Review of the novelties from the 2017 ECTRIMS Congress, presented at the 10th Post-ECTRIMS Meeting (I)

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Summary. The Post-ECTRIMS Meeting is an emblematic event in the field of multiple sclerosis in Spain. Its chief aim is bring together the country's leading specialised neurologists to analyse the main advances made in multiple sclerosis and to review the most important topics addressed at the ECTRIMS Congress. The tenth Post-ECTRIMS Meeting was held in November 2017. Over the years this event has firmly established itself as an important meeting point where experts from all over the country get together to foster communication, establish synergies and promote and enhance research ultimately aimed at improving the prognosis and quality of life of patients with multiple sclerosis. This first part reports on the publication of the new European and American clinical guidelines on the use of disease-modifying treatments and the new diagnostic criteria. It also discusses the strategies for following up patients treated with disease-modifying therapies, reviews cerebral atrophy and biomarkers of neurodegeneration and neuroinflammation, and analyses the role of neuroglia in pathogenesis and treatment. The study examines the natural history of the disease, with the evidence provided by registers, and we anticipate the future thanks to the progress being made in genetics and immunology.

Key words. ECTRIMS. Multiple sclerosis. Post-ECTRIMS.

Diagnosis and differential diagnosis

The diagnostic criteria for multiple sclerosis (MS) are defined for use in cases of patients with suspected MS, but were not specifically developed to differentiate MS from other diseases. The magnetic resonance imaging (MRI) criteria were developed in patients who begin with clinically isolated syndrome (CIS) and present the typical symptoms of MS, and should not be applied in patients with non-specific symptoms. MRI is often enough to confirm the diagnosis, provided that the characteristic lesions are accompanying a typical clinical syndrome. In patients with atypical manifestations, however, it is also necessary to conduct a laboratory test despite the fact that its performance may be low and could make it more difficult to interpret the data [1]. In these patients oligoclonal band analysis is particularly valuable, especially in subjects over the age of 50 who present vascular risk factors or migraine. It should be noted that the predictive positive value of the oligoclonal bands is higher than that of MRI, but the predictive negative value is also higher, which is to say that the risk of false positives is lower [2]. This is important because misinterpretation of the MRI often leads to the symptoms presented by a patient eventually being attributed to MS.

When it comes to diagnosis, it is important to take into account possible errors (some of the most frequent being the so-called red flags [3]), but also the fact that gadolinium-enhancing (Gd+) lesions are not characteristic of the disease, while the same can be said of meningeal enhancement or failure to detect black holes. The work by MAGNIMS that compared the McDonald-2010 criteria with those of Filippi-2010 concluded that the specificity of the diagnostic criteria is still low [4]. Data published after 2012 showed that approximately 10% of patients presented misdiagnosis of MS [5]. This occurred in patients with comorbidities that were difficult to diagnose, such as fibromyalgia, or with somewhat unclear symptoms or psychiatric problems, but a large percentage came from non-specific lesions of the white matter or small-vessel ischaemic lesions. A subsequent multicentre study with 110 patients showed that the diagnoses that could be confused with MS were not so different. The most notable finding was that a third of the patients had been diagnosed with MS for more than 10 years, 77% had received treatment for MS and some have even participated in clinical trials [6]. The atypical symptoms are the cause

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of misdiagnosis in up to two thirds of the patients, as the criteria have not been evaluated in patients with atypical presentations. Another factor to be taken into account is that over 50% of the patients with atypical symptoms present alterations in the MRI. The MRI criteria were not developed to distinguish MS from other diseases and rates of misdiagnosis reach 24% of all cases. Doubts regarding a possible overdiagnosis of radiologically isolated syndrome in clinical practice, given the importance of MRI in reaching a misdiagnosis, are ruled out provided that the diagnostic criteria are strictly fulfilled [7].

The differential diagnosis of neuromyelitis optica is MS. Hypothalamic lesions and extensive lesions or those involving three vertebral bodies are more characteristic of neuromyelitis optica, but patients with this disease can present brain lesions and paediatric patients with MS can even have an extensive spinal-cord lesion over three vertebral bodies.

Cases have been reported of encephalitis due to N-methyl D-aspartate antibodies with white matter lesions in MRI that can have anti-aquaporin-4 (AQP4+) or anti-myelin oligodendrocyte glycoprotein (MOG+) antibodies, and present a poorer therapeutic response profile. A review study compared two series of anti-MOG+ patients with very similar characteristics. The results showed that around 60% of patients begin with optic neuritis, 2% with clinical symptoms of the trunk, 15-20% may meet criteria for neuromyelitis optica, and 70-80% present a disease characterised by flare-ups [8]. Theoretically, optic neuritis-MOG+ is not very different from optic neuritis-AQP4+, although a great number of patients with MOG have anterior compromise and perineuritis [9]. Supratentorial or infratentorial lesions are different from MS and are more similar to those of neuromyelitis optica. Nevertheless, the percentage of false positives with commercial anti-MOG tests can reach 20%.

Some examples of infrequent clinical presentations include paralysis of the hypoglossal nerve, the presence of hemiageusia and itching or a myopathy. Infrequently, however, 3% of the patients with anti-AQP4 antibodies can present paraneoplastic syndromes, most of them males and with symptoms involving the trunk or patients with an extensive myelitis once over the age of 45 [10].

New diagnostic criteria for multiple sclerosis

The aim of reviewing the new diagnostic criteria is to simplify and optimise the use of the McDonald-2010 criteria, facilitate the early diagnosis of MS, preserve the specificity of these criteria and reduce the rate of false diagnoses. Table I shows the main incorporations, proposals that require more evidence and areas for future research.

As support for these new criteria, the 2017 review confirms the value of including oligoclonal bands in the diagnosis of MS in patients who met dissemination in space criteria, as the risk of MS and specificity of the diagnosis increase significantly [11,12]. To establish dissemination in space, the 2016 MAGNIMS MRI criteria [13] recommend confirmation of at least three periventricular lesions, involvement of the optic nerve, and the presence of juxtacortical and cortical lesions. These criteria are easy to implement and increase the diagnostic capacity if both symptomatic and asymptomatic lesions are taken into account. Including cortical lesions, however, does not provide much information about the juxtacortical lesions, although including three periventricular lesions instead of one single lesion reduces the sensitivity and increases the specificity of the diagnosis of MS. Nevertheless, in the McDonald-2017 criteria, dissemination in space with a periventricular lesion was finally accepted if there was another cortical or juxtacortical, infratentorial or spinal lesion. The role played by the compromise of the optic nerve in the diagnostic criteria for MS remains unclear.

Biomarkers

The search for biomarkers in MS is one of the aims of the research currently being conducted in this field, as they will allow faster progress to be made in the prognosis and treatment of patients, and in their tailored management. In this edition of the congress a number of aspects were reviewed ranging from general considerations concerning their development, validation and use (Figure) to the biomarkers identified to date in patients with MS (Tables II and III).

Genetics and advanced immunology in multiple sclerosis

Genetic map in multiple sclerosis and its role via the peripheral and central immune system

Data from the large Genome Wide Association Studies and the International Multiple Sclerosis Genetics Consortium have been grouped in 15 case (n = 14,802) and control (n = 26,703) datasets and a

Table I. New diagnostic criteria for multiple sclerosis.

Considerations for avoiding misdiagnosis	Main incorporations	Key proposals that require further evidence	Further areas of research
Perform an MRI scan of the spinal cord or examination of the cerebrospinal fluid when faced with: – Insufficient clinical and radiological evidence supporting the diagnosis of MS – Atypical presentations of MS, such as isolated radiological syndrome – Atypical forms of clinical presentation – Populations with a low prevalence and incidence of the disease	If a patient with typical clinically isolated syndrome and MRI criteria or DIS has oligoclonal bands, meets DIT criteria and, therefore, can be diagnosed with MS The symptomatic and asymptomatic lesions must be taken into account in the assessment of DIS and DIT criteria by MRI. In the 2010 criteria, symptomatic lesions were not taken into consideration when a patient presented attacks involving the trunk or the spinal cord Unlike the 2010 criteria, cortical lesions must be taken into account together with the juxtacortical lesions in order to fulfil the DIS by MRI The diagnostic criteria for primary progressive MS do not vary with respect to 2010, although the symptomatic + asymptomatic and cortical + juxtacortical lesions can be taken into consideration for the diagnosis The diagnosis of the clinical phenotype of the disease, according to Lublin's 2014 criteria, should be reassessed on the basis of new information obtained as the patient progresses	Value or relevance of the confirmation of more than one periventricular lesion (e.g. three) Role of the involvement of the optic nerve Management of atypical presentations, such as isolated radiological syndrome and solitary inflammatory lesions	Validation of the McDonald-2017 criteria in diverse populations Validation of the MAGNIMS-2016 criteria Different MS characteristics Utility of anti-MOG antibodies Utility of evoked potentials Diagnostic biomarkers (not imaging)

DIS: dissemination in space; DIT: dissemination in time; MOG: myelin oligodendrocyte glycoprotein; MRI: magnetic resonance imaging; MS: multiple sclerosis.

total of 8.6 million single nucleotide polymorphisms. A meta-analysis of these 15 sets showed 26,395 single nucleotide polymorphisms with genome-wide statistical significance.

The aim was to study the genes unrelated to the human leukocyte antigens (HLA). The strategy chosen for use in this case was to exclude a wide region around the major histocompatibility complex, isolate the non-relevant regions of the genome and repeat the procedure until the polymorphisms were isolated with a value $p < 0.05$, which were designated 'effects' (a total of 4,842 single nucleotide polymorphisms). Of these, the genome-wide ones showed higher statistical significance ($n = 200$) and the rest, i.e. the non genome-wide ones, were divided into suggestive genes, which could be highly or weakly suggestive, non-replicated, and with no data for replication. Finally there were a percentage of genes that provide heritability, some being related and unrelated to HLA [14].

These genes express proteins, above all in the immune system, with a fundamentally regulating action, and the pathways involved are those for development, maturation and terminal differentiation of cells in the immune system. The architecture of the genetic map of MS shows genes that are involved in the retroviral integration of the genome, intron splicing and co-activation of transcription factors. In sum, the genes have a regulatory potential, basically in the immune system and not so much so in the nervous system, which explains why MS is an immune-mediated disease, with a genetic predisposition linked to immunity.

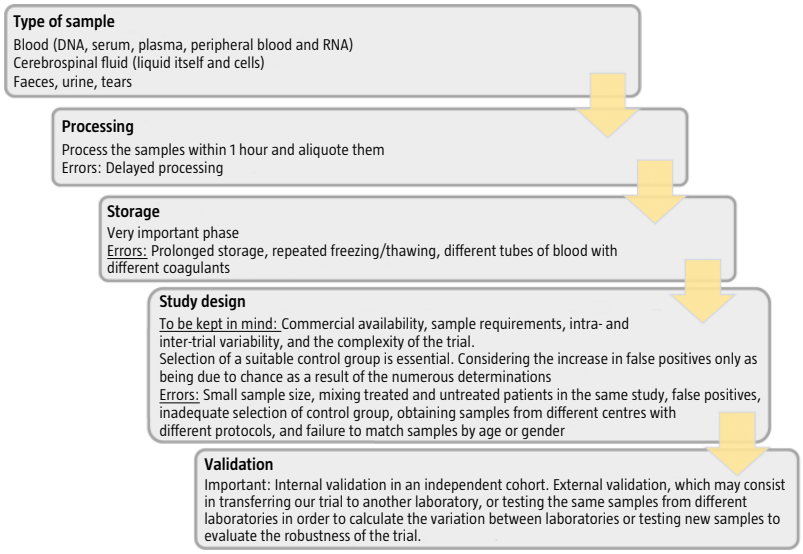
Pathogenic immune response

Today the relationship between HLA and autotolerance is not fully understood. In Goodpasture disease, an autoimmune disease that attacks the α_3 subunit of type IV collagen, HLA-DR15 confers a greater risk, while HLA-DR1 provides resistance to the disease in transgenic mice by increasing the production of tolerogenic cells [15].

Modulation of the tyrosine kinase 2 gene could represent a new therapeutic approach for the treatment of autoimmune diseases. There is a variant of this gene, whose protective C allele would favour a decrease in the activity of the protein, fundamentally mediated by Th2 cytokines [16].

The BAFF and APRIL cytokines play mediating roles in the survival and differentiation of B cells; a variant in TNFSF13B (a gene that codes for BAFF) is associated with MS and systemic lupus erythematosus. This risk allele, resulting from GCTGT→A deletion-insertion, is also associated with an overregulation of humoral immunity through the in-

Figure. General considerations for the development and use of biomarkers in multiple sclerosis.



crease in soluble BAFF, B lymphocytes and immunoglobulins. This area plays a role in protecting against malaria [17].

Granulocyte-macrophage colony-stimulating factor is necessary in the *in vivo* induction of experimental autoimmune encephalitis (EAE). It has recently been shown that the expression of Foxo3 plays a specific role in the polarisation of CD4+ T cells towards Thl Eomes+ pathogens, such as CD8, which produce interferon-γ and granulocyte-macrophage colony-stimulating factor [18]. Unlike T-bet, Eomes+ increases expression as regards the differentiation of B lymphocytes, which is a very interesting result because the cells are increased in the peripheral blood and the CSF of patients with progressive forms of the disease [19].

Follicular helper T lymphocytes also seem to play a role in MS. In comparison to healthy controls, follicular helper cells, and more especially those with the cell surface markers CCR7+ ICOS+, increase the production of B cells and interleukins. Their possible role as a therapeutic target is reflected in the fact that mitoxantrone lowers the number of these cells and the production of interleukin (IL)-21 [20]. The follicular Th17 cells are overrepresented in the progressive forms, unlike the follicular Th1 cells, which are observed in smaller proportions. These data point to them as a possible progression marker [21].

The Th17 lymphocytes are increased in active MS, and IL-17 is present in the active lesions from lymphocytes and glial cells [22]. Sodium chloride increases the proportion of Th17 cells and, in fact, the disease is seen to be more severe in animal models with EAE that follow a diet rich in salt. Salt-sensitive kinase plays a critical role in differentiating pathogenic Th17 cells and in the development of autoimmunity, as well as in the mechanism by which an environmental factor like a high-salt diet promotes inflammation [23].

Melatonin levels are negatively correlated with activity in MS. Treatment with melatonin improves the disease in an experimental model by directly interfering with the differentiation between human and murine T cells [24]. In humans, Th1 and Th17 have melatonin receptors that, by activating cellular signalling pathways, would inhibit the mechanisms that are set in motion due to the activation of these cells.

As regards the microbiota, one study conducted on monozygotic twins discordant for MS (n = 34 pairs) showed that the microbiota from twins with MS, and not that from their healthy siblings, contained factors that precipitate the development of an MS-type autoimmune disease in a transgenic murine model, such as lowered levels of IL-10 and a lower percentage of bacteria of the genus *Sutterella* with a protective immunoregulatory profile [25].

Early damage to the blood-brain barrier in multiple sclerosis lesions

The generalised belief that the blood brain barrier (BBB) prevents the entry of immune cells to the central nervous system (CNS) changed when it was discovered that activated T cells could cross the barriers of the CNS safeguarding the immune system.

Inflammation of the BBB precedes the passage of activated cells. The analysis of autopsies carried out within four hours in spontaneous relapsing-remitting EAE shows an early increase in Th1 and Th17 cytokines in the periphery of EAE before any neuropathological evidence [26]. In the following we describe other substances related to the passage of activated cells across the BBB that have been identified in experimental models or by means of proteomic and transcriptomic techniques.

The adhesion molecule DICAM (previously described as limitrin) is a new member of the superfamily of immunoglobulins that interacts with αvβ3 integrin expressed in the endothelial cells of the BBB. DICAM is typically expressed on the surface of potentially encephalitogenic Th17 lymphocytes,

Table II. Neuroinflammation biomarkers identified in patients with multiple sclerosis

	Biomarkers	Patients (*n*)	Outcome
Tintoré et al [64]	OCB IgG (CSF)	415 with CIS	Doubles the risk of a second episode, regardless of the findings in the MRI scan
Villar et al [65]	OCB IgM (CSF)	CIS	Shortens the time until a second episode
	OCB LS-IgM (CSF)	CIS	Advances the development of a second episode even more/strong relationship with the early appearance of a second relapse in MS
Villar et al [66]	KFLC (CSF)	25 with NIND, 78 with CIS	Advances conversion to MS
Brettschneider et al [67]	CXCL13 (CSF)	45 with CIS, 30 controls	High levels in patients with CIS that convert to MS
Khademi et al [68]	CXCL13 (LCR)	387 with MS, 79 with CIS, 357 with other neurological diseases, 14 healthy controls	High levels that predict conversion to CIS CXCL13 is associated with exacerbations of MS and unfavourable prognosis Does not appear to be MS specific
Piccio et al [69]	CXCL13 (CSF)	26	Levels in CSF diminish with rituximab
Sellebjerg et al [70]	CXCL13 (CSF)	15 with CIS, 27 with RRMS, 10 controls with NIND	Levels in CSF diminish with methylprednisolone and natalizumab
Romme Christensen et al [71]	MMP9 (CSF)	40 with PSMS, 21 with PPMS, 36 with RRMS, 21 with NIND	Increased levels in all the forms of MS, particularly during attacks
Fainardi et al [72]	MMP9 (CSF)	30 with Gd+ MS, 31 with Gd– MS	High levels in patients with Gd+ lesions
Szalardy et al [73]	Osteopontin (CSF)	75 with MS	Increased levels at the time of the attack, and correlates with the EDSS
Romme Christensen et al [74]	Osteopontin (CSF)	17 with progressive MS	Natalizumab reduces intrathecal levels
Van der Vuurst de Vries et al [75]	Soluble CD27 (CSF)	77 with CIS	High levels in CIS versus symptomatic controls, particularly in patients with conversion to MS Higher levels are associated with a shorter time until MS
Cantó et al [76]	CXCL13 (CSF)	800	Higher levels are associated with conversion to MS and a quicker development of disability
Burman et al [77]	CXCL13 (CSF)	62 with MS	Increased levels in attacks and in patients with more Gd+ lesions
Novakova et al [78]	CXCL13 (CSF)	43 with RRMS treated with fingolimod	Levels are modified with fingolimod
Komori et al [79]	CXCL13 (CSF)	40 with MS treated with daclizumab	Levels are modified with daclizumab
Stoop et al [80]	CHI3L1 (LCR)	28	Levels are modified with natalizumab

CIS: clinically isolated syndrome; CSF: cerebrospinal fluid; CXCL13: chemokine (C-X-C motif) ligand 13; EDSS: Expanded Disability Status Scale; KFLC: kappa free light chains; LS: lipid-specific; MMP9: matrix metallopeptidase-9; MRI: magnetic resonance imaging; MS: multiple sclerosis; NIND: non-inflammatory neurological disease; OCB: oligoclonal bands; PPMS: primary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: primary progressive multiple sclerosis.

and this expression is regulated by IL-23, IL-1b and IL-6, which are cytokines involved in autoimmune diseases of the CNS. It also responds to monoclonal antibodies and the Fab domain of the anti-DICAM antibody is currently undergoing humanisation for clinical trials [27].

Epidermal growth factor-like protein 7 (EGFL7) is a growth factor of the extracellular matrix that is expressed in the endothelium of the BBB, and protects its integrity. Knock-out EAE models for EGFL7 show a poorer progression, higher permeability of the BBB and greater cell infiltration. Treatment with recombinant EGFL7 promotes integrity of the BBB by anchoring CD4+ to the endothelium. This is yet another example of the complexity of the BBB that regulates the passage of cells to the CNS [28].

Table III. Neurodegeneration biomarkers identified in patients with multiple sclerosis.

	Biomarker	Patients (*n*)	Outcome
Rojas et al [81]	NfL (peripheral blood)	15 with PSP, 12 healthy controls Validation cohort: 147 with PSP	Increased levels in patients with the disease both at the baseline level and at one year of follow-up
Steinacker et al [82]	NfL (blood)	99 with primary progressive aphasias	The levels discriminate among different variants of aphasia
Steinacker et al [83]	NfL (blood)	42 with CJD, 55 controls with/without dementia	Increased levels in both sporadic and genetic CJD versus controls
Weydt et al [84]	NfL (blood and CSF)	76 with ALS	Significantly increased levels in symptomatic ALS versus mutation-carrying but asymptomatic relatives and versus non-carrier first-degree relatives
Disanto et al [85]	NfL (blood)	388 with MS, 254 healthy controls	Increased levels in MS, particularly in progressive forms Association regardless of levels of disability Gradation in relation to the number of T_2 and Gd+ lesions
Sormani [86]	NfL (blood)	Patients from the FREEDOMS study	Correlation at 24 months in T_2 (r = 0.45), cerebral atrophy (r = 0.41), in attacks (r = 0.25) and disability (HR = 1.7) Correlation with disability similar to the correlation with MRI Levels are reduced with fingolimod Candidate for use as an assessment variable in future phase II studies

ALS: amyotrophic lateral sclerosis; CJD: Creutzfeldt-Jakob disease; CSF: cerebrospinal fluid; HR: hazard ratio; MRI: magnetic resonance imaging; MS: multiple sclerosis; NfL: neurofilament light chain; PSP: progressive supranuclear palsy.

Integrin-α_8 is a new mediator of the migration of proinflammatory T lymphocytes across the BBB. Its main ligand, nephronectin, is a protein in the extracellular membrane that is expressed in endothelial cells in the BBB. Blockage of the binding site of α_8 diminishes Th1 and Th17, but not the migration of Th2 cells in an in vitro model of the BBB. Furthermore, injections of α_8-blocking peptide reduce the clinical severity and limit the infiltration of proinflammatory T lymphocytes in the CNS of EAE models [29].

In a murine model, the specific expression of the autoantigen haemagglutinin by the endothelial cells of the BBB activates antigen non-specific naïve TCD8 cells in vitro and in vivo, and induces their proliferation in vivo. The endothelial cells induce migration of antigen-specific cytotoxic TCD8 cells towards the CNS [30]. These findings underline the fact that the endothelial cells act as a sort of antigen-presenting cell and that they could be involved in infectious or inflammatory diseases of the CNS.

The factors secreted by the reactive astrocytes open the BBB by altering the endothelial tight junctions, but the mechanisms that control access across the glia limitans remain unknown. In inflammatory lesions a second barrier is induced in the glia limitans, consisting of reactive astrocytes that express claudin-1, claudin-4 and junctional adhesion molecule-A. In human co-cultures, the claudin-4 deficient astrocytes are unable to regulate the segregation of lymphocytes. In inflammatory models and models with MS, mice with deletion of the claudin-4 gene show exacerbated humoral and leukocytic infiltration [31]. For the first time, a second barrier inducible to the entrance of CNS at the level of the glia limitans is identified, which can be a therapeutic target in inflammatory diseases of the CNS.

Immune events within the CNS

The increase in CD4+ Th17 lymphocytes in the peripheral blood of patients with relapsing-remitting MS treated with natalizumab confirms the mechanism of action of the drug, that is, it blocks migration to the CNS [32]. This increase, however, does not appear to be related to disease relapse. Moreover, the CD11c+ antigen-presenting cells seem to play a safeguarding role in neuroinflammation; these CD11c+ cells are organised in perivascular groups and are a target for the T cells and strongly express proinflammatory cytokines. CD11c+ participate in the attraction of pathogenic T cells towards the CNS and in their survival; their depletion reduces the severity of the disease to a notable extent [33].

The direct action of Th17 on the neurons through the VCAM integrin activates potassium and calcium channels with the subsequent release of glutamate. In fact, the Th17 cells induce severe, localised and partially reversible fluctuations in the neuronal intracellular $Ca2^{+}$ concentration as an early sign of neuronal damage. These results highlight the key role of the effector phenotype of the Th17 cell in the neuronal dysfunction in chronic neuroinflammation [34].

Progressive multiple sclerosis and its relation to the recurring disease: how does neuroglial interaction underlie pathogenesis and treatment?

Glial cell and neuronal oxidative damage as the basis for the progression of the disease

Oxidative stress begins by means of the activated macrophages and microglial cells and augments through mitochondrial damage. In the very early stages of the inflammation changes are produced in the gene expression of the mitochondria towards an increase in the genes related to the production of oxygen reactive species. When mitochondrial damage occurs due to oxidative stress, the phenomenon expands and the number of mitochondria affected increases, which leads the cell to a state of greater vulnerability and the activation of apoptosis [35]. The neurons with mitochondrial deficiency are mainly found in cortical lesions and regions of the normal appearing grey matter, which is correlated with meningeal inflammation in MS [35].

As the individual gets older, the iron and ferritin deposits in the oligodendrocytes increase. In active lesions, the damaged oligodendrocytes release the iron deposits, cause microglial activation and perpetuate the cycle of the lesion by producing and stimulating more free radicals. Further knowledge of each stage of the cycle is helping in the design of new drugs.

Interactions of astrocytes with other glial cells and neurons in the development of progressive multiple sclerosis

Astrocytes are the most abundant cells in the CNS and are what provide the structural support for the grey matter. They also participate in the cohesion of the BBB and in intra- and extracellular homeostasis, as well as lending trophic support to neurons and oligodendrocytes, and playing a part in synaptogenesis, myelination and neurogenesis. There are differences in the patterns of expression of microRNA from one area of the brain to another, and also between the adult and the foetal brain [36]. The proinflammatory phenotype is especially harmful and is located in the innermost layers of the cortex and the white matter. The reactive astrocyte is activated by means of microglial cells through IL-1-α, tumour necrosis factor-α and C1q, which are currently being researched as possible therapeutic targets. The activated astrocyte loses its capacity to promote neuronal survival and takes on a neurotoxic function that will end up triggering neuronal death and that of the mature oligodendrocyte. Preclinical studies have shown that blockade of the activated astrocyte prevents neuronal death [37].

Glial cells as a therapeutic target for the progressive forms of the disease

Microglial cells form a resident group of cells in the CNS that, on becoming active, take on a macrophagic phenotype. In healthy controls, activated microglial cells in the normal appearing white matter increase with age. Inflammation and degeneration are also related to an increase in the activated microglial cells of the predominantly proinflammatory phenotype and to oxidative stress markers. They are also involved in the co-stimulation of T and B cells, in phagocytosis and in the presentation of antigens [38]. Many microglial cells with the inflammatory phenotype are present in active lesions while the number of those of the homeostatic phenotype diminishes. There is a steeply downward regulation of the genes associated with a homeostatic function of the microglial cells on the edge of the lesion and in the active centre of the lesion [38].

Imaging studies that combine positron emission tomography and 7T MRI show a greater enhancement of markers related to the activated microglial cells in areas where there is a lesion. Nevertheless, enhancement is diffuse in comparison to healthy controls and in different regions of the brain regardless of whether there are lesions present or not [39]. On comparing the number of immune cells from cerebrospinal fluid and their respective specific cellular soluble biomarkers between the progressive and recurring forms, surprisingly the number of intrathecal B and T cells is similar, although in the progressive forms they are preferably integrated within the tissue of the CNS [40]. The weak correlation between the active lesions in the MRI scan and the soluble markers of the cell surface suggests the absence of any rupture of the BBB and provides support for the phe-

nomenon of inflammation compartmentalisation. While such perivascular inflammation is infrequent, infiltration of T cells in brain tissue is usually present in progressive MS [40]. Meningeal inflammation also plays a role in the pathology of the progressive disease [41]. Cases of primary progressive MS with extensive meningeal lymphocyte infiltration display a more severe clinical course, with a shorter duration of the disease and death at an earlier age. Generalised diffuse inflammation of the meninges and the associated inflammatory medium in the subarachnoid compartment are involved in the pathogenesis of the cortical lesions of the grey matter [41].

Oligodendrocytes and oligodendrocyte precursor cells also exist in chronic lesions, although the number decreases with the time of disease progression. However, remyelination often fails, probably due to a lack of receptive axons [42]. The remyelination process is very heterogeneous depending on the patient and the form, although the general concept is that the primary progressive forms, and especially in the regions of the grey matter, are the ones that remyelinate the most.

With the development of drugs that are capable of crossing through to the CNS, of controlling activated microglial cells and free radicals, of promoting remyelination, and of reducing the T and B cells it would become possible to control the disease. Preclinical studies have shown that drugs that are potentially capable of inhibiting the microglial cells lower the severity of EAE, as is the case of laquinimod, hydroxychloroquine, dipyridamole or minocycline. The latest trial with minocycline in clinically isolated syndrome met the main objective of reducing the risk of conversion at six months versus placebo, but not at 24 months, although the assignation of patients to the different groups is questionable [43]. In EAE, the combination of minocycline with hydroxychloroquine shows synergic effects in the inhibition of microglial cells [44]. Remyelinating therapies represent a new direction and challenge in MS [45]. Domperidone, as a stimulant of the secretion of prolactin, and biotin with dual effects on remyelination or an increase in ATP synthesis in demyelinated axons are drugs currently under research [46].

Cerebral atrophy in clinical practice

The clinical relevance of brain volume measurements in multiple sclerosis

Cerebral atrophy occurs in MS from onset and progresses in a similar proportion in the different forms of the disease. Structures that are more susceptible to early atrophy, such as the thalamus, could be used to follow up disease progression; additionally, this could be considered a predictive factor of progression of the Expanded Disability Status Scale (EDSS) in the medium term, together with the volume of lesions in T_2. It should be remembered that measurements of brain volume are related to cognitive impairment in any of its domains, that is, both cortical atrophy and that of the deep structures of the grey matter.

Spinal atrophy, measured in 3 T MRI via the area of the upper cervical spinal cord, has proved to be useful for monitoring the progression of disability [47]. It can be measured in MRI scans of the cervical spinal cord and in the portion of the cervical spinal cord that is visible in MRI brain scans, with an excellent agreement between the two (absolute intraclass correlation index: 0.987) [48], which would result in reductions in the time needed to study a patient and the costs.

Value of the changes in brain volume to predict treatment response

Most of the drugs that have been approved in the last decade for the treatment of MS reduce cerebral atrophy, but in clinical trials. This measurement, however, may not be useful in the first year of treatment due to the pseudoatrophy effect, since many drugs, some of which have a strong anti-inflammatory effect such as natalizumab, give rise to a greater loss of brain volume in the first year of treatment. In clinical trials with natalizumab, this measurement does not reflect its protective effect in the development of cerebral atrophy until the third year [49]. A meta-analysis of 13 clinical trials with 13,500 patients evaluated whether the effect of drugs like fingolimod, cladribine, alemtuzumab and dimethyl fumarate in the progression of disability can be explained by their effect on cerebral atrophy [50]. The results show that 50% of the effect on disability can be explained by changes in brain volume and the figure rises to 75% if measurements of the lesions are added. That is, changes in brain volume improve the prediction of new lesions.

There is no clinically relevant threshold in clinical practice or at the individual level that allows its routine use. One study analysed the association between the loss of brain volume during the first year of treatment with interferon and the clinical outcomes at four years. The threshold identified and associated with greater EDSS progression in the fourth year was a loss of volume above 86%, with a

specificity of 65%, but with a low predictive positive value. As a result, many patients who lost brain volume above that figure remained stable. One of the explanations for this is the effect of pseudoatrophy, since the change in volume was measured in the first year of treatment [51]. Another study investigated the volume loss threshold that was useful in clinical practice by comparing the losses of volume among patients with MS and healthy controls during an average follow-up of seven years. A loss of volume above 0.4% up to 0.52% was shown to discriminate between patients and controls, with a specificity of 80-95% [52]. Whether or not this is useful in clinical practice has still to be determined.

Barriers to the use of brain volume in clinical practice

Heterogeneity in the measurement of brain volume, as a result of physiological variations, image acquisition or errors in readings, cannot be ruled out, as the changes that are measured in MS are not very large. For instance, variations in the level of hydration can lead to changes in the measurement of volume of up to 0.3% [53] and of 0.2% depending on the time of day at which the MRI scan was performed [54].

This variability could be resolved at the experimental and practical level. In sum, it is necessary to optimise image acquisition and interpretation, and to find standardised rates of atrophy that allow the use of this measurement in clinical practice.

New perspectives in neurobiology

How does the active brain stimulate repair?

Normal myelination of the CNS requires the formation of functionally mature oligodendrocytes from oligodendrocyte precursor cells. It is accepted, although the mechanisms are not fully understood, that oligodendrocytes preferably myelinate electrically active axons, that is to say, physiological myelination is dependent upon activity [55,56]. To evaluate whether remyelination is also a process dependent upon activity, an in vivo technique known as optogenetics is being used in murine models. This technique is a combination of optical and genetic methods for transferring the DNA that codes for several light-sensitive proteins of bacterial origin, called opsins, to a specific group of neurons. Their activation allows ions to cross the membrane, thereby producing activation or inhibition. This technique, which was considered technique of the year by the journal *Nature* in 2010 [57], entails the development of proteins and strategies for introducing the genes into target cells or tissues, thus resulting in their expression in some neurons but not in others.

The first step is to use a promoter to achieve the expression of the gene that codes for opsin, which uses a virus as a vehicle, and is introduced into a mouse. A fibre-optic cable is then attached to the animal to stimulate it with the appropriate wavelength; when stimulated, this ion channel opens, the ions flow and the cell is activated. In this murine model [58], a lesion is generated in the corpus callosum by injecting lysophosphatidylcholine to eliminate the myelin, but the axons are still alive and continue to express opsin within the lesion itself. In the mouse that is stimulated for three hours the number of oligodendrocyte precursor cells is significantly higher than in the control. Some days later, the number of differentiated oligodendrocytes and myelinated axons is also significantly higher. That is to say, neuronal activity induces proliferation and differentiation of oligodendrocyte precursor cells, as well as restoration of myelin during remyelination.

With a similar approach, another study evaluated whether there is evidence of adaptive myelination when a subgroup of axons in the CNS of healthy adults is stimulated, and whether it is limited to stimulated axons or also affects neighbouring axons. By means of a pharmacological model previously described elsewhere [59], a selective group of axons were stimulated to respond to clozapine-N-oxide instead of acetylcholine, resulting in a greater density of differentiated oligodendrocytes and a 70% increase in myelinated axons with respect to controls. The thickness of the myelin thus formed was greater in the active axons. This effect did not spread to the neighbouring axons but was, instead, specific to the stimulated axons. The authors concluded that the pharmacogenetic promotion of neuronal activity increases the proliferation of oligodendrocyte precursor cells, doubles the baseline rate of oligodendrocyte differentiation and confirms the preference for active axons in myelination, and that the myelin is thicker in active axons. Furthermore, the degree of activity and conduction blockade can have an impact upon remyelination in demyelinating diseases.

Can brain stimulation influence repair of the CNS?

A damaged CNS modifies its structure and function by means of changes in behaviour, including changes in rehabilitation or motor patterns. The question

therefore arises as to whether non-invasive brain stimulation, by means of simple repetitive magnetic stimulation or direct transcranial stimulation, could serve as an adjunct to rehabilitation. Although there are different techniques, they both have effects on the induction of synaptic plasticity, the production of neurotrophic factors, mainly brain-derived neurotrophic factor, gene expression and the modulation of levels of neurotransmitters [60]. Both of them have been approved by the US FDA for the treatment or other pathologies, but in MS the data published to date on their benefits in spasticity, working memory, fatigue and cognitive alterations are not conclusive [61-63].

Combining physical therapy and non-invasive brain stimulation can have synergic effects. Indeed, brain stimulation can prepare cortical excitability for a subsequent motor training task, thereby optimising the processes that are involved in standard rehabilitation therapies. Nevertheless, aspects such as the moment of application, the stimulation parameters, etc. are in need of further clarification. In addition, the outcomes can be task-dependent, hence the need for further preclinical and phase III studies.

Final observations

The most significant piece of data from the new diagnostic criteria is that oligoclonal bands satisfy the dissemination in time criteria, as they were not taken into account in the 2010 criteria, except in the primary progressive forms. The main problems of the diagnostic errors in MS include MRI and atypical symptoms. Yet the lack of a standard for complementary tests that are carried out systematically, over and beyond the value of the clinical features, leads the clinician to rely more on what can be explained and seen in the patient for guidance. The diagnostic error figures can also be explained by the exclusion of cerebrospinal fluid from the studies needed to diagnose MS. Cerebrospinal fluid is, however, fundamental and will be incorporated if the new diagnostic criteria are accepted.

As regards biomarkers, blood will possibly replace cerebrospinal fluid as a biological sample for quantifying the levels of neurofilament light chain and it seems clear that, in addition to measurements of inflammation, atrophy can also be used to predict therapeutic response. No clear-cut decision has been made regarding measurement of overall or regional brain volume, although experience to date uses measurement of overall brain volume. This is what will have to be implemented in clinical practice provided that thresholds are identified that make it possible to assess a suboptimal response to a drug or simply a progression.

References

1. Brownlee WJ, Hardy TA, Fazekas F, Miller DH. Diagnosis of multiple sclerosis: progress and challenges. Lancet 2017; 389: 1336-46.
2. Masjuán J, Álvarez-Cermeño JC, García-Barragán N, Díaz-Sánchez M, Espino M, Sádaba MC, et al. Clinically isolated syndromes: a new oligoclonal band test accurately predicts conversion to MS. Neurology 2006; 66: 576-8.
3. Rolak LA, Fleming JO. The differential diagnosis of multiple sclerosis. Neurologist 2007; 13: 57-72.
4. Preziosa P, Rocca MA, Mesaros S, Meani A, Montalban X, Drulovic J, et al. Diagnosis of multiple sclerosis: a multicentre study to compare revised McDonald-2010 and Filippi-2010 criteria: J Neurol Neurosurg Psychiatry 2018; 89: 316-8.
5. Solomon AJ, Klein EP, Bourdette D. 'Undiagnosing' multiple sclerosis: the challenge of misdiagnosis in MS. Neurology 2012; 78: 1986-91.
6. Solomon AJ, Bourdette DN, Cross AH, Applebee A, Skidd PM, Howard DB, et al. The contemporary spectrum of multiple sclerosis misdiagnosis: a multicenter study. Neurology 2016; 87: 1393-9.
7. Okuda DT, Mowry EM, Beheshtian A, Waubant E, Baranzini SE, Goodin DS, et al. Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. Neurology 2009; 72: 800-5.
8. Reindl M, Jarius S, Rostasy K, Berger T. Myelin oligodendrocyte glycoprotein antibodies: How clinically useful are they? Curr Opin Neurol 2017; 30: 295-301.
9. Jurynczyk M, Geraldes R, Probert F, Woodhall MR, Waters P, Tackley G, et al. Distinct brain imaging characteristics of autoantibody-mediated CNS conditions and multiple sclerosis. Brain 2017; 140: 617-27.
10. Sepúlveda M, Solá-Valls N, Escudero D, Rojc B, Barón M, Hernández-Echebarría L, et al. Clinical profile of patients with paraneoplastic neuromyelitis optica spectrum disorder and aquaporin-4 antibodies. Mult Scler 2017; Sep 1. [Epub ahead of print].
11. Huss AM, Halbgebauer S, Ockl P, Trebst C, Spreer A, Borisow N, et al. Importance of cerebrospinal fluid analysis in the era of McDonald 2010 criteria: a German-Austrian retrospective multicenter study in patients with a clinically isolated syndrome. J Neurol 2016; 263: 2499-504.
12. Tintoré M, Rovira A, Río J, Otero-Romero S, Arrambide G, Tur C, et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain 2015; 138: 1863-74.
13. Filippi M, Rocca MA, Ciccarelli O, De Stefano N, Evangelou N, Kappos L, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol 2016; 15: 292-303.
14. International Multiple Sclerosis Genetics Consortium. The multiple sclerosis genomic map: role of peripheral immune cells and resident microglia in susceptibility. BioRxiv 2017; Jul 13. doi: https: //doi.org/10.1101/143933.
15. Ooi JD, Petersen J, Tan YH, Huynh M, Willett ZJ, Ramarathinam SH, et al. Dominant protection from HLA-linked autoimmunity by antigen-specific regulatory T cells. Nature 2017; 545: 243-7.
16. Couturier N, Bucciarelli F, Nurtdinov RN, Debouverie M, Lebrun-Frenay C, Defer G, et al. Tyrosine kinase 2 variant influences T lymphocyte polarization and multiple sclerosis susceptibility. Brain 2011; 134: 693-703.
17. Steri M, Orru V, Idda ML, Pitzalis M, Pala M, Zara I, et al. Overexpression of the cytokine BAFF and autoimmunity risk. N Engl J Med 2017; 376: 1615-26.
18. Stienne C, Michieletto MF, Benamar M, Carrie N, Bernard I, Nguyen XH, et al. Foxo3 Transcription factor drives pathogenic

T helper 1 differentiation by inducing the expression of Eomes. Immunity 2016; 45: 774-87.
19. Raveney BJ, Oki S, Hohjoh H, Nakamura M, Sato W, Murata M, et al. Eomesodermin-expressing T-helper cells are essential for chronic neuroinflammation. Nat Commun 2015; 6: 8437.
20. Fan X, Jin T, Zhao S, Liu C, Han J, Jiang X, et al. Circulating CCR7+ICOS+ memory T follicular helper cells in patients with multiple sclerosis. PLoS One 2015; 10: e0134523.
21. Romme Christensen J, Bornsen L, Ratzer R, Piehl F, Khademi M, Olsson T, et al. Systemic inflammation in progressive multiple sclerosis involves follicular T-helper, Th17- and activated B-cells and correlates with progression. PLoS One 2013; 8: e57820.
22. Tzartos JS, Friese MA, Craner MJ, Palace J, Newcombe J, Esiri MM, et al. Interleukin-17 production in central nervous system-infiltrating T cells and glial cells is associated with active disease in multiple sclerosis. Am J Pathol 2008; 172: 146-55.
23. Wu C, Yosef N, Thalhamer T, Zhu C, Xiao S, Kishi Y, et al. Induction of pathogenic TH17 cells by inducible salt-sensing kinase SGK1. Nature 2013; 496: 513-7.
24. Farez MF, Mascanfroni ID, Méndez-Huergo SP, Yeste A, Murugaiyan G, Garo LP, et al. Melatonin contributes to the seasonality of multiple sclerosis relapses. Cell 2015; 162: 1338-52.
25. Berer K, Gerdes LA, Cekanaviciute E, Jia X, Xiao L, Xia Z, et al. Gut microbiota from multiple sclerosis patients enables spontaneous autoimmune encephalomyelitis in mice. Proc Natl Acad Sci U S A 2017; 114: 10719-24.
26. Álvarez JI, Saint-Laurent O, Godschalk A, Terouz S, Briels C, Larouche S, et al. Focal disturbances in the blood-brain barrier are associated with formation of neuroinflammatory lesions. Neurobiol Dis 2015; 74: 14-24.
27. Prat A. Blood brain barrier adhesion molecules as therapeutic targets in MS. ECTRIMS 2017; Paris, France.
28. Larochelle C. EGFL7: a novel player in multiple sclerosis implicated in CNS infiltration. ECTRIMS 2017; Paris, France.
29. Gowing E. Integrin alpha8 is a novel mediator of proinflammatory T lymphocyte migration across the CNS barriers. ECTRIMS 2017; Paris, France.
30. Meyer C. Antigen expression by endothelial cells of the blood brain barrier elicits activation and pathogenicity of CD8 T cells in the central nervous system. ECTRIMS 2017; Paris, France.
31. Chapouly C. Astrocytic tight junctions control inflammatory CNS lesion pathogenesis. ECTRIMS 2017; Paris, France.
32. Buhler U, Fleischer V, Luessi F, Rezk A, Belikan P, Graetz C, et al. Role of IL-17-producing lymphocytes in severity of multiple sclerosis upon natalizumab treatment. Mult Scler 2017; 23: 567-76.
33. Paterka M, Siffrin V, Voss JO, Werr J, Hoppmann N, Gollan R, et al. Gatekeeper role of brain antigen-presenting CD11c+ cells in neuroinflammation. Embo J 2016; 35: 89-101.
34. Siffrin V, Radbruch H, Glumm R, Niesner R, Paterka M, Herz J, et al. In vivo imaging of partially reversible th17 cell-induced neuronal dysfunction in the course of encephalomyelitis. Immunity 2010; 33: 424-36.
35. Campbell GR, Ziabreva I, Reeve AK, Krishnan KJ, Reynolds R, Howell O, et al. Mitochondrial DNA deletions and neurodegeneration in multiple sclerosis. Ann Neurol 2011; 69: 481-92.
36. Rao VT, Ludwin SK, Fuh SC, Sawaya R, Moore CS, Ho MK, et al. MicroRNA expression patterns in human astrocytes in relation to anatomical location and age. J Neuropathol Exp Neurol 2016; 75: 156-66.
37. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. Nature 2017; 541: 481-7.
38. Zrzavy T, Hametner S, Wimmer I, Butovsky O, Weiner HL, Lassmann H. Loss of 'homeostatic' microglia and patterns of their activation in active multiple sclerosis. Brain 2017; 140: 1900-13.
39. Herranz E, Gianni C, Louapre C, Treaba CA, Govindarajan ST, Ouellette R, et al. Neuroinflammatory component of gray matter pathology in multiple sclerosis. Ann Neurol 2016; 80: 776-90.
40. Komori M, Blake A, Greenwood M, Lin YC, Kosa P, Ghazali D, et al. Cerebrospinal fluid markers reveal intrathecal inflammation in progressive multiple sclerosis. Ann Neurol 2015; 78: 3-20.
41. Choi SR, Howell OW, Carassiti D, Magliozzi R, Gveric D, Muraro PA, et al. Meningeal inflammation plays a role in the pathology of primary progressive multiple sclerosis. Brain 2012; 135: 2925-37.
42. Chang A, Tourtellotte WW, Rudick R, Trapp BD. Premyelinating oligodendrocytes in chronic lesions of multiple sclerosis. N Engl J Med 2002; 346: 165-73.
43. Metz LM, Eliasziw M. Trial of minocycline in clinically isolated syndrome of multiple sclerosis. N Engl J Med 2017; 377: 789.
44. Faissner S, Mahjoub Y, Mishra M, Haupeltshofer S, Hahn JN, Gold R, et al. Unexpected additive effects of minocycline and hydroxychloroquine in models of multiple sclerosis: prospective combination treatment for progressive disease? Mult Scler 2017; Aug 1. [Epub ahead of print].
45. Plemel JR, Liu WQ, Yong VW. Remyelination therapies: a new direction and challenge in multiple sclerosis. Nat Rev Drug Discov 2017; 16: 617-34.
46. Sedel F, Bernard D, Mock DM, Tourbah A. Targeting demyelination and virtual hypoxia with high-dose biotin as a treatment for progressive multiple sclerosis. Neuropharmacology 2016; 110: 644-53.
47. Daams M, Weiler F, Steenwijk MD, Hahn HK, Geurts JJ, Vrenken H, et al. Mean upper cervical cord area (MUCCA) measurement in long-standing multiple sclerosis: relation to brain findings and clinical disability. Mult Scler 2014; 20: 1860-5.
48. Liu Y, Lukas C, Steenwijk MD, Daams M, Versteeg A, Duan Y, et al. Multicenter validation of mean upper cervical cord area measurements from head 3D T1-weighted MR imaging in patients with multiple sclerosis. AJNR Am J Neuroradiol 2016; 37: 749-54.
49. Sastre-Garriga J, Tur C, Pareto D, Vidal-Jordana A, Auger C, Río J, et al. Brain atrophy in natalizumab-treated patients: a 3-year follow-up. Mult Scler 2015; 21: 749-56.
50. Sormani MP, Arnold DL, De Stefano N. Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. Ann Neurol 2014; 75: 43-9.
51. Pérez-Miralles FC, Sastre-Garriga J, Vidal-Jordana A, Río J, Auger C, Pareto D, et al. Predictive value of early brain atrophy on response in patients treated with interferon beta. Neurol Neuroimmunol Neuroinflamm 2015; 2: e132.
52. De Stefano N, Stromillo ML, Giorgio A, Bartolozzi ML, Battaglini M, Baldini M, et al. Establishing pathological cut-offs of brain atrophy rates in multiple sclerosis. J Neurol Neurosurg Psychiatry 2016; 87: 93-9.
53. De Stefano N, Silva DG, Barnett MH. Effect of fingolimod on brain volume loss in patients with multiple sclerosis. CNS Drugs 2017; 31: 289-305.
54. Nakamura K, Brown RA, Narayanan S, Collins DL, Arnold DL. Diurnal fluctuations in brain volume: statistical analyses of MRI from large populations. Neuroimage 2015; 118: 126-32.
55. Hines JH, Ravanelli AM, Schwindt R, Scott EK, Appel B. Neuronal activity biases axon selection for myelination in vivo. Nat Neurosci 2015; 18: 683-9.
56. Wake H, Ortiz FC, Woo DH, Lee PR, Angulo MC, Fields RD. Nonsynaptic junctions on myelinating glia promote preferential myelination of electrically active axons. Nat Commun 2015; 6: 7844.
57. Lee JH, Durand R, Gradinaru V, Zhang F, Goshen I, Kim DS, et al. Global and local fMRI signals driven by neurons defined optogenetically by type and wiring. Nature 2010; 465: 788-92.
58. Herman AM, Huang L, Murphey DK, Garcia I, Arenkiel BR. Cell type-specific and time-dependent light exposure contribute to silencing in neurons expressing channelrhodopsin-2. Elife 2014; 3: 28.
59. Armbruster BN, Li X, Pausch MH, Herlitze S, Roth BL. Evolving the lock to fit the key to create a family of G protein-coupled receptors potently activated by an inert ligand. Proc Natl Acad Sci U S A 2007; 104: 5163-8.
60. Bolognini N, Pascual-Leone A, Fregni F. Using non-invasive brain stimulation to augment motor training-induced plasticity. J Neuroeng Rehabil 2009; 6: 8.
61. Hulst HE, Goldschmidt T, Nitsche MA, De Wit SJ, Van den Heuvel OA, Barkhof F, et al. rTMS affects working memory

performance, brain activation and functional connectivity in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 2017; 88: 386-94.
62. Iodice R, Dubbioso R, Ruggiero L, Santoro L, Manganelli F. Anodal transcranial direct current stimulation of motor cortex does not ameliorate spasticity in multiple sclerosis. Restor Neurol Neurosci 2015; 33: 487-92.
63. Lefaucheur JP, Chalah MA, Mhalla A, Palm U, Ayache SS, Mylius V. The treatment of fatigue by non-invasive brain stimulation. Neurophysiol Clin 2017; 47: 173-84.
64. Tintoré M, Rovira A, Río J, Tur C, Pelayo R, Nos C, et al. Do oligoclonal bands add information to MRI in first attacks of multiple sclerosis? Neurology 2008; 70: 1079-83.
65. Villar LM, Sadaba MC, Roldán E, Masjuán J, González-Porqué P, Villarrubia N, et al. Intrathecal synthesis of oligoclonal IgM against myelin lipids predicts an aggressive disease course in MS. J Clin Invest 2005; 115: 187-94.
66. Villar LM, Espino M, Costa-Frossard L, Muriel A, Jiménez J, Álvarez-Cermeño JC. High levels of cerebrospinal fluid free kappa chains predict conversion to multiple sclerosis. Clin Chim Acta 2012; 413: 1813-6.
67. Brettschneider J, Czerwoniak A, Senel M, Fang L, Kassubek J, Pinkhardt E, et al. The chemokine CXCL13 is a prognostic marker in clinically isolated syndrome (CIS). PLoS One 2010; 5: 0011986.
68. Khademi M, Kockum I, Andersson ML, Iacobaeus E, Brundin L, Sellebjerg F, et al. Cerebrospinal fluid CXCL13 in multiple sclerosis: a suggestive prognostic marker for the disease course. Mult Scler 2011; 17: 335-43.
69. Piccio L, Naismith RT, Trinkaus K, Klein RS, Parks BJ, Lyons JA, et al. Changes in B- and T-lymphocyte and chemokine levels with rituximab treatment in multiple sclerosis. Arch Neurol 2010; 67: 707-14.
70. Sellebjerg F, Bornsen L, Khademi M, Krakauer M, Olsson T, Frederiksen JL, et al. Increased cerebrospinal fluid concentrations of the chemokine CXCL13 in active MS. Neurology 2009; 73: 2003-10.
71. Romme Christensen J, Bornsen L, Khademi M, Olsson T, Jensen PE, Sorensen PS, et al. CSF inflammation and axonal damage are increased and correlate in progressive multiple sclerosis. Mult Scler 2013; 19: 877-84.
72. Fainardi E, Castellazzi M, Bellini T, Manfrinato MC, Baldi E, Casetta I, et al. Cerebrospinal fluid and serum levels and intrathecal production of active matrix metalloproteinase-9 (MMP-9) as markers of disease activity in patients with multiple sclerosis. Mult Scler 2006; 12: 294-301.
73. Szalardy L, Zadori D, Simu M, Bencsik K, Vecsei L, Klivenyi P. Evaluating biomarkers of neuronal degeneration and neuro-inflammation in CSF of patients with multiple sclerosis-osteopontin as a potential marker of clinical severity. J Neurol Sci 2013; 331: 38-42.
74. Romme Christensen J, Ratzer R, Bornsen L, Lyksborg M, Garde E, Dyrby TB, et al. Natalizumab in progressive MS: results of an open-label, phase 2A, proof-of-concept trial. Neurology 2014; 82: 1499-507.
75. Van der Vuurst de Vries RM, Mescheriakova JY, Runia TF, Jafari N, Siepman TA, Hintzen RQ. Soluble CD27 levels in cerebrospinal fluid as a prognostic biomarker in clinically isolated syndrome. JAMA Neurol 2017; 74: 286-92.
76. Cantó E, Tintoré M, Villar LM, Costa C, Nurtdinov R, Álvarez-Cermeño JC, et al. Chitinase 3-like 1: prognostic biomarker in clinically isolated syndromes. Brain 2015; 138: 918-31.
77. Burman J, Raininko R, Blennow K, Zetterberg H, Axelsson M, Malmestrom C. YKL-40 is a CSF biomarker of intrathecal inflammation in secondary progressive multiple sclerosis. J Neuroimmunol 2016; 292: 52-7.
78. Novakova L, Axelsson M, Khademi M, Zetterberg H, Blennow K, Malmestrom C, et al. Cerebrospinal fluid biomarkers of inflammation and degeneration as measures of fingolimod efficacy in multiple sclerosis. Mult Scler 2017; 23: 62-71.
79. Komori M, Kosa P, Stein J, Zhao V, Blake A, Cherup J, et al. Pharmacodynamic effects of daclizumab in the intrathecal compartment. Ann Clin Transl Neurol 2017; 4: 478-90.
80. Stoop MP, Singh V, Stingl C, Martin R, Khademi M, Olsson T, et al. Effects of natalizumab treatment on the cerebrospinal fluid proteome of multiple sclerosis patients. J Proteome Res 2013; 12: 1101-7.
81. Rojas JC, Karydas A, Bang J, Tsai RM, Blennow K, Liman V, et al. Plasma neurofilament light chain predicts progression in progressive supranuclear palsy. Ann Clin Transl Neurol 2016; 3: 216-25.
82. Steinacker P, Semler E, Anderl-Straub S, Diehl-Schmid J, Schroeter ML, Uttner I, et al. Neurofilament as a blood marker for diagnosis and monitoring of primary progressive aphasias. Neurology 2017; 88: 961-9.
83. Steinacker P, Blennow K, Halbgebauer S, Shi S, Ruf V, Oeckl P, et al. Neurofilaments in blood and CSF for diagnosis and prediction of onset in Creutzfeldt-Jakob disease. Sci Rep 2016; 6: 38737.
84. Weydt P, Oeckl P, Huss A, Muller K, Volk AE, Kuhle J, et al. Neurofilament levels as biomarkers in asymptomatic and symptomatic familial amyotrophic lateral sclerosis. Ann Neurol 2016; 79: 152-8.
85. Disanto G, Barro C, Benkert P, Naegelin Y, Schadelin S, Giardiello A, et al. Serum neurofilament light: a biomarker of neuronal damage in multiple sclerosis. Ann Neurol 2017; 81: 857-70.
86. Sormani MP. Blood NfL as a potential endpoint in phase 2 clinical studies in relapsing-remitting multiple sclerosis. ECTRIMS 2017; Paris, France.

Revisión de las novedades del Congreso ECTRIMS 2017, presentadas en la X Reunión Post-ECTRIMS (I)

Resumen. La reunión Post-ECTRIMS es una reunión emblemática en el ámbito de la esclerosis múltiple en España, con el claro objetivo de analizar, de la mano de reconocidos neurólogos especialistas nacionales, los principales avances en esclerosis múltiple y revisar los temas más importantes del congreso ECTRIMS. En noviembre de 2017, la reunión Post-ECTRIMS celebró su décima edición, y se ha consolidado como un importante foro de encuentro de expertos en nuestro país para favorecer la comunicación, establecer sinergias, y promover y potenciar la investigación para mejorar, en última instancia, el pronóstico y la calidad de vida de los pacientes con esclerosis múltiple. En esta primera parte se avanza la publicación de las nuevas guías clínicas europea y americana para el uso de los tratamientos modificadores de la enfermedad, y los nuevos criterios diagnósticos. Se discuten las estrategias para el seguimiento de los pacientes tratados con terapias modificadoras de la enfermedad, se revisan la atrofia cerebral y los biomarcadores de neurodegeneración y neuroinflamación, y se analiza el papel de la neuroglía en la patogenia y el tratamiento. Se hace un recorrido por la historia natural de la enfermedad, con la evidencia que aportan los registros, y nos adelantamos al futuro gracias a los avances en genética e inmunología.

Palabras clave. ECTRIMS. Esclerosis múltiple. Post-ECTRIMS.