Review of the novelties from the 2014 ECTRIMS-ACTRIMS Joint Congress, presented at the 7th Post-ECTRIMS Meeting (I)

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Summary. For the seventh year in a row the Post-ECTRIMS Meeting has been held in Madrid (Spain). Renowned specialists in multiple sclerosis and national leaders in this area have gathered once again to discuss the novelties presented at the 2014 ECTRIM-ACTRIMS World Congress. That meeting gave rise to this review, which will be published in two parts. One of the main conclusions in this first part is the deeper understanding of the genetic component of multiple sclerosis that we are acquiring, although it is still insufficient unless we bear in mind its interaction with the environmental risk factors of the disease or the impact of comorbidity and healthy habits on the patients' susceptibility and prognosis. In this respect, the authors insist on the fact that, in clinical practice, the cognitive and psychiatric disorders remain under-diagnosed and are rarely taken into account in clinical research. Yet, although scarce, the evidence we have points to the possible benefits of disease-modifying drugs and alternatives to treatment with selective serotonin reuptake inhibitors. Addressing the subpopulations in multiple sclerosis and variants of the disease enhances the importance of an early accurate diagnosis in order to offer patients a safer and more personalised prognosis and treatment. Paediatric multiple sclerosis is ideal for studying the risk factors of the disease but, given its low prevalence, the use of prospective studies raises a number of doubts and there is a preference for conducting collaborative studies.

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

Introduction

The Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) is the most important international congress regarding this disease. Its last meeting was held with its American counterpart, ACTRIMS, resulting in the largest meeting of Multiple Sclerosis (MS) professionals, with approximately 9,000 attendees from 90 countries.

The 7th Post-ECTRIMS meeting, a meeting that has been institutionalized through its clear scientific focus and practical interest for the MS collective and that depends on scientific endorsement from the Spanish Society of Neurology, was held in Madrid (Spain). As in previous years, this meeting involved the participation of national opinion leaders in the presentation and discussion of the topics presented at the 2014 ECTRIMS-ACTRIMS World Congress, which represents the forefront of MS research and treatment. The objectives of this review, which also contains a second part [1], are to summarize the most important aspects of the aforementioned congress under the criteria and experience of our country's specialists and to thereby develop a basis for updating the knowledge of medical professionals.

Role of genetics

Considerable advancements have been achieved in the identification of the genetic variants associated with MS [2,3], although additional studies are needed to understand how genetic factors interact with environmental factors. The HLA-DRB1*15:01 allele continues to be the allele that is most highly correlated with determining the genetic risk of developing the disease. The presence of HLA-DRB1*15:01 increases the risk of MS in smokers and obese patients, and this increased risk is greater if these patients are negative for the HLA-A*02 protector allele [4]. In the same respect, the humoral response against fragment 385-420 of the Epstein-Barr (EBNA-1) nuclear antigen 1, as well as the absence of A*02, increases the risk of MS and inter-

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acts with DRB1*15:01 [5]. The more than 110 variants associated with the disease in the HLA region identified in adults have been genotyped in the pediatric population, and an association has been demonstrated between the main genetic variants in adults and the risk of pediatric MS [6]. Whether the HLA-DRB1*15:01 (HLA-DRB1*15:03 the African population) allele modifies the association of the vitamin D levels with the prevalence rate, which has been observed in the adult population, has also been evaluated in the pediatric population [7]. Similarly, a decrease in vitamin D levels in children is associated with an increase in the prevalence rate only in patients carrying at least one copy of the 15:01 or 15:03 allele, and no interaction with non-HLA genes has been found [8].

Outside of the HLA region, the number of genetic variants consistently associated with the disease continues to increase, and the results of a not-yet-published meta-analysis places the number of variants associated with risk of the disease at close to 200. Among other innovations, the first analyses from Exome Chip stand out because these identified the perforin gene (PRF1) and the galactocerebroside (GALC) gene. Mutations in these genes have been associated with leukodystrophy in Krabbe Disease. Although the Exome Chip results are preliminary, these two genes are attractive candidates as risk genes for MS. Furthermore, the transition from the genetic map of MS to the genomic map of MS will allow the identification of the genetic risk distribution throughout the immune system and the brain.

Effect of comorbidity and healthy behaviors

Physical and psychiatric comorbidity in MS is related to a higher disability in the diagnosis and a faster progression of the disability [9,10]. This includes the lipid profile, particularly an increase in low-density lipoprotein and overall cholesterol levels, which have been associated with measures of inflammatory activity determined through the magnetic resonance imaging (MRI) of early MS [11]. The high impact of healthy behaviors and psychiatric comorbidities on the susceptibility to and prognosis of the disease, which may be modifiable factors, are then exhibited.

Healthy behaviors

Tobacco increases mortality in MS and risk of death for all of the causes related to MS [12]. Smokers have up to a 1.6-fold higher risk of developing MS than non-smokers. This risk increases with accumulative dose and is also observed in secondhand smokers (odds ratio, OR = 1.3). New data suggest an influence of tobacco on the risk of developing antibodies against natalizumab and indicate that this risk is greater in patients who are active smokers and ex-smokers compared with non-smokers, as demonstrated by the research conducted by Olson et al. [13]. This risk is reduced after two years of smoking cessation until reaching the level of non-smokers. One hypothesis notes the lung as an immunoreactive organ and the necessary autoactivation of T cells to enter the central nervous system. In fact, the injection of autoreactive T cells into the bronchial tubes of recently born rats triggers demyelinating lesions of the same type that is presented in MS [13].

With respect to obesity, women with a body mass index greater than 30 have a higher risk of MS compared to an 18-year-old woman with a normal weight (relative risk = 2.25). Similarly, extremely obese female children present a 3.7-fold greater risk of developing MS and a higher probability that the disease will begin with transverse myelitis than with optic neuritis or other isolated clinical syndromes [14].

In addition to the fact that an increase in the body mass index in infancy and adolescence decreases the levels of 25-hydroxyvitamin, the relationship between obesity and susceptibility to MS is explained by the chronic inflammatory state in obesity. The adipose tissue also constitutes a source of proinflammatory adipokines. In MS patients, a diet restricted in saturated fats has been associated with a better progression of the disease [15]. In experimental models, caloric restriction shows a clinical and histological benefit in inflammation, demyelination, and axonal damage, and intermittent deprivation improves experimental autoimmune encephalomyelitis [16].

Because the potential anti-inflammatory mechanisms of caloric restriction were found to be due to a reduction in leptin levels and an increase in adiponectin levels, there are studies currently underway to evaluate the impact of caloric restriction in patients with relapsing-remitting multiple sclerosis. This hypothetical role of the overall diet quality in MS risk has been researched in 185,000 individuals, but these are no conclusive data [17]. Therefore, further investigation is required to determine whether an association with diet patterns exists in the early years.

In line with recent studies that have found an elevated risk of MS in patients with a low level of edu-

Table I. Cognitive deterioration and neuropsychiatric changes in multiple sclerosis.

	Prevalence	Manifestations	Evaluations used in clinical practice	Therapeutic management
Cognitive deterioration	43-65%	Velocity in the processing of information, executive functions, and episodic memory	PASAT Selective Reminding Test Spatial Recall Test Brief Visuospatial Memory Test BICAMS	Treatment with DMD (limited evidence). Symptomatic treatment with drugs for Alzheimer's disease (contradictory results). Cognitive rehabilitation
Depression	50%	Five or more of the diagnostic criteria from the DSM-IV during at least two weeks	General questionnaire of health. Answering two questions: 'Are you depressed?' and 'Have you lost interest in things that you previously enjoyed?'. Beck Depression Inventory	Pharmacological [a]: tricyclic antidepressants, desipramine and paroxetine, sertraline, mirtazapine and bupropion. Psychotherapy
Sclerotic euphoria	9-13%	Excessive joy, impulsiveness, and childish behavior	Neuropsychiatric inventory	There is no effective treatment
Pseudobulbar affect	10%	Sudden and uncontrollable crisis of laughter or crying occurring spontaneously or in response to some type of stimulus	Center for Neurologic Study-Lability Scale	Low doses of amitriptyline, SSRI, levodopa, amantadine. In USA: dextromethorphan/quinidine (Nuedexta ®)

BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis; DMD: disease-modifying drug; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; PASAT: Paced Auditory Serial Addition Test; SSRI: selective serotonin reuptake inhibitors. a According to the American Academy of Neurology, there is no sufficient level of evidence to recommend pharmacological treatment.

cation, the EnviMS study has evaluated the association between level of education and MS after adjusting for known risk factors, such as tobacco addiction, infectious mononucleosis, and some indicators of a low vitamin D level, including the consumption of cod liver oil, a low intake of fish fat, scarce exposure to the sun, and an elevated body mass index [18]. The results showed a greater risk of developing MS in those patients with a lower level of education (OR = 1.79; confidence interval at 95%, CI 95% = 1.39-2.33), an association that was only moderately reduced after adjusting for the known risk factors (OR = 1.64; CI 95% = 1.16-2.27). This finding suggests that risk factors related to the level of education or socioeconomic status and are important in the etiology of the disease remain unknown.

Unlike for other chronic diseases, the impact that exposure to the parental disease can have on early childhood is not clear for MS. The recent work conducted by Razaz et al. [19] demonstrated that parental MS is not associated with adverse results in childhood development, expressed as vulnerability in five areas of child development at 5 years of age through the Early Child Development Instrument. Even so, the children of parents with MS affected by mental comorbidity were found to be more vulnerable in their social competence and emotional maturity. In addition, children exposed to a longer duration of the parental illness may exhibit a higher risk of developmental vulnerability.

Neuropsychiatric comorbidity and other symptoms

Depression is the most frequent psychiatric affectation in MS, and additional data are constantly emerging regarding common etiologies between both entities. Patients with MS and depression have a greater atrophy of the dentate gyrus and Ammon's horn and a higher level of plasmatic cortisol, which also correlates with inflammatory activity in the MRI. Other affective disorders much rarer than depression are pseudobulbar affect and sclerotic euphoria. Sclerotic euphoria differs from pseudobulbar affect in that it is more associated with serious cognitive deterioration or dementia (Table I).

Bipolar disorder and schizophrenia are also associated with MS. A large-scale study with 51 million patients from a database of statistical records of hospital admissions and death certificates in England between 1999 and 2011 has shown a higher risk of bipolar disorder and schizophrenia. This elevated risk was observed not only in the initial diagnosis of these psychiatric symptoms but also a year after the first MS exacerbation [21].

Although fatigue is undoubtedly the most frustrating symptom for patients with MS, patients also

complain of symptoms of the autonomic nervous system that are sometimes ignored by the clinics. This finding increases the evidence of a relationship between symptoms of the autonomic nervous system, quality of life, fatigue and disability. The work conducted by Cortez et al. [22] has demonstrated, along with a prevalence of orthostatic alterations of 50%, that symptoms of the autonomic nervous system (COMPASS scale 31 [23]) are inversely correlated with quality of life (Multiple Sclerosis Quality of Life 54; $R = -0.6$) and directly correlated with fatigue (Functional Systems Scores; $R = 0.51$) but not correlated with disability or duration of the disease.

Other non-corticospinal mechanisms that are not implicated in the pathophysiology of spasticity appear to exist. These conclusions were drawn by the Comi research group [24], which demonstrated that Sativex® significantly improves spasticity but not the amplitude of evoked motor potentials. Furthermore, it has been shown that no correlation exists between the clinical and neurophysiological parameters, even though a trend between changes in the modified Ashworth scale and the relationship of the H/M amplitude has been observed.

Cognitive deterioration and rehabilitation strategies

The cognitive alterations in MS are common and debilitating and have a great impact on the quality of life and employment situation of the patient. The velocity of information processing, attention, executive functions, and episodic memory are all affected. However, cognitive deterioration is under-diagnosed in clinical practice, and the incorporation of routinely implemented tools that aid in its early detection is recommended because beginning immunomodular treatment at an early stage can slow down the course of cognitive deterioration. In the BENEFIT study, early treatment with interferon β-1b showed a significant improvement in the Paced Auditory Serial Addition Test scores, which was maintained for five subsequent years. The evidence of reductions or improvements due to symptomatic treatment is limited, although, according to Cochrane's last review, cognitive rehabilitation serves as an alternative treatment to optimize the obtained results [26]. In support of these data, the MEMREHAB study has demonstrated that memory training with the modified story memory technique during five weeks improves learning, memory, and executive functions for more than six weeks [27]. Another study detected improvements in subjective measures of attention after submitting the patients to a training program specific to attention dysfunction [28]. The theory of cerebral and cognitive reserve in MS remains confirmed with recent data that demonstrate that a greater intellectual enrichment protects against cognitive deterioration [29].

Subpopulations in multiple sclerosis and variations of the disease

Radiologically isolated syndrome

The diagnostic criteria of radiologically isolated syndrome have not changed since the studies published by Okuda et al. in 2009 [30]. Although the prevalence is unknown, incidental discoveries have been noted in 0.06-0.7% [30,31] of the general population and in 2.9% of healthy subjects with at least one relative with MS [32].

A worldwide retrospective case study of 451 cases of radiologically isolated syndrome that took place over the course of five years has identified established predictive factors for a high risk of progression toward an isolated clinical syndrome or MS [33]. From the total population, 34% of the patients presented a demyelinating process in five years, and the disease in 9.6% of these patients converted to primary progressive forms. The most important independent predictive factors were age (< 37 years), masculine sex, and medullary affectation. After five years had passed, 45% of the patients treated with disease-modifying drugs developed MS compared with 31% of the non-treated patients. Because changes in natural history have not been demonstrated with any treatment, treatment with disease-modifying drugs is not a necessity, and management of these types of patients following Barkhof's criteria is suggested.

Clinically isolated syndrome: predictive factors

A younger age is one of the more obvious clinical predictive factors of a second exacerbation, even more so when it is combined with MRI and cerebrospinal fluid data [34].

A recent meta-analysis concluded that the presence of oligoclonal bands, which 69% of patients with clinically isolated syndrome present, is a predictive factor of a second exacerbation independent from the MRI [35]. Neurofilament light-chain and chitinase 3-like [36] are increased in patients with a higher risk of conversion. Various studies have demonstrated that a higher number of T_2 lesions in-

creases the risk of an earlier exacerbation [37,38], although a longer follow-up time indicates that the probability of conversion depends on the presentation of more than one lesion at the beginning of the disease [39]. The localization of infratentorial [40] and medullary lesions [41], atrophy [42], and low levels of N-acetyl-aspartate [43] are also considered predictive factors of clinically isolated syndrome.

More recent discoveries show an association between low levels of vitamin D in clinically isolated syndrome and a higher risk of a second exacerbation, T_2 lesions, atrophy and disability [44], which results in debates regarding the supplementation of patients with low vitamin D levels and with clinically isolated syndrome.

With respect to the management of this type of patients, the available evidence points toward the benefit of early treatment, and clinical practice indicates a patient preference for oral drugs from the start. The data from a clinical trial with teriflunomide in patients with first exacerbations show a delay in the appearance of a second exacerbation and a decrease of up to 43% in the risk of conversion [47]. Nevertheless, the proposal to abandon glatiramer acetate and interferons as a first-line therapy in the future is controversial [48,49], particularly from a pharmacoeconomic point of view, and the debate of whether convenience is an appropriate reason in this recession to switch from a more expensive treatment has not been resolved [50].

Neuromyelitis optica spectrum disorders

The international consensus criteria for neuromyelitis optica spectrum disorders attempt to establish a unifying term to stratify the criteria according to serological status and to follow up with periodic reviews.

The most comprehensive case study of neuromyelitis optica spectrum disorders, which included 290 patients categorized according to serological status (AQP4+: 57%; AQP4–: 43%) [51], showed that 26% of the patients negative for anti-AQP4 antibodies were positive for anti-MOG antibodies. In comparison with the AQP4+ patients, the anti-MOG patients showed different presentation characteristics, with a predominantly male sex, a lower number of exacerbations, the presence of a bilateral and simultaneous optical neuritis, and a generally better functional recovery after a first exacerbation. These results were similar to results previously obtained by the same author in a smaller case study [52].

New discoveries in discriminative MRIs of neuromyelitis optica revealed hyperintense medullary lesions [53]. These lesions are nonhomogeneous with a greater central hypersignal than that of the sequential cerebrospinal fluid in T_2 and a lower hypointense signal than that of the cerebrospinal fluid in T_1. The presence of hyperintense lesions or longitudinally extensive medullary lesions in 88% of the neuromyelitis optica patients may be useful in the differential diagnosis between MS and neuromyelitis optica spectrum disorders. However, the isolated presence of hyperintense lesions in 27.4% of the patients with neuromyelitis optica spectrum disorders compared with 0% in the patients with MS does not change the prognosis [53].

The current treatments include immunosuppressive agents, B cell depletion, and plasmapheresis [54]. The use of interferon β, natalizumab, and fingolimod can aggravate the course of the neuromyelitis optica spectrum disorder [54]. Anti-interleukin-6 receptor antibodies and anti-AQP4 antibodies, which are likely better etiopathogenic targets, are in the research phase [54].

Pediatric multiple sclerosis

Multiple sclerosis and other recurrent demyelinating diseases are rare in the pediatric stage, and a first episode of acute demyelination does not typically signify the start of MS. The importance of MRI in the diagnosis of MS in children and adolescents has been reflected through various studies conducted throughout the last five years with the publication of distinct criteria. MS diagnosis in children and adolescents currently follows the McDonald criteria, and the new Callen criteria are considered more useful in differentiating a first MS attack from acute monophasic disseminated encephalomyelitis [55].

Knowledge of all forms of presentation is essential for differential diagnosis with other acquired demyelinating diseases. These other diseases were first defined by the International Pediatric Multiple Sclerosis Study Group (IPMSSG) [56] and revised in 2013 [57]. With respect to this matter, the persistence or disappearance of anti-MOG antibodies have a demonstrated prognostic relevance in acute demyelination in childhood [58]. Previous studies showed elevated levels of antibodies in pediatric patients with acute disseminated encephalitis, which fall to undetectable levels in the recovery phase but persist in children with MS [58]. More recently, these antibodies, along with other serum antimyelin antibodies, have demonstrated their utility in the differential diagnosis between MS and acute

disseminated encephalitis [59]. The prognosis of pediatric MS is not as favorable as previously believed; thus, it is important to consider the possibility of treating the disease from the beginning, particularly due to the availability of treatments that are more efficient in the initial stages of the disease. The IPMSSG continues to insist on the consideration of first-line treatment with interferon β and glatiramer acetate following the diagnosis of the disease. We are witnessing a progress in treatment due to new clinical trial initiatives with other criteria and methodologies beyond the personal experiences reported and retrospective studies conducted over the past decade. The exploratory observational studies are very complicated given the low prevalence of pediatric MS, which is why collaborative studies are considered fundamental for the future.

Current controversy in the management of patients

Decision-making in the real world in regards to the selection of disease-modifying treatment and other clinical concerns that arise in the typical clinical practice MS has been reflected in an interactive debate of clinical cases (Table II). This idea-sharing session taught the MS community to elect the appropriate disease-modifying treatment based on indications and risk-benefit analysis, to remember that other causes of progressive neurological deficit should be considered before confirming the diagnosis of primary progressive MS, to implement the new phenotypes of the MS course in clinical practice and to improve the strategy and use of symptomatic treatments.

The first case covers a serious instance of MS, defined by one moderate/serious clinical exacerbation in a year or two exacerbations in two years, one or two gadolinium enhanced lesions in a year or two new T_2 lesions in two years, and a significant detriment in cognition, ambulation, or function of the superior extremities. An MRI is recommended 6-12 months from the start of treatment, and after detection of a suboptimal response based on the Canadian analog model of treatment optimization, a change in the disease-modifying treatment to natalizumab in the case of a negative JC virus is justified [60].

The second case corresponds to a primary progressive form that was suspected in an initial cranial MRI. However, it must be acknowledged that not all cranial resonances with lesions in the white matter are MS and that the lesions in MRI characteristic of primary progressive forms are not sufficient to define a primary progressive phenotype because there is a scarcity of lesion volume, little amounts of enhanced lesions, and the lesions are sometimes diffused at a cranial and medullary level.

It is known that 50% of the patients in early stages or during the progression of primary progressive form can present active lesions associated with young age and worse progression [61], and natural history studies show that 30% of the patients with primary progressive forms may experience exacerbations [62]. Furthermore, the subtypes of MS described in 1996 have changed. At present, researchers do not define cases based on recurrent progressive subtypes but rather primary progressive or secondary progressive phenotypes, whether these are active or inactive, and whether they present progression. No treatment has demonstrated concrete efficacy in primary progressive forms. However, the use of cannabinoids is recommended in the presence of spasticity and painful spasms, even though the evidence recommending their use is weak.

Conclusions

For 25 years, the ECTRIMS congress has served as Europe's and the world's largest professional organization dedicated to the understanding and treatment of MS, and its vision and mission have been strengthened by the participation of its American counterpart, ACTRIMS.

Some of the highly emphasized topics discussed in the meetings, conferences, and multidisciplinary sessions that were developed in the last meeting were exposed in the Post-ECTRIMS Meeting, which has been held in our country for seven years. In some way, the Post-ECTRIMS Meeting acts as a representative of the MS research community in our country, facilitates communication, and promotes and improves the research between health professionals to benefit MS patients.

A review of the GWAS genetic studies currently taking place in pediatric MS detected the principal genetic variants associated with MS found in the adult population. Given the role that the principal risk factor HLA-DRB1*15:01 plays in the susceptibility to MS and its interaction with environmental risk factors, it is no surprise that the rate of exacerbations in the pediatric population may be modulated by the interaction of HLA-DRB1 with vitamin D levels.

Together with the widespread work directed toward understanding the genetic component of MS,

Table II. Therapeutic and clinical decisions in the real world

		Therapeutic decision of the clinicians
Clinical case 1	18-year-old woman Without history of interest Normal neurological examination An initial cranial MRI showed new hyperintense T_2 lesions and no enhanced imaging	*In the event of IgG (–) oligoclonal bands:* 28% would treat this radiologically isolated syndrome *In the event of periventricular enhancing lesions:* 60% would treat this radiologically isolated syndrome
	The patient did not start disease-modifying treatment A year after developing a brain stem outbreak with cranial and medullary enhancing lesions	*In the year 2005:* 5% would not have started treatment and 50% would have elected for interferon β-1a three times/week *Currently and in the case of being a JCV (–) patient:* 2% would not have started treatment and 48% would elect natalizumab
	The patient recovered the deficit (EDSS 0) with a corticoid pulse and the start of subcutaneous interferon β After a month, a new brain stem outbreak developed with complete recovery and another brain stem outbreak at six months with right facial paralysis	*In this situation:* 88% would recommend a therapeutic change 73% would change to natalizumab in the case of JCV (–)
	The patient did not change treatment and continued with subcutaneous interferon β-1a Six months after (the year of interferon β initiation), the patient experiences a new outbreak with active lesions in the MRI	*In this situation:* 94% would change the treatment 80% would change to natalizumab in the case of JCV (–)
	The patient begins dimethyl fumarate After nine months, a new brain stem outbreak emerges	*In this situation:* 90% would recommend natalizumab in the case of JCV (–) 78% would not exchange natalizumab for alemtuzumab in the case of its availability
Clinical case 2	45-year-old male heavy smoker with a progressive disability in the inferior extremities and an unclear level of sensitivity in the neurological exam Suspecting myelopathy, the patient underwent a cranial MRI	*In this situation:* 79% consider that other etiologies must be ruled out
	Another MRI shows new lesions, and an analysis of cerebrospinal fluid shows an increase in the index of IgG and IgG oligoclonal bands	*In this situation:* Given the evidence, 71% would recommend quitting smoking [64]
	The motor deficit of the patient continues to worsen, and a new MRI shows two new enhancing lesions The patient decides not to undergo treat and gets worse, exhibiting fatigue and painful spasms	*In this situation:* 44% and 45% would treat with fampridine, oral baclofen or tizanidine
	The patient is treated with baclofen without satisfactory results, whereas nabiximol and fampridine improve the painful spasms and motion The patient is currently being treated by a multidisciplinary team with physical therapy and cognitive rehabilitation	

EDSS: Expanded Disability Status Scale; IgG: immunoglobulin G; JCV: JC virus; MRI: magnetic resonance imaging.

we are witnessing an evolution in the understanding of the effect of comorbidities and healthy behaviors on the susceptibility and prognosis of the disease. This finding reveals an important fact: there are potentially modifiable factors that also appear to be showing a therapeutic repercussion, as is the case with tobacco and caloric restriction. However, attempts to associate the disease with diet quality or parental illness have been unsuccessful.

The same does not occur with psychiatric comorbidities and cognitive changes, which, despite their impact on the quality of life and functionality of a

patient, are diagnosed in clinical practice and are hardly considered in clinical trials. The effect of the treatments is limited, and the rehabilitation strategies precede pharmacological management, specifically cognitive rehabilitation, which achieves better results. Furthermore, the theory of cerebral and cognitive reserve confirms the protection of cognitive rehabilitation against cognitive deterioration.

We are also more familiar with the risk factors from suffering a demyelinating event in patients with a radiologically isolated syndrome, which allows us to make a more precise follow up, avoiding presenting uncertainties to the patients and unnecessary tests or treatments. The use of disease-modifying treatments, particularly when implemented early, reduces the risk of suffering a second event and likely disability. This evidence causes strong controversy with the current proposal to abandon immunomodular treatments as the first-line therapy in the future.

The second part of this article revolves around the immunological phenomena involved in the pathogenesis and progression of the disease and discusses the remyelination processes and potential regenerative strategies. In the same respect, it touches upon the search for new biomarkers, alternatives to conventional treatments with stem cells, and the discovery of new medicines, all of which are exhibited without forgetting the present treatment for MS.

References

1. Fernández O, Álvarez-Cermeño JC, Arroyo-González R, Brieva Ll, Calles-Hernández MC, Casanova-Estruch B, et al. Revisión de las novedades del congreso conjunto ECTRIMS-ACTRIMS 2014, presentadas en la VII Reunión Post-ECTRIMS (II). Rev Neurol 2015 [in press].
2. 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.
3. Patsopoulos NA, Barcellos LF, Hintzen RQ, Schaefer C, Van Duijn CM, Noble JA, et al. Fine-mapping the genetic association of the major histocompatibility complex in multiple sclerosis: HLA and non-HLA effects. PLoS Genet 2013; 9: e1003926.
4. Hedstrom AK, Lima B, I, Barcellos L, Gianfrancesco M, Schaefer C, Kockum I, et al. Interaction between adolescent obesity and HLA risk genes in the etiology of multiple sclerosis. Neurology 2014; 82: 865-72.
5. Sundqvist E, Sundstrom P, Linden M, Hedstrom AK, Aloisi F, Hillert J, et al. Epstein-Barr virus and multiple sclerosis: interaction with HLA. Genes Immun 2012; 13: 14-20.
6. Barcellos LF. Genetic studies of pediatric onset MS. 2014 Joint ACTRIMS-ECTRIMS Meeting. Boston, MA USA, 2014.
7. Lin R, Taylor BV, Simpson S Jr, Charlesworth J, Ponsonby AL, Pittas F, et al. Association between multiple sclerosis risk-associated SNPs and relapse and disability –a prospective cohort study. Mult Scler 2014; 20: 313-21.
8. Graves J, Barcellos LF, Milazzo M, Mowry EM, Belman A, Rodriguez M, et al. HLA-DRB1*15:01/03 modifies association of vitamin D level with relapse rate in pediatric MS. 2014 Joint ACTRIMS-ECTRIMS Meeting. Boston, MA USA, 2014.
9. Marrie RA, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. Comorbidity delays diagnosis and increases disability at diagnosis in MS. Neurology 2009; 72: 117-24.
10. Marrie RA, Rudick R, Horwitz R, Cutter G, Tyry T, Campagnolo D, et al. Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis. Neurology 2010; 74: 1041-7.
11. Weinstock-Guttman B, Zivadinov R, Horakova D, Havrdova E, Qu J, Shyh G, et al. Lipid profiles are associated with lesion formation over 24 months in interferon-beta treated patients following the first demyelinating event. J Neurol Neurosurg Psychiatry 2013; 84: 1186-91.
12. Manouchehrinia A, Weston M, Tench CR, Britton J, Constantinescu CS. Tobacco smoking and excess mortality in multiple sclerosis: a cohort study. J Neurol Neurosurg Psychiatry 2014; 85: 1091-5.
13. Olsson T, Hedstrom AK, Alfredsson L, Ryner M, Fogdell-Hahn A, Hillert J. Smokers run increased risk of developing anti-natalizumab antibodies. 2014 Joint ACTRIMS-ECTRIMS Meeting. Boston, MA USA, 2014.
14. Marrie RA. Effects of comorbid disease and health behaviors on MS susceptibility and prognosis. 2014 Joint ACTRIMS-ECTRIMS Meeting. Boston, MA USA, 2015.
15. Swank RL, Dugan BB. Effect of low saturated fat diet in early and late cases of multiple sclerosis. Lancet 1990; 336: 37-9.
16. Cross AH. Leptin and other adipokines in EAE and MS. 2014 Joint ACTRIMS-ECTRIMS Meeting. Boston, MA USA, 2014.
17. Rotstein DL, Chiuve S, Chitnis T, Fung T, Munger KL. Dietary patterns not associated with the risk of multiple sclerosis. 2014 Joint ACTRIMS-ECTRIMS Meeting. Boston, MA USA, 2014.
18. Bjornevik K, Riise T, Casetta I, Drulovic J, Granieri E, Holmoy T, et al. Sun exposure and multiple sclerosis risk in Norway and Italy: The EnvIMS study. Mult Scler 2014; 20: 1042-9.
19. Razaz N, Tremlett H, Boyce WT, Guhn M, Joseph KS, Marrie RA. Impact of parental multiple sclerosis on early childhood development, a retrospective cohort study. 2014 Joint ACTRIMS-ECTRIMS Meeting. Boston, MA USA, 2014.
20. Gold SM, Kern KC, O'Connor MF, Montag MJ, Kim A, Yoo YS, et al. Smaller cornu ammonis 2-3/dentate gyrus volumes and elevated cortisol in multiple sclerosis patients with depressive symptoms. Biol Psychiatry 2010; 68: 553-9.
21. Ramagopalan S, Meier U, Goldacre R, Goldacre M. Co-associations of multiple sclerosis with schizophrenia and bipolar disorder: record linkage studies. 2014 Joint ACTRIMS-ECTRIMS Meeting. Boston, MA USA, 2014.
22. Cortez M, Goodman B, Nagi Reddy S, Carter J, Wingerchuk D. Autonomic symptom burden is associated with MS-related fatigue and quality of life. 2014 Joint ACTRIMS-ECTRIMS Meeting. Boston, MA USA, 2014.
23. Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W. COMPASS 31: a refined and abbreviated Composite Autonomic Symptom Score. Mayo Clin Proc 2012; 87: 1196-201.
24. Leocani L, Nuara A, Houdayer E, Del Carro U, Straffi L, Martinelli V, et al. Effect of THC-CBD oromucosal spray (Sativex) on measures of spasticity in multiple sclerosis: a double-blind, placebo-controlled, crossover study. 2014 Joint ACTRIMS-ECTRIMS Meeting. Boston, MA USA, 2014.
25. Penner IK, Stemper B, Calabrese P, Freedman MS, Polman CH, Edan G, et al. Effects of interferon beta-1b on cognitive performance in patients with a first event suggestive of multiple sclerosis. Mult Scler 2012; 18: 1466-71.
26. Rosti-Otajarvi EM, Hamalainen PI. Neuropsychological rehabilitation for multiple sclerosis. Cochrane Database Syst Rev 2014; 2: CD009131.
27. Chiaravalloti ND, Moore NB, Nikelshpur OM, DeLuca J. An RCT to treat learning impairment in multiple sclerosis: the MEMREHAB trial. Neurology 2013; 81: 2066-72.
28. Amato MP, Goretti B, Viterbo RG, Portaccio E, Niccolai C, Hakiki B, et al. Computer-assisted rehabilitation of attention in patients with multiple sclerosis: results of a randomized, double-blind trial. Mult Scler 2014; 20: 91-8.

29. Sumowski JF, Rocca MA, Leavitt VM, Dackovic J, Mesaros S, Drulovic J, et al. Brain reserve and cognitive reserve protect against cognitive decline over 4.5 years in MS. Neurology 2014; 82: 1776-83.
30. Okuda DT, Mowry EM, Beheshtian A, Waubant E, Baranzini SE, Goodin DS, et al. Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. Neurology 2009; 72: 800-5.
31. Granberg T, Martola J, Kristoffersen-Wiberg M, Aspelin P, Fredrikson S. Radiologically isolated syndrome –incidental magnetic resonance imaging findings suggestive of multiple sclerosis, a systematic review. Mult Scler 2013; 19: 271-80.
32. Gabelic T, Ramasamy DP, Weinstock-Guttman B, Hagemeier J, Kennedy C, Melia R, et al. Prevalence of radiologically isolated syndrome and white matter signal abnormalities in healthy relatives of patients with multiple sclerosis. AJNR Am J Neuroradiol 2014; 35: 106-12.
33. Okuda DT, Siva A, Kantarci O, Inglese M, Katz I, Tutuncu M, et al. Radiologically isolated syndrome: 5-year risk for an initial clinical event. PLoS One 2014; 9: e90509.
34. Ruet A, Arrambide G, Brochet B, Auger C, Simon E, Rovira A, et al. Early predictors of multiple sclerosis after a typical clinically isolated syndrome. Mult Scler 2014; 20: 1721-6.
35. Dobson R, Ramagopalan S, Davis A, Giovannoni G. Cerebrospinal fluid oligoclonal bands in multiple sclerosis and clinically isolated syndromes: a meta-analysis of prevalence, prognosis and effect of latitude. J Neurol Neurosurg Psychiatry 2013; 84: 909-14.
36. Comabella M, Fernandez M, Martin R, Rivera-Vallve S, Borras E, Chiva C, et al. Cerebrospinal fluid chitinase 3-like 1 levels are associated with conversion to multiple sclerosis. Brain 2010; 133: 1082-93.
37. Optic Neuritis Study Group. The 5-year risk of MS after optic neuritis. Experience of the optic neuritis treatment trial. Neurology 1997; 49: 1404-13.
38. Tintoré M, Rovira A, Río J, Nos C, Grive E, Téllez N, et al. Baseline MRI predicts future attacks and disability in clinically isolated syndromes. Neurology 2006; 67: 968-72.
39. Fisniku LK, Brex PA, Altmann DR, Miszkiel KA, Benton CE, Lanyon R, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. Brain 2008; 131: 808-17.
40. Tintoré M, Rovira A, Arrambide G, Mitjana R, Río J, Auger C, et al. Brainstem lesions in clinically isolated syndromes. Neurology 2010; 75: 1933-8.
41. Sombekke MH, Wattjes MP, Balk LJ, Nielsen JM, Vrenken H, Uitdehaag BM, et al. Spinal cord lesions in patients with clinically isolated syndrome: a powerful tool in diagnosis and prognosis. Neurology 2013; 80: 69-75.
42. Sbardella E, Tomassini V, Stromillo ML, Filippini N, Battaglini M, Ruggieri S, et al. Pronounced focal and diffuse brain damage predicts short-term disease evolution in patients with clinically isolated syndrome suggestive of multiple sclerosis. Mult Scler 2011; 17: 1432-40.
43. Wattjes MP, Harzheim M, Lutterbey GG, Bogdanow M, Schmidt S, Schild HH, et al. Prognostic value of high-field proton magnetic resonance spectroscopy in patients presenting with clinically isolated syndromes suggestive of multiple sclerosis. Neuroradiology 2008; 50: 123-9.
44. Ascherio A, Munger KL, White R, Kochert K, Simon KC, Polman CH, et al. Vitamin D as an early predictor of multiple sclerosis activity and progression. JAMA Neurol 2014; 71: 306-14.
45. Correale J. If I had clinically isolated syndrome with magnetic resonance imaging diagnostic of multiple sclerosis, I would take vitamin D 10,000 IU daily: yes. Mult Scler 2013; 19: 137-9.
46. Papeix C, Lubetzki C. If I had a clinically isolated syndrome with MRI diagnostic of MS, I would take vitamin D 10,000 IU daily: no. Mult Scler 2013; 19: 140-2.
47. Miller AE. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol 2014; 13: 977-86.
48. Fox RJ. In the coming year we should abandon interferons and glatiramer acetate as first-line therapy for MS: yes. Mult Scler 2013; 19: 24-5.
49. Hillert J. In the coming year we should abandon interferons and glatiramer acetate as first line therapy for MS: no. Mult Scler 2013; 19: 26-8.
50. Hutchinson M. In the coming year we should abandon interferons and glatiramer acetate as first line therapy for MS: commentary. Mult Scler 2013; 19: 29-30.
51. Sato DK, Callegaro D, Lana-Peixoto MA, Waters PJ, Tanaka S, Jorge FMH, et al. Autoantibodies against MOG and aquaporin-4 identify distinct neuromyelitis optica spectrum disorders subgroups. 2014 Joint ACTRIMS-ECTRIMS Meeting. Boston, MA USA, 2014.
52. Sato DK, Callegaro D, Lana-Peixoto MA, Waters PJ, De Haidar Jorge FM, Takahashi T, et al. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. Neurology 2014; 82: 474-81.
53. Yonezu T, Ito S, Mori M, Ogawa Y, Makino T, Uzawa A, et al. 'Bright spotty lesions' on spinal magnetic resonance imaging differentiate neuromyelitis optica from multiple sclerosis. Mult Scler 2014; 20: 331-7.
54. Papadopoulos MC, Bennett JL, Verkman AS. Treatment of neuromyelitis optica: state-of-the-art and emerging therapies. Nat Rev Neurol 2014; 10: 493-506.
55. Ketelslegers IA, Neuteboom RF, Boon M, Catsman-Berrevoets CE, Hintzen RQ. A comparison of MRI criteria for diagnosing pediatric ADEM and MS. Neurology 2010; 74: 1412-5.
56. Krupp LB, Banwell B, Tenembaum S. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. Neurology 2007; 68 (Suppl 2): S7-12.
57. Krupp LB, Tardieu M, Amato MP, Banwell B, Chitnis T, Dale RC, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler 2013; 19: 1261-7.
58. Probstel AK, Dornmair K, Bittner R, Sperl P, Jenne D, Magalhaes S, et al. Antibodies to MOG are transient in childhood acute disseminated encephalomyelitis. Neurology 2011; 77: 580-8.
59. Van HK, Tomooka BH, Kidd BA, Banwell B, Bar-Or A, Chitnis T, et al. Serum autoantibodies to myelin peptides distinguish acute disseminated encephalomyelitis from relapsing-remitting multiple sclerosis. Mult Scler 2013; 19: 1726-33.
60. Freedman MS, Selchen D, Arnold DL, Prat A, Banwell B, Yeung M, et al. Treatment optimization in MS: Canadian MS Working Group updated recommendations. Can J Neurol Sci 2013; 40: 307-23.
61. Ingle GT, Sastre-Garriga J, Miller DH, Thompson AJ. Is inflammation important in early PPMS? A longitudinal MRI study. J Neurol Neurosurg Psychiatry 2005; 76: 1255-8.
62. Cottrell DA, Kremenchutzky M, Rice GP, Koopman WJ, Hader W, Baskerville J, et al. The natural history of multiple sclerosis: a geographically based study. 5. The clinical features and natural history of primary progressive multiple sclerosis. Brain 1999; 122: 625-39.
63. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sorensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014; 83: 278-86.
64. Manouchehrinia A, Tench CR, Maxted J, Bibani RH, Britton J, Constantinescu CS. Tobacco smoking and disability progression in multiple sclerosis: United Kingdom cohort study. Brain 2013; 136: 2298-304.

Revisión de las novedades del congreso conjunto ECTRIMS-ACTRIMS 2014, presentadas en la VII Reunión Post-ECTRIMS (I)

Resumen. Por séptimo año consecutivo se ha celebrado en Madrid (España) la Reunión Post-ECTRIMS. Reconocidos especialistas en esclerosis múltiple y líderes de opinión nacionales se han reunido un año más para exponer las novedades presentadas en el Congreso Mundial ECTRIMS-ACTRIMS 2014, y fruto de esa reunión se genera esta revisión que sale publicada en dos partes. Como principales conclusiones de esta primera parte se destaca el mayor entendimiento del componente genético de la esclerosis múltiple al que estamos asistiendo, el cual no resulta suficiente si no se considera su interacción con los factores ambientales de riesgo de la enfermedad, ni el impacto de la comorbilidad y de las conductas saludables en la susceptibilidad y pronóstico de los pacientes. Al respecto, los autores insisten en que, en la práctica clínica, las alteraciones cognitivas y psiquiátricas están infradiagnosticadas y son poco consideradas en la investigación clínica; no obstante, la evidencia, aunque escasa, apunta hacia posibles beneficios de los fármacos modificadores de la enfermedad y alternativas al tratamiento inhibidor selectivo de la recaptación de serotonina. El abordaje de las subpoblaciones en esclerosis múltiple y variantes de la enfermedad refuerza la importancia del diagnóstico precoz y preciso para ofrecer a los pacientes un pronóstico y un tratamiento más seguros y personalizados. La esclerosis múltiple pediátrica es idónea para estudiar factores de riesgo de la enfermedad, pero dada su baja prevalencia, se cuestionan los estudios prospectivos y se aboga por los estudios colaborativos.

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