, Bass B, Rice GP, *et al.* The natural history of multiple sclerosis: a geographically based study. 1. Clinical course and disability. Brain 1989; 112: 133-146.

[2] Weinshenker BG, Bass B, Rice GP, *et al.* The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of early clinical course. Brain 1989; 112: 1419-1428.

[3] Eriksson M, Andersen O, Runmarker B. Long-term follow up of patient with clinically isolated syndromes, relapsing-remitting and secondary progressive multiple sclerosis. Multiple Sclerosis 2003; 9: 260-274.

[4] Kantarci OH, Weinshenker BG. Natural history of multiple sclerosis. Neurol Clin 2005; 23: 17-38.

[5] Sayao AL, Devonshire V, Tremlett H. Longitudinal follow-up of "benign" multiple sclerosis at 20 years. Neurology 2007; 68: 496-500.

[6] Kister I, Chamot E, Salter AR, et at. Disability in multiple sclerosis. A reference for patients and clinicians. Neurology 2013; 80: 1018-1024.

[7] The International Multiple Sclerosis Genetics Consortium. Risk alleles for multiple sclerosis identified by a genomewide study. NEJM 2007; 357: 851-862.

[8] The International Multiple Sclerosis Genetics Consortium and the Wellcome Trust Case Control Consortium 2. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. Nature 2011; 476: 214-219.

[9] Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: the role of infection. Ann Neurol. 2007; 61: 288-299. doi: 10.1002/ana.21117.

[10] Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part II: noninfectious factors. Ann Neurol 2007; 61: 504-513. doi: 10.1002/ana.21141.

[11] D'Netto MJ, Morrison KM, Ramagopalan SV, *et al.* Risk alleles for multiple sclerosis in multiplex families. Neurology 2009; 72: 1984-1988.

[12] De Silvestri A, Capittini C, Mallucci G, *et al.* The involvement of HLA Class II alleles in multiple sclerosis: a systematic review with meta-analysis. Disease Markers 2019; doi: 10.1155/2019/1409069.

[13] Lucchinetti C, Bruck W, Parisi J *et al.* Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol 2000; 47: 707-717.

[14] Frisher JM, Bramov S, Dal-Bianco A et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain 2009; 132: 1175-1189. doi.org/10.1093/brain/awp070.

[15] Lublin FD, Reingold SC, Cohen JA, *et al.* Defining the clinical course of multiple sclerosis. The 2013 revisions. Neurology 2014; 83: 278-286.

[16] McFaul D, Hakopian NN, Smith JB, Nielsen AS, Langer-Gould A. Defining benign/burnt-out MS and discontinuing disease-modifying therapies. Neurol Neuroimmunol Neuroinflamm. 2021; 8: e960. doi: 10.1212/NXI.0000000000000960.

[17] Magliozzi R, Howell O, Vora A *et al*. Menigeal B-cell follicles in secondary progressive multiple sclerosis associate with early osent of disease and severe cortical pathology. Brain 2007; 130: 1089-1104.

[18] Mahad DH, Trapp BD, Lassmann H. Pathological mechanisms in progressive multiple sclerosis. Lancet Neurol 2015; 14: 183-93. doi: 10.1016/S1474-4422(14)70256-X.

[19] Tintore' M, Rovira A, Rio J, *et al.* Baseline MRI predicts future attacks and disability in clinically isolated syndrome. Neurology 2006; 67: 968-972.

[20] Wattjes M, Rovira A, Miller D, *et al.* MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis—establishing disease prognosis and monitoring patients. Nature Reviews Neurology 2015; 11: 597-606.

[21] Tintore M, Rovira A, Rio J, *et al.* Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain 2015: 138: 1863-1874.

[22] Bekker I, Sombekke MH, Balk LJ, et al. Infratentorial and spinal cord lesions: cumulative predictors of long term disability? Mult Scler 2020: 26: 1381-1391.

[23] Fisniku LK, Brex PA, Altmann DR, Miszkiel KA, Benton CE, Lanyon R, Thompson AJ, Miller DH. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. Brain 2008; 131: 808-817. doi: 10.1093/brain/awm329.

[24] Barkhof F. The clinical-radiological paradox in multiple sclerosis revisited. Curr Opin Neurol 2002: 15: 239-245.

[25] Bielekova B, Kadom N, Fisher E, *et al.* MRI as a marker for disease heterogeneity in multiple sclerosis. Neurology 2005; 65: 1071-1076.

[26] Lavorgna L, Bonavita S, Ippolito D, et a. Clinical and magnetic resonance imaging predictors of disease progression in multiple sclerosis: a nine-year follow-up study. Mult Scler. 2014; 20: 220-226.

[27] Sastre-Garriga J, Pareto D, Rovira A. Brain atrophy in multiple sclerosis: Clinical relevance and technical aspects. Neuroimaging Clin N Am 2017; 27 (2): 289-300. doi: 10.1016/j.nic.2017.01.002.

[28] Popescu V, Agosta F, Hulst HE *et al.* Brain atrophy and lesion load predict long term disability in multiple sclerosis. J Neurol Neurosurg Psychiatry 2013; 84: 1082-1091. doi: 10.1136/jnnp-2012-304094.

[29] Perez-Miralles F, Sastre-Garriga J, Tintore M et al. Clinical impact of early brain atrophy in clinically isolated syndrome. Mult. Scler 2013: 19: 1878-1886.

[30] Cole JH, Raffel J, Friede T et al. Longitudinal assessment of multiple sclerosis with brain-age paradigm. Ann Neurol 2020: 88: 93-105.

[31] Cortese R, Battaglini M, Parodi F, et al. Mild gray matter atrophy in patients with long-standing multiple sclerosis and favorable clinical course. Mult Scler 2022; 28: 154-159.

[32] Cree BA, Hollenbach JA, Bove R et al. Silent progression in disease activity-free relapsing multiple sclerosis. Ann Neurol 2019; 85: 653-666.

[33] Giorgio A, Stromillo ML, Bartolozzi ML et al. Relevance of hypointense brain MRI lesions for long-term worsening of clinical disability in relapsing multiple sclerosis. Mult Scler 2014; 20: 214-219. DOI: 10.1177/1352458513494490.

[34] Dekker J, Eijlers AJC, Popescu V et al. Predicting clinical progression in multiple sclerosis after 6 and 12 years. Eur Journal Neurol 2019; 26: 893-902 doi.org/10.1111/ene.13904.

[35] Elliott C, Belachew S, Wolinsky JS et al. Chronic white matter lesion activity predicts clinical progression in primary progressive multiple sclerosis. Brain 2019; 142: 2787-2799.

[36] Scalfari A, Romualdi C, Nicholas RS, *et al.* The cortical damage, early relapses, and onset of the progressive phase in multiple sclerosis. Neurology 2018; 90: e2107-e2118.

[37] Rocca MA, Valsasina P, Meani A, Gobbi C, Zecca C, *et al*. on behalf of the MAGNIMS Study Group. Association of gray matter atrophy patterns with clinical phenotype and progression in multiple sclerosis. Neurology 2021; 96: doi.org/10.1212/WNL.0000000000011494.

[38] Sechi E. Keegan BM, Kaufmann TJ, *et al.* Unilateral motor progression in MS. Association with a critical corticospinal tract lesion. Neurology 2019; 93: e628-e634.

[39] Eden D, Gros C, Badji A, *et al.* Spatial distribution of multiple sclerosis lesions in the cervical spinal cord. Brain 2019: 142: 633-646.

[40] Enzinger C, Fazekas F, Matthews PM et al. Risk factors for progression of brain atrophy in aging: six-year follow-up of normal subjects. Neurology 2005; 64: 1704-1711.

[41] Fox RJ, Salter AR, Tyry T, Sun J, et al. Treatment discontinuation and disease progression with injectable disease-modifying therapies: findings from the north american research committee on multiple sclerosis database. Int J MS Care 2013; 15: 194-201.

[42] Hatcher SE, Waubant E, Nourbakhsh B et al. Rebound syndrome in patients with multiple sclerosis after cessation of fingolimod treatment. JAMA Neurol 2016; 73: 790-794.

[43] West TW, Cree BAC. Natalizumab dosage suspension: are we helping or hurting? Ann Neurol 2010; 68: 395-399.

[44] Goodin DS. Disease-modifying therapy in multiple sclerosis. Update and implications. Neurology 2008; 71 suppl 3: S8-13.

[45] Inojosa H, Proschmann U, Akgun K et al. The need for a strategic therapeutic approach: multiple sclerosis in check. Ther Adv Chronic Dis 2022; 13: 20406223211063032.

[46] Scalfari A, Knappertz V, Cutter G, *et al.* Mortality in patients with multiple sclerosis. Neurology 2013; 81: 184-192.

[47] Harding K, Zhu F, Alotaibi M, Duggan T, et al. Multiple cause of death analysis in multiple sclerosis. A population-based study. Neurology 2020: 94: e820-e829.

[48] Stankiewicz JM, Weiner HL. An argument for broad use of high efficacy treatments in early multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm* 2020; 7: e636.

[49] Brown JWL, Coles A, Horakova D *et al*. Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. JAMA 2019: 32: 175-187.

[50] Kalincik T, Diouf I, Sharmin S, Malpas C, Spelman, T, *et al*. Effect of disease-modifying therapy on disability in relapsing-remitting multiple sclerosis over 15 years. Neurology 2021; 96: e783-797.

[51] Burt RK, Balabanov R, Burman J, *et al.* Effect of nonmyeloablative hematopoietic stem cell transplantation vs continued disease-modifying therapy on disease progression in patients with relapsing-remitting multiple sclerosis. A randomized clinical trial. JAMA 2019; 321: 165-174.

[52] Krieger SC, Cook K, De Nino S, Fletcher M. The topographical model of multiple sclerosis. A dynamic visualization of disease course. Neurol Neuroimmunol Neuroinflamm 2016; 3: e279.

[53] Marrie RA, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer TL. Comorbidity, socioeconomic status and multiple sclerosis. Mult Scler 2008; 14: 1091-1098.

[54] Marrie RA, Rudick R, Horwitz R, Cutter G, *et al.* Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis. Neurology 2010; 74: 1041-1047.

[55] Salter A, Kowalec K, Fitzgerald KC, Cutter G, Marrie RA. Comorbidity is associated with disease activity in MS. Findings from the CombiRx trial. Neurology 2020; 95: e446-e456.

[56] Poser CM. Trauma to the central nervous system may result in formation or enlargement of multiple sclerosis plaques. Arch Neurol 2000; 57: 1074-1077.

[57] Gratch D, Do D, Khankhanian P *et al.* Impact of cervical stenosis on multiple sclerosis lesion distribution in the spinal cord. Mult Scler Relat Disord 2020; 45: 102415. doi: 10.1016/j.msard.2020.102415.

[58] Bomprezzi R, Chen AP, Hemond CC. Cervical spondylosis is a risk factor for localized spinal cord lesions in multiple sclerosis. Clin Neurol Neurosurg 2020; 199: 106311 doi: 10.1016/j.clineuro.2020.106311.

[59] Chataway J, De Angelis F, Connick P, *et al.* Efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis (MS-SMART): a phase 2b, multiarm, double-blind, randomised, placebo-controlled trial. The Lancet Neurology 2020; 19: 214-225.

[60] Rissanen E, Tuisku J, Vahlberg T, *et al.* Microglial activation, white matter tract damage and disability in MS. Neurol Neuroimmunol Neuroinflamm 2018; 5: e443. doi: 10.1212/NXI.0000000000000443.