Review of the novelties presented at the 27th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) (I)

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Summary. The new insights presented at the 5th Joint Triennial Congress of the European and Americas Committees on Treatment and Research in Multiple Sclerosis (ECTRIMS and ACTRIMS) held in Amsterdam, the Netherlands, 19-22 October 2011, have been summarized at the fourth edition of Post-ECTRIMS meeting held in Madrid in November 2011. Further evidence from epidemiological studies yield a possible relationship between nutrition and alterations of the microbiota that may result in the development of multiple sclerosis (MS) and that may trigger the exacerbation of disease symptoms. Also show the magnitude of impact of comorbidities in multiple sclerosis course as well as the impact of early identification and management. Review of current data on chronic cerebrospinal venous insufficiency and MS sclerosis concludes that there is no role of chronic cerebrospinal venous insufficiency in either multiple sclerosis risk or MS severity. New diagnostic criteria for MS have simplified requirements for demonstrating dissemination of lesions in time. High-field magnetic resonance imaging improves cortical visualization and become a promising tool to detect remyelinization and cortical and medullary lesions, and optical coherence tomography is established as a powerful tool for neuroprotection trials. Diffuse meningeal inflammation through B-cell follicle-like structures is associated with cortical pathology and an accelerated clinical course in secondary progressive MS sclerosis. Systemic inflammation may contribute to neurodegeneration processes in MS, and with regard to grey matter damage recent findings conclude that occurs early in disease course, and correlates with future MS-related disability.

Key words. Diagnosis. ECTRIMS. Epidemiology. Multiple sclerosis.

Introduction

The Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) is the most important international meeting on this pathology. The last Congress, held in October 2011, was attended by 7991 specialists in multiple sclerosis (MS) from 95 countries.

The Post-ECTRIMS experts meeting, which has been held in Madrid for the last four years and enjoys the scientific backing of the Spanish Neurology Society, provides a setting where renowned national leaders in this area can present the most significant data addressed at ECTRIMS 2011.

New advances in the epidemiology of multiple sclerosis

One of the most notable items dealt with, and one that has aroused a great deal of interest from an epidemiological point of view, is the relationship between diet and changes in the intestinal microbiota, which could favour the appearance of diseases like MS. Recent findings in the model of experimental autoimmune encephalitis by the group led by Ochoa-Reparaz [1] suggest that alterations affecting certain populations of bacteria in the intestine can trigger a proinflammatory response or protect against inflammation, which are responses that are also modified by antibiotics. In this line, Riccio [2] proposed a model in which the metabolic changes derived from alterations in the microbiota due to diet would lead to a breakdown in the correct communication between the microbiota and the intestine, mild endotoxemia and a systemic autoimmune inflammation.

Another significant aspect is the effect of comorbidity on the prognosis of the disease. Recent epidemiological studies conducted with small series and over short periods of time have reported an increase in the frequency of autoimmune diseases

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and allergies, as well as certain sleep disorders associated to MS. Using information from the NARCOMS (North American Research Committee on Multiple Sclerosis) registry, which contains data on a total of 8983 patients, the Marrie group [3] found that concomitant pathologies are frequent from the onset of the disease and increase over time, sometimes delaying diagnosis. All of them were associated with a higher degree of disability, vascular and visual comorbidities being the ones that produced greater physical compromise, as shown by the fact that patients with vascular comorbidities reached a score of 6 on the Expanded Disability Status Scale (EDSS) six years earlier than those without any associated vascular pathology. The impact on quality of life is seen to be highly significant and increases in proportion to the number of associated pathologies, the most relevant in terms of their frequency and impact being rheumatoid arthritis, fibromyalgia, migraine, depression and anxiety.

The environmental risk factors with the most scientific evidence pointing to their role in the onset (causal factors) or in the development of the disease (modifying factors), and which can act independently, in association or as cofactors in MS, are the Epstein-Barr virus (EBV), vitamin D and tobacco smoking. Munger, a member of Ascherio's team at Harvard [4], presented the analysis he had carried out applying the Bradford Hill causality criteria to these three factors, not only to determine the degree of causality (if any), but also to identify a possible relationship between the causal agent and the heterogeneity of the disease (Table I).

With regard to the EBV, the work of Levin et al. [5] revealed the temporality by manifesting that 100% of the patients with MS EBV(–) became seropositive before the onset of the disease. The strength of association is shown by the extremely low risk of MS in EBV(–) patients, which increases before the onset of the disease, particularly if they are suffering from infectious mononucleosis [6]. The biologic gradient is reflected in an increased risk of the disease that is proportional to the antibody titre. These results have been replicated in many other studies conducted with patients of both sexes and different origins [7]. The plausibility of this hypothesis is very high, since the EBV affects the immune function, because it remains latent in the memory B lymphocytes and can have an epigenetic or direct effect on the DNA and the transcription of the genes involved [7].

As regards vitamin D, there is evidence to show that the levels of 25(OH)D in healthy individuals predict the risk of MS, with a month of birth effect reflected by a 19% reduction in the number of births in November versus those born in May [8,9]. These findings have been confirmed in studies conducted in Canada, the United Kingdom, Sweden and Denmark [10], as well as nationally, in Vigo, Spain. The strength of association is important, with levels of 25(OH)D in serum 50-60% lower than those of healthy individuals [11]. The intake of > 400 IU/day of vitamin D reduces the risk by 40% as compared to not taking it (p = 0.006). Exposure to the sun's rays reduces the risk by 40-60%, which is a finding that was confirmed (in order to give the study a higher degree of validity) by the level of actinic-damaged skin, which seems to be a fairly clear marker of exposure to the sun's rays [12]. The involvement of vitamin D in MS processes is quite feasible due to its role as an immunomodulator, with receptors in the activated T and B lymphocytes, macrophages and dendritic cells, and owing to its effect on lowering Th1 cytokines and on increasing the regulatory Th2 cells. Moreover, there is evidence showing that a deficit of vitamin D speeds up the onset of experimental autoimmune encephalitis and increases its development [13], and that vitamin D supplements prevent experimental autoimmune encephalitis, although this only occurs in females [14].

At this point the EPIC study should be considered. This study was designed to analyse the relation between the levels of vitamin D and magnetic resonance imaging (RMI) activity; its findings were reported by Mowry et al. [15]. It was a prospective, longitudinal study conducted over five years to compare clinical activity, 3T MR activity and levels of 25(OH)D in serum. Data showed that each 10 ng/mL increase in the levels of 25(OH)D was associated with a 15% reduction in new lesions in T_2 (p = 0.005), 32% in new GD^+ lesions (p = 0.001) and 34% in the rate of attacks (p = 0.13).

As far as the relation between smoking and MS is concerned, active smokers are at a higher risk than passive smokers, and the latter have an even higher risk than non-smokers [16,17]. Nevertheless, the strength of association is moderate, with a risk that is lower than twice [18]. There is a dose-response effect that depends on the number of cigarettes and findings are consistent because they have been replicated in several population-based studies [19]. These results are plausible because the free radicals in tobacco smoke could increase the level of toxicity through nitric oxide, since nicotine increases the permeability of the blood-brain barrier and also because of the direct toxic effects on immunity [20,21].

A negative interaction between infectious mononucleosis and smoking in the risk of MS was found in the work by Riise et al. [22], which is a case-control study conducted with patients from Italy, Norway, Serbia, Sweden and Canada. An analysis of 2125 patients with MS and 4455 healthy control subjects showed that both tobacco and infectious mononucleosis were, individually, important risk factors in all the participating populations, with an age- and sex-adjusted odds ratio of 2 for infectious mononucleosis and 1.8 for smoking. Using a multiplicative model of interaction, the effect of infectious mononucleosis was seen to be significantly higher in non-smoking patients (2.4; 95% confidence interval, CI 95% = 1.8-3.2) versus smokers (1.6; CI 95% = 1.3-2.1; p = 0.04), which was a negative interaction that was observed in all the countries and separately in men and women.

In another line, new data concerning the post-natal increase in the rate of relapses were reported in the form of a study by Portaccio et al. [23] and the findings from a study designed to verify the protective value of exclusive breastfeeding in post-natal attacks [24]. A follow-up carried out over at least one year on a total of 349 pregnant patients showed that 42% suffered at least one attack in the year following childbirth; the only factors associated with the risk of post-natal attacks were the initial EDSS score (p = 0.001), the number of attacks before the pregnancy ($p < 0.0001$) and the number of attacks during pregnancy (p = 0.001). Moreover, 12% progressed one point on the EDSS scale during the first year and 27.5% had done so at five years. Therefore, it can be seen that, in patients with a high rate of attacks and disability before and during their pregnancy, immunomodulatory treatment, and not breastfeeding, decreased the post-natal attacks and development of the disability. It would thus be recommendable to begin treatment as soon as possible after pregnancy in this type of patients.

Gene and environment interaction

In epidemiology, an interaction occurs when the influence of two variables upon a third deviate the expected value, depending on the specific model under consideration. As an example, taking the work by De Jager et al. [26] on the interaction of risk factors HLA-DRB1*1501 and EBV in MS as a starting point, Ascherio [25] concluded that, although high anti-EBV antibody titres and being HLA-DR15 positive raises the risk of suffering from MS considerably, it cannot be said that interaction takes place between them because they fit a multiplicative model, that is to say, we find ourselves before an expected value.

Table I. Bradford Hill causality criteria. Causal relationships of the heterogeneity of multiple sclerosis.

	Epstein-Barr Virus	Vitamin D	Smoking
Temporality	+++	++	+++
Strength of association	+++	++	++
Biologic gradient	+++	+	++
Consistency	+++	+	+++
Plausibility	++	++	++

+++ very good; ++ good; + more evidence needed.

With respect to vitamin D, and providing further support for the evidence of a higher prevalence of MS at higher latitudes, Ebers [27] reported on the work by Orton et al. [28], which was carried out in France on families of farmers because of their scarce migration and homogeneity. The results of this study showed a strong association between prevalence of MS and average annual UV radiation. In the same line, Lucas [29] presented the Australian study entitled Ausimmune, which confirms the presence of a latitudinal gradient in the incidence of MS, especially for patients with a first demyelinating event [30]. Moreover, the risk of suffering a first demyelinating episode decreases with high levels of vitamins D [8] and increases with high anti-EBV and HLA-DR15 or HLA-A antibody titres [12].

The fact that the incidence of the disease is higher in the spring months than in the autumn, and given that this effect is more pronounced in familial cases of MS, led to the hypothesis of a relation between the month of birth and the MS susceptibility gene HLA-DRB1. Results showed a higher prevalence of MS in patients who were carriers of the HLA-DRB1*15 allele born in April [31]. These data suggest an interaction, either during gestation or just after birth, between a seasonal risk factor, which could be lower levels of vitamin D in the mother of patients born in spring, and the locus HLA-DRB1. This interaction is confirmed following the recent identification of a vitamin D response element (VDRE) in the promoter region of the *HLA-DRB1* gene [32].

Furthermore, and starting out from the hypothesis of a common genetic origin or some common factor that predisposes the individual to suffer MS

and infectious mononucleosis in order to explain the relation between EBV and MS, Giovannoni [33] reported on the recent work carried out by Ramagopalan et al. [34] on the role played by the HLA system in the association between MS and infectious mononucleosis. Of a total of 457 EBV seronegative individuals, 175 developed infectious mononucleosis and 179 seroconverted asymptomatically. The analysis revealed a frequency of the HLA-DRB1*01:01 allele that was significantly higher in patients who developed infectious mononucleosis than in those who seroconverted but did not manifest the disease. Taking into account the fact that several studies have associated this allele as a protecting factor for MS, the hypothesis of a common genetic origin would not hold. Nevertheless, interaction has been observed between EBV and genetic risk factors. Thus, the work by Sundqvist et al. [35] provided evidence that in patients with high EBV antibody titres, with HLA-DRB1*15 positive and HLA-A*02 negative, there is an increased risk of suffering from MS.

Chronic cerebrospinal venous insufficiency

A review of the current data on chronic cerebrospinal venous insufficiency and MS concludes that there is no evidence of a causal relationship in the pathogenesis of the disease [36], an idea initially proposed by Zamboni et al. [37], and therefore neither venous angioplasty nor the placement of stents is indicated in MS.

Doepp [38] criticised the ultrasound criteria proposed by Zamboni to define chronic cerebrospinal venous insufficiency on the grounds that they did not include Doppler studies in the longitudinal plane and Doppler spectral analysis, as well as failing to take into account the fact that the continuous reflux in the internal jugular vein could be a physiological phenomenon. Moreover, the cut-off point used to detect reflux in the internal jugular veins was adapted from chronic venous insufficiency of the lower limbs, the direction of the blood flow in certain venous structures of the brain is unknown, adjacent structures give rise to important physiological variations in the area of the internal jugular vein, position of the body, intrathoracic pressure and central venous pressure, and the absence of blood flow in the internal jugular veins can be physiological in some cases.

Miller [39], on the other hand, also criticised Zamboni's initial study on the grounds that it is a procedure that is carried out open (not blind) and depends heavily on the researcher it is conducted by; the normal venous anatomy of the brain is not well defined; there are no previous descriptions of chronic cerebrospinal venous insufficiency; venous drainage of the brain is redundant and dependent on the posture; blockage of the internal jugular veins has never been associated to MS; patients with MS do not present clinical or radiological findings compatible with an increase in pressure in the veins of the brain; and, more especially, the fact that the sensitivity, specificity, predictive positive value and predictive negative value are all 100%. Likewise, Miller criticised the release procedure in Zamboni's study due to the fact that it is a non-randomised pilot study conducted in a single centre, with this procedure there is no control group, no benefits are reported in the progressive forms and there is a high percentage (47%) of restenosis.

Several recent studies that contradict Zamboni's hypothesis were reviewed, such as the one published by Doepp et al. [40] with 56 MS patients and 20 healthy controls, in whom extra and transcranial Doppler scans were performed in order to analyse the volume of extracranial venous flow, the area of the internal jugular vein and the flow in the internal jugular vein during the Valsalva manoeuvre, as well as the criteria for chronic cerebrospinal venous insufficiency. Findings did not reveal any differences between groups in terms of the parameters that were analysed and none of the patients fulfilled more than one criterion for chronic cerebrospinal venous insufficiency. Another study by Doepp et al. [41] compared MR venography with extracranial Doppler to determine the stenosis of the internal jugular vein and of the azygos vein in 40 patients. Results of the Doppler showed that only 10% of patients fulfilled the criterion for chronic cerebrospinal venous insufficiency and none of them fulfilled two criteria. Moreover, MR venography was more sensitive than the Doppler for detecting stenosis of the internal jugular vein, and no causal relationship was found between chronic cerebrospinal venous insufficiency and MS.

Centonze et al. [42] studied chronic cerebrospinal venous insufficiency in 84 patients with MS and 56 healthy controls and no significant differences were found between the two groups as far as chronic cerebrospinal venous insufficiency was concerned. Likewise, no relevant clinical differences were observed among patients with chronic cerebrospinal venous insufficiency and controls as regards the remitting or progressive course, duration or severity of the disease. On the other hand, two notable pieces of work were carried out by Barcchini's group. One of them, conducted on patients with isolated

demyelinating syndrome [43], found no evidence of a cause-and-effect relation with chronic cerebrospinal venous insufficiency, while the second, which was designed in the progressive forms of the disease [44], did not find any evidence of its being a late second phenomenon of MS or that it is associated with greater disability in patients.

Zivadinov et al. [45] failed to find any significant differences in terms of internal jugular vein stenosis, venous asymmetries or the collateral circulation between patients with MS and healthy control subjects using MR venography.

As a last reference to current data, we should mention a meta-analysis of studies that analyse chronic venous insufficiency of the brain in patients with MS [46], the results of which show a positive association between chronic venous insufficiency of the brain and MS, although the heterogeneity of the studies analysed and open (non-blind) studies does not allow any definitive conclusions to be reached. High-quality studies using identical ultrasound protocols therefore need to be conducted.

With regard to the anatomical and histological analysis of the structures associated to chronic cerebrospinal venous insufficiency, the group led by Diaconu [47] has designed a study aimed at developing a procedure for obtaining veins related with the theory of chronic cerebrospinal venous insufficiency post-mortem, as well as describing venous abnormalities and determining their prevalence. For this purpose they used seven donors with MS and six healthy controls. The different venous abnormalities that were identified were hypoplasia and valvular rings, abnormal valve closure, membranes, septum and intraluminal sheaths, which were observed both in donors with MS and in control subjects, and most of them were not associated to changes in the wall or narrowing of the vessel. The limitations of the study include a small sample size, the fact it is not a blind study and a possible bias due to pre-mortem medical treatment.

Diagnosis of MS

New diagnostic criteria

A proposed set of new diagnostic criteria (Table II) has recently been published. These new guidelines were drawn up by a panel of experts [48] and were deemed to be necessary mainly owing to the development of MRI, the modification of some definitions (in particular the role of spinal MRI in diagnosis) and the simplification of the definitions of space and time, which several different works have contributed to since the year 2006.

Table II. 2010 review of the McDonald criteria.

Dissemination in space demonstrated by:
≥ 1 lesion in at least two of the typical locations: periventricular, juxtacortical, infratentorial or spinal cord
Dissemination in space demonstrated by:
Simultaneous presence of lesions in T_2 and Gd^+ lesions at any time
New lesion in T_2 or Gd^+ lesion in a second follow-up magnetic resonance scan regardless of the time

The findings of an evaluation of the diagnostic precision of the criteria put forward by McDonald in 2001 [49], McDonald in 2005 [50] and the new criteria drawn up by the MAGNIMS group show that the new criteria improve sensitivity without reducing specificity to any notable extent (Table III). Hence, when faced with a subject with a typical isolated demyelinating syndrome and a baseline MRI scan that fulfils criteria of dissemination in space and time, a diagnosis of MS can be established with a predictive positive value of 79%. This simplification of criteria is also applied for the primary progressive form.

The new revised criteria maintain the concepts that hold that the diagnosis of MS is reached by exclusion and must fulfil criteria of dissemination in space and time. The new current criteria are presumably more easily applicable in non-Caucasian populations (Latin-American and Asian), as well as in paediatric populations, which is also subject to debate. They must only be applied to patients with a typical isolated demyelinating syndrome, with special attention being paid to unspecific MRI findings and treatment by non-experts.

Differential diagnosis of MS

Vukusic [54] suggested incorporating into the spectrum of neuromyelitis optica what are considered to be incomplete disorders or forms, such as recurring, bilateral, simultaneous, severe, anti-aquaporin-4 antibody positive optic neuritis – anti-AQP4(+), longitudinally extensive transverse myelitis with anti-AQP4(+) or longitudinally extensive optic neuritis or transverse myelitis without antibodies, but with typical lesions in the MRI. The same author also proposed incorporating the so-called overlap syndromes, such as the Asian optic-

Table III. Diagnostic precision of the new criteria for dissemination in space and time (2010).

	Sensitivity	Specificity	Precision	Predictive positive value
McDonald 2001	47.1% (36.1-58.1)	91.1% (84.6-95.5)	73.1% (66.5-79.0)	78.4% (64.7-88.7)
McDonald 2005	60.0% (48.8-70.5)	87.8% (80.7-93.0)	76.4% (70.1-82.0)	77.3% (65.3-86.7)
New criteria	71.8% (61.0-81.0)	87.0% (79.7-94.2)	80.8% (74.8-85.9)	79.2% (68.5-87.6)

spinal form of MS, and the neuromyelitis optica syndromes in other, essentially rheumatic, pathologies like systemic lupus erythematosus. Other possible non-neuromyelitis optica phenotypes with anti-AQP4(+) antibodies should be considered under the proposed denomination of aquaporinopathies. This would be the case, for example, of anti-AQP4(+) and images that are characteristic of periaqueductal involvement in cases of untreatable hiccupping/vomiting or of anti-AQP4(+) with involvement of the hemispheric white matter in cases of adult encephalopathy. In short, since anti-AQP4 antibodies became available, neuromyelitis optica can be said to be a condition that is distinct from MS and it is suggested that anti-AQP antibodies in 'at-risk' phenotypes should be determined.

Continuing with the differential diagnosis of MS, Mueller-Lenke et al. [52] addressed the problem that may arise from abnormal venous drainage in relation to acute MS plates in MRI and presented the results of their study on the prevalence of abnormal venous drainage in patients with MS, with figures of 13.45%, with a supratentorial (78%) and infratentorial location (22%). Special attention was paid to the morphology characterising abnormal venous drainage, which can typically be seen as tubular structures resembling a "Medusa's head", a feature that often allows them to be distinguished from an acute plaque.

Contributions from the use of high-field MRI

The high field reduces exploration time, is improving image quality and is going to optimise the use of sequences such as diffusion, functional resonance, spectroscopy, molecular radiology, and USPIO (ultrasmall superparamagnetic iron oxide), which will make it possible for imaging to come close to the true pathogenic substrate of MS.

The detection of cortical lesions has been successively optimised from T_2, in which one cortical lesion was detected for every 12 in the white matter, to FLAIR, DIR, which appeared to be the most appropriate tool, and more recently PSIR in T_1. These last two may become, together with 3T MRI, the tools for detecting cortical lesions. Thus, PSIR achieves four times as many findings as the DIR in all clinical forms of the disease. Yet, up to 10% of the total number of lesions visible in high-field MRI can be artefacts, especially vascular lesions. In this respect, a comparison between 3T and 7T in 138 patients showed that 17 lesions in DIR 3T were reclassified as blood vessels with the 7T MP-RAGE [53].

The cortical lesions detected in 7T MRI were divided into four types [54]. Type I are leukocortical lesions, which account for 36%, and juxtacortical lesions that extend towards the cortical region. Type II are intracortical, which account for 13%, and type III and IV lesions are subpial lesions that are spread partially (type III) or totally (type IV) over the entire cerebral cortex. Type III and IV lesions are the most frequent and are represented in all the different types of the disease, although they are only present to a significant degree in secondary progressive forms.

Diagnosis with high-field MRI increases the number of lesions observed with 3T. The use of 7T MRI now makes it possible to distinguish the extent to which the subcortical lesions are spread over the cortex [55]. Likewise, it also enables the central vein present in most lesions to be distinguished, even when the lesions are somewhat larger (> 1 cm), as well as offering higher performance in strategic lesions, such as infratentorial lesions. While on changing from 0.5 to 1.5T, the evidence available on an increase in the number of lesions observed is not homogeneous, on changing from 1.5 to 3T and even 4T, the increase in the number of lesions can be observed in practically all the studies. Thus, with 3T, the number of lesions in T_2 increases by 13-46%, and the number of Gd-enhancing lesions, by 7.5-21% compared to 1.5T.

In supratentorial lesions, FLAIR has always been superior to T_2, both at 1.5 and 3T, and T_2 is superior to FLAIR in infratentorial lesions; on applying 3T for infratentorial lesions the strength of both sequences becomes equal. Hence, with 3T more infratentorial lesions are observed and cortical compromise can be distinguished from the supratentorial lesions, and more especially from juxtacortical ones. This increase in the lesion load could have an impact on the diagnostic criteria, since the number of patients who fulfil Barkhof criteria of dissemination in space increases, although the number of those who fulfil dissemination in time does not. In this regard and based on the fact that 36% of patients with isolated demyelinating syndrome present cortical lesions, Filippi et al. [56] proposed a set of new diagnostic criteria that include these cortical lesions in the criteria for dissemination in space, since they are considered to be very specific to MS, together with other items that have already been defined in previous criteria for dissemination in space, such as ≥ 1 infratentorial lesion, ≥ 1 Gd^+ lesion and ≥ 1 spinal cord lesion.

By applying these new diagnostic criteria, they achieved a very high specificity, with only slight loss of sensitivity, and they managed to identify with a high degree of precision patients with isolated demyelinating syndrome who were going to become clinically defined MS. Since all the patients with new cortical lesions have, over time, also developed white matter lesions, the proposed criteria do not represent any kind of gain in the identification of patients with dissemination in time with respect to the present criteria. Hence, Filippi et al. [56] suggested including their criteria for dissemination in space, which stress the finding of cortical lesions, and maintaining the current criteria for dissemination in time.

Up to 91% of cortical lesions are invisible in MRI, and this is especially true of those of type III and IV. Seewann et al. [57] determined that the visibility of cortical lesions in MRI is determined by the size of the lesion and not by the underlying pathology and, furthermore, that visible lesions are associated with greater cortical damage. Accordingly, visible cortical lesions would represent the tip of the pathological iceberg, with a poorer prognosis.

Schmierer et al. [58] used 9.4T to detect cortical lesions in post-mortem samples of motor cortex from patients with MS. Furthermore, they obtained sequences in T_1, T_2 and magnetisation transfer studies, and correlated these indexes with the results of the quantitative histology analysis for myelinated content (intensity of the immunostaining for a basic protein in myelin) and neural density and axonal damage (phosphorylated neurofilaments). There is a correlation between myelin content and neural density, and a correlation is also observed between the T_2 indexes with the myelin content and the T_1 indexes with the neural density.

With respect to the behaviour of the blood-brain barrier, Gaitán et al. [59] have shown that for focal lesions there are only two spatiotemporal patterns of contrast uptake: centripetal and centrifugal. By means of MRI performed on days 1, 5 and 25 with a contrast sequence lasting between half and one hour, they observed that early small-sized lesions presented a centrifugal pattern with initial central uptake that expanded to form a nodule, whereas uptake in later and larger lesions was centripetal, with a thin peripheral enhancement that filled the middle of the lesion. This pattern of uptake throughout the spatiotemporal development in the MRI scan corresponds to different stages of a single pathogenic process rather than to different types of lesion.

Optical coherence tomography in MS

Balcer [60] highlighted the interest in optic neuritis in neuroprotection trials, on the basis of evidence of an axonal and neuronal degeneration that is characteristic in all forms of MS, which is especially frequent in the visual pathways of patients with a history of acute optic neuritis. Optical coherence tomography (OCT) provides a fast reproducible reconstruction of the anatomy of the retina. In systematic reviews on OCT in MS patients, both the thickness of the retinal nerve fibre layer and the total macular volume are reduced over time in MS, even without optic neuritis. Fibre loss is more pronounced if contrast vision is affected and in patients with greater brain atrophy, which is the case of those who present the secondary progressive form of the disease, in comparison with isolated demyelinating syndrome and relapsing-remitting MS, even in the unaffected eye [61].

Involvement of both the layer of fibres and the total macular volume become apparent in three months, and this time course has been proposed as a therapeutic window concept with which to act in neuroprotection trials [62]. Longitudinal studies on the thickness of the retinal nerve fibre layer by means of OCT in patients with MS reflect a progressive loss of the thickness of the layer of fibres as time goes by, even without a history of optic neuritis, and it is associated to a significant loss of visual acuity [63]. Similar findings are obtained from the

study of the involvement of the layer of ganglionic cells, both in the macular and in the internal plexiform layer [64].

The interest in OCT goes beyond the study of the retinal nerve fibre layer to focus on the neuronal study, given the pathological evidence of a loss of ganglionic cells and the inner nuclear layer in 79% and 40% of the eyes of patients with MS, respectively, and which suggest the presence of alterations in the central nervous system. One notable study in this regard is that conducted by Saidha et al. [65], which was designed to establish a correlation between grey matter atrophy and changes in the retina. The purpose was to compare measurements with conventional OCT (peripapillary retinal nerve fibre layer) and with segmentation (macular study with thickness of the ganglionic and outer plexiform, inner nuclear, outer plexiform and outer nuclear layer) with MRI measurements of the volume of the substructures of the brain, and to relate the OCT measurements with the intracranial volume, taking into account the size of the brain. The findings indicate that changes in the retina, particularly in eyes without optic neuritis, seemed to reflect the global changes in the central nervous system with data suggesting a correlation between atrophy of the cortical grey matter and loss of neuronal cells, but not fibres. Likewise, the different OCT measurements are related with the volume of the brain; a thickening of the inner nuclear layer is related with the volume in T_2 and atrophy of apparently normal white matter and thinning of the outer nuclear layer are related to atrophy of the caudate and thalamus, in addition to an increase in the ventricular volume and lesions in T_2.

Few studies have been carried out to examine the patterns of retinal alterations in the different subtypes of MS. There are OCT data in isolated demyelinating syndrome with findings that are generally speaking similar to those from control subjects, and low reliability data derived from studies with problems when it comes to their interpretation, due to the type of OCT, the size of the sample or a heterogeneous statistic. On this foundation, Oberwahrenbrock et al. [66] designed a cross-sectional study to analyse the thickness of the retinal nerve fibre layer and the total macular volume in the different subtypes of MS and isolated demyelinating syndrome by means of high-resolution OCT; three centres and a total of 441 patients with MS took part in the study. Results showed that the eyes of patients with MS and a history of optic neuritis presented a significant reduction in macular volume and thickness of the layer of fibres in comparison to control subjects in the relapsing-remitting, secondary progressive and isolated demyelinating syndrome forms. This reduction was also found in the eyes of patients without optic neuritis for the relapsing-remitting, secondary progressive and primary progressive forms, that is to say, there is also independent involvement of optic neuritis. Similarly, differences were found in the thickness of the layer of fibres between the relapsing-remitting and secondary progressive forms without optic neuritis, and as regards the total macular volume between controls and isolated syndromes without optic neuritis, which is an important finding because even in these patients there is neuronal involvement.

Given the scarce amount of information available on the follow-up carried out to examine the association between the retinal nerve fibre layer and brain volume, Ratchford et al. [67] conducted a longitudinal study to determine whether the thickness of the retinal nerve fibre layer predicts the development of brain atrophy in a two-year follow-up study. This work, with a total of 162 patients with relapsing-remitting MS and isolated demyelinating syndrome, together with a weekly OCT scan until the 18th month and a (3T) MRI scan in 190 patients, showed that the rate of change in the retinal nerve fibre layer was related with prior optic neuritis and that operations in the ganglionic cell and inner plexiform layers were related to the development of Gd-enhancing lesions and new lesions in T_2, as well as with a one-point increase on the EDSS, although this was not the case with brain volume. Moreover, and in spite of the fact that the baseline OCT was not a factor predicting the risk of relapses or the worsening of the EDSS score or of an increase in brain atrophy, the rate of change in the retinal nerve fibre layer was associated to the rate of change in brain volume. This meant that each micron that was lost in the retinal nerve fibre layer annually was related to a 3.3 cm^3 increase in the amount of brain volume lost each year.

Importance of B cells in MS

The role of B cells in MS is made apparent by the persistent intrathecal synthesis of immunoglobulin G (IgG) in over 90% of patients, the presence of B cells in the cerebrospinal fluid of patients with active disease, immunoglobulin deposits, the accumulation of B and plasmatic cells in type II white matter lesions, according to Lucchinetti et al. [68], the existence of ectopic B-cell follicles in the meninges of patients with secondary progressive forms,

and the effectiveness of treatments against B cells, such as rituximab.

Given the absence of a recognised autoantigen in MS, Aloisi [69] proposed that the intrathecal activation of B cells could be secondary to an inflammatory process, in response to an infectious agent, as in other diseases of the central nervous system in which there exists detection of oligoclonal bands, or perhaps induced by infection of EBV.

Traditionally, the role of B cells in the pathogenesis of MS has been reported as associated to the production of autoantibodies, yet studies conducted with animal models and experimental models in patients have shed light on other 'antibody-independent' mechanisms involved, such as an antigen-presenting function, a regulating function, a bystander activation promoting the production of proinflammatory cytokines, and a process of lymphogenesis, contributing to the formation of ectopic lymphoid follicles.

With respect to the process of lymphogenesis, Howell et al. [70] conducted a study based on the hypothesis that meningeal inflammation in the form of ectopic follicles is related to cortical pathology in MS. Accordingly, they analysed 150 post-mortem cases with the secondary progressive form, grouped according to the presence or absence of ectopic B-cell follicles, and found differences in terms of the development of the disease. Thus, the presence of meningeal follicles was significantly associated to an earlier age of onset and development of the disease, as well as to a younger mean age at death. From their results, the authors concluded that ectopic B-cell follicles are a factor leading to poor prognosis in MS. Together with the oligoclonal IgM bands against lipids, they are related to greater meningeal inflammation, to greater microglial cell activation, and to greater cortical alterations associated to greater development and severity of MS.

Molnarfi et al. [71] addressed the B-cell antigen presenting function in the absence of antibody secretion using an experimental model of experimental autoimmune encephalitis induced by myelin oligodendrocyte glycoprotein (MOG) in wild-type mice and in three transgenic models: B-cell deficient, MOG-IgM transgenic (they express specific receptors for MOG in their B cells and only secrete IgM against MOG, but do not produce antibodies) and MOG-BCR knock-in transgenic, capable of secreting all the isotypes. The results show that B-cell deficient mice were resistant to the development of experimental autoimmune encephalitis, thus confirming the direct involvement of B cells in the pathogenesis of the disease. Nevertheless, the development of the disease both in the wild-type and the MOG-IgM and MOG-BCR knock-in transgenics points to an 'Accessory' cellular function of the B cells that is independent of the humoral function involved in the pathogenesis of experimental autoimmune encephalitis.

Bar-Or [72] focused the clinical experience of effective treatments against B cells in MS on rituximab, ocrelizumab and ofatumumab. The therapeutic approach by means of depletion induced by rituximab is observed by flow cytometry for CD19 following its administration, as well as by MRI, with fewer new lesions and Gd-enhancing lesions compared to placebo; similar results to these last findings were obtained for ocrelizumab and ofatumumab.

Not all the treatments, however, that act upon B cells are effective, or at least that is what can be concluded from the results of the ATAMS study conducted by Kappos et al. [73]. This is a phase II study involving atacicept, a recombinant fusion protein made up of the extracellular domain of the TACI receptor that is capable of recognising two soluble factors that inhibit B cells: BLyS and APRIL. At 25, 75 and 100 mg doses, atacicept is associated with an unexpected progressive increase in attacks, although the reduction in immunoglobulins in serum and mature B cells was as expected. The MRI results were partially consistent with the clinical activity of the disease and the effects of treatment were found to be reversible.

Neurodegeneration

Pathological substrates of neurodegeneration

Stadelmann [74] reviewed the available evidence on the pathological substrate underlying neurodegeneration. Notable works included that of Scalfari et al. [75], which showed that the total number of attacks is not related to the time elapsed before reaching disability, unlike the number of attacks in the first two years or the time lapse between them. This suggests that the processes of inflammation and neurodegeneration are independent, involving different pathogenic mechanisms, as well as the possibility of a causal and non-causal relationship, and the possibility of compartmentalising the inflammation at the outset of the disease.

DeLuca et al. [76] did not find any relationship between lesion load and the weight of the brain or between lesion load and the axonal loss in different segments of the spinal cord. They did, however, report a loss of spinal cord axons that was both sym-

metrical and selective as regards the size of the axons involved. This finding means that the neurodegeneration that leads to the loss of functioning could be related to a metabolic toxic disorder affecting the axons, independently of the focal demyelination. Hence, one of the possible causes of axonal damage is long-term demyelination, which places excessive stress on the demyelinated axons when it comes to maintaining their membrane potentials, the consequences of a cortical demyelination in dendritic and synaptic deterioration, and the participation of innate/adaptive immunity that can induce the release of inflammatory toxic mediators and activate mitochondrial oxidative damage mechanisms.

With regard to the axonal damage in the spinal cord, Schirmer et al. [77] examined spinal cord tissue from patients with MS, amyotrophic lateral sclerosis and healthy controls, and found substantial neuronal loss in the ventral horn of the spinal cord that did not progress with the patient. Furthermore, in the areas of inflammation, they detected c-Jun and GAP43 immunoreactivity in the grey matter and in areas adjacent to the active demyelinating lesions, which pointed to neuronal damage and regeneration as an early response to the formation of lesions. This lack of any relationship between neuronal loss and the neurodegeneration that is present led them to carry out a second study, in which they classified lesions as being more or less inactive, depending on the number of microglial cells and macrophages with myelin. They found intense axonal involvement in the more inactive lesions and attributed this phenomenon to a (probably metabolic) aggression of the Exons in areas that were chronically very demyelinated and in no way related with the inflammation.

The hypothesis that the neurodegeneration is caused by inflammation has been addressed in several studies. Some of the most notable recent publications include the works by Magliozzi et al. [78] and Howell et al. [70], which analysed the number of patients with lymphoid pseudo-follicles in the meninges and found that the figure ranges between 40-50%. Howell et al. demonstrated a correlation between the presence of lymphoid follicles and involvement of the cerebral cortex in gradient, which is an aspect that indicates infiltration of the lymphoid cells from the inflamed meninges towards the cortex. Magliozzi et al., on the other hand, found involvement of the glial limiting membrane due to an immune-mediated aggression, which suggested the involvement of antibodies or cytotoxic factors. Moreover, the existence of lymphoid follicles leads to a poorer prognosis, in this particular case, the development of a secondary progressive form of the disease. Frischer et al. [79] observed that, in the progressive phase of MS, active demyelination and neurodegeneration were only seen in patients with pronounced inflammation. Likewise, in elderly patients in the final phases of the disease, the inflammation dropped to levels observed in age-paired control subjects, which led them to conclude that there was a close relationship between the processes of inflammation and neurodegeneration.

From all this, doubts arise as to whether anti-inflammatory treatments play any useful role in the progression of the disease, some of the main reasons being: limited access across the blood-brain barrier to a very compartmentalised inflammation, a limited role of the peripheral immune system, inappropriate therapeutic targets or the activation or deactivation of regulatory mechanisms at the outset of the disease.

Perry [80] set out from the hypothesis that microglia play a very important role in neurodegeneration. It is well known that, in the presence of an infection, an inflammatory response is produced that is mediated by the release of proinflammatory cytokines, which in a certain way reach the brain and activate the microglia. Perry [80] claimed that this is the process underlying the 'sickness behaviour syndrome', which is an adaptive behaviour against infection without any consequences in a healthy brain, although in brains that have been damaged by prions or in experimental models of amyotrophic lateral sclerosis or Parkinson's disease (in short, within the context of a degenerative disease), the hyperactivated microglia accelerate cognitive impairment, as has been shown in the case of Alzheimer's disease [81]. In other words, the contribution made by a systemic inflammatory process to the process of neurodegeneration could be explained as having an organic basis. In an attempt to find an answer to this issue, Moreno et al. [82] designed an experimental model of experimental autoimmune encephalitis and systemic inflammation by means of lipopolysaccharide. Their results showed that in a high percentage of cases activity starts up again but without breaching the blood-brain barrier and all of them show an increase in neurodegenerative damage. Furthermore, immunohistochemical analyses of the brains of animals show a pattern of cytokine secretion of the activated microglia that differs from zone to zone, even when they are very close to each other, and therefore the microenvironment could modify the impact of the systemic inflammation. These findings are very important, especially if they are confirmed

in the case of MS, since the frequency of infections in this kind of patient is very high.

In the same line, and outside the theoretical framework, Tiwari-Woodruff et al. [83] have shown that the beneficial effect of laquinimod in laboratory animals is related to the inhibition of microglia and to the inhibition of the activation of astrocytes, which also play an important role in the whole cascade that gives rise to axonal loss.

Grey matter compromise in MS

Measurements of cerebral atrophy show an annual loss of cerebral tissue of around 0.1-0.3% in a normal individual, while this figure increases fourfold in a patient with MS, reaching values of 0.5-1.3%. If we turn to look at the loss of grey matter, the increase in loss is around 4-14 times that of a healthy individual.

This grey matter compromise is correlated with clinical forms of the disease. Thus, if the fraction of brain parenchyma is recorded as a global measurement of atrophy, greater loss is observed in the secondary progressive forms and, in the same way, the secondary progressive forms are also the ones that most increase the rate of grey matter atrophy over a period of four years [84]. Another longitudinal study of cerebral atrophy at four years that uses the CLADA programme, which was specifically designed to measure grey matter atrophy, revealed that isolated demyelinating syndromes present less atrophy than the secondary progressive forms. Similarly, several studies have been published that show a correlation between grey matter compromise and clinical disability, as well as its value in predicting the conversion of isolated demyelinating syndrome into the relapsing-remitting form.

Geurts [85] highlighted the fact that MS does not offer an exact view of the pathological mechanisms that affect the grey matter, based on the results of a pathological verification study conducted in 211 post-mortem samples of grey matter lesions. MRI techniques, including both DIR and FLAIR, were found to be quite specific for identifying these lesions, with a specificity of 90% and 81% respectively, although pathological sensitivity values were low, i.e. 37% and 18% respectively. A relative comparison of the techniques that are already used in clinical practice showed 3D-DIR to be the best technique for measuring intracortical lesions, with a comparative advantage of 538% with respect to T_2 and 152% compared to FLAIR.

As criteria for grey matter lesions, Geurts et al. [86] proposed the use of a hyperintensity compared to the underlying tissue that covered ≥ 3 pixels (based on ≤ 1 mm resolution). Furthermore, it is necessary to compare with other techniques, look in multiple sequences and define the artefacts well.

In order to approach the pathology of apparently normal grey matter, Calabrese et al. [87] used the fractional anisotropy technique as a direct measure in control subjects and patients with relapsing-remitting MS both with and without cortical lesions. Their findings showed that the anisotropy fraction was altered in all the patients with relapsing-remitting MS, although to a greater extent in those with cortical lesions. Accordingly, diffusion tensor imaging is proposed for the measurement of the anisotropy fraction as a better method for analysing apparently normal grey matter than purely morphological techniques.

On the other hand, Gray et al. [88] analysed the changes that occur in the cerebral cortex linked to the process of neurodegeneration in MS, taking as their starting point the association between peroxisomal dysfunction and certain neurological diseases, such as adrenoleukodystrophy, reported in some studies. To do so, they evaluated PMP-70 expression and the gene expression of peroxisomes in cortex samples from controls and MS patients, their results showing lower PMP-70 expression and lower expression of peroxisomal transcripts in the affected cortex. This finding is probably related to microglia activity, the alteration of which is highly dependent on myeloperoxisome activity, which led the authors to suggest that peroxisomal dysfunction would be associated to neuronal dysfunction and to degeneration in MS, at least in the cortex.

With the aim of evaluating whether grey matter and white matter atrophy share the same patterns of regional distribution, Riccitelli et al. [89] used voxel-based morphology in patients with relapsing-remitting MS and control subjects to obtain in vivo a precise description of the distribution and behaviour of grey matter and white matter atrophy. Thus, they observed that, in patients with relapsing-remitting MS, grey matter and white matter atrophy presents different patterns of regional distribution, with predominance of grey matter involvement in the anterior areas and of the white matter in the posterior areas. These data suggest that different mechanisms are involved in the two types of lesion.

Conclusions

Recent epidemiological evidence reveals a possible relationship between diet and changes in the intes-

tinal microbiota, which could favour the appearance of MS due to different molecular mechanisms involved in the inflammatory and autoimmune processes of the disease. Additionally, it also highlights the effect of comorbidity on the prognosis of MS, which it would be important to recognise and treat in order to draw up risk programmes with new drugs. The hypothesis of a genetic and environmental interaction would be shown by the identification of a vitamin D response element (VDRE) in the promoter region of the MS susceptibility gene *HLA-DRB1*.

A review of the current data on chronic cerebrospinal venous insufficiency and MS concludes that there is no evidence of a causal relationship in the pathogenesis of the disease and, therefore, neither venous angioplasty nor the placement of stents is indicated in MS.

New diagnostic criteria for MS have simplified the criteria for dissemination in time, and high-field magnetic resonance imaging is a promising tool allowing better detection of cortical and spinal cord lesions. OCT is a powerful tool in neuroprotection trials and, although baseline OCT has no predictive value, the thickness of the retinal nerve fibre layer is correlated with cerebral atrophy.

The role played by B cells in the pathogenesis of MS has been reported as being associated to an antigen-presenting function, to a regulating function and to a process involving the maturation of those cells in ectopic follicle-like structures, which are present in the meninges of the secondary progressive forms. The presence of organised meningeal inflammation leads to further neuronal damage and loss.

The slow continual loss of axons and the progressive increase in neuroaxonal dysfunction are still not fully understood. 'Malnutrition' or energy failure have been suggested as possible causes of long-term demyelination. Likewise, a systemic inflammatory process has also been considered as contributing to the process of neurodegeneration.

It can be concluded, on the other hand, that grey matter compromise takes place early in the course of the disease, is partially related to the lesions, predicts the conversion of the isolated demyelinating syndrome, and correlates with future disability. It is considered to be an attractive measurement as a result that should be measured in clinical trials with MS, and its evaluation with currently available drugs is recommended.

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

Resumen. Los datos más relevantes presentados en el V Congreso Trianual de los Comités Europeos y Americanos para el Tratamiento y la Investigación en Esclerosis Múltiple (ECTRIMS/ACTRIMS), celebrado en Ámsterdam del 19 al 22 de octubre de 2011, han sido resumidos en la cuarta edición de la reunión Post-ECTRIMS celebrada en Madrid en noviembre de 2011. Las nuevas aportaciones en epidemiología revelan una posible relación entre la dieta y los cambios en la microbiota intestinal, que podría favorecer la aparición de la esclerosis múltiple, así como el efecto de la comorbilidad sobre el pronóstico de la enfermedad, y la importancia de su reconocimiento y manejo. La revisión de los datos actuales sobre insuficiencia venosa cerebroespinal crónica y esclerosis múltiple concluye que no existe evidencia de una relación causal en la patogenia de la enfermedad. Los nuevos criterios diagnósticos facilitan los criterios de diseminación en tiempo, y las perspectivas de la resonancia magnética de alto campo pasan por detectar mejor las lesiones corticales y medulares. La tomografía de coherencia óptica se constituye como una herramienta poderosa en ensayos de neuroprotección. El papel de los linfocitos B en la patogenia de la esclerosis múltiple se ha descrito asociado a un proceso de maduración de dichas células en estructuras tipo folículos ectópicos, presentes en las meninges de las formas secundarias progresivas. Por otro lado, se ha planteado la contribución de una inflamación sistémica al proceso de la neurodegeneración, y respecto a la afectación de la sustancia gris, recientes hallazgos han concluido que ocurre de forma temprana en el curso de la enfermedad y se correlaciona con la discapacidad futura.

Palabras clave. Diagnóstico. ECTRIMS. Epidemiología. Esclerosis múltiple.