12th Post-ECTRIMS Meeting: review of the novelties from the 2019 ECTRIMS Congress (I)

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Introduction. Like every year, after the ECTRIMS Congress, renowned Spanish neurologists who are experts in multiple sclerosis presented the main novelties in research in this field at the Post-ECTRIMS Meeting.

Aim. To summarise the content presented at the 12th edition of the Post-ECTRIMS Meeting, which took place in September 2019 in Sevilla and is presented in two parts.

Development. This first part addresses the latest studies on vitamin D deficiency and the discrepancies that currently exist regarding its treatment. The advances made in epigenetics allow us to present this approach as a possible biomarker of multiple sclerosis. An account is provided to explain the growing importance of imaging techniques to detect atrophy and other phenomena that occur during the disease, such as changes in iron concentration or remyelination processes, which allow us to further our understanding of the mechanisms of cortical pathology, and the dimensionality of neurodegeneration during its course. Findings related to immunological mechanisms and advances in potential antigen-specific therapies are discussed. The contribution presents the latest studies on the assessment of cognitive impairment and its rehabilitation, which are becoming increasingly important due to the high prevalence of these disorders and the absence of their systematic assessment in clinical practice. Finally, the unmet social and health needs of multiple sclerosis patients in our country are presented, with emphasis on the current deficits in the system of social protection.

Key words. Biomarkers. Cognition. ECTRIMS. Multiple sclerosis. Pathophysiology. Post-ECTRIMS. Remyelination.

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Introduction

The 12th edition of the Annual Post-ECTRIMS Meeting was held in Sevilla (Spain) on the 27th and 28th of September 2019. There, a group of neurologists, experts in multiple sclerosis (MS), presented the latest developments from the Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), the largest congress in Europe devoted to MS, held in Stockholm on 11, 12 and 13 September 2019.

The relevance of the Post-ECTRIMS Meeting lies in two main aspects. On the one hand, it provides easy access to a summarised form of the main results of the more than 1,500 presentations (including oral communications and posters) at the ECTRIMS Congress. On the other hand, it serves as a meeting place for experts on multiple sclerosis (MS) in Spain, and in turn lays down the foundations for this article, which is presented in two parts. This first part summarises the latest developments related to the pathology of the disease and to the different ways of measuring it, from imaging biomarkers to neuropsychological evaluation, including the patient's own perception of their disease.

Risk factors of multiple sclerosis: vitamin D deficiency

MS is a complex disease, the causation of which remains unknown. There are several environmental factors that, in combination with genetic factors, increase the risk of the disease. The most widely recognised environmental risk factors are Epstein-Barr virus infection, exposure to tobacco, obesity during adolescence, lack of exposure to sunlight and low levels of vitamin D [1,2].

There is an inverse relationship between 25-hydroxyvitamin D levels in serum and the risk of MS or disease activity [3-6]. In the phase 3 clinical trials BENEFIT [4], BEYOND [5] and FREEDOMS [6] in

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patients treated with interferon β-1b [4,5] or fingolimod [6], high levels of vitamin D were found to be associated with improvements in magnetic resonance imaging parameters (MRI). Nevertheless, both these clinical trials and the observational studies present a series of limitations that make it difficult to establish consensual recommendations on complementary treatment with vitamin D. In the case of observational studies, the causal relationship between levels of vitamin D and progression of MS may be inverse (for example, patients with more severe MS could have less exposure to sunlight, and therefore lower vitamin D synthesis), and there are also variations in vitamin D levels across individuals over time. The clinical trials, however, have a small sample size, a short duration, include mostly Caucasian patients and exclude those with vitamin D deficiency.

Considering the available evidence, some experts conclude that the risk/benefit of moderate-dose vitamin D supplements is favourable and should be part of the treatment of most patients with MS [7], while others believe that there is insufficient data on the impact of administering vitamin D supplements and thus it should not be considered standard practice [8]. If the decision is made to establish treatment with vitamin D supplements, it is suggested that this decision be made taking into account the individual characteristics of the patient and the benefit/risk in patients at risk of excess vitamin D. Specifically, recommendations include administration of doses of between 2,000 and 5,000 IU/day, and maintaining vitamin D levels between 40 and 60 ng/mol with reassessment every three months [9].

Epigenetics: implications for the pathogenesis and treatment of the disease

Epigenetics is the study of the mechanisms that regulate gene expression without any modification of the DNA sequence. Environmental factors can promote epigenetic changes that will determine which genes are activated or inactivated.

One of the major epigenetic events is DNA methylation, the evaluation of which offers a unique opportunity to examine in situ the neural pathology underlying MS. A post mortem study conducted on brains found that, with respect to controls, in MS patients there were changes in DNA methylation associated with a reduction in CREB (cAMP response element-binding) activity in white matter neurons [10]. The relevance of these findings lies in the fact that it is precisely CREB activity that most predominantly underlies synaptic plasticity and axonal guidance.

Through the study of DNA methylation in blood samples, different methylation groupings have been classified among healthy subjects and patients with MS, and among the diverse developmental courses of MS. While the differences between patients with MS and controls appeared in the lymphocyte signalling pathways and in T cell activation and migration, when the group with relapsing-remitting MS was compared to the group with secondary progressive MS, it was found that patients with this latter type show more changes involved in the metabolism and myeloid cell functions, and in genes and pathways related to neuronal/neurodegenerative processes [11]. Detection of demethylated myelin oligodendrocyte glycoprotein (MOG) in serum from patients with MS indicates that methylation patterns in the blood could be used to detect cell loss in autoimmune processes such as MS, and as prognostic biomarkers of disease activity

An algorithm has been developed which, by introducing methyloma data, allows calculation of the epigenetic age of a tissue. This 'epigenetic clock' has been shown to predict the chronological age quite accurately. In some neurodegenerative diseases, such as Parkinson's disease, it predicts an age that is greater than the chronological age, which is known as accelerated epigenetic ageing. In the case of MS, data from research conducted with three different cohorts of patients indicated that there was no accelerated epigenetic ageing. Although one of the cohorts showed a correlation between such acceleration and the Expanded Disability Status Scale, no evidence of the correlation was found in the other two cohorts [12].

Remyelination

What cells, what regions and in what patients

There is evidence showing that myelin that has been destroyed by the immune system in MS is able to regenerate and recover its neurological function [13]. Murine models of demyelinating diseases have been used to show that myelin is regenerated in particular by new oligodendrocytes and not by mature oligodendrocytes [14]. However, differences between rodents and humans as regards the dynamics of oligodendrocyte generation calls into question its extrapolation to MS. According to a study conducted on post mortem tissue from pa-

tients with MS, the dynamics of oligodendrocytes in humans would be very different from that seen in murine models [15]. The authors noted that the oligodendrocytes in the shadow plaques (which are believed to represent remyelinated areas) were mature and so, unlike what occurs in animal models, remyelination would be carried out by pre-existing oligodendrocytes rather than new ones.

It seems that there are different subtypes of mature oligodendrocytes in humans, and that this heterogeneity could be altered in MS [16]. Patients with MS have a low representation in some subpopulations of oligodendrocytes, while others are more prevalent. This could indicate different functional states of mature oligodendrocytes in MS lesions.

The capacity of oligodendrocytes for repair in different regions of the brain also differs. The use of positron emission tomography with 11C-PiB and 3T MRI has revealed that the capacity for remyelination depends on the proximity to the periventricular areas. In periventricular areas this capacity is low, and increases in white matter lesions the further they are from the ventricles. They also observed that patients with high remyelination rates in periventricular areas had better preservation of the grey matter, which suggests a close relationship between myelin repair and neuroprotection [17]. There may be common factors in the cerebrospinal fluid that block remyelination while at the same time generating cortical damage. Alternatively, early remyelination in periventricular regions may protect against axonal and Wallerian degeneration and help preserve the grey matter.

With regard to the profile of patients with remyelination, it has been seen that the generation of new oligodendrocytes increases considerably in the normal-appearing white matter only in patients with aggressive MS [15]. These data are in line with what was observed in vivo in another 7T MRI study, where remyelination occurred selectively in one out of every seven patients [18]. Therefore, there seems to be an inherent potential for generating oligodendrocytes, but it is not present in all patients.

Remyelination mechanisms and therapeutic targets

One of the mechanisms that has been postulated during remyelination is the interaction between the nodes of Ranvier and microglial cells. This proposal is grounded on three observations:

– The interaction is stable and predominates in remyelination phases.
– The number of interactions is greater in patients with MS than in controls.
– The phenotype of the microglial cell that interacts with the node of Ranvier is predominantly the restorative one more than the proinflammatory one [19].

Thanks to advances in the understanding of the mechanisms underlying remyelination, several therapeutic options aimed at promoting myelin regeneration and with the potential to prevent neurodegeneration [20] have emerged in recent years [21]. These treatments may be administered in monotherapy or in combination with anti-inflammatory therapies [22]. The table shows some of the most significant clinical trials involving remyelinating treatments. As can be seen, the evaluation of the primary endpoint varies greatly from one study to another. While some choose to assess efficacy through neurophysiological tests, such as evoked potentials [23], others evaluate it through clinical tests, such as the Expanded Disability Status Scale, and other physical and cognitive tests [24]. This variability highlights the need to define the evaluation variables for remyelination in clinical trials in a more homogeneous and appropriate manner, in order to ensure that the measures used are sensitive enough to be able to find what is being sought [25]. One of the cell markers postulated for assessing active remyelination is BCAS1-positive (breast carcinoma amplified sequence 1) oligodendrocytes, as they have been found in a proportion of chronic white matter lesions in MS patients, including those in advanced stages of the disease [26].

Immunopathology and therapeutic perspectives

Immunological mechanisms

The acute inflammatory response triggered to protect the organism against a foreign agent requires an efficient resolution to avoid chronic inflammation. This resolution process appears to be orchestrated by specialised pro-resolving lipid mediators synthesised by omega-3 fatty acids. Up until now, knowledge about this resolution process and how it is related to the progression of MS has been limited. For the first time, thanks to the use of metabololipidomic techniques in the cerebrospinal fluid, evidence has been found showing that the resolution of inflammation is altered, and that there is a unique 'footprint' of lipid mediators for relapsing and progressive forms of MS [27]. In particular, alterations in the biosynthesis of specialised pro-re-

Table. Clinical studies with remyelinating treatments in multiple sclerosis.

	Treatment	Phase	Mechanism of action	Primary endpoint	Outcomes
S56.003 [79]	Liothyronine	Ib	Regulation of oligodendrocyte differentiation and maturation by triiodothyronine (T3)	Rate of adverse side effects at 24 weeks	Well tolerated, with no serious treatment-related adverse effects or evidence of disease activation or clinical deterioration
MS-SPI [80]	Biotin/MD1003	III	Activation of the Krebs cycle to increase energy production in demyelinated axons and intensify myelin production in mature oligodendrocytes	Reversal of disability at 9 months, confirmed at 12 months, defined as a decrease in EDSS ≥ 1 point (≥ 0.5 for EDSS 6-7) or an increase ≥ 20% in the T25FW	12.6% of patients had their disability reversed, compared to none in the untreated group
ReBUILD [23]	Clemastine	II	Induces OPC differentiation and increases remyelination	Changes in P100 latency across the entire field of visual evoked potentials	The primary endpoint was reached. Significant reduction in latency of 1,7 ms per eye
SYNERGY[81]	Opicinumab	II	Induces OPC differentiation and remyelination	Improvement in disability confirmed at 72 weeks, assessed with the EDSS, the T25FW, the 9HPT and the 3 s PASAT	The primary endpoint was not reached. Improvement in disability was observed in 49% of the placebo group, 47% of the 3 mg/kg opicinumab group, 63% of the 10 mg/kg opicinumab group, 65% of the 30 mg/kg opicinumab group and 40% of the 100 mg/kg opicinumab group
AFINITY [82]	Opicinumab	II	Induces OPC differentiation and remyelination	Improvement or exacerbation in disability, evaluated with the EDSS, the T25FW and the 9HPT	Awaiting results

9HPT: 9-Hole Peg Test; EDSS: Expanded Disability Status Scale; OPC: oligodendrocyte progenitor cells; PASAT: Paced Auditory Serial Addition Task; T25FW: Timed 25-Foot Walk.

solving lipid mediators have been observed in the epithelial cells of the choroid plexuses and an increase in eicosanoids. The administration of these mediators reduced the inflammatory profile of the innate (microglial cells) and adaptive (Th1 and Th17) immune systems under conditions of inflammation in experimental autoimmune encephalomyelitis, the murine model of MS [27].

Another observation on the immunopathology of MS that is garnering an increasing amount support is the heterogeneity of myeloid cells (macrophages derived from monocytes and dendritic cells) and the evolution of their phenotype throughout the course of the disease. Although myeloid cells have generally been considered pro-inflammatory, polarised subpopulations may contribute to non-inflammatory or restorative processes [28]. Using immunohistochemistry in experimental autoimmune encephalomyelitis, it has been observed that myeloid cells expressing inducible nitric oxide synthase, indicative of an inflammatory phenotype, were detected in the active demyelinating ring of chronic lesions, while macrophages expressing the mannose receptor (CD206), a marker of polarised myeloid cells, were found in inactive lesions. Throughout the course of the disease, there was a change in the infiltrated myeloid cells from expressing pro-inflammatory to non-inflammatory markers immediately prior to clinical remission. Myeloid cells expressing the alternative lineage marker arginase-1 (Arg1), partially derived from inducible nitric oxide synthase precursors, were deficient when it comes to activating T cells compared to $Arg1^{-}$ [29]. Future therapeutic strategies could be aimed at accelerating the transition of myeloid cells from a pro-inflammatory to a non-inflammatory state.

One change in the pathological mechanisms that seems to occur during the course of the disease is the type of inflammation. It has been suggested that there are two types of inflammation that develop in parallel, but in a partially independent manner. The first type, which dominates during the acute and relapsing phase, consists in an invasion by T and B lymphocytes with deep filtration in the blood-brain barrier, affects mainly the white matter and causes active demyelinated plaques. The other type of inflammation, present at the onset of the disease and gradually increasing as the disease progresses, is based on the slow accumulation of T and B lymphocytes in the absence of damage to the blood-brain barrier in the connective tissue spaces, and is associated with the formation of subpial demyeli-

nated lesions, the expansion of pre-existing lesions in the white matter and diffuse neurodegeneration of the white matter or normal-appearing grey matter [30]. One of the hypotheses that have been proposed is that B lymphocytes could propagate demyelination and neurodegeneration through the production of soluble neurotoxic factors [30].

Implications of the brain's inflammatory response in pathogenesis and treatment

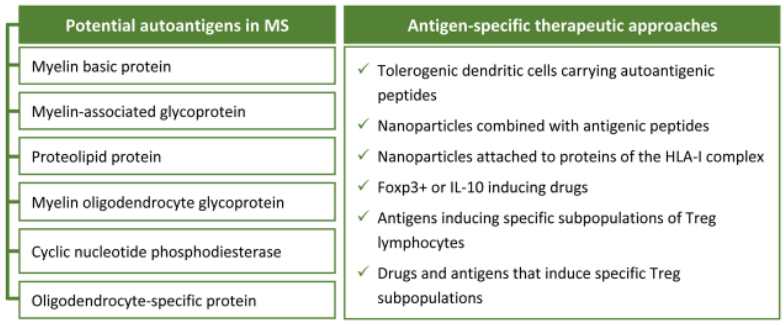
Although it is well known that inflammation is caused by the infiltration of lymphocytes in the brain, little is known about their phenotype and function. Machado-Santos et al. [31] observed a dominance of CD8+ T cells and a significant contribution of CD20+ B cells in all disease courses and stages of inflammatory demyelinating lesions, and deemphasised the relevance historically attributed to CD4+ T cells as components of the inflammatory reaction. In line with this, clinical trials of treatments for MS specifically targeting CD4+ T cells have not shown any convincing results, while treatments that reduce memory B cells (CD19+ and CD27+) or CD20 B cells show a beneficial effect [32].

Antigen-specific therapies

The goal of antigen-specific therapies is to restore immune tolerance, a mechanism by which specific pathogens are eliminated while maintaining a correct unresponsiveness to autoantigens. Most clinical trials on antigen-specific therapies in MS conducted to date have shown no clinical efficacy for immune tolerance. Some of the challenges faced by these studies are the definition of the target antigens, our understanding of the aetiopathogenesis and pathophysiology, and the delimitation of the dosages, intervals and optimal routes of administration of the treatments [33].

In recent years, thanks to the growing knowledge of potential autoantigens in MS and the new theoretical approaches to the design of antigen-specific therapies [34,35] (Fig. 1), a number of preliminary, but nevertheless promising, results have been obtained. An example of this is ATX-MS-1467 immunotherapy, consisting of four peptides derived from the myelin basic protein, which, in two clinical trials (phase 1b and phase 2a), reduced the number and volume of gadolinium-enhancing lesions (Gd+) in T_1, with good results in terms of safety [36]. Another example is the Phase Ib clinical trial ETIMS red trial, which has shown that a treatment involving peptides attached to autologous red blood cells has an excellent level of tolerance in patients with relapsing-remitting MS [37].

Figure 1. Potential autoantigens and therapeutic approaches.



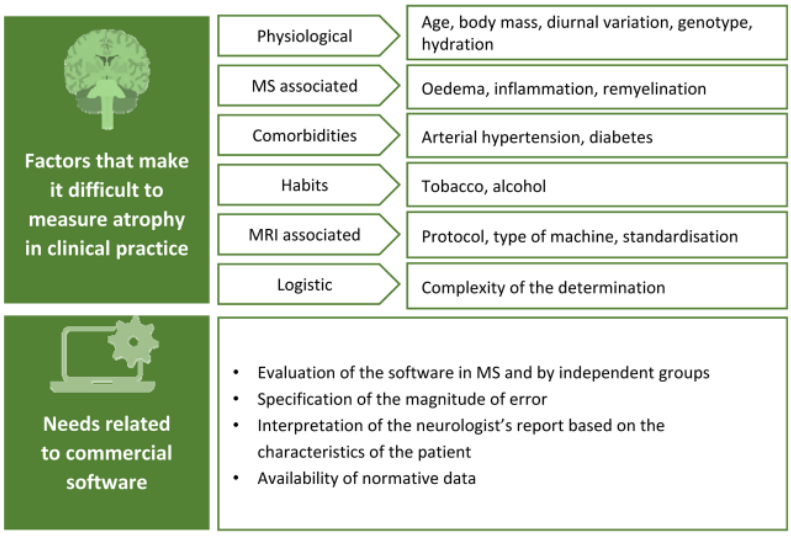
Quantitative image biomarkers

Grey matter atrophy: when, where and why

Cortical grey matter lesions are recognised as one of the main pathological features and as a marker of disease severity that accurately predicts future disability [38]. These lesions, along with the meningeal inflammation associated with activation of microglial cells and macrophages, are visible in early stages, even at two years after diagnosis [39]. It has recently been seen that the long-term exacerbation that characterises relapsing-remitting MS is independent of relapses, but is significantly associated with an accelerated rate of brain atrophy [40]. Based on these observations, the term silent progression has been proposed to describe the insidious cumulative disability in patients who continue to meet criteria for relapsing-remitting MS. Thus, the same process that underlies secondarily progressive MS could begin much earlier than previously thought, thus supporting a unitary view of the biology of MS, where inflammation and neurodegeneration would occur across the spectrum of the disease.

Some areas appear to be more susceptible to grey matter degeneration than others. On the one hand, one of the first regions where atrophy appears is the thalamus [41,42]. Studies carried out in the paediatric population confirm the presence of microstructural thalamic lesions from the earliest stages [42,43], and note that the damage is located preferentially in the bands closest to the cerebrospinal fluid and the white matter [44], thus suggesting the existence of inflammation-mediated mechanisms of

Figure 2. Challenges of incorporating biomarkers of neurodegeneration into clinical practice.



Wallerian degeneration. On the other hand, the regions of the brain adjacent to deep folds could also be more susceptible to neurodegeneration due to the presence of inflammatory mediators and immune cells in the neighbouring meninges [45]. Not only specific regions, but also certain types of neurons appear to be more vulnerable, as shown by the increased loss of excitatory neurons in the upper layer of cortical lesions in patients with MS [46].

Although brain atrophy and white matter lesions are two established parameters in MS, the causal interaction between the two is not clear. With the aim of understanding this interaction, a longitudinal cross-sectional study was conducted in which maps of white matter lesions were combined with data from the Human Connectome Project to predict brain atrophy in patients with clinically isolated syndrome and all the different forms of MS [47]. A strong relationship was found between local grey matter atrophy and maps of white matter disconnection. It could be that lesions in the white matter contribute to atrophy in the grey matter through disconnection, as a close temporal relationship was seen between local grey matter atrophy and new lesions in the white matter with projection fibres.

Despite the accumulation of evidence showing that brain atrophy is a useful marker of progression, just how applicable its use is in clinical practice remains unknown. Figure 2 shows the main limitations and possible solutions to be considered before it can be implemented. The use of artificial intelligence algorithms is a promising tool for identifying atrophy and its implications in the progression.

Spinal cord atrophy

The annual rate of spinal cord atrophy (1.78%) is higher than that of cortical atrophy (0.5%) [48], it is more apparent in progressive forms and more aggressive courses, and is related to the disability progression [49]. Spinal cord lesions are more difficult to detect. The progress being achieved in various MRI techniques is allowing improvements to be made in the assessment of spinal cord atrophy (using magnetisation transfer contrast, diffusion imaging or T_1 and T_2 weighted imaging), and its functional connectivity (with resting-state functional MRI). These advances have led to the measurement of spinal atrophy being included as an outcome in clinical trials, especially in progressive forms [50], and its inclusion is expected to increase in future studies.

Advances in the detection of the condition in vivo with imaging techniques

Thanks to the increasing development of 7T MRI sequences, such as quantitative susceptibility mapping, the effective transverse relaxation rate (R2*) [51] and new positron emission tomography radioligands (11C-PK11195) [52], the relationship between changes in the iron concentration and the progression of MS has been observed in vivo. The changes in iron include increases in deep grey matter, decreases in the normal-appearing white matter, release of iron in the acute lesions and the presence of iron rings in certain MS lesions [53]. With regard to iron-ring lesions, it should be noted that they expand significantly over the years compared to lesions without rings, and the latter are more frequent in remyelinated shadow plaques [54].

A high presence of ringed lesions is associated with more severe MS [55]. In support of this claim, a retrospective in vivo study showed that patients with four or more iron-ring lesions had greater cognitive and motor disability at a younger age [56]. The time during which iron-ring lesions continue to expand was limited, and it was observed that after a period of expansion for three or four years, it gradually declines, and at seven years most of the lesions had lost the ring [57]. Despite the greater accuracy of the above-mentioned sequences in 7T MRI, it should be noted that, using a sequence in T_1 in 3T MRI, the expansion of the iron-ring lesions can be observed up to four years after the basal measurement [53].

Paediatric multiple sclerosis

The characteristics and disease course in paediatric MS are different from those of adults. They take longer to progress and recover better from flare-ups, although they are at greater risk of physical and cognitive disability in adulthood and of progressing to secondarily progressive MS at a younger age [58,59]. One of the risk factors for paediatric MS that must be taken into account is obesity. Paediatric MS patients with obesity who are treated with a first-line therapy have a worse prognosis, with a higher rate of flare-ups and a greater likelihood of receiving second-line therapy than patients with a normal weight [60]. The diagnosis of paediatric MS is becoming more and more accurate, thanks to the increased availability of biomarkers.

Myelin oligodendrocyte glycoprotein antibodies

Measurement of MOG antibodies makes it possible to rule out the diagnosis of MS versus other demyelinating syndromes acquired in childhood [61]. In acquired demyelinating syndromes in which MOG antibodies are common, they are transient in half the cases, and most children have a monophasic disease [61]. In monophasic forms of acquired demyelinating syndromes, immunosuppressive treatment is not recommended for the time being, and discussion continues about immunosuppressive maintenance treatment in relapsing forms (sequelae, relapses and the persistent presence of antibodies) [62]. There is growing evidence that disease due to MOG antibodies is a distinct entity with a better prognosis than MS.

Neurofilament light chain

Neurofilaments light chain are one of the most promising biomarkers of early axonal damage for monitoring MS. According to the latest evidence, patients with clinically isolated syndrome with elevated levels of neurofilaments light chain in cerebrospinal fluid were diagnosed with MS earlier than those with lower levels. Among patients with clinically isolated syndrome with a subsequent diagnosis of MS, children showed higher values of neurofilaments light chain than adults [63], so acute axonal degeneration may occur earlier and be more severe in paediatric MS. Neurofilament levels appear as a potential biomarker not only for MS in adults, but also for MS in children, and could be used as a tool for monitoring the disease and making therapeutic decisions.

Cognitive impairment

Epidemiology and risk factors

Cognitive impairment is a very common symptom in people with MS. Its prevalence (two or more affected domains) in people over 55 years of age is 77.4% and it is influenced by comorbidities such as conditions related to the ageing process [64]. However, the prevalence of cognitive impairment is higher in MS that begins in the paediatric age than in adulthood [65]. There are a number of both non-modifiable (e.g. ApoE4 and Val66Met polymorphism) and modifiable risk factors (e.g. alcohol, tobacco and recreational cannabis) that affect the development and course of cognitive impairment [66]. Identifying these factors is essential to be able to develop preventive strategies and guide clinical treatment. For example, abstinence from cannabis for 28 days has been shown to significantly improve cognition and cause changes in brain activity (in functional MRI) in habitual smokers [67].

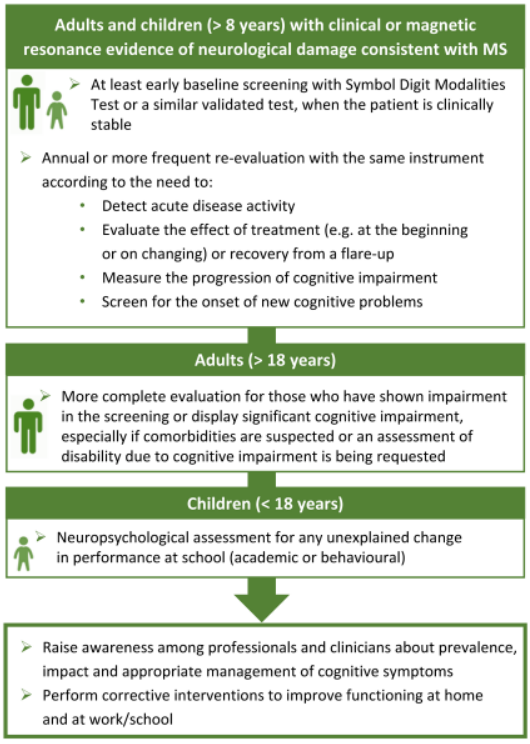
Diagnosis and follow-up

Despite the high prevalence of cognitive impairment as of the diagnosis of MS, in clinical practice neuropsychological assessment is not performed systematically. There are batteries, such as the Minimal Assessment of Cognitive Function in Multiple Sclerosis or the Brief International Cognitive Assessment for Multiple Sclerosis, which include widely used and validated tests, although their application requires a lot of time, making them difficult to use in clinical practice. One of the tests included in these batteries is the Symbol Digit Modalities Test, which is known for being a rapid test (administered in less than five minutes) that is particularly sensitive to the detection of the decrease in information processing speed that characterises MS [68]. A validated electronic version is also available (Processing Speed Test), which is easy to administer and store in databases for use in research [69]. Current recommendations advocate the regular administration of the Symbol Digit Modalities Test, or a similar validated scale, in the diagnosis and during follow-up [70]. Figure 3 shows the recommendations for cognitive assessment in the adult and paediatric population.

Impact of rehabilitation and treatments on cognition

Cognitive rehabilitation has been shown to be effective in patients with MS, although the effect varies from one individual to another. The patient pro-

Figure 3. Recommendations for cognitive assessment in multiple sclerosis. The recommendations were proposed by a group of experts (clinicians, researchers and patients with multiple sclerosis) gathered by the National Multiple Sclerosis Society.



file most likely to benefit from a cognitive restorative rehabilitation programme at home is the patient with a relapsing course, increased volume of grey matter and personality traits with a tendency to be careful and orderly [71].

There is no evidence to show that physical exercise has any influence on cognition in patients with MS. Studies examining this effect are scarce and do not include patients with proven objective cognitive impairment. In recent years, clinical trials have been conducted that include an active control group, neuroimaging measures, results for quality of life or daily functioning and long-term follow-up, but to date there is no single study that includes all these elements together [72].

The evidence on the impact of disease-modifying treatments on cognition has not yet allowed any valid conclusions to be drawn, since the design of clinical trials and observational studies on this matter has certain methodological limitations. The impact of symptomatic treatments on cognition appears to be positive, with 86% of patients treated with dalfampridine improving their score by up to four points on the Symbol Digit Modalities Test [73], and this difference is significant compared to the control group. However, it should be noted that 60% of the patients in the control group also achieved a four-point improvement in this test, so more evidence is needed.

The voice of the patient

Patient-reported outcome measures are increasingly used to assess their perception of health-related issues. They allow us to know their preferences, values and needs, placing their experience at the centre of health care and research. The information thus obtained complements traditional medical measures and provides insight into the actual impact that the disease and treatments have on the patient [74]. Health authorities, such as the Food and Drug Administration, are beginning to require that the voice of the patient be taken into account and are advising the inclusion of patient-reported outcome measures as an outcome variable in clinical trials [75].

The main challenges at present include, on the one hand, the comprehensive selection of validated outcome measures that provide added value and do not unnecessarily overburden patients and health professionals and, on the other hand, their implementation in clinical practice and their integration into electronic medical records [75]. To address these and other challenges, the European Charcot Foundation, the Italian Multiple Sclerosis Society and the International Multiple Sclerosis Federation have launched 'PROMs: a joint global initiative' [76].

The unmet needs most demanded by patients in Spain are, first of all, access to quality information that helps them to make decisions about their disease and possible treatments, and about healthy habits and quality of life. Despite the fact that there is an overwhelming amount of information available today, patients consider their neurologists to be the most reliable source of information. The second most popular unfulfilled need is to promote rehabilitation, which, although it is becoming increasingly significant [77], patients believe is still deficient. Virtual reality and robotics are expected to open up a new range of possibilities for physical and cognitive rehabilitation in these patients; and, finally, patients demand recognition of the complexity of their situation after diagnosis and the degree of disability they suffer. To alleviate these needs, a map of social and health resources could be drawn up, and more efficient action and coordination pro-

tocols could be generated to improve the patient's quality of life [78].

Conclusions

At this latest edition of the ECTRIMS, speakers presented advances in the knowledge of the pathology of MS and the biomarkers that allow us to track its progression.

Novel biomarkers include epigenetic changes, such as DNA methylation, and the unique 'footprint' of lipid mediators for different forms of MS. One of the topics that attracted a larger number of presentations was that of the advances being made in imaging techniques, where the new 7T MRI sequences stand out. Through the combination of biomarkers based on cortical and spinal degeneration, inflammation and iron concentration in the grey matter and white matter, it could be possible to predict which newly diagnosed MS patients are most at risk of progressing. Unfortunately, the issue of how to apply imaging techniques in clinical practice has not yet been resolved, although it is likely that the use of artificial intelligence will facilitate their incorporation in the near future.

Regarding the underlying pathological processes, it has been seen that myeloid cells evolve throughout the disease, so one therapeutic strategy could be to accelerate the transition of these cells from a pro-inflammatory to a non-inflammatory phenotype. On the other hand, while there is a capacity for remyelination, it seems that it is not present in all regions or in all patients to an equal extent, and is greater in regions further away from the ventricles and in patients with aggressive MS.

Cognitive alterations, which are more frequent than initially believed, should be evaluated, at least with the Symbol Digit Modalities Test, both at diagnosis and during follow-up. Cognitive rehabilitation appears to be efficient, although its effect varies from one individual to another. There is a need to establish a set of minimum standards on the type of exercises and the optimal frequency for each type of patient, together with a set of biomarkers to evaluate the response to rehabilitation.

Along with the evaluations carried out by health professionals, it is crucial to take into account the patient's perception of his or her situation. The tendency to include patient-reported outcome measures in both clinical practice and research is increasing, but it is important to limit their use to those that have been validated and to select them carefully in order to avoid overburdening the patient.

Based on all these developments, we can expect the future management of MS to be more holistic and to address a broader spectrum of underlying pathological mechanisms.

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XII Reunión Post-ECTRIMS: revisión de las novedades presentadas en el Congreso ECTRIMS 2019 (I)

Introducción. Como cada año, tras la celebración del Congreso ECTRIMS, reconocidos neurólogos españoles expertos en esclerosis múltiple expusieron en la Reunión Post-ECTRIMS las principales novedades en investigación en este ámbito.

Objetivo. Sintetizar el contenido presentado en la XII edición de la Reunión Post-ECTRIMS, que tuvo lugar en septiembre de 2019 en Sevilla y que se presenta en dos partes.

Desarrollo. Esta primera parte aborda los últimos estudios sobre el déficit de vitamina D y las discrepancias existentes acerca de su tratamiento. Los avances en epigenética realizados permiten presentar esta aproximación como un posible biomarcador de la esclerosis múltiple. Se explica el creciente protagonismo de las técnicas de imagen para detectar la atrofia y otros fenómenos que acontecen durante la enfermedad, como los cambios en la concentración de hierro o los procesos de remielinización, que nos permiten ganar comprensión sobre los mecanismos de la patología cortical, y sobre la dimensionalidad de la neurodegeneración durante su evolución. Se discuten los hallazgos relacionados con los mecanismos inmunológicos y los avances realizados en las potenciales terapias específicas del antígeno. Se presentan los últimos estudios sobre la evaluación del deterioro cognitivo y su rehabilitación, que cobran cada vez más importancia por la alta prevalencia de estas alteraciones y por la ausencia de su evaluación sistemática en la práctica clínica. Por último, se exponen las necesidades sociosanitarias no cubiertas de los pacientes de esclerosis múltiple en nuestro país, poniendo el acento en los déficits actuales del sistema de protección social.

Palabras clave. Biomarcadores. Cognición. ECTRIMS. Esclerosis múltiple. Patofisiología. Post-ECTRIMS. Remielinización.