Review of the novelties presented at the 2018 ECTRIMS Congress: 11th Post-ECTRIMS Meeting (I)

Óscar Fernández, Mar Tintoré, Albert Saiz, M. Carmen Calles-Hernández, Manuel Comabella, Lluís Ramió-Torrentà, Agustín Oterino, Guillermo Izquierdo, Nieves Téllez, Juan A. García Merino, Lluís Brieva, Carmen Arnal-García, Yolanda Aladro, María del Mar Mendibe-Bilbao, José E. Meca-Lallana, Lucía Romero-Pinel, M. Luisa Martínez-Ginés, Rafael Arroyo, Celia Oreja-Guevara, Lucienne Costa-Frossard, Pedro Carrascal, Alfredo Rodríguez-Antigüedad

Summary. The Post-ECTRIMS Meeting is an emblematic event in Spain which seeks to review and disseminate the main advances in multiple sclerosis presented at the ECTRIMS annual congress. In October 2018, the eleventh Post-ECTRIMS meeting was held in Madrid and was attended by the country's leading experts in multiple sclerosis. As a result of this meeting, we present two articles which outline the most interesting novelties discussed there. This first part includes the latest results obtained regarding the influence of modifiable and non-modifiable risk factors in multiple sclerosis, with emphasis on the progress made in the field of genetics, where the discovery of genes associated with multiple sclerosis has increased exponentially. The complexity of the immune system is addressed and some contributions are made on autoimmunity mechanisms, in which bidirectional relations are observed between immune cells and cells residing in the central nervous system, such as microglial cells and astrocytes. Biomarkers, both in serum and cerebrospinal fluid as well as in imaging, are gaining more and more attention due to their current and, above all, potential role in the diagnosis and prognosis of the disease and in the evaluation of the efficacy of treatments. Finally, the observations made regarding changes in structural and functional connectivity in patients and their relationship with clinical alterations are presented.

Key words. Autoimmunity mechanisms. Biomarkers. ECTRIMS. Multiple sclerosis. Post-ECTRIMS. Risk factors. Structural and functional connectivity.

Introduction

The 34th Congress organised by the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) was held in Berlin from 10 to 12 October, 2018. ECTRIMS is the annual meeting of experts on multiple sclerosis (MS) with the highest attendance and international impact.

As has been the tradition for the last eleven years, a few days after the ECTRIMS Congress (26-27 October 2018), the Post-ECTRIMS meeting was held in Madrid, sponsored by TEVA Neuroscience. The objectives of this meeting were for it to serve as a forum where national experts in MS could meet, to present a summary of the most relevant information presented at the ECTRIMS Congress and to disseminate the contents of the Post-ECTRIMS meeting simultaneously and through this publication.

The summarised content of the Post-ECTRIMS meeting is published in two parts. This first part presents the most outstanding novelties in relation to risk factors, pathophysiology and autoimmunity mechanisms, the development of biomarkers sensitive to diagnosis and prognosis, and the relationship between changes in brain connectivity and clinical manifestations.

Risk factors in multiple sclerosis

Although the causes of MS remain unknown, the body of information collected in recent years suggests that its origin is the result of complex interactions between genetic and environmental factors, the integration of which occurs at the epigenetic level [1].

Environmental factors

Numerous environmental factors present at a given time during ontogenesis could influence the devel-

Hospital Universitario Carlos Haya; Málaga (O. Fernández). Cemcat-Hospital Universitari Vall d'Hebron; Barcelona (M. Tintoré, M. Comabella). Hospital Clínic; Barcelona (A. Saiz). Hospital Universitari Son Espases; Palma de Mallorca (M.C. Calles-Hernández). Hospital Universitari Dr. Josep Trueta; Hospital Santa Caterina de Salt; Institut d'Investigació Biomédica de Girona, IDIBGI; Universitat de Girona; Girona (Ll. Ramió-Torrentà). Hospital Universitario Marqués de Valdecilla; Santander, Cantabria (A. Oterino). Unidad de Esclerosis Múltiple; Hospital Vithas-NISA; Castilla la Cuesta, Sevilla (G. Izquierdo). Hospital Clínico Universitario; Valladolid (N. Téllez). Hospital Universitario Puerta de Hierro; Madrid (J.A. García-Merino). Hospital Universitari Arnau de Vilanova; Lleida (Ll. Brieva). Hospital Universitario Virgen de las Nieves; Granada (C. Arnal-García). Hospital Universitario de Getafe; Madrid (Y. Aladro). Hospital Universitario de Cruces; Bilbao (M.M. Mendibe-Bilbao, A. Rodríguez-Antigüedad). Hospital Universitario Virgen de la Arrixaca; Murcia (J.E. Meca-Lallana). Hospital Universitari de Bellvitge; L'Hospitalet de Llobregat, Barcelona (L. Romero-Pinel). Hospital General Universitario Gregorio Marañón; Madrid (M.L. Martínez-Ginés). Hospital Universitario Quirónsalud; Madrid (R. Arroyo). Hospital Clínico Universitario San Carlos; Madrid (C. Oreja-Guevara). Hospital Universitario Ramón y Cajal; Madrid (L. Costa-Frossard). Esclerosis Múltiple España; Madrid, Spain (P. Carrascal).

Corresponding author:
Dr. Óscar Fernández Fernández. Instituto de Investigación Biomédica de Málaga. Hospital Universitario Regional de Málaga. Universidad de Málaga. Avda. Carlos Haya, s/n. E-29010 Málaga (Spain).

E-mail:
oscar.fernandez.sspa@gmail.com
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opment of MS. The most firmly established risk factors are Epstein-Barr virus during adolescence and early young adulthood [2], obesity in adolescence, active and passive exposure to tobacco smoke, and low levels of vitamin D caused by insufficient exposure to sunlight [3]. For the correct identification of the role played by each of the environmental factors in the disease, long-term prospective studies are needed.

An example of this type of research is that carried out with a subpopulation of patients from the BENEFIT study with clinically isolated syndrome (CIS), followed up over a period of 11 years. In that study it was shown that elevated vitamin D levels predicted increases in cognitive function (according to the Paced Auditory Serial Addition Test) and axonal integrity (20% lower levels of neurofilaments light chain – NfL), while smoking was associated with greater cognitive impairment and axonal damage, with levels of NfL being 29% higher. Seropositivity for Epstein-Barr virus was not associated with changes in cognitive function or long-term axonal damage [4].

Genetic factors

The influence of genetics on susceptibility to MS has been demonstrated over the last few years [5], from the discovery of the role of three human leukocyte antigen (HLA) alleles encoded in the major histocompatibility complex (MHC) in the early 1970s to the more than 200 non-MHC genetic variants discovered by the genome-wide association study (GWAS) [6,7] (Fig. 1). Each of these variants has a modest effect on the disease and their different combinations contribute to the susceptibility developed by each patient [8].

Although GWAS have been effective in identifying risk alleles for MS, they have not been so effective in determining the genetic components of susceptibility to different forms of MS. Thanks to a recent transcriptomics study, we have learned that gene expression in peripheral blood mononuclear cells is different in patients with CIS and in the different clinical forms of MS (relapsing-remitting, primary progressive and secondary progressive). In fact, only six of the 162 genes identified by GWAS and examined in this study were expressed in all patients compared to controls. Each clinical course was characterised by dysregulation in the expression of a different set of GWAS genes, thus indicating that alteration of gene expression does not occur homogeneously in the disease, but is selective for each of its stages [9].

Pathophysiology and autoimmunity mechanisms in the central nervous system

The demyelination and neurodegeneration that occur during MS are associated with the presence of perivascular and parenchymal inflammatory infiltrates composed of T- and B-lymphocytes.

The traditional view of the role of T cells as mediators of the flare-ups in MS has been updated to a more complex view in which bidirectional interactions occur between various types of immune cells, including T cells, B cells and peripheral myeloid cells, as well as cells residing in the central nervous system (CNS) such as microglial cells and astrocytes.

T cells

Based on studies conducted with patients and animal models, it has been seen that flare-ups are mainly mediated by the aberrant or insufficiently regulated activity of pro-inflammatory CNS effector cells, such as CD4+ T cells and CD8+ T cells, which travel to the CNS parenchyma and cause demyelination, oligodendrocyte destruction and axonal damage [10]. However, given the immune-privileged status of the CNS, provided by the blood-brain barrier, the question arises as to how the T-cell response to non-self or self-antigens expressed in the CNS originates. In view of this situation, two possible scenarios are considered [11,12]. In the first, the antigen could be derived from CNS cells infected with a virus or self-antigens, released as a result of an oligodendrocyte alteration or a neurodegenerative process that would trigger the subsequent inflammation, autoreactive cells having been found in the cerebrospinal fluid (CSF) of patients with Parkinson's disease and Alzheimer's disease [13,14]. It could be that the local inflammatory response in neurodegeneration is carried out through innate immunity and that acquired immunity only modulates and does not initiate the inflammation. In the second scenario, CNS reactive T cells could be activated in the peripheral immune compartment by antigens derived from peripheral tissues such as the skin, lungs or intestine. The peripheral origin of the antigen would determine the phenotype of the cells that infiltrate the CNS. This latter scenario seems the most likely, since single nucleotide polymorphisms point more to alterations of the acquired immune response than to structural or functional alterations of the CNS [12].

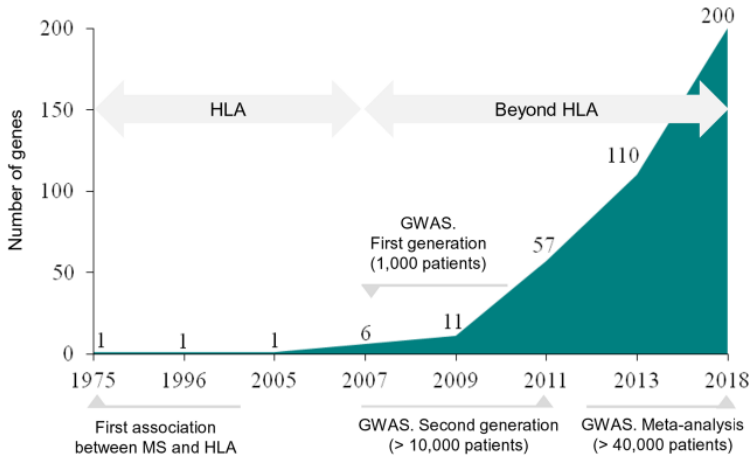
Important advances have also been made in understanding the differentiation of CD4+ T cells into cooperating –T helper (T_h)– cells, which in turn are

divided into groups of T_h cells with different specialised functions. In addition, different types of T_h cells seem to employ different pathways. For example, although both T_h17 and T_h1 cells are involved in inflammation induction in the CNS during autoimmunity, only T_h17 access the CNS parenchyma through the choroid plexuses and CSF [11]. At the site of the inflammation, effector T cells could be reprogrammed into regulatory T cells to express interleukin-10 and contribute to the resolution of inflammation.

On the other hand, an increasing amount is known about CD8+ T tissue-resident memory (T_{RM}) cells, which persist in the CNS parenchyma after clearance of viral infections [15]. Phenotypic analyses of CD8+ T cells suggest that T_{RM} cells could be reactivated in acute MS lesions and in both the recurrent and the progressive forms of MS, while B cells, at least in part, are gradually transformed into plasma cells [16].

Systemic memory populations, including central memory T cells (T_{CM}) and effector memory T cells (T_{EM}), are found in the CSF. Of all the T cells in CSF, 90% are T_{CM} cells and 10% are T_{EM} cells. However, patients with MS have fewer T_{EM} cells in CSF, suggesting that T_{EM} cells in MS patients may have left the CSF space to invade the CNS parenchyma after undergoing specific antigen interactions in the meningeal compartment [17].

Figure 1. Number of genes associated with multiple sclerosis (MS) identified in recent years. The increasing development of genome-wide association studies (GWAS) since 2007 has made it possible to explore the whole genome and identify which parts of it are associated with MS. The figure shows the large number of non-MHC genetic variants that have been discovered thanks to GWAS, with a total of more than 200 variants to date (data obtained from [7]). HLA: human leukocyte antigens.



B cells

There is an increasing amount of evidence suggesting that B cells contribute to the pathogenesis of MS. B cells not only increase inflammation through the production of interleukin-6 cytokines, but may also decrease inflammation by producing interleukin-10 [19], although the pro-inflammatory effects of B cells appear to predominate in MS. A recent study has shown that CD20 B cells make a prominent contribution to the inflammatory response of MS, especially in the early stages, but also in the progressive phase. An important finding in this same study was that the density of B cells within an active lesion is greater in the perivascular space of the central vein, while T cells infiltrate more diffusely in the parenchyma of the lesion and at the initial site of demyelination [16].

It is not yet clear how the aetiological factors (genetics and environment) contribute to generating a repertoire of self-reactive CD4+ T cells. There is what is called automatic reactivity, defined as 'autoproliferation' of peripheral Th1 cells, which is mediated by B cells and elevated in patients carrying the HLA-DR15 haplotype. In fact, it is precisely memory B cells that cause CD4+ T_h1 T cells to auto-proliferate, and it has been observed, both *in vitro* and *in vivo*, that the decrease in B cells effectively reduces the autoproliferation of T cells [19].

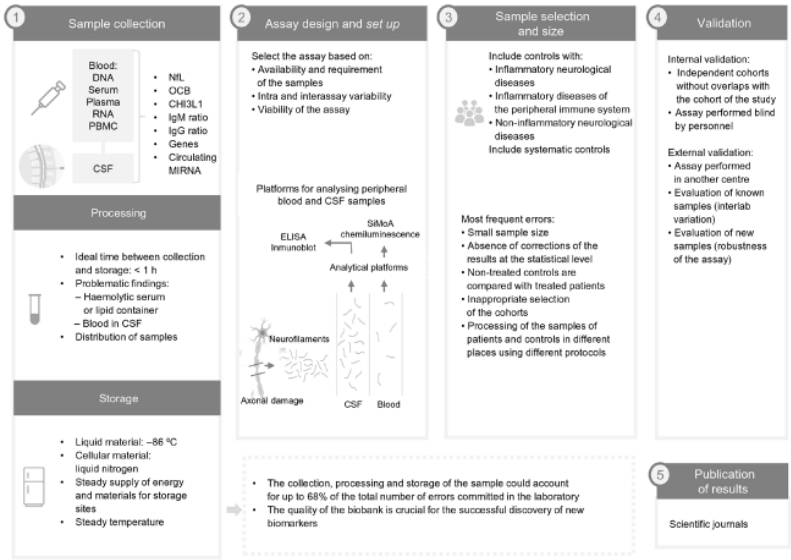
Autoantibodies

Evidence of the existence of autoantibodies in a certain percentage of patients with MS has been detected in studies on the pathogenic effects of anti-MOG (myelin oligodendrocyte glycoprotein) antibodies and by observed responses to therapeutic apheresis.

Regarding apheresis, a cohort study has shown that the response to treatment based on plasma exchange or immunoadsorption is associated with different patterns of immunopathology: patients with lesion patterns 1 and 2 (pattern 1: demyelination associated with T cells and macrophages; pattern 2: demyelination associated with complement deposits and immunoglobulins) showed clinical improvement after treatment with plasmapheresis (up to 31% of patients with type 1 and 55% with type 2), while patients with type 3 lesions (oligodendrocyte degeneration) showed no benefit [20].

Regarding the pathogenic effects of antibodies, it has been observed that anti-MOG autoantibodies, present in certain patients with inflammatory demyelinating diseases, induced pathological chang-

Figure 2. General considerations in research on biomarkers in cerebrospinal fluid (CSF) and serum. IgG: immunoglobulin G; IgM: immunoglobulin M; MiRNA: microRNA; NfL: neurofilament light chain; OCB: oligoclonal bands; PBMC: peripheral blood mononuclear cell.



es *in vivo* in murine models, such as increased infiltration of T cells [21].

Myeloid cells

Along with the T and B cell response of the adaptive immune system, there are also responses in the traditionally less studied innate immune system, consisting of myeloid cells. Disease-modifying therapies have an influence on T and B cells, but they also influence myeloid cells. The little attention paid to the innate immune system in the therapeutic setting of MS is probably due to the fact that the number of myeloid cells after treatment is replaced more rapidly compared to the persistent long-term decrease in the number of lymphocytes [22].

One aspect to consider is the fact that ageing does not have the same impact on the proinflammatory activity of the various myeloid cells. While with age macrophages are less able to produce proinflammatory responses, microglial cells show an exacerbated inflammatory response, although it is true that age decreases phagocytic and chemotactic function in both cell types [23]. Consequently, therapeutic strategies aimed at selectively stimulating macrophages and microglial cells to correct the changes that occur with age may be promising approaches in the area of immune system regeneration [24].

Biomarkers in serum and cerebrospinal fluid

For a biomarker to be incorporated into clinical practice, it must be a faithful reflection of the underlying biological or pathological processes, it must allow for easy and safe measurement and it must be economically sustainable. Together with the need to increase collaboration between researchers to develop new biomarkers in serum and CSF, again emphasis was placed on the need to take into account a series of general considerations when undertaking the different steps that make up the studies aimed at developing a biomarker (Fig. 2) [25].

Chitinase CHI3L1

Chitinase CHI3L1 (*chitinase 3-like 1*), or YKL-40, is a marker of glial activity expressed primarily by astrocytes and microglial cells in white matter lesions, whose function appears to be related to tissue changes during inflammation. As a result of the studies discussed below, CHI3L1 has been proposed as a biomarker of MS conversion in CIS patients [26]. A cohort study of 813 CSF samples confirmed that levels of CHI3L1 in CSF, but not in serum, were higher in CIS patients who progressed to MS than in those who remained stable [27]. Similarly, elevated levels of CHI3L1 in CSF independently predicted a shorter MS conversion time, faster development of disability [27] and long-term physical and cognitive impairment [28]. However, the findings on the predictive value of CHI3L1 levels in peripheral blood are not conclusive [27,29], and so today CHI3L1 in blood is not as informative as in CSF and its usefulness is remains uncertain.

In patients with radiologically isolated syndrome, the CHI3L1 in CSF does not appear to show the same predictive value of conversion to MS as in CIS patients, since conversion rates to CIS or to MS are similar in patients with high and low levels of CHI3L1 [30].

In MS, CHI3L1 levels are increased in patients with the relapsing-remitting form (RRMS), especially during flare-ups, and also correlate with the number of gadolinium-enhancing lesions [31]. On the other hand, disease-modifying treatments such as daclizumab, natalizumab and fingolimod significantly reduce levels of CHI3L1 in CSF [32-34].

Neurofilaments light chain

Another very promising biomarker in CSF and serum, not only in MS but also in other neurological diseases [35], is neurofilaments, which are the main

components in the cytoskeleton of the neurons that are released after axonal damage. The available evidence shows that high CSF levels of NfL (68 kDa), rather than heavy chain (205 kDa), constitute an independent risk factor for conversion from CIS to MS [36] and for the emergence of CIS and MS in patients with radiologically isolated syndrome, especially beyond the age of 37 [30]. High levels of NfL in CSF also correlate with the number of lesions in magnetic resonance and the degree of disability [37] and decrease with the administration of disease-modifying treatments such as daclizumab, natalizumab, fingolimod or rituximab [32,38-40].

Thanks to the fourth generation SiMoA (single molecule array) technique, NfL can be detected in blood more accurately, with a sensitivity up to 126 and 25 times higher than ELISA and electrochemiluminescence assays, respectively [41]. Although NfL concentration in serum is up to 50-100 times lower than in CSF [35], they can be used as markers of brain damage because there is a strong relationship between NfL levels in serum and in CSF [42-44]. The cumulative evidence from recent studies supporting the use of NfL as a biomarker in MS is shown in table I.

Coordinated research is currently being carried out at different centres to establish standardised and precise measures of NfL for application in clinical trials and in individualised therapeutic decision-making [45].

Oligoclonal bands

The revision of the 2010 McDonald Diagnostic Criteria, conducted in 2017 [46], included oligoclonal bands in CSF as a biomarker of MS, based on evidence that it is an independent predictor of a second flare-up in CIS patients, and its high specificity in combination with dissemination in space in the diagnosis of CIS [47]. According to the 2017 criteria, a patient with CIS who meets clinical criteria for dissemination in space or for MS, with no other better explanation for the clinical presentation, and with oligoclonal bands, in the absence of atypical CSF findings, may be diagnosed with MS. In fact, a study comparing the proportion of CIS patients diagnosed with MS using the 2010 and 2017 criteria showed that the latter increase the diagnostic accuracy of MS by 25%, which allows an earlier diagnosis without the need to wait for the appearance of a new lesion in T_2 or gadolinium-enhancing lesions [48].

It has been highlighted that the inclusion of oligoclonal bands instead of dissemination in time entails the need for neurologists to ensure that CSF analyses are performed according to the analytical quality standards [49] shown in figure 2.

Magnetic resonance imaging biomarkers

Differential diagnosis of multiple sclerosis

Dissemination in time and dissemination in space of white matter lesions, in addition to being a crucial biomarker of MS, occur in other diseases, from the most common age-related vascular pathologies and migraine to neuromyelitis optica spectrum disorders and other less common conditions. The location of the lesion, as well as its characteristics and behaviour under different sequences, can help in the differential diagnosis of MS. Thus, lesions in the optic nerve, juxtacortical areas, with an irregular shape, periphery of the brain stem and posterolateral cervical spinal cord point to MS rather than other conditions, such as small-vessel vascular diseases [50,51].

The percentage of periventricular lesions and the presence of cortical lesions identified with SWI (susceptibility-weighted imaging) and DIR (double inversion recovery) sequences also aid in the differential diagnosis [52]. In this sense, the percentage of patients with MS and periventricular lesions is much higher (median: 88%) than that of patients with inflammatory vascular diseases of the nervous system (14%) [53]. On the other hand, the thickening of the meninges, undefined lesions that increase in size over time, macro and microbleeds, heart attacks, cavities, symmetrical lesions without affecting U-fibres and extensive lesions in the spinal cord suggest a diagnosis other than MS [52].

Optic nerve involvement in MS has been widely demonstrated and at least one third of patients present with optic neuritis as their first symptom [54]. However, to date, there are insufficient data on the accuracy of the different tests (magnetic resonance, visual evoked potentials and optical coherence tomography) in improving the diagnosis of MS [55]. Therefore, the 2017 McDonald criteria do not include the optic nerve as one of the typical regions of the CNS to establish dissemination in space in the diagnosis of MS.

Prognosis of patients with clinically isolated syndrome or newly diagnosed multiple sclerosis: results of cohort studies

For most patients with MS, the progressive course of the disease can take more than ten years to ap-

Table I. Evidence supporting the use of neurofilaments light chain (NfL) as a biomarker of multiple sclerosis (MS).

	Patients	NfL	Results	Value
Novakova et al [43]	MS (*n* = 286), other neurological conditions (*n* = 45), healthy controls (*n* = 42)	Serum	NfL levels were significantly higher in patients with RRMS (16.9 ng/L) and with progressive MS (PPMS and SPMS) (23 ng/L) than in controls (10.5 ng/L)	Diagnosis
			Serum and CSF NfL levels decreased with DMT in patients who had not been previously treated and in patients scaled to a more effective DMT, while they remained stable in patients who did not receive DMTs and in those who switched to DMTs with a similar level of efficacy	Treatment response
Chitnis et al [69]	MS (*n* = 122)	Serum	Correlation between NfL levels in the early stages of the disease and brain lesions detected ten years later, including the cerebral parenchymal fraction and the volume of hyperintense lesions in T_2	Prognosis
Barro et al [70]	RRMS (*n* = 189), progressive MS (*n* = 70), healthy controls (*n* = 259)	Serum	During an average follow-up period of 6.5 years, NfL levels above the 90th percentile of the control values were an independent predictor of worsening of the EDSS the following year in MS patients. Lesions were independently associated with increased NfL. The higher the percentile of NfL is, the more pronounced the loss of brain and spinal volume will be	Prognosis
Varhaug et al [71]	RRMS (*n* = 85)	Serum	NfL levels were associated with the presence of T_1 gadolinium-enhancing lesions up to two months before and one month after biomarker measurement	Prognosis
Hakansson et al [44]	MS or CIS (*n* = 41), healthy controls (*n* = 22)	CSF	NfL were associated with new lesions in T_2 and loss of brain volume during four years' follow-up	Prognosis
			There was a correlation between NfL levels in serum and NfL levels in CSF. NfL levels in CSF showed a stronger association with NEDA-3 status, new lesions in T_2 and loss of brain volume than NfL levels in serum	Disease activity
Hakansson et al [72]	MS or CIS (*n* = 41), healthy controls (*n* = 22)	CSF	Baseline NfL levels correctly classified 85% of patients who showed disease-related activity during two years' follow-up	Prognosis
Kuhle et al [73]	RRMS or CIS with riluzole (*n* = 22), RRMS or CIS with placebo (*n* = 20)	Serum	There was a correlation between changes in NfL over 24 months and changes in EDSS and neuropsychological outcomes. Brain volume decreased more rapidly in patients with higher baseline levels of NfL, an association that became stronger at 24 months. Higher and increasing NfL levels over time predicted a greater number of gadolinium-enhancing lesions	Prognosis
Disanto et al [42]	Cross-sectional MS cohort (*n* = 142), longitudinal MS cohort (*n* = 246), healthy controls (*n* = 254)	Serum	There was a correlation between NfL levels in serum and NfL levels in CSF. Patients with gadolinium-enhancing lesions in the brain or spinal cord displayed higher levels of NfL. These NfL levels were independently associated with the EDSS and the presence of flare-ups. Patients with NfL levels above the 80th, 90th, 95th and 97.5th percentiles and the 99th percentile of the controls had an increased risk of flare-ups and poorer EDSS. The NfL levels were associated with time since the start of DMT, regardless of the flare-ups	Disease activity Treatment response
Calabresi [74]	RRMS (*n* = 594) [a], CIS (*n* = 319) [a], RRMS (*n* = 164) [a], RRMS (*n* = 122) [a]	Serum	LBaseline NfL levels were associated with the number of gadolinium-enhancing lesions and with the accumulation of new lesions in T_2. Patients with a high rate of cerebral atrophy had high levels of NfL	Disease activity
			NfL levels decreased with DMT. Natalizumab reduced NfL levels below 16 pg/mL in 96% of patients. Levels of NfL > 16 pg/mL were associated in the long term with progression on the EDSS (12 years), brain volume in T2 (10 years) and brain atrophy (5 years)	Treatment response Prognosis
Disanto et al [42]	RRMS (*n* = 594) [a], CIS (*n* = 319) [a], RRMS (*n* = 164) [a], RRMS (*n* = 122) [a]	Serum	NfL levels decreased with injectable DMT, fingolimod, natalizumab and rituximab to a similar extent. There was a negative correlation between NfL levels during follow-up and treatment time	Treatment response

CIS: isolated clinical syndrome; CSF: cerebrospinal fluid; DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; NEDA: no evidence of disease activity; PPMS: primary progressive multiple sclerosis; RRMS: recurrent remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis. [a] Patients taking part in the following phase III clinical trials: ADVANCE (*n* = 594), CHAMPS (*n* = 319), MSCRG (*n* = 164) and SENTINEL (*n* = 122).

Table II. Predictors of disease course in early stages, based on data from cohort studies.

	Patients (*n*)	Mean follow-up	Predictors
London CIS cohort [75]	120	30 years	The best predictors of disease development (EDSS > 3.5) were baseline infratentorial lesions and deep white matter lesions at one year
Verona MS cohort [76]	219	7.9 years	Extensive initial cortical damage was associated with inflammatory activity and predisposed the patient to a rapid onset of the progressive phase. In addition, the age at diagnosis and the number of early flare-ups made it possible to identify patients at higher risk of progression
Barcelona CIS cohort [77]	1300	10 years	Its prognostic model for risk assessment of a second flare-up includes: age, sex, oligoclonal bands, number of MRI lesions, disease-modifying therapies, presence of new lesions in T_2 during the first year, topography of the lesion and activity, vitamin D and cotinine levels in serum

CIS: clinically isolated syndrome; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; MS: multiple sclerosis.

pear and may develop over several decades. Cohort studies with an extensive follow-up and carried out in real-life conditions have the potential to identify the factors that contribute to disability progression and the patients who may benefit most from available treatments. Table II highlights the cohort studies focused on the prognosis of patients with CIS or MS in the early stages that were presented in this edition of the ECTRIMS Congress.

Changes in structural and functional connectivity and their impact on cognitive alterations

Cognitive deficits are present in 40-70% of MS patients and have a significant impact on the performance of activities of daily living. The pathology of MS in the form of focal lesions, damage to normal-appearing tissue and atrophy affect both the white and the grey matter. White matter lesions, diffuse damage and atrophy in deep grey matter already occur early in the disease, while cortical demyelination and cortical atrophy are more prevalent in later stages. A five-year longitudinal study showed that different structural damage predicted cognitive impairment based on the duration of MS symptoms. In those patients with RRMS and symptoms during a period of less than 10 years, the best predictor of cognitive impairment was damage to white matter integrity and atrophy of deep grey matter, while in patients with RRMS and symptoms for more than 10 years, and in those with progressive MS, cortical atrophy was the best predictor [56].

One of the major advances in the evaluation of the structural connections of white matter tracts is probabilistic tractography, as opposed to deterministic tractography, which was previously used [57]. Thanks to improvements in this technique, MS patients have been found to have a less efficient structural network for transferring local and global information due to widespread alterations in white matter connections and grey matter structures, which affects attention and executive function [58].

Together with the decrease in the capacity to transmit information, the integration of global information between different regions is also affected. This is due to changes in the organisation of central neurocortical nodes, or hubs, which are highly connected ('rich-club') and which play a fundamental role in integrating the global information among different parts of the structural network. MS patients show decreases in the strength of the 'rich-club' connections associated with cognitive impairment [59]. Interestingly, one of the network nodes whose connections have been altered in both MS and CIS patients is the thalamus [59]. The importance of the thalamus in MS has been reported in many other studies, where its atrophy has been seen to occur prematurely and consistently [60], its hypoperfusion has an impact on disability [61], its volume is the best predictor of the evolution from RRMS to secondary progressive MS in five years [62] and its functional connectivity to resting-state networks is associated with disability and cognitive impairment [63].

Regarding the functional connectivity of the thalamus, a study of two independent cohorts of MS patients showed that disability (Expanded Disability Status Scale) was associated with increased functional connectivity of the thalamus to the motor network, while cognitive impairment was associated with increased connectivity between the thal-

amus and the ventral and dorsal attention network [63]. These increases in thalamic functional connectivity are not observed in the same way in all MS patients. In fact, when MS patients were divided according to their cognitive impairment (preserved, mild or severe), only patients with severe cognitive impairment showed increases in thalamic functional connectivity, which could be interpreted as a sign of maladjustment [64].

In addition to increases in the thalamic connections, increases in the functional connections of activated resting-state networks have been seen in both RRMS patients [65] and CIS patients [66]. This increase in functional connectivity that is initially manifested in patients seems to decrease, after having reached a maximum level, as the disease progresses. Thus, patients with an initially greater disability show a decrease in connectivity two years later, this pattern being associated with an increase in disability [67]. Since changes in functional networks in the early stages of MS are initially associated with maintenance of overall brain efficiency, it has been suggested that these changes may have a compensatory mechanism. However, the minimum degree of pathology required to trigger these functional changes and the maximum degree of pathology from which increases in functional connectivity go from being compensatory and help to maintain cognitive processes to becoming aberrant and accentuate cognitive alterations and disability are still unknown.

Although there is a strong association between atrophy and cognitive impairment, there are also patients without atrophy who have cognitive impairment, and vice versa. This can be seen by the fact that, in patients without atrophy, the level of education predicts cognitive alterations, while in patients with atrophy cognitive decline is predicted by alterations in the white matter [68]. This study focuses on the importance of considering the cognitive reserve, through the level of education, in patients' vulnerability to cognitive impairment.

Final observations

The 2018 edition of ECTRIMS shed more light on the understanding of genetic and environmental risk factors. On the one hand, more than 200 genetic variants have already been identified in relation to the development of MS thanks to the GWAS and, on the other hand, it has been confirmed that vitamin D levels and smoking in the first years after CIS play an essential role in long-term cognitive function and neural damage.

In terms of autoimmunity mechanisms, it is worth highlighting the data indicating that autoreactive T cells are characterised by an increase in self-proliferation driven by memory B cells.

One of the aspects that was received with the most expectation was the presentation of favourable evidence on the use of serum NfL as a biomarker for diagnosis, prognosis, disease activity and treatment response.

Despite the important methodological advances in the analysis of structural and functional alterations with imaging techniques, the conclusion is that their real impact on clinical practice remains limited.

There is still a long way to go in the development of standardised data collection and analysis models that make it possible to determine the individual risk of MS based on clinical, radiological, neurophysiological and transcriptomic information. These findings will open up new areas in clinical research, where big data will play a fundamental role in resolving a number of questions that remain unanswered about risk factors and biomarkers of the disease, in order to bring us closer to a precision medicine that improves the treatment of MS.

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Revisión de las novedades presentadas en el congreso ECTRIMS 2018: XI Reunión Post-ECTRIMS (I)

Resumen. La reunión Post-ECTRIMS es un encuentro emblemático en España que persigue revisar y difundir los principales avances en esclerosis múltiple presentados en el congreso anual ECTRIMS. En octubre de 2018, la reunión Post-ECTRIMS celebró en Madrid su undécima edición, contando con los mayores expertos de ámbito nacional en esclerosis múltiple. Como resultado de esta reunión, se presentan dos artículos donde se recogen las novedades más destacadas en la misma. En esta primera parte se incluyen los últimos resultados sobre la influencia de los factores de riesgo modificables y no modificables en la esclerosis múltiple, destacando los progresos realizados en el ámbito genético, donde el descubrimiento de genes asociados a la esclerosis múltiple ha aumentado exponencialmente. Se aborda la complejidad del sistema inmune y se realizan algunas aportaciones sobre los mecanismos de autoinmunidad, en los que se observan relaciones bidireccionales entre las células inmunes y las células residentes del sistema nervioso central, como la microglía y los astrocitos. Los biomarcadores, tanto en suero y líquido cefalorraquídeo como de imagen, ganan cada vez más atención por su papel actual, y sobre todo potencial, en el diagnóstico y pronóstico de la enfermedad y en la evaluación de la eficacia de los tratamientos. Por último, se presentan las observaciones realizadas respecto a los cambios en la conectividad estructural y funcional en los pacientes y su relación con las alteraciones clínicas.

Palabras clave. Biomarcadores. Conectividad estructural y funcional. ECTRIMS. Esclerosis múltiple. Factores de riesgo. Mecanismos de autoinmunidad. Post-ECTRIMS.