Review of the novelties presented at the 29th 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 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), held in October 2013 in Denmark, were summarised at the sixth edition of the Post-ECTRIMS Expert Meeting, held in Madrid in October 2013, resulting in this review, to be published in three parts. This first part of the Post-ECTRIMS review presents an update on gender differences in multiple sclerosis (MS) as well as new evidence on the impact of sex hormones on the disease. We should consider that there is still much to discover with regard to the genetic components of the disease. Similarly, possible infections and lifestyle habits are added as triggers of the known environmental risk factors for MS. The interaction between genetics and the environment has been increasingly implicated as a cause of susceptibility to MS. With regard to the mechanisms of inflammation, axo-glial proteins, instead of myelin proteins, may be the early antigenic targets, and B cells have been implicated in the production of cytokines toxic to oligodendrocytes. Chitinase 3-like 1 (CHI3L1) is validated as a prognostic marker of conversion to MS, and immunoglobulin M oligoclonal bands and L-selectin could be incorporated as possible measures of the risk stratification strategy in patients treated with natalizumab.

Key words. Epigenetics. Inflammation. Multiple sclerosis. Sex. Tissue damage.

Introduction

The Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) is the most important international meeting on this disease. In its last edition, held in Denmark in October 2013, over 8,000 specialists in multiple sclerosis (MS) gathered from around the world.

For the sixth consecutive year, the Post-ECTRIMS Expert Meeting was held in Madrid, a meeting that is scientifically supported by the Spanish Society of Neurology and that invites recognised national experts to assemble to present the most relevant data addressed at the ECTRIMS Congress.

This article incorporates a full review, to be published in three parts, including the latest developments in basic and clinical research presented at the largest international conference devoted to the understanding and treatment of MS.

Sex and multiple sclerosis

Sex influences susceptibility to MS and its phenotypic expression. This is reflected both in cross-sectional studies of prevalence and longitudinal studies of incidence showing that MS is more common in women, especially the relapsing-remitting (RR) form, a disparity that has increased in recent decades. There are exceptions, as shown by the study conducted by Mackenzie et al. [1] in an English cohort during the 1990–2000 period, with increased prevalence figures, perhaps because of increased life expectancy and access to health services, albeit with a decreased incidence similar between men and women. In contrast, a recent systematic review of the incidence and prevalence of MS in Europe, in which 123 studies conducted between 1985 and 2001 were analysed, concludes that, with rare exceptions, the incidence of MS is higher among women at a 3:1 ratio and that the prevalence has increased in more recent studies [2]. Whereas this 3:1 ratio is overrepresented in the RR form, the sex ratio is almost equal in the primary progressive (PP) form of the disease, a difference that could be attributed to a lower probability of relapse in men. The retrospective cohort study conducted by Kalincik et al. [3], designed to analyse the effect of sex on the incidence

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of relapse, included 23,000 patients from 176 centres in 65 countries. Their results showed a higher frequency of relapse among women (17.7%), accompanied by more benign symptoms, largely affecting the visual and sensory pathways; conversely, in men, relapses were found to be less common and more severe, affecting the pyramidal tract, brain stem and cerebellum, which are classically associated with poor prognosis due to more severe sequelae.

The relationship between sex and long-term disability is reflected in cohort studies, having shown a slower progression in women [4,5], even though the study of gender differences in terms of radiological evolution shows that grey matter atrophy in relapsing-remitting multiple sclerosis (RRMS) does not depend on gender. [6].

In sum, there is enough evidence to conclude that sex influences susceptibility and phenotypic expression as well as the course of MS. The causes are still unknown, but the notion that it can be accounted for by changes in diagnostic criteria is refutable by considering the disease onset adjusted for year of birth, as well as increased life expectancy, rather than the date of diagnosis; such analysis merely suggests modified prevalence. All evidence implicates the influence of sex hormones, beyond the role of chromosomes, and genetic-environmental or epigenetic interactions.

New evidence on the effect of sex hormones

According to preclinical studies, progesterone promotes an anti-inflammatory Th2 phenotype *in vitro* and reduces the severity of chronic and acute experimental autoimmune encephalomyelitis. Observational studies in pregnant women show its remyelinating and protective role. However, the results of the POPARTMUS [7] study have failed to demonstrate postpartum improvement in 300 patients treated with high doses of progesterone (10 mg/day) and low doses of estradiol (100 µg transdermally administered once per week). In the experimental autoimmune encephalomyelitis model, the results are controversial because some studies support the clinical benefit and neuroprotective effect of progesterone, which is especially apparent in combination with estradiol E2 [8], whereas others suggest its influence lies in the increased neural vulnerability to apoptotic damage [9] or its lack of effect [10].

Oestrogens in experimental autoimmune encephalomyelitis behave as peripheral immunomodulators and as neuroprotective agents in the central nervous system. In MS, low oestrogen levels during the postpartum period are associated with an increase in attacks, as in menopause (especially induced menopause), which is accompanied by new or worsening symptoms, such as impaired concentration and memory, fatigue, depression, and headaches, among others [11].

Testosterone has been shown to promote remyelination in an animal model of cuprizone-induced demyelination by inducing an increase in oligodendrocyte progenitors and glial fibrillary acidic protein (GFAP). In MS, an empirical study of the effect of testosterone treatment in 10 RRMS patients showed a decrease in brain atrophy, cognitive improvement, and an increase of the ciliary neurotrophic factor, although it had no effect on active lesions [12]. The study by Bove et al. [13], presented at this year's ECTRIMS Congress, found an inverse correlation between the results of the *Symbol Digit Modality Test* and baseline free testosterone, but not with the testosterone/estradiol ratio, in addition to identifying a high prevalence of hypogonadotropic hypogonadism (HH) in MS patients (39%); these findings associate testosterone with worse clinical outcomes, although its possible role as a neuroprotector or as a marker of the severity of the disease is yet to be determined.

Genetic component, triggers and epigenetic factors

Genetic contribution

Much remains to be done regarding the study of the genetic component of MS. This is made evident by the following facts:

- Studies have observed a decrease in λ_s estimates, which reflect familial aggregation—i.e., the risk of recurrence when a sibling of an MS patient has the disease has significantly decreased from initial values of 20–40 to 6.3 in recent studies [14].
- A higher probability of finding true associations between common alleles and the disease is found with larger sample sizes [15].
- Increased numbers of genetic associations have been identified in recent years, exceeding 100 in 2013 [16].
- The list of genes associated with MS outside the human leukocyte antigen (HLA) region has grown, as shown by the ImmunoChip study (considered the largest experiment to date on the genetic analysis of common variants of MS) [17].

This last study has provided the most comprehensive genetic susceptibility map of MS, expanding

the list of genes associated with MS to 110 common genetic variants outside the HLA region, most of them (54%) located in intergenic regions, 43% in intronic regions, and only 3% in exonic coding regions. These findings suggest the existence of unidentified rare variants that will contribute to a better characterisation of the genetic component of MS.

The underlying mechanisms by which the HLA-DRB*15:01 allele confers an increased risk for developing the disease are still unknown. Researchers at the Multiple Sclerosis Centre of Catalonia [18] have investigated the gene expression profile with microarrays in peripheral blood cells of patients stratified according to the presence of this allele, with results of a significantly higher differential expression of the HLA-DRB1 gene in HLA-DRB1*15:01(+) patients compared to HLA-DRB1*15:01(–) patients; these results were validated by allele-specific polymerase chain reaction in patients heterozygous for the *15:01 allele.

Pharmacogenetics is considered an open door to the identification of genetic variants that respond to treatment. To date, there are two published studies of genome-wide association in relation to interferon-β [19,20], with identified associations that have yet to be validated in large cohorts of patients. However, above all, pharmacogenetics has achieved prominence in the development of neutralising antibodies in patients treated with interferon, most likely mediated genetically by HLA class II alleles, as seen in the study by Hoffmann et al. [21] of patients with the HLA-DRB1*0401 and HLA-DRB1*0408 alleles, who were at increased risk of developing neutralising antibodies. In line with this effect of HLA alleles favouring the development of neutralising antibodies, the recently published findings of Link et al. were shown. [22]. These results replicate those previously reported by Hoffmann et al. [21], showing an association between an increased risk of developing neutralising antibodies and the DRB1*0401 allele in patients treated with interferon β-1b as well as an association with the main genetic risk allele for MS, DRB1*15, in patients treated with interferon β-1a. Additionally, a study of genetic variants in Toll-like receptors (TLR) shows TLR6 polymorphism association and increased risk of developing neutralising antibodies. [23].

The relationship between genetic polymorphisms associated with MS and the expression of proximal genes has been investigated by James's team [24] to understand the impact of genetics on the pathogenesis of MS. To do this, they analysed the transcriptome through RNA sequencing of mononuclear cells of 120 MS patients: 105 with RRMS, nine with secondary progressive multiple sclerosis (SPMS) and six with primary progressive multiple sclerosis (PPMS). For each genetic variant associated with the disease that was identified within the Immuno-Chip project, they studied the expression of genes located within 400 kb on each side of the variant or polymorphism (*single-nucleotide polymorphism*). The main results show the r201202118 region in linkage disequilibrium with other polymorphisms associated with the differential expression of *CYP27B1*, *METTL21B*, *TSFM* genes, and in particular, *METTL21B*, whose expression is markedly reduced in patients carrying the risk genotype. These results confirm the previous findings of a Spanish study involving members of the Spanish Network of Multiple Sclerosis [25].

Multiple sclerosis triggers: new and more effective approaches to prevent the disease

Rigorous epidemiological research is critical because it helps to improve the understanding of environmental factors involved in MS, being at the level at which the prevention or risk reduction of developing the disease can be more easily achieved.

The involvement of viruses in the pathogenesis of MS is recognised; however, the relationship between viral infections as triggers of the disease, among other factors, remains unresolved because the stage of the disease in which they exert their effect and the mode of interaction with other environmental and genetic factors are unknown. There is growing evidence of viruses being involved in the disease, especially the Epstein-Barr virus (EBV) and human endogenous retroviruses. The latter can modulate the immune response by innate or adaptive response mechanisms or can alter the expression of nearby genes. The association of human endogenous retroviruses with MS has been shown in numerous published studies showing the presence of retroviral particles in lymphocyte cell cultures from MS patients that are absent in control subjects [26,27].

EBV infection is one of the best documented risk factors in the onset of the disease. As a potential underlying biological mechanism, the expansion of viral-specific autoreactive T cells is proposed as a response to the infection of B lymphocytes, which cross the blood-brain barrier and may trigger MS. EBV seroprevalence and the elevated levels of both the viral capsid antigen (VCA) and the Epstein-Barr nuclear antigen (EBNA) are common in the paediatric MS population [28,29]. Patients with infectious

mononucleosis have 2–3 times higher risk of developing MS [30], and MS patients have increased levels of Epstein-Barr nuclear antigen (EBNA-1) that may precede the onset of the disease [31]. The increase of the selective immune response to EBNA-1 in patients with clinically isolated syndrome suggests its potential role as a prognostic marker of the conversion to clinically definite multiple sclerosis (CDMS) [32]. However, a study by Khule et al. [33] to define variables that can better predict the conversion from clinically isolated syndrome to CDMS studied the following factors as possible independent contributors to the risk associated with immunoglobulin G (IgG) oligoclonal bands (OCB) and T_2-hyperintense lesions suggestive of demyelination in baseline magnetic resonance imaging (MRI): EBV systemic humoral response, serum vitamin D, biochemical evidence of tobacco consumption (cotinine), and the determination of cytomegalovirus-IgG. The results showed that the presence of OCB and lesions on MRIs independently increased the risk of conversion to MS, and a weak association with vitamin D was also found. Serum cotinine and anti-EBNA-1 antibodies were not predictors of conversion to MS, although patients with higher EBNA-1 IgG titres had a higher percentage of OCB (+).

The epidemiological link between MS and human immunodeficiency virus (HIV) infection and antiretroviral treatment is very weak, despite a similar age of onset and prevalence in both entities, as only 10 cases of patients with HIV and MS have been described in the past 30 years. The latest data from the Danish National Registry (in which 5,018 HIV patients were matched with 50,194 controls by age and sex) showed only one HIV patient who developed MS, thus conferring a fairly low relative risk of 0.3. These results are similar to those found in an English registry, where a relative risk of developing the disease of 0.38 was calculated, which had diminished to 0.22 after a one-year follow-up –a time in which such patients should have been on antiretroviral treatment. These results have been the starting point to design the first clinical trial aiming to investigate infections as a cause of MS. This is the CHARCOT INSPIRE project, a pilot study on the relapsing forms of the disease that uses raltegravir, whose results will be presented in the next edition of ECTRIMS.

The results of the study presented by Alfredsson's team [34] added to the already clear relationship established with smoking, showing that the duration and intensity of tobacco consumption independently contribute to increased disease risk, a detrimental effect that decreases a decade after quitting.

Salt intake has been associated with increased clinical and radiological MS activity in a recent study by Farez et al. [35], which showed higher attack rate, MRI activity and T_2 lesion load in a group of patients with higher salt intake and an increase of 3.65 in the number of lesions on MRI per gram of salt consumed daily; the same data did not correlate with serum sodium.

A recent analysis of possible factors with predictive value for the age of onset of MS in 2,511 Danish patients, presented by Oturai et al. [36], has determined that a high body mass index at age 20, prior mononucleosis, high alcohol consumption between 15 and 19 years, and being homozygous for HLA-DRB1*15.01 are associated with disease onset at a younger age.

Genetic-environmental interactions as causes of multiple sclerosis

Fortunately, an increasing number of risk factors that could lead to the clinical syndrome are being identified. The current objective is to deepen our understanding of intermediate phenotypes, i.e., the molecular mechanisms or altered cellular functions that might be involved in the development of paraclinical features such as T_2 demyelination and asymptomatic lesions, which will often later lead to an isolated neurological syndrome and/or MS. Ambitious studies are being developed that aim to identify new genetic variants associated with MS, such as the above-mentioned ImmunoChip study [17], although new areas of study should be directed to identify where risk alleles exert their effect (in the central or in the peripheral nervous system) and the molecular level at which they act (protein expression, mRNA expression, transcriptional or post-transcriptional). For example, the study by Ottoboni et al. [37] demonstrated that monocyte stimulation with tumour necrosis factor α (TNF-α) alters the expression of different MS risk genes, although for some of these genes, the sensitivity to TNF-α was unknown; these findings suggest a relationship between different genes involved in the disease. With the aim of understanding the functional consequences of MS susceptibility genetic variants, De Jager currently has several projects underway. In line with the above, the ImmVar Project, a systematic review of susceptibility *loci*, and the PhenoGenetic and CLIMB projects, to identify the molecular pathways affected by genetic susceptibility *loci*, are notable. The fact that fewer than 40% of MS risk alleles directly influence gene expression, whereas the rest are involved in regulatory functions, is re-

markable. Another notable result is that the myeloid line plays an important role in disease susceptibility.

The importance of genetics and the environment in MS has given way to evidence that disease susceptibility is determined by epigenetic changes, or heritable changes in gene expression that do not correspond to changes in the DNA sequence and are usually due to environmental factors. Many epigenetic changes in MS are considered to be located in the major histocompatibility complex (MHC) region, not only because of new studies but also based on previous data that showed intergenerational changes in the frequency of the HLA-DRB1*15 allele in women [38] and increased female:male ratio in MS in HLA-DRB1*15(+) patients versus HLA-DRB1*15(–) patients [39]. In addition to the increased female:male ratio that genetic epidemiology has demonstrated in recent decades [40], an effect of parental origin has been found in disease susceptibility insofar as those siblings who share a mother with MS have higher risk of developing the disease than those who share an affected father [41]. All data relating to females in MS involve epigenetic mechanisms.

It has been shown that tobacco and diet (vitamin D and folate) are environmental risk factors that influence gene expression via epigenetic mechanisms such as DNA methylation, histone or micro-RNA modification [42]. For example, DNA methylation at CpG dinucleotides in CD4+ T cells isolated from RRMS patients and their contribution to the pathogenesis of the disease have been investigated by Graves's team, who found a differential methylation signal on chromosome 6 between patients and control subjects that corresponded to the HLA region, particularly the *HLA-DRB1* gene, and that was more hypomethylated in MS patients, especially in carriers of the HLA-DRB1*15:01 allele.

Genetic interaction with vitamin D is documented. The risk of disease is associated with the month of birth and the HLA-DRB1 genotype [43], an interaction that began to be understood following the discovery of an element of response to vitamin D in the promoter region of the *HLA-DRB1* gene [44] but that is becoming increasingly complicated as new findings appear; such complicating findings include those derived from a study of the genomic map of the vitamin D receptor, showing the existence of 2,776 genomic regions occupied by this receptor and 229 genes that change their expression in response to vitamin D, especially in certain autoimmune diseases or cancers [45]. A recent study in adolescents has shown that severe vitamin D deficiency causes changes in DNA methylation in leukocytes [46], which shows that this deficiency leads to epigenetic changes involved in the regulation of immune cells.

The interaction between obesity in adolescence and HLA-risk genes increases the likelihood of developing MS. This finding comes from new data from the Swedish EIMS study, which has been underway since 2005 with the aim of studying genetic and environmental factors and their interactions in relation to the risk of developing MS; to date, this study has sampled a total of 2,400 incident cases of MS and 4,800 controls. Specifically, EIMS cohort data, coincident with those derived from a cohort at the University of California (KPNC), have shown that elevated BMI in adolescence increases the risk of susceptibility to MS, especially in HLA-DRB1*15(+) and HLA-A*02(–) patients. Among the possible explanations, it is suggested that obesity may induce a state of chronic, low-grade inflammation that would favour the activation of central nervous system autoimmunity; that leptin could be a link between obesity, metabolic status and autoimmunity; or that obesity could be linked to low vitamin D, the latter being unlikely, as the results do not change with regard to sun exposure.

Paediatric multiple sclerosis

Between 4.5 and 9% of all MS starts before age 18. In 2007, the International Paediatric Multiple Sclerosis Study Group published a reference study in which consensus definitions were established for the various demyelinating diseases occurring during the paediatric age [47]. This group of patients has special epidemiological and clinical features. Whereas in adulthood, MS is more common in females, this female:male ratio is almost balanced prior to age 11; MS only becomes more common in females upon reaching adolescence. Most patients start with the RR form, although cases of PP evolution are anecdotal. Those affected suffer a greater attack rate in the first two years, the interval between the first and second attack is smaller, and they may develop some disability at a younger age. In recent years, there have been several studies on cognitive impairment in this patient population, and it has been observed that 30–70% have cognitive impairment from early stages of the disease, with the consequent academic and social sequelae that could be anticipated for this age.

Differential diagnosis requires the exclusion of other characteristic demyelinating diseases in children, such as acute disseminated encephalomyelitis, with much better prognosis. There are different

MRI criteria specific for the paediatric age [48,49], but those of Barkhof-Tintoré are still being used, although it is known that they have lower sensitivity in this paediatric stage than in adulthood. It is common to observe diffuse, ill-defined and more oedematous lesions with increased inflammation and a greater number of lesions in the posterior region. [50]. In the early stages, fewer black holes, fewer cortical lesions and less brain atrophy are observed. Cerebrospinal fluid may show some peculiarities. In one reference study by Chabas [51], patients under 11 years of age had a different inflammatory profile than adolescents. In children under 11 years of age, neutrophilic pleocytosis, a lower percentage of positive OCB and intrathecal IgG secretion could be found; similar findings to adults were observed in teenagers, with increased IgG and intrathecal OCB synthesis. These findings have an immunological explanation that is related to the fundamental role of innate immunity in younger patients versus adaptive immunity.

With regard to prognosis in this patient population, it should be mentioned that there are few longitudinal studies on the natural history of the disease. It has been described that they can evolve to SP form at an earlier age. Patients had the RR form much longer, but they could have had the SP form approximately 10 years earlier than the adult population, with an average of 35 years.

In terms of disease-modifying treatment, the International Paediatric Multiple Sclerosis Study Group [47] recommends that all paediatric MS patients should be considered for treatment with interferon-β or glatiramer acetate upon being diagnosed with the disease. These drugs have demonstrated efficacy in reducing the annual relapse rate, similar to that observed in adults. Unfortunately, a high percentage of these patients discontinue treatment due to intolerance, persistent relapse and non-adherence. Several studies have reported personal experiences with drugs, such as natalizumab, which can be effective when following the directions of the Summary of Product Characteristics (SMPC), similar to those in adults. The first clinical trial with fingolimod is being conducted in this patient population. Innovative oral drugs may be an interesting alternative in the future.

Inflammation and tissue damage in multiple sclerosis

Mechanisms of inflammation

Bar-Or [52] focused on the study of paediatric cohorts because of the possibility to study events at very early stages of the disease; this approach could identify potential antigenic targets and study the role of different cell types involved in the mechanisms of inflammation. The increased response of T cells against myelin antigens that is observed not only in children with demyelinating diseases but also in those with non-inflammatory processes of the central nervous system and in autoimmune diseases, such as type 1 diabetes mellitus, involves immune dysregulation mechanisms shared and combined by different diseases and challenges the existing vision that autoreactive cells in the central nervous system inherently mediate the disease in the early stages of MS. Interestingly, proteomic techniques in cerebrospinal fluid do not show proteins from compact myelin, which would act as early antigenic targets; rather, they show proteins of the axoglial apparatus, such as neurofascin and contactin, among others, that could indicate a pathogenic role in the disease [53] and pose the alternative pathogenic theory model based on a primary disturbance in the central nervous system triggering an immune response and the subsequent inflammatory lesion of the central nervous system [54]. MS is an ongoing inflammatory process, as we can see by the epitope expansion reflected in serum only three months after the onset of a clinically isolated syndrome in children (Quintana, unpublished data).

In recent years, Th17 cells have been implicated in a fundamental role. The Th17 response decreases in patients undergoing bone marrow transplantation, but not the Th1 response, thus Th17 cells being implicated in a mechanism underlying the decrease in disease activity observed in these patients. [55]. Meanwhile, B cell involvement goes beyond the known processes of antibody production and antigen presentation. It has been shown that they produce cytokines toxic to oligodendrocytes in vitro [56] and that they form ectopic germinal centres whose presence contributes to both the pathology of the subpial grey-matter and the development of a rapid clinical course of the disease [57].

Mechanisms of tissue damage

Kerschensteiner [58] considered neuroinflammatory tissue damage in the axon essential in the process and focused on how new microscopy techniques *in vivo* may help to better understand the mechanisms involved. For example, the study by Nikic et al. is noteworthy [59]: through *in vivo* imaging in a mouse model of MS, the authors identified a form of axonal injury not previously described that they called 'fo-

cal axonal degeneration'. They described it as a sequential process, which begins with focal oedema and progresses to axon fragmentation. Interestingly, not all swollen axons progress—instead, 30% recover spontaneously. The first sign of damage appears to be a mitochondrial morphological alteration restricted to areas of inflammatory infiltration even when the myelin is intact, elicited by reactive species of activated microglia. In fact, treatment with antioxidants recovers 80% of the axons in the phase of inflammatory damage. Likewise, blocking the influx of calcium into the axon prevents mitochondrial oxidation, which shows the causal relationship between the two mechanisms.

Oxidative damage associated with mitochondrial DNA damage has been shown to be the dominant pathway of tissue damage and degeneration in cortical lesions in a study by Wimmer et al. [60] designed to identify specific mechanisms leading to primary plaque-like demyelination and neurodegeneration. Neuropathological analysis, combined with the study of gene expression in *post-mortem* brains of patients with MS, meningitis, Alzheimer's disease and control subjects, has identified 301 differentially expressed genes associated with MS, most of which are involved in inflammation and oxidative stress processes.

Additionally, microglial inflammation may be involved in diffuse white matter inflammation, which, according to a study by Bramow et al. [61], would be associated with less permanent remyelination and reduced survival, at least in progressive MS. Immunohistochemical analyses of samples from patients with progressive forms showed lower demyelination in white matter areas with the formation of microglial nodules as well as areas of demyelination in apparently remyelinated zones with residual inflammation.

The pathogenesis of cortical atrophy is still unknown, although new MRI findings of the study provided by Klaver et al. [62] in 11 *post-mortem* brains conclude that although histological distribution is heterogeneous, the predominant underlying substrate of grey matter atrophy visible on MRI is axonal and neuronal loss that does not correlate with demyelination.

The immune demyelinating pattern is also heterogeneous among individuals, suggesting that the mechanisms and targets of tissue damage in early MS lesions may differ between different groups of patients [63]. The longitudinal analysis of the damage pattern in sequential biopsies or biopsy and autopsy samples by immunohistochemistry shows histopathological homogeneity that is maintained for each patient, an observation with potentially important implications for an individualised therapeutic approach.

Biomarkers in cerebrospinal fluid: current status and clinical application

Diagnosis and prognosis of the disease

The KIR4.1 potassium channel has proven to be a target of autoantibody response in a group of MS patients [64], with higher serum levels compared to other neurological diseases and control subjects. However, although the results have been replicated in two independent groups, it is necessary to evaluate them in other series. IgM OCB predicts greater disability and increased disease activity [65,66] (Table).

Chitinase 3-like 1 has been validated as a prognostic marker for conversion to MS and disease severity in patients with clinically isolated syndrome [67]; the neurofilament light subunit (NfL) appears as a good prognostic marker for evolution to MS of isolated neurological syndromes [68] (Table).

The usefulness of glial fibrillary acidic protein (GFAP) in cerebrospinal fluid in the diagnosis and prognosis of inflammatory demyelinating diseases (neuromyelitis optica, seronegative neuromyelitis optica, MS, tumefactive demyelinating lesions and Behçet's disease) was studied by Nishiyama et al. [69] on the basis of prior pathological studies on neuromyelitis optica that showed extensive loss of GFAP and aquaporin-4 (AQP-4), particularly in perivascular regions [70]. The main results were elevated GFAP levels observed in the cerebrospinal fluid of patients with neuromyelitis optica and one case of seronegative neuromyelitis optica with high GFAP levels that later seroconverted. These findings reflect astrocyte injury and the possible role of GFAP as a biomarker for neuromyelitis optica in certain cases.

Pathogenesis and immune activation

Anti-myelin-oligodendrocyte-glycoprotein (anti-MOG) antibodies may be associated with a wide range of demyelinating diseases of the central nervous system. A recent study showed high titres in paediatric patients with acute disseminated encephalitis, MS, neuromyelitis optica, AQP-4(–), isolated optic neuritis or transverse myelitis, but not in adults with these diseases [71].

Other studies, using DNA *arrays*, have demonstrated a heterogeneous antibody response against

Table. Role of biomarkers in serum and cerebrospinal fluid.

Immune activation and tissue damage	Immune activation	Serum surface markers, mRNA, microRNA, etc.; CSF levels of cytokines/chemokines, MMP, etc.
	Soluble immune factors	Serum levels of cytokines, antibodies, micro-RNA, etc.
	Tissue damage	Serum neurofilaments; CSF levels of MBP, neurofilaments, etc.
Diagnosis/prognosis	KIR4.1	
	Intrathecal oligoclonal bands	
	IgG index	
	Chitinase 3-like 1 in clinically isolated syndrome	
	Neurofilament light subunit in clinically isolated syndrome	
Pharmacovigilance	Initial screening	Monoclonal gammopathy (interferon-β)
		VZV serology, JCV (immunosuppression)
Monitoring	JCV serology (natalizumab)	
	CD56 bright (daclizumab)	
	Neutralising antibodies (interferon-β and natalizumab)	
Potential surrogate markers of treatment	Axonal degeneration	CSF neurofilaments levels
Potential future markers of baseline response	Specific of type 1 interferon	
	Peripheral blood mononuclear cells transcriptomic profiles	

CSF: cerebrospinal fluid; JCV: John Cunningham virus; MBP: myelin basic protein; MMP: matrix metalloproteinase; mRNA: messenger RNA; VZV: varicella zoster virus.

various myelin antigens, such as 2', 3'-cyclic nucleotide 3'-phosphodiesterase (CNP), myelin basic protein (MBP), MOG, and proteolipid protein (PLP) [72]. It is important to note that methylprednisolone treatment clearly decreases autoantibody reactivity; this is leveraged in clinical practice to perform lumbar puncture in patients treated with corticosteroids to prevent possible negative outcomes.

Axonal injury and neuroprotection

The presence of NfL in cerebrospinal fluid as a possible marker of neurodegeneration, together with preclinical findings pointing to the loss of neuronal volume suggestive of a possible neuroprotective effect of fingolimod, were incorporated into the development of a study that aimed to show a reduction in NfL levels in patients from the FREEDOMS study treated with fingolimod (0.5 mg and 1.25 mg) for one year [33]. After 12 months of treatment, a significant reduction of NfL levels was observed versus placebo (p = 0.001), which was associated with both doses of fingolimod. In line with the above, treatment with natalizumab also clearly decreases NfL levels in cerebrospinal fluid and possibly the accumulation of axonal injury in relapsing forms of MS [73]. These findings reinforce the rationale for determining NfL as a measure of neurodegeneration and its use in monitoring the possible neuroprotective effect of treatment. Furthermore, the release of NfL into the cerebrospinal fluid has been closely associated with the presence of IgM OCB [74].

Risk prediction

IgM OCBs against lipids have proven to be a protective factor against the development of progressive multifocal leukoencephalopathy in patients treated with natalizumab. One national study of 365 MS patients treated with natalizumab demonstrated that the percentage of patients with progressive multifocal leukoencephalopathy is higher among patients negative for IgM OCB against lipids than in those IgM OCB(+). Additionally, the combination of IgM with the risk stratification factor of progressive multifocal leukoencephalopathy in the presence of anti-John Cunningham virus (anti-JCV) antibodies showed a similar risk of developing progressive multifocal leukoencephalopathy between anti-JCV(–) patients and between anti-JCV(+) and IgM(+) patients, whereas the group at highest risk were anti-JCV(+) and IgM(–) patients.

Another novelty in the identification of new biomarkers for predicting the risk of progressive multifocal leukoencephalopathy comes from the study of Schneider et al. [75], who evaluated the role of L-selectin (CD62L) levels. They analysed and compared L-selectin levels in patients treated with natalizumab who developed progressive multifocal leukoencephalopathy with those who did not develop the disease. Additionally, they compared MS patients not being treated and patients who developed progressive multifocal leukoencephalopathy without treatment with natalizumab against controls. Surprisingly, L-selectin (CD62L) exhibited a strong correlation with the development of progressive multifocal leukoencephalopathy. The per-

centage of expression of L-selectin (CD62L) by $CD4^+$ T cells was significantly lower in patients who developed progressive multifocal leukoencephalopathy prior to diagnosis compared with patients treated with natalizumab without progressive multifocal leukoencephalopathy, findings suggesting that a lack of expression of L-selectin (CD62L) may be a biomarker for individual risk assessment of progressive multifocal leukoencephalopathy and could therefore be incorporated as a possible measure of the risk stratification strategy adopted for patients treated with natalizumab. In fact, the authors conclude that a determination of selectin levels < 15% after 18 months of treatment, being repeated after one month, is reason to consider treatment discontinuation. Obviously, these data require validation in a larger cohort of patients.

Conclusions

MS is more common in women, although it manifests in a more benign form, with sex hormones being partially involved in these changes and being dependent on the dose and patient age in clinical trials. Overall, the available evidence suggests that female sex hormones have more anti-inflammatory effect and that testosterone has more neuroprotective activity.

Studies characterising the genetic component of the disease find new associations or rare genetic variants, and the list of risk genes for the disease expands to 110 outside the HLA region. New evidence on the main genetic risk factor for MS underscores epigenetic changes that modify gene expression.

Apart from the known environmental risk factors for MS, new trigger point of infections and lifestyle habits have been identified, such as high tobacco consumption and salt intake, higher body mass index, and alcohol consumption in youngsters. The importance of genetics and the environment in MS has given way to evidence showing that disease susceptibility is determined by epigenetic changes, many of which are considered to be located in the MHC region, although the molecular confirmation of these mechanisms and their precise location remain difficult to ascertain.

Regarding the mechanisms of inflammation, axoglial proteins act as early antigenic targets instead of myelin proteins, and the Th17 response is involved in decreasing disease activity. B cells have been implicated in the production of cytokines toxic to oligodendrocytes. Mitochondrial oxidation induced by reactive species from microglia precedes morphological change of the axon and triggers local axonal degeneration that may be reversible. This oxidative damage is the dominant pathway of tissue damage and degeneration in cortical MS lesions. Grey matter atrophy is explained by the axonal and neuronal loss, not being correlated with demyelination, and in the progressive forms, diffuse inflammation is associated with less permanent remyelination.

Among the novelties of biomarkers in cerebrospinal fluid, the validation of chitinase 3-like 1 as a prognostic marker of conversion to MS is noteworthy. IgM OCB and L-selectin could be incorporated as possible measures of the risk stratification strategy in patients treated with natalizumab.

The second part of this article [76] focuses on diagnostic imaging and differential diagnosis, clinical and paraclinical monitoring of neurodegeneration, progression and disability, and functional imaging and neural connectivity. Finally, the third part [77] discusses the effects of immunomodulatory therapy on the natural history of MS, collects possible future therapeutic strategies that go through the experimental models, and discusses clinical trials currently underway as well as future treatments.

References

1. Mackenzie IS, Morant SV, Bloomfield GA, Macdonald TM, O'Riordan J. Incidence and prevalence of multiple sclerosis in the UK 1990-2010: a descriptive study in the General Practice Research Database. J Neurol Neurosurg Psychiatry. 2013 Sep 19. [Epub ahead of print].
2. Kingwell E, Marriott JJ, Jette N, Pringsheim T, Makhani N, Morrow SA, et al. Incidence and prevalence of multiple sclerosis in Europe: a systematic review. BMC Neurol 2013; 13: 128.
3. Kalincik T, Vivek V, Jokubaitis V, Lechner-Scott J, Trojano M, Izquierdo G. Relapse incidence in women and men throughout the course of multiple sclerosis: an MSBase cohort study. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
4. Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain 2003; 126: 770-82.
5. Leray E, Yaouanq J, Le PE, Coustans M, Laplaud D, Oger J, et al. Evidence for a two-stage disability progression in multiple sclerosis. Brain 2010; 133: 1900-13.
6. Dolezal O, Gabelic T, Horakova D, Bergsland N, Dwyer M, Seidl Z. Development of grey matter atrophy in relapsing remitting multiple sclerosis is not gender-dependent: results of a five-year follow-up study. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
7. Wattjes M. How and when should brain and spinal cord MRI be performed in the diagnostic process? 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
8. Garay L, Gonzalez Deniselle MC, Gierman L, Meyer M, Lima A, Roig P, et al. Steroid protection in the experimental autoimmune encephalomyelitis model of multiple sclerosis. Neuroimmunomodulation 2008; 15: 76-83.
9. Hoffman GE, Le WW, Murphy AZ, Koski CL. Divergent effects of ovarian steroids on neuronal survival during experimental allergic encephalitis in Lewis rats. Exp Neurol 2001; 171: 272-84.

10. Voskuhl RR, Pribyl TM, Kampf K, Handley V, Liu HB, Feng J, et al. Experimental autoimmune encephalomyelitis relapses are reduced in heterozygous golli MBP knockout mice. J Neuroimmunol 2003; 139: 44-50.
11. Bove R, Secor E, Vaughan T, Katic B, Chitnis T, Wicks P. Menopause may worsen the symptoms of multiple sclerosis. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
12. Sicotte NL, Giesser BS, Tandon V, Klutch R, Steiner B, Drain AE, et al. Testosterone treatment in multiple sclerosis: a pilot study. Arch Neurol 2007; 64: 683-8.
13. Bove R, Musallam A, Healy BC, Radhavan R, Glanz B, Weiner H, et al. Testosterone is associated with worse disease severity in men with early relapsing onset multiple sclerosis. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
14. Sawcer S, Ban M, Wason J, Dudbridge F. What role for genetics in the prediction of multiple sclerosis? Ann Neurol 2010; 67: 3-10.
15. Sawcer S. The complex genetics of multiple sclerosis: pitfalls and prospects. Brain 2008; 131: 3118-31.
16. Parkes M, Cortes A, van Heel DA, Brown MA. Genetic insights into common pathways and complex relationships among immune-mediated diseases. Nat Rev Genet 2013; 14: 661-73.
17. Beecham AH, Patsopoulos NA, Xifara DK, Davis MF, Kemppinen A, Cotsapas C, et al. Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. Nat Genet 2013; 45: 1353-60.
18. Nurtdinov R, Urcelay E, Costa C, Tur C, Malhotra S, Castilló J, et al. Gene expression profiling in peripheral blood mononuclear cells of multiple sclerosis patients positive and negative for HLA-DRB1*15:01. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
19. Byun E, Caillier SJ, Montalban X, Villoslada P, Fernandez O, Brassat D, et al. Genome-wide pharmacogenomic analysis of the response to interferon beta therapy in multiple sclerosis. Arch Neurol 2008; 65: 337-44.
20. Comabella M, Craig DW, Morcillo-Suarez C, Rio J, Navarro A, Fernandez M, et al. Genome-wide scan of 500,000 single-nucleotide polymorphisms among responders and non-responders to interferon beta therapy in multiple sclerosis. Arch Neurol 2009; 66: 972-8.
21. Hoffmann S, Cepok S, Grummel V, Lehmann-Horn K, Hackermuller J, Stadler PF, et al. HLA-DRB1*0401 and HLA-DRB1*0408 are strongly associated with the development of antibodies against interferon-beta therapy in multiple sclerosis. Am J Hum Genet 2008; 83: 219-27.
22. Link J, Lundkvist RM, Fink K, Hermanrud C, Lima I, Brynedal B, et al. Human leukocyte antigen genes and interferon beta preparations influence risk of developing neutralizing anti-drug antibodies in multiple sclerosis. PLoS One 2014; 9: e90479.
23. Enevold C, Oturai AB, Sorensen PS, Ryder LP, Koch-Henriksen N, Bendtzen K. Polymorphisms of innate pattern recognition receptors, response to interferon-beta and development of neutralizing antibodies in multiple sclerosis patients. Mult Scler 2010; 16: 942-9.
24. James T, Liinden M, Huss M, Brandi M, Khademi M, Tegner J, et al. Impact of genetic risk loci in multiple sclerosis on expression of proximal genes. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
25. Alcina A, Fedetz M, Fernandez O, Saiz A, Izquierdo G, Lucas M, et al. Identification of a functional variant in the KIF5A-CYP27B1-METTL1-FAM119B locus associated with multiple sclerosis. J Med Genet 2013; 50: 25-33.
26. Christensen T, Tonjes RR, Zur MJ, Boller K, Moller-Larsen A. Reverse transcriptase activity and particle production in B lymphoblastoid cell lines established from lymphocytes of patients with multiple sclerosis. AIDS Res Hum Retroviruses 1999; 15: 285-91.
27. Perron H, Jouvin-Marche E, Michel M, Ounanian-Paraz A, Camelo S, Dumon A, et al. Multiple sclerosis retrovirus particles and recombinant envelope trigger an abnormal immune response in vitro, by inducing polyclonal Vbeta16 T-lymphocyte activation. Virology 2001; 287: 321-32.
28. Banwell B, Krupp L, Kennedy J, Tellier R, Tenembaum S, Ness J, et al. Clinical features and viral serologies in children with multiple sclerosis: a multinational observational study. Lancet Neurol 2007; 6: 773-81.
29. Lunemann JD, Huppke P, Roberts S, Bruck W, Gartner J, Munz C. Broadened and elevated humoral immune response to EBNA1 in pediatric multiple sclerosis. Neurology 2008; 71: 1033-5.
30. Thacker EL, Mirzaei F, Ascherio A. Infectious mononucleosis and risk for multiple sclerosis: a meta-analysis. Ann Neurol 2006; 59: 499-503.
31. Levin LI, Munger KL, Rubertone MV, Peck CA, Lennette ET, Spiegelman D, et al. Temporal relationship between elevation of epstein-barr virus antibody titers and initial onset of neurological symptoms in multiple sclerosis. JAMA 2005; 293: 2496-500.
32. Lunemann JD, Tintore M, Messmer B, Strowig T, Rovira A, Perkal H, et al. Elevated Epstein-Barr virus-encoded nuclear antigen-1 immune responses predict conversion to multiple sclerosis. Ann Neurol 2010; 67: 159-69.
33. Khule J, Dobson R, Bestwick J, Topping J, Dalla Costa G, Khademi M, et al. Multivariate clinically isolated syndrome (CIS) risk factor study: towards individual prognosis and treatment indication in CIS. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
34. Hedström A, Hillert J, Olsson T, Alfredsson L. Smoking and multiple sclerosis susceptibility. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
35. Farez M, Quintana J, Correale J. Sodium intake is associated with increased disease activity in multiple sclerosis. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
36. Oturai A, Hejgaard J, Sellebjerg F, Albrectsen A, Petersen E, Koch-Henriksen N. High body mass index and alcohol consumption at age 15-19 and previous mononucleosis are important factors for age at onset in Danish multiple sclerosis patients. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
37. Ottoboni L, Frohlich IY, Lee M, Healy BC, Keenan BT, Xia Z, et al. Clinical relevance and functional consequences of the TNFRSF1A multiple sclerosis locus. Neurology. 2013; 81: 1891-9.
38. Chao MJ, Ramagopalan SV, Herrera BM, Lincoln MR, Dyment DA, Sadovnick AD, et al. Epigenetics in multiple sclerosis susceptibility: difference in transgenerational risk localizes to the major histocompatibility complex. Hum Mol Genet 2009; 18: 261-6.
39. Chao MJ, Ramagopalan SV, Herrera BM, Orton SM, Handunnetthi L, Lincoln MR, et al. MHC transmission: insights into gender bias in MS susceptibility. Neurology 2011; 76: 242-6.
40. Koch-Henriksen N, Sorensen PS. The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol 2010; 9: 520-32.
41. Ebers GC, Sadovnick AD, Dyment DA, Yee IM, Willer CJ, Risch N. Parent-of-origin effect in multiple sclerosis: observations in half-siblings. Lancet 2004; 363: 1773-4.
42. Huynh JL, Casaccia P. Epigenetic mechanisms in multiple sclerosis: implications for pathogenesis and treatment. Lancet Neurol 2013; 12: 195-206.
43. Ramagopalan SV, Link J, Byrnes JK, Dyment DA, Giovannoni G, Hintzen RQ, et al. HLA-DRB1 and month of birth in multiple sclerosis. Neurology 2009; 73: 2107-11.
44. Berlanga-Taylor AJ, Disanto G, Ebers GC, Ramagopalan SV. Vitamin D-gene interactions in multiple sclerosis. J Neurol Sci 2011; 311: 32-6.

45. Ramagopalan SV, Heger A, Berlanga AJ, Maugeri NJ, Lincoln MR, Burrell A, et al. A ChIP-seq defined genome-wide map of vitamin D receptor binding: associations with disease and evolution. Genome Res 2010; 20: 1352-60.
46. Zhu H, Wang X, Shi H, Su S, Harshfield GA, Gutin B, et al. A genome-wide methylation study of severe vitamin D deficiency in African American adolescents. J Pediatr 2013; 162: 1004-9.
47. Chitnis T, Tenembaum S, Banwell B, Krupp L, Pohl D, Rostasy K, et al. Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis. Mult Scler 2012; 18: 116-27.
48. Callen DJ, Shroff MM, Branson HM, Li DK, Lotze T, Stephens D, et al. Role of MRI in the differentiation of ADEM from MS in children. Neurology 2009; 72: 968-73.
49. Mikaeloff Y, Adamsbaum C, Husson B, Vallee L, Ponsot G, Confavreux C, et al. MRI prognostic factors for relapse after acute CNS inflammatory demyelination in childhood. Brain 2004; 127: 1942-7.
50. Callen DJ, Shroff MM, Branson HM, Lotze T, Li DK, Stephens D, et al. MRI in the diagnosis of pediatric multiple sclerosis. Neurology 2009; 72: 961-7.
51. Chabas D, Ness J, Belman A, Yeh EA, Kuntz N, Gorman MP, et al. Younger children with MS have a distinct CSF inflammatory profile at disease onset. Neurology 2010; 74: 399-405.
52. Bar-Or A. Mechanisms of inflammation. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
53. Dhaunchak AS, Becker C, Schulman H, De FO Jr, Rajasekharan S, Banwell B, et al. Implication of perturbed axoglial apparatus in early pediatric multiple sclerosis. Ann Neurol 2012; 71: 601-13.
54. Bar-Or A. Immunology of multiple sclerosis. Neurol Clin 2005; 23: 149-75.
55. Darlington PJ, Touil T, Doucet JS, Gaucher D, Zeidan J, Gauchat D, et al. Diminished Th17 (not Th1) responses underlie multiple sclerosis disease abrogation after hematopoietic stem cell transplantation. Ann Neurol 2013; 73: 341-54.
56. Lisak RP, Benjamins JA, Nedelkoska L, Barger JL, Ragheb S, Fan B, et al. Secretory products of multiple sclerosis B cells are cytotoxic to oligodendroglia in vitro. J Neuroimmunol 2012; 246: 85-95.
57. Howell OW, Reeves CA, Nicholas R, Carassiti D, Radotra B, Gentleman SM, et al. Meningeal inflammation is widespread and linked to cortical pathology in multiple sclerosis. Brain 2011; 134: 2755-71.
58. Khalil M. State-of-the-art and opinion on clinical applicability of biomarkers. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
59. Nikic I, Merkler D, Sorbara C, Brinkoetter M, Kreutzfeldt M, Bareyre FM, et al. A reversible form of axon damage in experimental autoimmune encephalomyelitis and multiple sclerosis. Nat Med 2011; 17: 495-9.
60. Wimmer I, Fischer M, Höftberger R, Gerlach S, Haider L, Zrzavy T. Disease-specific mechanisms in cortical multiple sclerosis lesions. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
61. Bramow S, Frischer J, Lassmann H, Sørensen P, Laursen H. Diffuse inflammation is associated with less permanent remyelination and reduced survival in progressive multiple sclerosis. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
62. Klaver R, Popescu V, Galis Y, Knol D, Versteeg A, Voorn P. Pathological substrate of grey matter atrophy in multiple sclerosis. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
63. Metz I, Weigand S, Popescu B, Stadelmann D, Frischer J, Parisi J. Immunopathologic heterogeneity persists in early active multiple sclerosis lesions. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
64. Srivastava R, Aslam M, Kalluri SR, Schirmer L, Buck D, Tackenberg B, et al. Potassium channel KIR4.1 as an immune target in multiple sclerosis. N Engl J Med 2012; 367: 115-23.
65. Villar LM, Masjuan J, González-Porque P, Plaza J, Sadaba MC, Roldan E, et al. Intrathecal IgM synthesis predicts the onset of new relapses and a worse disease course in MS. Neurology 2002; 59: 555-9.
66. Villar LM, Masjuan J, González-Porque P, Plaza J, Sadaba MC, Roldan E, et al. Intrathecal IgM synthesis is a prognostic factor in multiple sclerosis. Ann Neurol 2003; 53: 222-6.
67. Cantó E, Tintore M, Costa C, Arrambide G, Villar LM, Álvarez-Cermeño JC, et al. Validation of cerebrospinal fluid chitinase 3-like 1 as a prognostic biomarker of conversion to multiple sclerosis and disease severity in patients with clinically isolated syndromes. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
68. Arrambide G, Espejo C, Eixarch H, Villar L, Álvarez-Cermeño J, Simon E, et al. Neurofilament light subunit and evolution of CIS to MS. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
69. Nishiyama S, Misu T, Simizu Y, Yokoyama K, Kageyama T, Takai Y, et al. A multicentric cross-sectional study of the usefulness of cerebrospinal fluid-glial fibrillary acidic protein (CSF-GFAP) in the diagnosis and prognosis of inflammatory demyelinating diseases. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
70. Misu T, Takahashi T, Nishiyama S, Takano R, Nakashima I, Fujihara K, et al. [New insights into the pathogenesis of neuromyelitis optica]. Brain Nerve 2010; 62: 921-31.
71. Reindl M, Di PF, Rostasy K, Berger T. The spectrum of MOG autoantibody-associated demyelinating diseases. Nat Rev Neurol 2013; 9: 455-61.
72. Quintana FJ, Farez MF, Izquierdo G, Lucas M, Cohen IR, Weiner HL. Antigen microarrays identify CNS-produced autoantibodies in RRMS. Neurology 2012; 78: 532-9.
73. Gunnarsson M, Malmestrom C, Axelsson M, Sundstrom P, Dahle C, Vrethem M, et al. Axonal damage in relapsing multiple sclerosis is markedly reduced by natalizumab. Ann Neurol 2011; 69: 83-9.
74. Villar L, Picón C, Costa-Frossard L, Alenda R, García-Caldentey J, Kawiorsky M, et al. CSF immunological biomarkers associated with axonal damage in multiple sclerosis. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
75. Schneider-Hohendorf T, Schwab N, Wiendl H. Dynamic biomarkers for clinical efficacy and individual PML prevention under natalizumab therapy. 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Copenhagen, Denmark. 2013.
76. Fernández O, Álvarez-Cermeño JC, Arnal-García C, Arroyo-González R, Brieva Ll, Calles-Hernández MC, et al. Revisión de las novedades presentadas en el XXIX Congreso del Comité Europeo para el Tratamiento e Investigación en Esclerosis Múltiple (ECTRIMS) (II). Rev Neurol 2014 [in press].
77. Fernández O, Álvarez-Cermeño JC, Arnal-García C, Arroyo-González R, Brieva Ll, Calles-Hernández MC, et al. Revisión de las novedades presentadas en el XXIX Congreso del Comité Europeo para el Tratamiento e Investigación en Esclerosis Múltiple (ECTRIMS) (III). Rev Neurol 2014 [in press].

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

Resumen. Los datos más relevantes presentados en la XXIX edición del Congreso del Comité Europeo para el Tratamiento e Investigación en Esclerosis Múltiple (ECTRIMS), celebrado en octubre de 2013 en Dinamarca, se han resumido en la sexta edición de la Reunión de Expertos Post-ECTRIMS celebrada en Madrid en octubre de 2013, fruto de la cual nace esta revisión, que se publica en tres partes. Esta primera parte de la revisión Post-ECTRIMS presenta una visión actualizada de las diferencias de género en la esclerosis múltiple (EM), así como las nuevas evidencias sobre el impacto de las hormonas sexuales en la enfermedad. Podemos asumir que aún queda mucho por descubrir con relación al componente genético de la enfermedad. De la misma manera, a los ya conocidos factores ambientales de riesgo para la EM se unen posibles infecciones y hábitos de vida como desencadenantes. La interacción entre la genética y el ambiente cada vez cobra más fuerza como causa de susceptibilidad a la EM. En cuanto a los mecanismos de inflamación, las proteínas del complejo axoglial pueden ser las dianas antigénicas iniciales en lugar de las proteínas de mielina, y las células B se han visto implicadas en la producción de citocinas tóxicas para los oligodendrocitos. La quitinasa 3-*like* 1 se valida como marcador pronóstico de conversión a EM, y las bandas oligoclonales de inmunoglobulina M y la L-selectina podrían incorporarse como posibles medidas dentro de la estrategia de estratificación del riesgo en pacientes tratados con natalizumab.

Palabras clave. Daño tisular. Epigenética. Esclerosis múltiple. Inflamación. Sexo.