Review of the novelties presented at the 28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) (I)

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Summary. The most relevant data presented at the 28th edition of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), held in October 2012 in France, have been summarized in the fifth edition of the Post-ECTRIMS Expert Meeting held in Madrid in October 2012. The present review summarizes the views and results of the meeting and is being published in three parts. This first part of the Post-ECTRIMS review addresses the incidence and prevalence of multiple sclerosis (MS), which has increased at the global level, largely due to the increased incidence in women because the risk of developing the disease is increased in females, with minimal concurrent effect on the progression of MS. Sexual dimorphism is evident in MS, and all evidence points to an interaction between hormonal, genetic, and environmental factors. The paediatric population represents an ideal group to study susceptibility factors to the disease, which is why collaborative studies designed to increase the patient samples are being considered, given its low prevalence. In this review, inflammatory and neurodegenerative phenomena involved in the pathogenesis of the disease and that have a cause-and-effect or shared relationship with the disease are being discussed. Current hypotheses suggest a phenomenon of compartmentalization, presumably inaccessible to current immunomodulatory therapy. Among the possible mechanisms involved in these processes of inflammation and demyelination, the role of Th17 cells, mitochondrial dysfunction, early disruption of astrocytic processes, and chronic hypoxia are discussed.

Key words. Environment. Genes. Hormones. Inflammation. Multiple sclerosis. Neurodegeneration.

Introduction

The Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) is the most important international conference on this disease. The last edition, held in October 2012, brought together a total of 7,500 specialists in multiple sclerosis (MS) from 96 countries.

For the fifth consecutive year, the Post-ECTRIMS Expert Meeting was held in Madrid. This is an annual meeting that brings together renowned national opinion leaders to present the most relevant data discussed at the Congress of ECTRIMS and has the scientific backing of the Spanish Society of Neurology.

This paper incorporates a full review, which is being published in three parts, and includes the latest developments in basic and clinical research presented at the largest international conference devoted to the understanding and treatment of MS.

Genetic aspects and gender differences in MS

The incidence and prevalence of MS has increased worldwide, mainly in women. However, this gender-biased increase has not been due to a decrease in the incidence and prevalence in men, which has remained stable from 1950 to 2000. Pregnancy has a beneficial effect on MS attacks, but the attacks increase after delivery. In women, the onset of disease is earlier, primary progressive forms are less frequent, and disability progression is slower. These three observations suggest that the study of factors associated with gender could provide significant information on the pathophysiology of the disease. The existence of sexual dimorphism, with an effect on individual susceptibility for the development and progression of the disease, could be due to differences in the immune response to external or environmental stimuli, to differences in gonadal hormones, or to differences dependent on sex chromosomes (Table).

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Table. Sexual dimorphism and pregnancy in the susceptibility and progression of multiple sclerosis.

	Incidence of multiple sclerosis	Activity (attack rate)	Disability progression
Gender	Female > male	Female > male	Male > female (resistance mechanism)
Pregnancy	Reduction	Reduction	Contradictory data (beneficial effect versus lack of long-term benefit)
Postpartum	Increase	Increase	None
Reproductive history	No change or decrease in the number of pregnancies	Unknown effect	No change or improvement with a greater number of pregnancies

Genes affecting the susceptibility to MS

The genetic contribution to MS susceptibility has been well documented since a strong association with genes of the major histocompatibility complex (MHC) was discovered in the 70s. The HLA region is considered the major genetic risk factor for MS, and the HLA-DRB1*15:01 allele exhibits a substantial and additive risk for the disease (*odds ratio*: 3.1), although it is not related to the progression or severity of the disease or to the month of birth. However, in male carriers of the HLA-DRB1*15:01 allele, greater progression on the Expanded Disability Status Scale (EDSS) has been reported, which increases with the presence of oligoclonal bands in the cerebrospinal fluid [1].

No relationship has also been found between certain non-MHC genes, such as *ILR-2, ILR-7 CLEC 16A, CD226*, and the progression of disability [2]. However, the HLA-B*44 allele has been shown to moderate the course of the disease, reducing brain atrophy and lesions in T_2 [3].

Genetic differences between subgroups of patients with MS have been studied for many years, although many of the studies lack relevance due to small sample sizes as a result of dividing the cohort into subgroups. More convincingly, a genome-wide association study (GWAS) has identified an association between the HLA-DRB1*1 15:01 allele and early onset of the disease and has proven that each copy of HLA-DR15 decreases the age of onset by 10.6 months [4]. Other studies with candidate genes have focused on those genes encoding interferon-γ and have reported polymorphisms that reduce susceptibility to MS only in men [5].

The different response to treatment observed among individuals may be due to genetic differences. Studies of allelic combinations of the *JAK2*, *IL10RB*, *GBP1,* and *PIAS1* genes have reported differences between responders to interferon therapy. However, two GWAS studies to detect genetic differences between patients who were responders and non-responders to interferon-1 therapy did not produce any conclusive results, although certain regions of interest were identified for future studies [6,7]. Patients homozygous for the HLA-DRB1*15:01 allele are better responders to treatment with glatiramer acetate [8].

Genetic and molecular mechanisms of sexual dimorphism in MS

Epigenetic modifications of DNA by external factors that differ by gender could explain the gender difference in MS. Indeed, men and women respond differently to sun exposure and vitamin D intake [9].

The role of chromosome X in the induction of autoimmunity has also been investigated. In the experimental autoimmune encephalitis model, the presence of two X chromosomes increases susceptibility to this disease. Furthermore, X chromosome inactivation in females induces the overrepresentation of susceptibility genes. Similarly, according to Spach et al., [10] the Y chromosome could reduce the susceptibility to develop experimental autoimmune encephalitis.

The expression of peroxisome proliferator-activated receptors (PPAR) has been proposed as the molecular mechanism of immune sexual dimorphism in MS. Studies in animal and human models suggest that sexual dimorphism in the production of Th1 and Th17 cytokines depends on androgen levels and the expression of PPAR-γ in CD4+ T cells [11].

Effect of sex hormones, the menstrual cycle, and pregnancy

Sexual dimorphism is present in autoimmune dis-

eases with an obvious hormonal role. Testosterone exerts a protective effect in the experimental autoimmune encephalitis model, and castrated males exhibit more severe progression [12,13]; in patients with MS, testosterone treatment slows progression of brain atrophy, although it has no effect on activity [14]. Estrogens are believed to differentially regulate the immune response during pregnancy and the menstrual cycle and after menopause. Low levels of estrogen and prolactin favour a Th1 proinflammatory response, whereas high levels during pregnancy are associated with the anti-inflammatory Th2 response and an upregulation of the regulatory T cell response [15-17].

The influence of menarche in MS is demonstrated by an increased risk of developing the disease in women with precocious puberty [18] and a decreased risk of disease progression in those with delayed puberty, with a greater time span to reach an EDSS score of 6 [19]. Another study with results from a large population survey demonstrated that MS symptoms are not modified during menstruation, when taking oral contraceptives, or when receiving hormone replacement therapy in menopause; however, symptoms during menopause and the postpartum period worsened by 45 and 33%, respectively, compared with only 10% during pregnancy. Moreover, in this period, 25% of women reported a relief of symptoms [20].

Pregnancy

As mentioned above, the state of immune protection during pregnancy appears to be mediated by a significant increase in gonadal steroids, which favours the anti-inflammatory Th2 response, inhibiting the Th1 response associated with MS; its decline postpartum would explain the increase in attacks. Another question is whether pregnancy and associated prenatal biological phenomena could influence the development of MS. Foetal chimerism is believed to contribute to autoimmunity and has been associated with MS in a Canadian study of twins who were discordant for MS [21]. This raises the hypothesis of an increased risk of MS in multiparous patients. However, this approach has not been confirmed in further research. The AusImmune study [22] reported a 49% reduction in the risk of experiencing a first demyelinating event with each pregnancy, a relationship that is independent of HLA and other risk factors, such as the Epstein-Barr virus (EBV). Another study also found that people with reproductive histories had a lower risk of MS than those without children [23].

Nowadays, it is widely accepted that the relapse rate is reduced during pregnancy, at least in the second and third trimester, and increases significantly in the first six months after delivery, until reaching the pre-pregnancy rate [24]. Clinical predictors of postpartum attacks include higher relapse rates in the year before pregnancy, higher relapse rates during pregnancy, and higher scores on the EDSS in early pregnancy [25,26]. The final results of the POPARTMUS multicentre study, designed to determine clinical activity in women treated with progesterone and estriol (in the form of 17-β-estradiol) during the three months following delivery, were presented at the conference. This clinical trial demonstrated no efficacy of treatment with sex steroid supplements to prevent postpartum attacks [27]. There is thus currently no treatment that has demonstrated efficacy in the prevention of postpartum attacks. In clinical practice, some authors propose to start or restart treatment with disease-modifying drugs as soon as possible and to use intravenous immunoglobulins compatible with breastfeeding [28] or to use monthly pulses of methylprednisolone [29].

The impact of pregnancy on short-term disability was demonstrated in the PRIMS study [26], which showed an average increase of 0.7 points on the EDSS, consistent with the expected range, during a two-year follow-up, a progression that was not influenced either by breastfeeding or by epidural analgesia. However, the impact of pregnancy on the long-term course and disability is contradictory, as there are studies supporting its possible beneficial effect, in contrast to other studies, such as the one presented by Karp et al. [30], which does not describe any effect. Specifically, this study collected data from a cohort of patients included in the database of the Notre-Dame Hospital in Montreal (Canada) between 1977 and 2010, who were followed for 10 years. The results demonstrated that pregnancy improved the course of the disease in the short term, with no long-term benefit. After 10 years of follow-up, the cumulative incidence rate for irreversible disability progression was 15% in both pregnant and non-pregnant patients, whereas the rate of transition to the secondary progressive form was reduced in non-pregnant women (8%) in contrast to 16% reported for pregnant women.

Lactation

The evidence on the role of breastfeeding on postpartum attacks is contradictory. Although some studies have reported no effect or even an increase

in the relapse rate, other studies have reported a protective effect, especially of exclusive breastfeeding, significantly reducing the risk of a second postpartum attack by up to 50% [31,32]. It should be noted that there might have been a selection bias in these studies, as patients with a more benign MS are those who choose to proceed with further breastfeeding.

Special situations

In optic neuromyelitis and other antibody-mediated autoimmune diseases of the central nervous system, pregnancy might have a negative effect on progression, with an increase in the risk of having an attack and increased disability one year after delivery [33]. Epidural anaesthesia and breastfeeding do not seem to worsen the prognosis. Prospective studies are needed, however, to confirm these data.

The treatments used during assisted reproductive techniques could influence the course of MS, given that they modify hormonal status. There are studies with series of patients cautioning that assisted reproductive techniques might increase the attack rate [34]. However, a recent French study involving 13 medical research centres and 48 women reported an increase in the attack rate associated with the use of GnRH agonists and failure of *in vitro* fertilization. In another recent study, assisted reproductive techniques increased the number of attacks by seven-fold and gadolinium uptake by nine-fold. Such activity was correlated with an increase in the secretion of IL-8, IL-12, interferon γ, TGF-β, and VEGF and plasma levels of CXCL-12 [35]. Again, the possible effect of assisted reproductive techniques on the disease should be confirmed by well-designed prospective studies.

Exposure to treatment during pregnancy

Most current symptomatic treatments besides the disease-modifying treatments are considered class C or D by the US Food and Drug Administration (FDA), except glatiramer acetate (class B). Exposure to magnetic resonance imaging (MRI) and gadolinium, although not considered drugs, should be considered in terms of safety for pregnancy outcomes. MRI should be avoided in the first trimester of pregnancy due to its potential teratogenic effect. Gadolinium, considered class C by the US FDA, should be avoided throughout pregnancy, delaying breastfeeding 24 hours after administration.

Waubant [36] advised that disease-modifying treatment should be discontinued before conception: one menstrual cycle prior to conception in the case of classical immunomodulators, two months in the case of natalizumab and fingolimod, and as soon as possible in those patients who become pregnant while being treated, keeping in mind that there is no current evidence for pregnancy termination.

Furthermore, Waubant urged active participation in gathering global records on treatment exposure during pregnancy, which, together with postmarketing surveillance studies, is an important source of reliable safety data. In this edition, the records shown included exposure to natalizumab [37], fingolimod [38], and intramuscular interferon β-1a, the results of which, although limited and preliminary, suggest a rate of spontaneous abortions and congenital abnormalities consistent with what has been reported for the overall population. It should be noted that additional data are needed before reaching definitive conclusions about the effect of exposure to these drugs on pregnancy outcomes.

Environmental risk factors and temporal changes in the epidemiology of MS

Genetic predisposition is not sufficient to explain the prevalence and risk of MS, and all evidence points to an interaction between genetic and environmental factors in the development of the disease. Among the environmental risk factors, EBV infection has appeared as one of the most interesting, thanks to the results of numerous studies over the past 20 years that have evaluated its role in MS, identifying a strong epidemiological relationship with the appearance of the disease. The main mechanism that has been implicated in the pathogenic process is antigenic mimicry between EBV and myelin molecules, in addition to a possible relationship between EBV and genetic susceptibility (HLA), as Jilek et al. reported in their study [39], where the results suggest an EBV-specific CD8(+) poor functional response in patients with the HLA-B*0702 allele. Additionally, viral particles may exert a proinflammatory effect. An innovative finding is the possible association of cytomegalovirus with a low risk of MS. In this regard, a study by Sundqvist et al. [40] demonstrated that seropositivity to cytomegalovirus might protect against the disease in patients carrying the HLA-DRB1*15 allele, although the mechanism of the protective effect is unknown.

The role of vitamin D in MS is supported by reports of a lower prevalence with respect to increased exposure to annual average ultraviolet radiation [41]; reports of an increased risk depending

on the time of gestation in Northern Europe and Canada [42], which points to a genetic predisposition to suffer the disease in the months of lower sun exposure; and reports of a decreased risk of MS with high levels of vitamin D in women. Studies evaluating the possible protective effect of vitamin D supplements in patients treated with other drugs do not provide conclusive evidence because, among other reasons, of the small sample sizes; it is worth mentioning the SOLAR study [43], currently underway in patients with relapsing-remitting MS treated with Rebif® and Vigantol® Oil supplement (vitamin A + vitamin D_3 + vitamin E) versus placebo.

Among the mechanisms of action of vitamin D studied by Ramagopalan [44], perhaps the most relevant is the need for 75 nmol of hydroxycholecalciferol to achieve full activation of the vitamin D receptor, which is directly involved in the immune process. Another novel aspect is that EBV can compromise the effects of vitamin D. In short, there is a genetic and environmental interaction with vitamin D, which could modulate DNA methylation, a process known as epigenetic regulation, and which may result in changes in phenotype and disease development.

Sun exposure as an indirect measure of vitamin D status at different ages during childhood and adolescence and the risk of MS has been described by Bjørnevik et al. using data from the well-known EnviMS case-control study [45] and specifically with the group of patients from Italy and Norway. In both countries, sun exposure was inversely associated with MS, an association that was observed in summer and in winter in Italy, but observed only in summer in Norway. In Norway, the use of sunscreen in children 0-6 years was associated with an increased risk of MS after adjustment for exposure time. These findings suggest that age at solar exposure may be related to a deficiency of vitamin D and the risk of developing MS.

Contrary to the effect of sun exposure is the fact that the NS gradient is inverted at latitudes > 55° N [46], a finding that may be associated with an increased intake of vitamin D in these countries; moreover, the Danish Cancer record figures demonstrate an increase in the incidence of skin cancer, correlated with solar exposure, which theoretically clashes with the increase in the incidence of MS detected in recent years. These results are confirmed by those in a cohort of the Basque Country, which demonstrate an MS risk independent of daylight hours.

Smoking is a risk factor clearly related to MS, as has been reported in several studies that present conclusive data of the interaction between tobacco and the MS HLA-DRB1*15 susceptibility allele. In patients who smoke, there is an increased risk of conversion, both from a clinically isolated syndrome to clinically definite MS and from the relapsing-remitting form to the secondary progressive form and a greater accumulation of disability. Outside the clinical and epidemiological context, MRI results demonstrate higher lesion load and increased brain atrophy in these patients. A recent survival analysis by Manouchehrinia et al. [47] determined that smoking is a significant, although preventable, risk factor for death. As a remarkable finding, the study concludes that the death rate among smokers with MS is 5.3/1,000 vs. 2.07/1,000 among non-smokers, a risk that is also increased in males; hence, the estimated survival times of 16 years for men and 24 years for women. In contrast with this association, the inverse relationship between lung cancer and MS is prominent. According to comparative data from the Danish MS and cancer registers, it appears that MS patients exhibit a lower risk of lung cancer than the overall population.

Urbanization would be another possible contributing factor, as reflected in the study of Kotzamani et al. [48], with data that demonstrate a further increase in the incidence of MS in urban areas compared with rural areas. However, several studies have found that a high body mass index during childhood and adolescence doubles the risk of MS in adulthood, especially in women; therefore, obesity would be another possible factor responsible for these changes in the epidemiology of MS.

The absence of a causal relationship between chronic cerebrospinal venous insufficiency and MS, which was described by Zamboni in 2008, even etiologically, is again revealed in the COSMO study [49], a multicentre case-control study promoted by the Italian MS Foundation. Thirty five (35) Italian centres have participated, with a total of 1,202 patients with MS (72.6% relapsing-remitting, 13.5% secondary progressive, 5.2% primary progressive, and 8.7% clinically isolated syndrome), 232 with other neurological diseases, and 382 healthy controls. A protocol for carrying out the Doppler was prespecified to establish compliance with the Zamboni criteria, with specifically trained local sonographers and centralized blind evaluation by one of the three assigned experts, who were blinded to access to the Doppler images. In case of disagreement, the Doppler was assessed independently by the two other central sonographers to establish a diagnosis. The prevalence of chronic cerebrospinal venous insufficiency was similar in all groups stud-

ied, except for cases of clinically isolated syndrome, where there was no diagnosis. There were no differences between the centres, although evaluation bias was present locally, given that the centre where the test was done reported the greatest risk factor for chronic cerebrospinal venous insufficiency. Furthermore, there was no association between this and any subtype of MS.

Paediatric MS

Paediatric MS patients accounts for approximately 5% of all MS patients. By consensus [50], MS is classified as paediatric when the disease begins before age 18 years, although for certain etiopathogenic studies, it is preferred to differentiate between childhood (< 11 years) and adolescent MS (11-18 years). This group of patients represents an ideal population to study the various etiopathogenic aspects involved in the disease as environmental risk factors, including infections, vitamin D deficiency, and exposure to various toxic agents, because the interval between exposure to the risk factor and biological disease onset is shorter.

As is the case in the adult population, the prevalence is higher in females. The female:male ratio tends to be balanced primarily in children less than 11 years of age and increases as they reach adolescence, a fact that suggests a hormonal influence. The annualized rate of attacks is higher than the one experienced by adult patients, especially in the early years. Recovery from the attacks is faster, probably associated with higher brain plasticity. Most cases begin with a relapsing-remitting progression. The widespread idea that existed a few years ago about a better prognosis in paediatric vs. adult MS is questionable, as indicated by studies of the natural history of MS, including one published by the French group of Renoux [51], who stated that paediatric disease has a better prognosis because it takes longer to reach a secondary progressive form, but a significant percentage reaches this disability. This aspect should be taken into account now that effective drugs are available in the inflammatory phase. Patients starting with paediatric disease advance to a secondary progressive phase more slowly than adults. It is estimated to take 10 years more to progress, but the patients do so at a younger age, with a mean age of 35 years.

There are some differences in MRI features, especially in younger patients [52]. The lesions are more swollen, with an increased inflammatory component, more diffuse and oedematous, less defined, and may exhibit a favourable outcome in 4-5 months. Fewer cortical lesions are observed, and in the early stages, there are fewer black holes than in adults. In adolescents, MRI begins to resemble that of adults. For the paediatric population, there are different specific MRI criteria [53,54], and the criteria of Barkhof-Tintoré are less sensitive in this patient population. A differential diagnosis with acute disseminated encephalomyelitis is required.

Regarding studies on cerebrospinal fluid in children with MS, the study published by Chabas et al. in 2010 is considered a reference study [55] and demonstrates a different inflammatory profile in children under 11 years and adolescents. The cerebrospinal fluid of patients under 11 years of age exhibits more unique characteristics and greater pleocytosis at the expense of polymorphonuclear cells and a lower percentage of oligoclonal bands. In patients older than 11 years, there is a higher lymphocyte cellularity and presence of oligoclonal bands. These findings presumably are related to increased activation of innate immunity in children less than 11 years of age versus adaptive immunity.

Regarding the therapeutic management of these patients, all current information comes from personal experiences that have not been protocolized. It has been observed that first-line treatments, such as interferons and glatiramer acetate, are safe and well tolerated after 12 years of age. There have been reports of some isolated cases of hepatotoxicity in children under 11 years. Recent studies have examined the efficacy of natalizumab in the paediatric population, given that seronegativity for the JC virus is more common in children in comparison with adults. New clinical trials are being advanced with immunosuppressive drugs, such as fingolimod [56,57]. Because of their safety and efficacy data, BG12 might be an interesting drug for a clinical trial in this patient population.

The treatment algorithm to be followed is similar to that in adults, beginning with first-line drugs and proceeding to a second line in case of treatment failure [58]. It should be noted that in this patient population, safety monitoring is especially important because of the key role that the thymus plays in the maturation of T cells at this age, as this may generate premature immune senescence phenomena.

The characteristics of paediatric optic neuromyelitis are similar and use the same diagnostic criteria of 2006 as for adults. On the MRI of paediatric optic neuromyelitis, lesions can be observed that are much more diffuse, large, poorly demarcated, oedematous, and swollen; brain lesions can be ob-

served in the hypothalamus and diencephalon. As is the case with MS, progression is slower, with severe long-term prognosis.

From inflammation to neurodegeneration

In MS, there are inflammatory and neurodegenerative phenomena that likely exhibit a cause-and-effect or shared relationship. It is also true that there is growing evidence of the contribution of a phenomenon of the compartmentalization of inflammation that may be inaccessible to current immunomodulatory therapy. Identifying the mechanisms involved might help to understand the fact that the onset of disability changes across patients over time and does not follow a similar course.

Neuronal adhesion of T cells and lack of compensation of endogenous repair mechanisms

MRI studies, as well as *ex vivo* studies and experimental models, reveal that brain atrophy, a sign of neurodegeneration, appears early, even in patients with less than five years of disease progression. Experimental data by Zipp [59] have demonstrated that T cell adhesion to neurons triggers an inflammatory cascade that leads to neurodegeneration and, moreover, that there is a lack of compensation of endogenous repair mechanisms. Constant invasion and survival of these pathological T cells would be responsible for the progression of local inflammation to neurodegeneration. Other mechanisms include increased local plaque size and a lack of nutrient supply, with the resultant disconnection of the neural network by Wallerian degeneration. The results of their work illustrate how Th17 cells traverse vessels and invade the brain parenchyma, triggering inflammatory processes that accumulate mainly in the margins of demyelination; hence, the role of Th17 cells is increasingly recognized in the phenomena of inflammation.

Mitochondrial dysfunction and inhibition of oligodendroglial progenitor cells

In myelinated axons, 90% of mitochondria are located in internodal and juxtaparanodal regions; in cases of inflammatory aggression and demyelination, the axon mitochondrial content is reduced and fails to return to basal levels even in cases of remyelination. In addition, functional changes occur in mitochondria, including mitochondrial DNA deletions and a decrease in COX1 activity in complex IV of the respiratory chain. According to Mahad [60], during the course of the disease, there is a growing accumulation of these mitochondrial deletions, which translate into a loss of ATP production, thus leading to energy failure and contributing to the increase in demand for ATP by the demyelinated axon and the inability to produce ATP by the affected neurons. This mitochondrial dysfunction can induce tissue damage through three mechanisms: energy failure, free radical production, and induction of apoptosis, likely of oligodendrocytes; therefore, mitochondrial dysfunction is involved in the processes of demyelination and, according to the authors, in remyelination failure. Thus, hypothetically, mitochondrial failure is involved in the inhibition of oligodendroglial progenitor cells.

Oligodendrocyte apoptosis

According to Kuhlmann [61], loss of oligodendrocytes is heterogeneous in both chronic and active acute injuries, and the *PUMA* gene has been defined as a gene involved in apoptosis, although the mechanisms involved are not well established. Thus, in the cuprizone (CPZ)-induced demyelination animal model, no oligodendrocyte apoptosis occurs in *PUMA*-deficient animals, and therefore, there is no demyelination. As potential treatment options, two oral drugs are prominent: fingolimod, which in the CPZ-induced demyelination model reduces oligodendrocyte death and demyelination, and laquinimod, which produces a similar effect by downregulation of astrocyte activity.

Astrocytic processes

The possible link between astrocyte damage and demyelination in MS, optic neuromyelitis, and Balo's disease has been investigated by Masaki et al. [62] based on the results of a previous study in which the authors observed a loss of aquaporin-4 (AQP4) with no perivascular deposit of complement or immunoglobulins in the three entities. In this report, they studied the association between astrocytopathy and demyelination, examining the expression of connexins (Cx). All cases of Balo's disease exhibited hypertrophic astrocytes, loss of perivascular extensions, extensive loss of Cx43 and AQP4, which are expressed only or predominantly in astrocytes, and preferential loss of myelin-associated glycoprotein, related to distal oligodendropathy. MS exhibited a perivascular inflammatory infiltrate and astrocytopathy with loss of AQP4 and Cx43 in active lesions, and optic neuromyelitis exhibited

vascular astrocytopathy with complement deposition and distal oligodendropathy. The study's authors concluded that early disruption of astrocytic processes may precede demyelination and contribute to the pathogenesis of demyelinating disorders.

In this line, the receptor-mediated response of sphingosine 1-phosphate (S1PR) can help promote or inhibit the severity of inflammatory disorders of the central nervous system, a conclusion that is derived from the study designed by Wu et al. [63] for evaluating *in vitro* impact of fingolimod (FTY720) in astrocyte proliferation. The results demonstrate that fingolimod has a dual agonist/antagonist effect; its agonist binding to the S1PR receptor promotes the permanent internalization of the receptor, therefore acting as a functional antagonist by eliminating S1PR from the cell surface and thereby inhibiting excessive astrocyte proliferation.

Diffuse inflammation

Diffuse neurodegeneration develops in part independently of focal demyelinating lesion. In MS, this diffuse neurodegeneration is reflected by biochemical disorders and axonal loss in normal-appearing white matter, especially in the spinal cord and corpus callosum, and by diffuse general atrophy seen in MRI. An example is the cuprizone-induced reversible demyelination model in which, after remyelination, basal levels of myelin are not recovered [64]. The impact of isolated or repeated episodes of reversible demyelination on locomotor performance and neuroaxonal integrity has been investigated by Manrique-Hoyos et al. [65], who found that even after complete remyelination, axonal degeneration continues to advance at a slow pace and accumulates over time to become apparently functional in the long term. They studied three groups of animals: a normal diet control group, a group subjected to two cuprizone treatment periods separated by an intervening period of remyelination, and a third group treated with a single episode of demyelination. Mobility was assessed by the MOSS technique in the short and long term. Short-term results revealed that animals of both experimental groups exhibited reduced mobility compared to the control group, which recovered over the medium term; however, long-term mobility decreased again even more substantially. In addition, the numbers of neurofilaments after remyelination did not reach the numbers expressed by the control animals. These results suggest that remyelination does not prevent neurodegeneration, a finding that suggests the existence of specific neurodegenerative phenomena that are independent of inflammatory phenomena, apart from those directly affecting the neurodegenerative process (Figure).

Periplaque and plaque findings in the cortical area

The role of periplaques in MS has been studied by Lhuillier et al.[66], who analysed normal-appearing white matter, plaque, and periplaque in *post mortem* samples of the spinal cord of patients with progressive forms of the disease. The periplaque area exhibited less myelin than normal-appearing white matter, but surprisingly, myelinated axons of the periplaque had a thicker myelin sheath, although the sheath was abnormal according to the authors. Furthermore, there was an accumulation of macrophages and microglia. These results did not correlate with either the shape or the size or with inflammatory processes in the areas of the plaques.

Meanwhile, Clarner et al. [67] found plaques in the cortical area, focusing on leukocortical plaques on the boundary between white matter and gray matter. The aim of their study was to analyse the association between myelin deposits and the inflammatory response in an experimental model of demyelination and MS lesions. The results of the cuprizone model demonstrated that myelin loss correlated positively with microgliosis. In MS, there was less inflammatory activity in leukocortical plaques in contact with the gray matter, which is perhaps one of the reasons why remyelination phenomena are more frequent in gray matter than in white matter areas. Finally, the direct application of myelin debris in the corpus callosum or cortex induces an inflammatory response [68]. These findings suggest that myelin debris plays an important role in the inflammatory response during demyelinating processes.

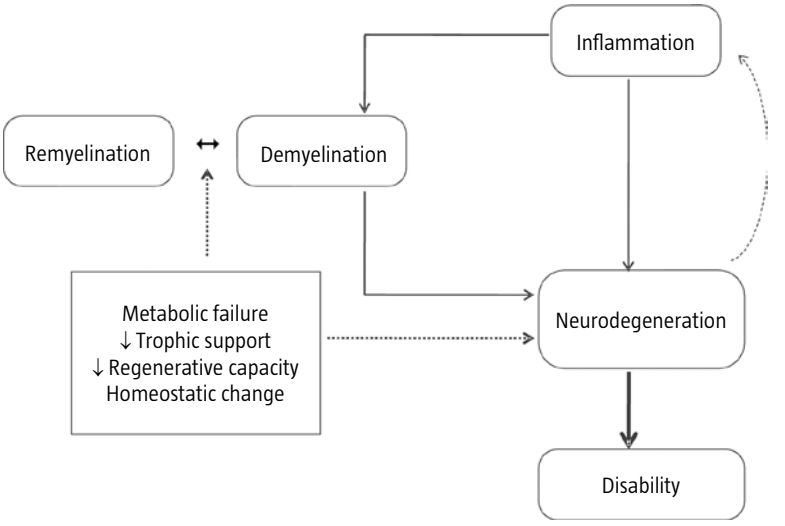
The differential role of macrophages

Macrophages, together with dendritic cells, are key components of cellular immunity, and they are believed to originate and renew themselves from hematopoietic stem cells. However, some macrophages develop in the embryo, as suggested by the earlier establishment of definitive hematopoietic stem cells. In a paper published in 2012, Schulz et al. [69] found that the MYB transcription factor was necessary for the development of hematopoietic stem cells and the whole cell line of monocytes and macrophages but that it was dispensable for the formation of microglial cells.

Ransohoff [70] has highlighted the importance of understanding the differential role of hematoge-

nous and brain macrophages as a future therapeutic strategy directed at neuroinflammatory processes. Both microglia and monocytes differentiate into macrophages, but there are functional differences between the two populations [71]. However, no immunohistochemical markers have been identified that differentiate macrophages derived from monocytes and those derived from resident microglia. New murine genetic models discriminate between resident microglia and infiltrating monocytes both in the healthy brain and in autoimmune inflammation. Using specific markers and the SBFSEM technique for 3D reconstruction, Lang et al. [72] examined the role of both cell lines in experimental autoimmune encephalitis. The results suggest that, although infiltrating monocytes invade and surround intact axons in early experimental autoimmune encephalitis, the contribution of microglia takes place later and is associated with cleaning myelinated debris, an essential function for remyelination. Furthermore, microglial cells are CX3CR1^{+}, but CCR2^{-} receptors are required for entry into the central nervous system and are present on macrophages derived from monocytes [72].

Figure. Inflammation and neurodegeneration in multiple sclerosis.



Chronic hypoxia and activation of Na^{+} channels

Assuming that axonal injury is not associated with complete demyelination, as there are viable axons in demyelinated areas and as areas where there is demyelination also exhibit reversible axonal dysfunction, Siffrin et al. [73] advanced potential targets for the prevention of neurodegeneration monitoring by two-photon laser scanning microscopy of the immune attack process on the axon in transgenic mice and of the steps involved in the axonal degeneration cascade. The results, in line with the assumption of energy failure but independent of mitochondrial dysfunction, demonstrate that chronic relative hypoxia is triggered in the demyelinated axon and Na^{+} channels, consequently activating Ca^{2+} channels and disturbing axonal flow, which may contribute to neurodegeneration.

The identification of Na^{+} channels as a possible contributor to the pathogenesis and development of clinical deficits in MS has led researchers to consider them as possible candidates for therapeutic targets for functional recovery in MS. At present, there are Na^{+} channel antagonists (phenytoin and lamotrigine) and NMDA receptor antagonists (memantine), among others, which can block the entry of Ca^{2+} into the axon and potentially and still very theoretically could help prevent neurodegeneration and the occurrence of MS deficits.

The family of Na^{+} channels includes nine isoforms (Nav1.1 to Nav1.9) differing in voltage dependence, kinetics, and pharmacological properties as well as in the developmental pattern and regional expression in neurons and glial cells of the immune system [74]. Microglia expresses voltage-dependent sodium channels both in vivo and in vitro, and blockade of these channels can attenuate some of their effector functions, such as proliferation of CD4+ T cells, the production of proinflammatory cytokines, nitric oxide, and reactive species, antigen presentation, and phagocytosis [75]. Specifically, Nav1.6 is the isoform primarily expressed in activated microglia and likely plays an important role in microglial activation associated with inflammation, as its blockade in experimental models by phenytoin reduces the inflammatory infiltrate. Furthermore, in Nav1.6-deficient animal models, phagocytosis and microglial migration are inhibited [75].

Cerebellar dysfunction in MS appears to be associated with sodium ion channelopathy. Shields et al. [76] observed the expression of the Nav 1.8 sodium channel in Purkinje cells in both animal models and in MS lesions, which is normally limited to the peripheral nervous system. Assuming that the upregulation of Nav1.8 in the cerebellum would have functional consequences, the authors developed a new transgenic mouse model overexpressing the Nav1.8 channel in Purkinje cells, with results of cell hyperexcitability accompanied by im-

paired coordination; in a contrary manner, Nav1.8 knock-out mice exhibited reduced clinical deficits. Physiologic and clinical abnormalities were reversed with the pharmacological blockade of Na^+ channels.

Conclusions

In recent decades, there has been a significant increase in the prevalence and incidence of MS, with doubts about the existence of a latitudinal gradient. The female to male sex ratio is increasing, but we still do not understand the exact mechanisms underlying the increased incidence of MS in women, although the available evidence points to an interaction between hormonal, genetic, and environmental factors. Female sex confers an increased risk for developing the disease, but does not have any negative effect on its progression. Pregnancy exhibits a protective effect on the disease, and assisted reproductive therapies increase the number of attacks. Exposure to current treatments during pregnancy does not lead to serious adverse effects on the newborn, although it is recommended to stop treatment beginning one menstrual cycle prior to the administration of classical immunomodulators and two months in the case of natalizumab and fingolimod.

The risk of MS, based on the additive and combined effect of the three major environmental risk factors (EBV, vitamin D deficiency, and smoking) on different genetic markers, greatly increases the risk of developing the disease. Paediatric MS constitutes an ideal population group for the study of susceptibility factors to disease and is teaching us that we should encourage collaborative studies due to the low prevalence of the disease to allow us to obtain a critical and relevant sample population.

In the pathogenesis of MS, there are inflammatory and neurodegenerative phenomena that exhibit a likely cause-and-effect or shared relationship. Th17 cells are heavily involved in processes of inflammation, leading to neurodegeneration and the presence of periplaques and myelin debris. Hypothetically, mitochondrial dysfunction would be involved in the process of demyelination and remyelination failure, which, however, does not prevent neurodegeneration. Meanwhile, early disruption of the astrocytic processes may precede demyelination and contribute to the pathogenesis of demyelinating disorders, and resident microglia are related to myelin debris cleaning, an essential function for remyelination. The phenomena that trigger chronic hypoxia activate Na^+ channels, which, as potential contributors to the pathogenesis and clinical deficits, are considered candidates for therapeutic targets for functional recovery in MS. At present, there are Na^+ channel antagonists (phenytoin and lamotrigine) that potentially and very theoretically could help prevent neurodegeneration in MS.

In the next two parts of this paper [77,78], the different strategies of repair and endogenous and exogenous remyelination will be discussed, addressing the current and future use of biomarkers in MS and presenting the results of recent studies with disease-modifying treatments.

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

Resumen. Los datos más relevantes presentados en la XXVIII edición del Congreso del Comité Europeo para el Tratamiento e Investigación en Esclerosis Múltiple (ECTRIMS), celebrado en octubre de 2012 en Francia, se han resumido en la quinta edición de la Reunión de Expertos Post-ECTRIMS celebrada en Madrid en octubre de 2012, fruto de la cual nace esta revisión, que se publica en tres partes. Esta primera parte de la revisión Post-ECTRIMS aborda la incidencia y prevalencia de la esclerosis múltiple (EM), que, en el ámbito mundial, ha aumentado a expensas de las mujeres, ya que el sexo femenino aumenta el riesgo de desarrollar la enfermedad, aunque no afecta de forma negativa a su evolución. El dimorfismo sexual en la EM es evidente, y todo apunta a una interacción entre factores hormonales, genéticos y medioambientales. La población pediátrica representa un grupo idóneo para el estudio de factores de susceptibilidad a la enfermedad, razón por la que se están planteando estudios colaborativos ideados para aumentar la muestra de pacientes, dada su baja prevalencia. En esta revisión se discute sobre los fenómenos inflamatorios y de neurodegeneración que intervienen en la pa-

togenia de la enfermedad, y que probablemente estén relacionados, bien de forma compartida o como causa efecto. Las hipótesis actuales apuntan a un fenómeno de compartimentación presumiblemente inaccesible a la terapia inmunomoduladora actual. Entre los posibles mecanismos involucrados en estos procesos de inflamación y desmielinización se discute el papel de las células Th17, disfunción mitocondrial, disrupción precoz de procesos astrocitarios e hipoxia crónica.

Palabras clave. Esclerosis múltiple. Genes. Hormonas. Inflamación. Medioambiente. Neurodegeneración.