Review of the novelties presented at the XXVI Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) (I)

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Summary. The new insights presented at European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), held in the city of Gothenburg, Sweden, in October 2010, have been summarized at the third edition of Post-ECTRIMS meeting held in Madrid in November 2010. The age is an important factor related to the course and prognosis of multiple sclerosis (MS). The evolution to progressive disease persists more than 50 years after diagnosis of MS and a reduction in the delay of diagnosis has been detected. Several strategies have been proposed in order to improve the efficacy of magnetic resonance regarding prognosis and course of disease. The studies presented at the Congress reflect the influence of gender on course and severity of disease symptoms, showing an increase of worldwide prevalence of MS in women. Neuroprotective action of estrogen receptor beta has been reported. The genome wide association studies have allowed investigators to identify numerous susceptible alleles. In this regard, HLA class II genes, seems to contribute to genetic risk for developing neutralizing antibodies against beta-interferon. Vitamin D deficiency and Epstein-Barr virus have been highlighted as risk factors for MS in the reported findings. On the subject of the ongoing controversy regarding the role of inflammation and degeneration in MS, several arguments have been found to support the role of CNS autoimmunity to explain the presence of inflammatory phenomenon. The available data hold the potential therapeutic role of mesenchymal cells given the involvement of these stem cells in CNS repair.

Key words. Diagnosis. ECTRIMS. Genetics. Multiple sclerosis. Progression.

Introduction

The Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) is the most important international congress for this pathology.

The third edition of the Post-ECTRIMS meeting, held in Madrid, has the objective of summarising the most outstanding data presented at the XXVI Congress of the ECTRIMS, which was held in October 2010 in the Swedish city of Gothenburg. The congress was attended by over 6,500 multiple sclerosis (MS) professionals.

At this event, which had the scientific endorsement of the Spanish Society of Neurology for the second consecutive year, twenty speakers, all specialists in MS, presented new findings. We ultimately aim to institutionalise this meeting because of its clear scientific focus and interest for the MS community, as well as to consolidate a network of MS experts.

This document has the main goal of documenting the most relevant data presented at the 2010 ECTRIMS, where different issues related to the natural course of the disease were presented and discussed, as well as infections related to the aetiopathogenesis of MS, advances in the description of biomarkers, and new treatment strategies and the risk-benefit relationships of these strategies. In addition, the advancement of therapies used for the management of symptoms that significantly affect quality of life were highlighted.

The natural course of multiple sclerosis

The majority of the patients who initially present with relapsing-remitting MS transition into secondary progressive MS. Normally, this transition occurs at a rate of 2 to 3% per year, with a median transition time of 19 years.

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Relapses occur in approximately 40% of cases during the secondary progressive stage of the disease. Such relapses minimally contribute to the accumulation of irreversible disability. The mean lengths of time to reach the irreversible levels of 4, 6, and 7 on the *Expanded Disability Status Scale* (EDSS) are 8, 20, and 30 years, respectively.

The beginning of the relapsing-remitting stage of the disease (whether followed by secondary progression or not), the beginning of the progressive stage (whether primary or secondary) and the appearance of irreversible levels of disability essentially depend on age.

MS is a disease with different categories of clinical phenotypes. In this context, the idea of the complexity of the disease prevails over the idea of the true heterogeneity of the disease. Several Japanese MS experts believe that the phenotype of the disease has changed in Japan, arguing that there are two different MS phenotypes in Asian patients: optico-spinal MS (OSMS) and conventional MS (CMS). The most recent national survey conducted in Japan showed a fourfold increase in the estimated number of patients with clinically definite MS (CDMS) in 2003 compared to 1972 and a change in the mean age of the onset of the disease from 30 years in 1989 to 20 years in 2003. The anticipated age of onset is present in patients without medullary lesions (LESCLs–) independently of the CMS or OSMS phenotype, but not in those with medullary lesions (LESCLs+). Additionally, a proportional decrease in optico-spinal affection is observed in patients with CDMS, and a north-south gradient is important for the CMS/OSMS relationship in that northern residents show a higher frequency of cerebral lesions based on the Barkhof criteria than do residents from the south.

Patients with MS are characterised by extreme variability in the course and prognosis of the disease. As a result, the spectrum of the disease ranges from silent cases to fatal forms with acute demyelination. Therefore, exact prognostic predictions for any individual patient are impossible.

Charcot described 'frustrated forms' of MS, such as the truly benign sclerosis, which has been observed in the last few decades, although it has not been strictly demonstrated. After onset, this form varies with regard to clinical and radiological characteristics that are described. An unbiased incidence cohort in which almost all of the patients reside within a well-defined geographical area and are evaluated within a well-defined period of time is essential for the epidemiological analysis of MS. Such a cohort should be used as the basis for a longitudinal follow-up without withdrawal or bias.

A cohort of 307 patients from Gothenburg with the most benign form of MS whose onset began during the period of 1950 to 1964 were analysed in a longitudinal study with 50 years of follow-up. Of the total cohort, 202 patients, excluding those with clinically isolated syndrome (CIS) and the primary progressive form of MS, presented an initial diagnosis of relapsing-remitting MS (RRMS) based on the Poser criteria. In this cohort, the probability of remaining benign (without progression) 45 years after onset was 18%. In the most recent follow-up of the patients with RRMS (2009-2020), three patients had converted to the secondary progressive stage, two had died, thirteen had no disease progression, nine had RRMS disability scores of 0 to 2.5, and four showed residual damage from exacerbations suffered in previous decades, presenting with disability scores of 3 to 3.5 (EDSS).

Magnetic resonance images (MRI) met the Barkhof criteria in 10/11 patients, with a predominance of an absence of lesions at the periventricular region and the corpus callosum. However, some subcortical lesions and the presence of lesions at the callosomarginal region extending from the inferior medial face of the corpus callosum were present in almost all of the cases, except in two patients.

Five decades after the appearance of MS, approximately 10% of the patients with MS in this essentially unbiased cohort had minimal neurological and neuro-psychiatric disabilities, despite the presence of neuro-radiological signs of MS lesions.

Given the current scenario, the question has been raised of whether the currently available immunomodulators could delay progression of the disease to the secondary progressive stage (SPMS). However, it would be unrealistic and unethical to test this hypothesis in the long term with randomised studies. On the other hand, the use of historical controls could lead to erroneous results, making it necessary to develop new techniques for adequately using historical data. For example, in Sweden, a method for the use of natural history data has been developed with its own predictors.

The time from the onset of symptoms to the definitive diagnosis of MS depends on many factors, such as the time that it takes for patients to become aware of their symptoms and to then contact their primary care providers, the time taken for a referral to be made to a specialised MS unit, and the time required for the final diagnosis.

A Danish MS registry has been generated, which contains all of the diagnosed cases of MS between 1965 and 2004. In this registry, the diagnostic delay has been defined as the difference between the year

in which the patient first became aware of MS symptoms and the year of the diagnosis [1]. The results showed a decrease, albeit a moderate one, in the diagnostic delay during the period from 1965 to 2004. In certain cases, the use of the McDonald criteria allows for a CDMS diagnosis only after an exacerbation, which, along with the generalised use of MRI in the following years, could reduce the time until diagnosis. The time from the patient's awareness of symptoms to the time of contact with a primary care provider may have also been reduced as a result of greater knowledge of the disease among the population.

The work presented by Dr. H. Butzkueven [2] validates the use of MRI and the analysis of cerebrospinal fluid (CSF) as predictors of the time to relapse following CIS (Clinicaly Isolated Syndrome) in neurological practice. The significant predictors in this study were the following: the presence of at least one gadolinium-enhancing lesion (Gd+), 3-8 or > 9 T_2 lesions, the presence of oligoclonal bands, and the presence of at least one T_2 spinal lesion. The presence of infratentorial subcortical U-fibres or periventricular lesions were not predictive of the time to relapse in a multivariate analysis.

Gender and multiple sclerosis

With respect to the implication of gender in MS, it has been observed that women are more susceptible than men, although a reduction in the activity of the disease during pregnancy has been reported. Therefore, there seems be a gender influence over the course and severity of the disease, with MS being more frequent in women at a proportion of 4:1, whereas in men, the course of MS is more severe, and primary progressive MS is most frequent. A general increase in the percentage of women with MS has been confirmed in the past three decades, especially in geographical areas located in the northern latitudes (60 to 45° N) and for relapsing-remitting MS.

An example of how gender and sexual hormones influence the disease is represented by the trends observed during gestation; a noticeable reduction in relapses has been observed, especially during the third trimester of pregnancy, when oestrogen levels increase the most [3].

In relation to the function of sex hormones in models of experimental autoimmune encephalomyelitis (EAE), two published animal studies stand out. In the first, it was reported that sex hormones modulate the expression, severity, and course of EAE. Oestrogens act through α and β receptors. The exogenous administration of α receptor ligands has effects in the early phase of EAE, preventing inflammatory infiltration of the central nervous system (CNS) and microglial activation [4]. Another published study has revealed that the exogenous administration of ligands for oestrogen receptor β exerts its effects in the late phase of EAE, such that certain ligands act as neuroprotectors by activating remyelination [5].

In this scenario, sex hormones could be used as anti-inflammatory and neuroprotective agents in the treatment of MS, especially the ligands for oestrogen receptor β, considering that they obviate the risk of breast and uterine cancer mediated by the oestrogen α receptor.

Several controversies exist with respect to whether the prevalence and incidence of MS are increasing worldwide, if the percentage of affected women is increasing, and if a north-south difference is still present. Furthermore, the implications of previous findings and the lines of research that should be pursued in the future continue to be the subject of debate.

A number of speculative ideas have been proposed, such as the notion that changes are not likely to be related to genetic factors, given that their effects are slow. On the other hand, there could be an increase in the frequency of exposure in women or the existence of new risk factors that affect women. In addition, a decreased exposure to protective factors has been observed, given that there are currently fewer pregnancies overall, more pregnancies later in life, less sun exposure during infancy, and fewer parasitic infections [6,7]. Thus, it is necessary to continue investigating the causes for these findings through epidemiological studies with appropriate designs.

Dr. G. Graziano [8] presented a registry that included 15,322 patients in October 2010 (MSBase). His objectives were to study the significance of birth year as a predictor of the proportion of men and women affected by MS in different geographical areas around the world over a period of 60 years and to compare the distribution and trends in gender proportions throughout the 60-year-period amongst different geographical areas. The results reflect a global increase in the proportion of women among patients with MS that is more accentuated in northern countries. From the data presented, it can be concluded that there is a need for case-control studies to identify environmental factors and lifestyle changes in women, such as exposure to sunlight, age at the time of pregnancies, dietary changes, tobacco

use, and contraceptive use, that could contribute to the increase in incidence seen in some countries.

Genetics in multiple sclerosis

Dr. L. Fugger presented a study, using humanised mouse models, of the interactions between class I and class II genes of the major histocompatibility (HLA) complex expressed in T cells isolated based on their reactions with myelin basic protein in patients with MS HLA+. This study included the interaction between HLA-DR2a (DRB5*0101) and HLA-DR2b (DRB1*1501). The results showed that mice that expressed HLA-DR2 followed a more aggressive disease course, similar to the primary progressive forms of MS. In contrast, mice that expressed HLA-DR2b followed a more benign disease course similar to that of patients with RRMS.

A possible explanation for these phenotypes could be that the HLA-DR2b antigen-presenting cells (APCs) activate the immune response, giving rise to a more aggressive phenotype. On the other hand, the interaction between HLA-DR2a and HLA DR2b would produce a more benign phenotype due to the elimination of pathogenic T cells by activation-induced cell death. Therefore, the results represent an example of an epistatic interaction between two genes in which *HLA-DR2a* acts as a modifier of the actions of *HLA-DR2b.*

The results presented by Dr. L. Fugger also addressed the interactions between the class I HLA genes. In MS, the HLA-A*0201 allele is considered protective against MS (RR=0.6), while the HLA-A*0301 allele confers an increased risk for the disease. It was observed that transgenic mice for HLA-A*0301 developed the disease, while doubly transgenic mice for HLA-A*0301 and HLA-A*0201 did not develop EAE. These findings show an epistatic interaction between these two alleles of class I genes, in which the HLA-A*0201 allele modulates the effect of the HLA-A*0301 allele. The proposed hypothesis is that an elimination of autoreactive T cells occurs at the central level of the thymus, thus leading to their almost-total disappearance at the periphery.

In the most recent meeting of the ECTRIMS, Dr. S. Sawcer [9] reported the current state of genetic research at the International Multiple Sclerosis Genetic Consortium (IMSGC), which has almost been completed. The genotypes of over 10,000 patients with MS have been identified through the use of microarray technology (implicated groups, case and control contribution of each group, quality control, target replication). A comparison of the genetic components of MS that have been determined to date and the new genetic components found as a result of this study were presented.

In a study published in 2007 by the IMSGC [10], single nucleotide polymorphisms (SNPs) were genotyped by chromosome. An HLA signal was detected on chromosome 6, as were other, minor signals. In addition, other noteworthy signals have been observed. In total, 102 signals have been detected, of which 21 are known, but 81 correspond to new signals. These results are quite promising. Some major associations identified in previous studies have been validated by Swacer's study, but a list of the new genes has not yet been made available.

Upon defining the genetic components of MS, a new and equally important chapter will be opened for defining the biological and clinical utility of genes that contribute to the genetic risk of this disease.

For example, the German group led by Dr. B. Hemmer [11] has identified three SNPs that are associated with the development of neutralising antibodies (NABs) against interferon (IFN)-β therapy in MS patients. Two of these are found on chromosome 6, and one is on chromosome 8. None are located within genes. Through genotyping and HLA typing, these results could help to identify patients at risk for developing NABs against IFN-β [12].

Neuropathology of multiple sclerosis

Currently, there is controversy regarding the pathogenesis of MS and the relationship between degeneration and inflammation. Several experts believe that the inflammatory and autoimmune components are the fundamental basis of MS, and they associate these components with the presence of immune infiltrates that breach the blood-brain barrier (BBB) and glial activation. However, other experts support the idea of degeneration as the fundamental cause of the disease. A recent study has suggested a close relationship between inflammation and degeneration in all of the lesions and stages of the disease [13], whereas Henderson et al. have suggested that the formation of the plaque is mediated by cellular destruction directed against myelin and other oligodendrocytes, implicating degeneration as a fundamental component of the pathogenesis of MS [14]. In any case, a dynamic relationship between degeneration and inflammation has been proposed.

There are several arguments that support the idea of the disease as fundamentally degenerative. The presence of cellular infiltrates associated with

the phenomenon of axonal transection in experiments on the facial nerve, as well as infiltrates in other types of myelin degenerative responses, point towards the existence of inflammatory processes following degeneration. However, there have been findings that contradict this hypothesis. There are also arguments against degeneration related to the absence of clonal expansion and the lack of any known genetic susceptibility to degeneration, which is observed in immunologic phenomena.

Dr. H. Wekerle [15] affirms that autoimmunity may be sufficient for explaining the presence of inflammatory phenomena that are not necessarily associated with neurodegenerative processes. Some arguments in favour of this hypothesis are the presence of CD8+ cells in MS plaques, which are present in up to 75% of the plaques in necropsy; the immunologic control associated with class II HLA antigens and IL-2R, amongst others; the presence of B cells probably associated with IgG oligoclonal bands; and other phenomena associated with antibodies, such as those against MOG, AQP4/NMO, and anti-CD20 (rituximab). Therefore, three steps in autoimmunity have been proposed. First, clones of T cells that react against CNS structures appear and are activated in the intestinal lymphoid tissue. This step is followed by the activation of T cells, and lastly, demyelination and axonal degeneration.

Currently, the role of innate immunity is gaining increasing attention, given its probable relationship with the neurodegenerative phenomena of MS.

The aspect of innate immunity in the CNS most relevant to MS is the role of microglia, and thus, the role of macrophages. Macrophages play a crucial role in EAE. M1 macrophages are primarily pro-inflammatory and are activated by the classical pathway (endotoxin, lipopolysaccharide, or IFN-γ), while M2 macrophages facilitate the production of growth factors through an alternate mode of activation (IL-10 or corticoids). The balance between M1 and M2 macrophages is implicated in the chronic, recurrent forms of EAE. In addition, macrophages, specifically M2 macrophages, have a close relationship with axonal damage activated by the classic route. It is now clear that in MS, M1 macrophages are linked to neurotoxicity, and M2 macrophages are linked to neuroprotection.

The local reactivation of T cells by contact with macrophages is essential for the development of EAE [16].

Different transgenic models allow us to distinguish the importance of B cells in the APC aspect of EAE and as producers of immunoglobulins. In a recent study exploring the benefit of rituximab in MS, MOG-induced EAE models were used (peptide 35-55 and complete recombinant mouse proteins that induce different B responses). In the second case, its APC action promotes Th1 and Th17 responses, which result in the depletion of harmful and helpful B cells, respectively [17].

The presence of cortical pathology in MS has recently generated great interest. The findings by Dr. C. Reali [18], presented at the ECTRIMS, point towards a relationship between meningeal inflammation phenomena and spinal medullary lesions that trigger permanent inflammatory activity through T cells that maintain the inflammation. This aspect is interesting, as it could serve as the starting point for the search for biomarkers for the treatment of the progressive stage of MS.

Mitochondrial pathology has been related to oxidative processes. The study presented at ECTRIMS by Dr. M.E. Witte [19] brings to light a series of molecules, including peroxidise-3 (Prx3) and thioredoxin-2 (Tnx2), whose expression is increased during the active stage of the disease and subsequently is reduced in the chronic lesions. Therefore, mitochondria could be a susceptible point for the treatment of SPMS, mainly through the targeting of other intermediate enzymes, such as PGC-1α which could become, due to this reason, a possible biomarker for the secondary progressive form of the disease.

Mechanisms in the progression of multiple sclerosis

Amongst the mechanisms of MS progression, the role played by astrocytes in the generation and maintenance of the inflammatory processes characteristic of MS are of particular interest, based on an experimental model in which an axonal lesion induces an inflammatory reaction.

Astrocytes are cells of neuroectodermal lineage. Historically, structural functions and roles in support, nutrition, regeneration, and contributions to the BBB have been attributed to astrocytes. In addition, we have recently begun to discover their important immunological functions in neuroprotection, the formation of the *glia limitans* together with the vascular endothelial cells, restriction of the migration of molecules and inflammatory mediators through the BBB, and as limiting agents of parenchymal leukocyte infiltration.

In general, when a lesion is produced in the CNS, astrocytes increase in size, extend processes towards the affected area, and induce local reactive astrogliosis.

An experimental rodent model of an axonal lesion at the prefrontal cortex has been developed in which a denervation of the entorhinal cortex is induced. It has been shown that this model of neurodegeneration induces an inflammatory response; in addition to astrogliosis at the denervated zone, it also produces microglia and lymphocyte infiltration. Therefore, it has been developed an experimental model with neurodegenerative lesions that result in the production of an inflammatory response. In this context, it has been demonstrated that astrocytes have a determining role in the release of inflammatory mediators and in lymphocyte and microglial infiltration at the affected sites. When a lesion is produced, astrocytes express receptors and release cytokines, which are implicated in the innate immune response.

Using this model, it has also been demonstrated that inhibition of the IFN astrocyte receptor produces an increase in microglial and leukocyte proliferation. On the other hand, the inhibition of astrocyte transcription factors like NF-κB, leads to a decrease in the release of pro-inflammatory mediators and cytokines, resulting in reduced microglial infiltration.

It has been confirmed that after an axonal lesion is produced in this experimental mouse model, macrophages express angiotensin II and type I angiotensin receptor (AT1), whereas astrocytes only express AT1.

Thus, in this experimental model, it has been demonstrated that inhibition of the astrocyte AT1 (with candesartan) induces an increase in the number of macrophages that infiltrate the denervated hippocampus of the murine model two days after the lesion. From this, we have concluded that the stimulus produced by angiotensin II over the astrocyt AT1 plays an important role in the regulation of leukocyte infiltration in the CNS after a neurodegenerative stimulus, leading to the possibility of identifying new therapeutic targets.

Other studies have shown the following that stimulation of the AT1 inhibits the migration of molecules through the BBB, the inflammatory processes produced in MS lead to a decrease in the number of immunopositive perivascular astrocytes for angiotensinogen and that this constitutes one of the immunopathogenic mechanisms involved in the disruption of the BBB in MS.

In classical experimental models of EAE, the astrocytes and their processes act as true barriers, in the sense that they surround the perivascular spaces and contain the extravasation of inflammatory mediators and inflammatory cells, limiting the extension of the adjacent parenchymal inflammation.

In a study presented at the congress and recently published by Dr. R.R. Voskuhl's group [20], it was observed that the depletion of reactive perivascular astrocytes with ganciclovir led to aggravation of EAE in an experimental model. This observation probably reflects a secondary mechanism, given that when reactive perivascular astrocytes are lost, an expansion of inflammatory mediators and inflammatory cells is produced in the adjacent parenchyma.

Repair of the central nervous system

MS is a chronic inflammatory and neurodegenerative disease. Repair processes (remyelination) that are observed at the beginning disappear over time. Therefore, the progression of MS may be the consequence of a defect in intrinsic repair mechanisms.

We are beginning to understand the cellular and molecular mechanisms that are involved in the intrinsic regeneration of the CNS, mostly with respect to inflammation, CNS plasticity, and neuro(glio)genesis. It is apparent that some of the aspects of CNS repair are directly related to inflammation, which initially produces tissue destruction. However, this profile may change throughout the inflammatory process, and it may give way to tissue repair through the production of neurotrophic factors. On the other hand, CNS plasticity is necessary to establish new dendritic and axonal connections that allow for the reconstruction of damaged neural circuits. In neuro(glio)genesis, brain precursor cells may migrate to damaged areas and repair them. The mechanisms that might lead to this repair are, on the one hand, the proliferation and maturation of different types of precursor cells (endogenous neural stem/precursor cells) and, on the other hand, immunomodulation and neuroprotection (Figure).

With respect to remyelination in MS, a primary line for regenerative treatment has not yet been found, and research is still in its very initial stage; the most innovative target areas have not yet been linked with the prevention of inflammation.

In unpublished data from a study led by Dr. D. Buchet, pluripotent cells that were extracted from embryonic brain or the neural crest boundary and injected into an experimental mouse model with a demyelinated posterior spinal cord were found to migrate through a single intrathecal injection and proliferate. In addition, once injected into the CSF, the cells migrated, implanted, and proliferated as

adult oligodendrocytes independent of the embryonic precursor cell extraction zone.

When pluripotent cells are used that have been extracted from an embryonic zone that could typically give rise to cells of the peripheral nervous system, the cells are similarly observed to migrate to the CNS and convert into oligodendrocytes [21].

Thus, it has been demonstrated that precursor cells of the CNS and peripheral nervous system display great plasticity; despite the inhospitable environment of the adult context, these cells slowly migrate to the CNS and become adult oligodendrocytes.

The disruption of the BBB constitutes an initial factor in the formation of a plaque, and for this reason, an understanding of the mechanisms involved in BBB disruption could aid in the identification of new therapeutic targets.

The available data suggest that the extracellular environment of the oligodendrocyte determines its capability for remyelination. A study conducted by Kalgari et al. analysed how the reduction in chondroitin sulphate proteoglycan (CSPG) in demyelinated lesions promotes remyelination. CSPGs create dense CISrs in chronic plaques and inhibit axonal regeneration at the sites of traumatic lesions. Laminin, which is found in the extracellular matrix, has the opposite effect of CSPG, promoting the proliferation and maturation of *in vitro* oligodendrocytes.

In relation to remyelination, the *in vivo* effect of laminin on the role of CSPG is not known. In this context, the dynamics of CSPG and laminin have been studied in a toxic model of CNS demyelination (lysolecithin in the spinal dorsal cord), and the effect of reduction with xylosidase of CSPG expression is that CSPGs reduce the afference and differentiation of oligodendrocyte precursors.

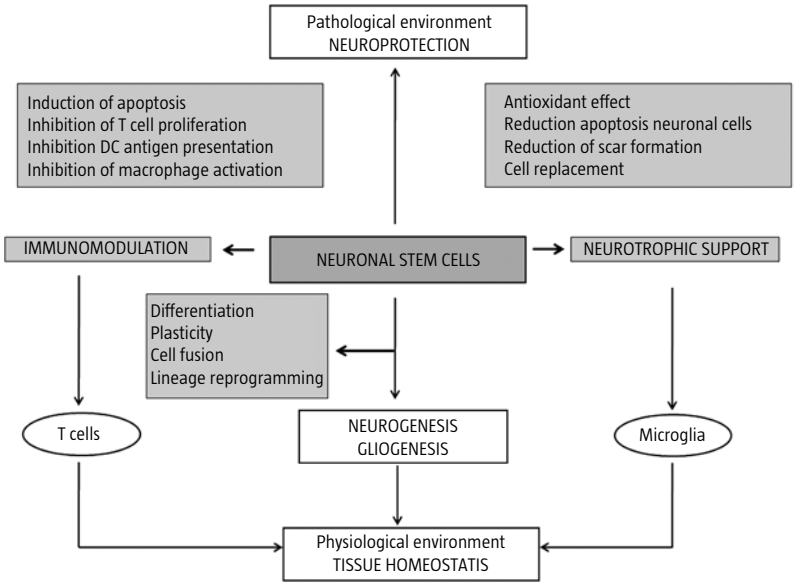
Mesenchymal stem cells (MSCs) are a subtype of stromal cells that may be isolated from amniotic fluid or different adult tissues, such as bone marrow, adipose tissue, and almost any other organ that contains connective tissue. Mesenchymal cells constitute a CISrce population. In the haematopoietic niche, they are less than 0.01% of all bone marrow cells. Mesenchymal cells can be isolated relatively easily, and they multiply well *in vitro*. *In vitro,* mesenchymal cells may differentiate into cells of the mesodermal lineage, such as cartilage, bone, and adipocytes. In certain conditions, they may also differentiate into neural cells.

Many studies have indicated that most probably is not possible for mesenchymal cells to transdifferentiate into neurons *in vivo* and provide a substitute for destroyed neurons. However, in experimental models, it has been observed that MSCs penetrate the interior of the CNS, and that although they cannot transdifferentiate into neurons, they protect neurons and other CNS cells. MSCs might achieve this effect through at least three different mechanisms of action: a neuroprotective effect, an induction effect, and an immunomodulator effect, which in some cases may become immunosuppressive.The neuroprotective effect of MSCs is characterised by the release of trophic factors, anti-apoptotic molecules, and antioxidant molecules, as well as by the induction and mobilisation of the proliferation of cellular precursors.

On the other hand, an inductive effect has been observed in many experimental models upon the administration of MSCs, demonstrating that they promote the proliferation, migration, and survival of neuronal stem cells. In addition, the implantation of human MSCs into murine models increases the synthesis of trophic factors. Recently, it has been shown that MSCs from bone marrow promote oligodendrogenesis and inhibit astrogliosis in EAE models [22].

MSCs act as true immunomodulators, given that they inhibit an antigen's specific T cell response. Data not yet published by Dr. Casazza suggest that, in addition, they reduce microglial activation in ex-

Figure. Repair of the central nervous system (presented by Dr. G. Martino at ECTRIMS 2010).



perimental EAE models. This inhibition of the T cell response by MSCs is able to overcome the interspecies barrier [23]. In fact, EAE may be inhibited by syngeneic, allogeneic, and xenogeneic MSCs. The interspecies jump is based on the low level of immunogenicity of MSCs. In fact, MSCs do not express the class II HLA, and they barely express class I 1.

At the congress, a consensus document was presented that had been created by a panel of experts, which discussed how treatment of MS patients with MSCs should be performed, how clinical studies of these treatments should be designed, what types of patients could benefit from such treatment and should be included in the clinical studies, and the ideal characteristics of the mesenchymal cells to be administered. Amongst the aspects discussed in this document, it is noteworthy that any form of MS may be included, as long as there are symptoms of progression, clinical activity, and radiological activity. On the other hand, this panel of experts also urged that the primary objective of any MS study with MSCs should be safety, and the clinical and radiological variables should be considered secondary variables [24].

Use of magnetic resonance in the diagnosis and progression of multiple sclerosis

Dr. Fisniku et al. [25] described the difficulty that clinical neurologists face in obtaining information based on MRI studies related to the evolution and prognosis of the disability of a determined MS patient, and they proposed three strategies to improve the use of MRIs. The first is to plan longer longitudinal studies because disability develops over many years. Secondly, the authors propose the use of more sensitive clinical CISles that take the complexity of MS into account with respect to cognitive aspects and fatigue, for example. The third strategy is the improvement of MRI studies to increase the sensitivity of the detection of lesions with higher resolution and newer sequences to study the relationship between the location of infratentorial or medullary lesions and the disability. The authors recommend the use of unconventional MRI to better characterise the pathological heterogeneity of the lesions to analyse the utility of measurement combinations as composite indices. The authors emphasised the need for a paradigm shift with respect to MS as a diffuse disease of the CNS with involvement of the white and grey matter. The study published by Dr. Fisniku [25] compared grey matter and white matter atrophy in MS patients and found that grey matter atrophy was greater in patients with secondary progressive MS than in RRMS patients with CIS. In addition, only grey matter atrophy correlated with the MS functional composite [26].

Other aspects of MRI that need improvement are the T1,T2, DTI, MT quantitative acquisition, post-processing of images of the grey matter with regional segmentation techniques, and the production of probability maps of lesion distribution. In addition, there is a fundamental need to increase the specificity of MRI without losing sensitivity. Dr. Pelletier [27] presented a study on the content of glutamate in the brain through spectroscopy by MRI in patients with MS. Glutamate is an excitatory neurotransmitter, and its metabolism in oligodendrocytes plays a role in MS. The increase in glutamate levels during the infiltration of inflammatory cells and microglia, together with the decrease in glutamate in oligodendrocytes, is probably the cause of the increase in glutamate levels in active lesions and their vicinity, as well as its decrease in chronic lesions. In Pelletier's study, an increase in glutamate was found in all the patients with MS (SPMS, RRMS, or CIS). In addition, a relationship was established between the increase in basal glutamate in grey and white matter and the loss of N-acetylaspartate in the grey matter after two years of follow-up. However, this relationship was not observed in white matter, which could result in a useful predictive biomarker of neuroaxonal damage to the grey matter.

Another noteworthy issue with respect to the future use of MRI is the possibility of detecting iron deposits as markers of neurodegeneration using high-field machines (7T) with gradient echo sequences that quantify the distortion of the magnetic field caused by the magnetic components. It has been observed that the basal ganglia of patients with MS are more paramagnetic than the controls and that the hypersignal extension correlates with the length of time of the disease evolution.

In the coming years, it would be of interest to define the *in vivo* profiles of metabolites, such as N-acetylaspartate, glutamate, iron, glutathione, and other macromolecules that are associated with neurodegeneration or neuroprotection.

With the goal of evaluating the neuronal pathology in grey matter, the use of positron emission tomography (PET) with flumazenil (FMZ), an antagonist of the benzodiazepine receptor (BZR) that is part of the γ-aminobutyric acid complex of the CNS neurons, has been studied. A decrease in the total number of BZRs in patients with RRMS and SPMS has been found, along with a loss of BZRs in the earliest stages of the disease, even before evident

brain atrophy. The findings suggest that the use of PET with FMZ could be useful for the detection of early axonal damage in longitudinal studies and in studies of neuroprotection.

On the other hand, the 3D DIR sequence obtained a gain of 240% with respect to 3D FLAIR for the detection of intracortical lesions without finding false positives. A clear increase in sensitivity without loss of specificity was inferred from these results.

In addition, the use of high-field MRI machines of 7T with a multiplanar RAGE sequence (MPRAGE) was discussed in terms of the detection of additional smaller lesions in seemingly normal white matter that cannot be detected by 3T MRI.

Biomarkers in multiple sclerosis

Biomarkers can provide information regarding the diagnosis, pathophysiology, and prognosis of CIS and MS, as well as the response to treatment.

Amongst the diagnostic biomarkers, the oligoclonal bands are noteworthy. The presence of oligoclonal bands in the CSF has been associated with a higher risk of exacerbation and a worse clinical evolution. In addition, a distinct sensitivity has been observed as a function of race.

The group led by Dr. G. Izquierdo [2] found promising results in their informatics analysis of oligoclonal band patterns. The data obtained showed that the analysed patterns may have a different significance in patients with CIS that progresses to MS compared to those who remain with CIS, and this discrepancy could serve as the basis for identifying differences in the CNS pathophysiology in these patients.

Levels of the chemokine CXCL13 in the CSF are increased in patients experiencing MS exacerbations in the active phase; CXCL13 levels show a correlation with the number of B cells in the CNS. We should point out that the increase in CXCL13 exhibits a significant correlation with some parameters of disease activation, such as the number of lesions captured by gadolinium or the level of myelin basic protein. In addition, a significant correlation with several biomarkers of immune activation has been observed, such as the concentration of MMP-9 and the rate of intrathecal synthesis of IgG in the CSF.

The discovery of new biomarkers reveals new pathways in the pathophysiology of MS. The levels of CD8+DR+ lymphocytes in the CSF, which are highly correlated with axonal damage, display a significant correlation with the EDSS score.

It has been observed that each heavy chain of neurofilaments NfHSMI35 correlates with the EDSS and with the volume of active lesions (gadolinium enhancing) in resonance, which is why it has been proposed as a biomarker for disease activation.

There is an increasing number of studies reporting predictors of CIS evolution and disability, as well as treatment response. The presence of the HLA-DRB*15 allele and vitamin D levels are risk factors that are independent of conversion to MS. In addition, it has been shown that neurofilament and cystatin C levels in the CSF (CIS-myelitis) are good predictors of conversion to MS.

With respect to biomarkers of treatment response, the group led by Dr. F. Weber found a series of SNPs (in the HLA region) that are associated with the production of anti-IFN antibodies. In contrast, the expression of VLA-4 decreases in patients who respond to IFN and show less activity by MRI. Dr. C. Oreja-Guevara [28] reported an increase in Th1 and Th2 cytokines after treatment with natalizumab.

Dr. I.R. Kasper et al. observed that patients who secreted high amounts of IL-17 and IFN exhibited the best response to treatment with glatiramer acetate [29]. In addition, it was found that treatment resulted in increased levels of IFN-γ. Dr. S. Dhib-Jalbut et al. found that patients with the HLA-DQ6 allele responded to glatiramer acetate and that IL-17 and TNF-α levels decreased during the course of treatment [30].

Currently, there are no efficient diagnostic biomarkers, and there is a need to establish new biomarkers that are predictive of response.

Infections in the aetiopathogenesis of multiple sclerosis

Data that support the implication of viral agents in the aetiopathogenesis of MS are based on the following observations: exacerbations commonly follow episodes of viral infection, the development of EAE in 100% of transgenic mice in a non-sterile environment compared to the absence of EAE in a sterile environment, and the existence of demyelinating diseases caused by viruses (including JC virus, measles, HTLV-1, and HIC),

The mechanisms implicated in the possible role of viruses in the pathogenesis of MS include direct viral infection, molecular imitation, and 'innocent' activation of the immunologic system by a viral infection, which produces an inflammatory cascade that leads to myelin damage and the activation of other mechanisms as an unwanted consequence of the viral infection.

The Epstein-Barr virus (EBV) and the torque teno virus (TTV) have been proposed to be involved in the aetiopathogenesis of MS. However, there is controversy regarding EBV infection with respect to whether it truly results in the direct involvement of lymphocytes, and whether lymphocytes are responsible for the appearance of lymphoid follicles, which ultimately lead to a more aggressive disease. TTV is a small DNA virus that shares genetic similarities with many prokaryotic and eukaryotic organisms and that could act as an imitator molecule. TTV can be detected in different tissues and fluids, including the CSF in patients with MS.

In conclusion, although various infectious agents have been serologically and pathologically associated with MS, none of the associations are conclusive. On the other hand, the difficulty of identifying a single microorganism as the cause of MS suggests that Koch's paradigm of 'one organism-one disease' does not apply to this complex disease. In this sense, the current data suggest that MS could be induced or exacerbated by different infectious agents that are probably prevalent in the general population.

The results of a study published by Sundstrom et al. [31], which analysed the question of whether there is sufficient evidence to implicate viral infections in the pre-symptomatic stage of MS, showed that only the extractable EBV antigen had a correlation with the presence of MS [32]. In accordance with this study, Dr. Sundqvist presented research at the ECTRIMS that analysed the reactivity of immunoglobulins against EBNA-1 as a function of different fragments or peptides of the antigen that generate different responses. It was found that the fragment of the EBNA-1 Ig 385-420 antibody had a higher correlation with the risk of developing MS than other antigens of the same virus. However, it was pointed out that contradictory evidence exists regarding the implication of the EBV in the aetiology of MS, due to the interaction of amino acid sequences containing an EBNA-1 fragment with the HLA DRB1*15 allele. As a result, it would be impossible to confirm that EBNA-1 is responsible for the risk, rather than the HLA factor.

A study that explored the B lymphocyte response to the EBNA-1 antigen in patients with MS and discordant twins found that EBNA fragments exist in patients with MS that do not appear in the controls. It has been observed that the levels of antibodies against the 401-411 epitope of EBNA-1 are higher in patients with MS than in controls, and they are higher in twins with MS than in healthy twins.

Environmental and lifestyle contributions to multiple sclerosis

In addition to the genetic component, a series of factors have been implicated in the aetiology of MS, such as serum vitamin D levels, dietary intake of animal fats, a history of trauma, and exposure to toxic agents (including tobacco, heavy metals, and organic solvents). Of these, the factors with the greatest consistency are the EBV (++), vitamin D (+) and tobacco.

Vitamin D deficit is a prominent risk factor for MS. Ultraviolet radiation is implicated in the synthesis of vitamin D, which is also synthesised from dietary components, mainly fish oils.

There are many studies that have looked at the protective effects of solar radiation against MS, and a decrease in the amount of effective ultraviolet radiation in countries at higher latitudes is associated with a greater risk of MS [33].

Vitamin D also has a prominent role as a regulator of immune function. Vitamin D influences both adaptive and innate immunity. It acts as an immunomodulator, exerting its effect on APC and decreasing the maturation of dendritic cells. The effects of vitamin D on T cells involve decreases in Th1 proliferation, which reduces IFN-γ and IL-2 levels. In addition, vitamin D stimulates innate immunity.

In EAE animal models, vitamin D intake was shown to be protective only in female rats with EAE. Observational ecological studies (case-control and prospective) have shown the importance of environmental factors, specifically vitamin D synthesis, in the development of MS in humans, but bias associated with other environmental factors cannot be excluded. Ultimately, a randomised study is needed to better understand the possible preventive value of vitamin D, and it would be justified to begin such a study at the early stages of life.

Only modest evidence relating each of the factors involved in MS to the disease has been demonstrated. However, these factors may interact with each other and increase the risk of MS, which would explain the mechanisms of disease development. As such, the possibility is presented that the interaction between these factors could explain the variability in risk for the development of MS.

Dr. M. Baarnhielm [32] presented the results of a recent epidemiological case-control study (EIMS) that included 2,109 cases and 4,388 controls in Italy, Norway, Sweden, Serbia, and Canada. The objective of the study was to evaluate the relationship between previous exposure to ultraviolet radiation and vitamin D levels and the risk of developing MS.

In addition, the interaction of these factors with the DRB1*15 allele was evaluated. It was observed that individuals exposed to less ultraviolet radiation exhibited a greater risk of MS. However, no interaction was observed between the DRB1*15 allele and previous vitamin D exposure, as determined in serum , for an increase in the risk of developing MS.

Environmental and genetic factors, especially the DRB1*15 allele, independently influence the risk of developing MS. However, there is no evidence of interaction between the risk factors, and a multifactorial cause with different mechanisms of action has been suggested.

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Revisión de las novedades presentadas en el XXVI Congreso del Comité Europeo para el Tratamiento e Investigación en Esclerosis Múltiple (ECTRIMS) (I)

Resumen. Las novedades presentadas en el XXVI Congreso del Comité Europeo para el Tratamiento e Investigación en Esclerosis Múltiple (ECTRIMS), celebrado en octubre de 2010 en la ciudad sueca de Gotemburgo, han sido resumidas durante la tercera edición de la reunión Post-ECTRIMS celebrada en Madrid en noviembre de 2010. La edad es un factor muy importante relacionado con el curso y pronóstico de la esclerosis múltiple (EM). La transición a la etapa progresiva persiste más de 50 años después del diagnóstico de EM, y se ha detectado una disminución de la demora en el diagnóstico. Se han propuesto varias estrategias para poder mejorar la utilidad de la resonancia magnética respecto al pronóstico y al curso de la enfermedad. Los estudios presentados reflejan la influencia del género sobre el curso y gravedad de los síntomas de la enfermedad, observándose un incremento de la prevalencia mundial de EM en mujeres. Se ha destacado la acción neuroprotectora de los ligandos del receptor estrogénico beta. Los estudios genéticos de asociación han permitido identificar numerosos alelos susceptibles. En este sentido, los genes del complejo mayor de histocompatibilidad de clase II parecen contribuir al riesgo genético de desarrollar anticuerpos neutralizantes contra el interferón beta. Se ha destacado, además, el déficit de la vitamina D y la infección por virus de Epstein-Barr como factores de riesgo para la EM en los estudios realizados. En relación con la controversia generada en torno al papel de la inflamación y la degeneración en la EM, se han expuesto argumentos a favor de la autoinmunidad para explicar la presencia de fenómenos inflamatorios. Los estudios realizados apoyan el potencial efecto terapéutico de las células mesenquimales, dada su implicación en la reparación del sistema nervioso central.

Palabras clave. Diagnóstico. ECTRIMS. Esclerosis múltiple. Genética. Progresión.