Review of the novelties presented at the 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) (II)

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Summary. The most relevant data presented at the 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), held in October 2013 in Denmark, were summarised at the sixth edition of the Post-ECTRIMS Expert Meeting, held in Madrid in October 2013, resulting in this review, which is being published in three parts. This second part of the Post-ECTRIMS review focuses on diagnostic imaging and differential diagnosis, the clinical and paraclinical monitoring of neurodegeneration, progression and disability, and functional imaging and neural connectivity. It is clear that conventional multiple sclerosis sequences remain essential for the diagnosis, differential diagnosis and disease monitoring, that new MRI techniques help to assess the neurodegenerative process, and that some of the new sequences are more specific to neuroaxonal injury. Very high field magnetic resonance imaging allows better understanding of the lesion load, distribution and heterogeneity of the lesions, and positron emission tomography studies offer new insight into the pathophysiology of the disease. Functional imaging and neural connectivity studies show that there is cortical reorganisation in multiple sclerosis, whose equilibrium with structural damage is responsible for the impairment.

Key words. Functional imaging. Magnetic resonance imaging. Multiple sclerosis. Neural connectivity. Optical coherence tomography. Positron emission tomography.

Introduction

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

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

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

Diagnostic imaging, differential diagnosis, disease monitoring and response to treatment

Magnetic resonance imaging

In general, there is a magnetic resonance imaging (MRI) pattern quite specific to MS that, together with established diagnostic criteria [1] and laboratory tests, provides a reliable diagnosis of MS. However, differential diagnosis is extensive, and false diagnoses are common, mainly due to the inadequate interpretation of diagnostic imaging criteria [2]. The perivenular location of lesions in high-field MRI (3-7 T) allows the discrimination between MS lesions and nonspecific white matter lesions [3] or lesions due to other causes, such as those of vascular origin [4]. In iron susceptibility-weighted imaging (SWI) sequences, MS lesions show a hypointense image inside, differentiating them from other vascular lesions or those associated with migraine.

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Declaration of interest:
The Post-ECTRIMS working group has received unconditional funding for continuing medical education

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from Teva Neuroscience Spain. O.F. reports having received fees as a consultant, advisor, speaker or moderator and having participated in clinical trials and other research projects promoted by Biogen-Idec, Bayer-Schering, Merck-Serono, Teva, Novartis, Almirall, and Allergan. The remaining authors declare no conflicts of interest concerning the present article.

Note:
All authors of the Post-ECTRIMS group contributed equally to the preparation of the manuscript.

Accepted:
14.07.14.

How to cite this paper:
Fernández O, Álvarez-Cermeño JC, Arnal-García C, Arroyo-González R, Brieva LI, Calles-Hernández MC, et al. Review of the novelties presented at the 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) (II). Rev Neurol 2014; 59: 307-16.

Versión española disponible en www.neurologia.com

The location of the lesions at the intracortical level is of particular importance, which can be identified with high field 3-7 T techniques and the DIR and PSIR sequences. Different studies have shown identification increases MS diagnostic accuracy in patients with clinically isolated syndrome [5]. Additionally, MS lesions have a highly suggestive gadolinium-enhanced pattern: an incomplete ring open towards the cortex in cortical or juxtacortical lesions and open towards the ventricle in periventricular lesions. After mentioning some recommendations about cranial and spinal MRI in the study of MS patients (Table I), Wattjes [4] suggested that at the spinal level, high-field MRI does not add much to the diagnosis of MS. Other considerations to keep in mind are the importance of MRI in radiologically isolated syndrome (RIS), that currently a single MRI allows the diagnosis of MS if criteria for dissemination in time and space are met, and that spinal MRI is more useful in the initial evaluation of a patient with MS than during follow-up.

Baseline MRI is currently the biomarker that provides more medium- and long-term information, more even than the presence of oligoclonal bands and clinical data. This is demonstrated by the follow-up of isolated neurological syndromes from the CEM-Cat cohort of Barcelona, to date the largest prospective cohort described, with a total of 1,000 patients with clinically isolated syndromes [6]. The various studies conducted on immunomodulatory drugs (BENEFIT [7], REFLEX [8], PRECISE [9], TEMSO [10], FREEDOMS [11], TRANSFORMS [12] and CARE-MS I-II [13,14]) provide evidence to conclude that baseline MRI does not predict response to treatment. However, the control MRI scan within the first year of treatment does help us to more reliably obtain this information, together with other clinical data, as demonstrated by studies using the Rio score [15-17] and its modified version [18].

Because new results add to the evidence of markers of the response to treatment in patients initiating immunomodulatory therapy, the study by Romeo et al. [19], which retrospectively observed 700 patients with RRMS with mean follow-ups of eight years, confirms the ability of MRI to predict worsening of long-term disability. Additionally, clinical activity and MRI activity were found to be the major predictors of long-term treatment failure, as reflected by the fact that patients who were disease-free within the first two years showed lower long-term treatment failure.

The current challenge is to determine whether MRI usefulness in monitoring the disease and response to treatment can be applied individually and as part of personalised medicine.

Optical coherence tomography

The diagnostic accuracy of optical coherence tomography (OCT) is still discussed for each individual case, although it allows developing different disease patterns for MS, neuromyelitis optica, and Susac's syndrome, which show a significant reduction in the thickness of the retinal nerve fibre layer and/or total macular volume compared with MS [20]. It is a useful tool in monitoring treatment, as shown by some studies with findings pointing to a possible neuroprotective effect of erythropoietin on optic neuritis and control of macular volume with fingolimod [21], hence its potential in studies of neuroprotective utility.

Clinical and paraclinical monitoring of neurodegeneration, progression, and disability

Neurodegenerative phenomena appear to be present from the onset of the disease; however, there is still no measure available to determine axonal loss with easy application and low cost. Evoked potentials have shown good correlation with the progression of disability in MS, and OCT measures the retinal nerve fibre layer and the thickness of the ganglion cell layer. The correlations among a clinical measure of disability progression –the Expanded Disability Status Scale (EDSS)– OCT measurements and evoked potentials has been investigated by Fernandez et al. [22]. In addition to detecting axonal loss in MS patients, both in the eyes affected and those unaffected by optic neuritis, their study revealed good correlation of OCT with the EDSS, especially in the ganglion cell layer, and of motor evoked potentials with OCT and the EDSS. Additionally, the amplitude of motor evoked potentials is the measure that best correlates with clinical progression and, therefore, could be a good biomarker for MS progression.

In another line of research, there are certain conventional and non-conventional MRI biomarkers at the brain and spinal levels. At issue are their specificity to evaluate an underlying process of neuronal involvement and axonal injury, their sensitivity to change, and, therefore, their usefulness for assessing the patient in the long-term and their use in the evaluation of neuroprotective drugs (Table II).

Biomarkers of neurodegeneration in brain MRIs

T_1 hypointense lesions exhibit 40% axonal density [23], which indicates that they are chronic lesions characterised by marked, irreversible neuroaxonal damage. Their clinical relevance is determined by their high predictive value: the 10-year EDSS score change correlates with the combination of the number of baseline T_1 lesions and the volume increase of these lesions [24].

The clinical relevance of brain volume loss is demonstrated by its good correlation with physical and cognitive disabilities [25] and by its sensitivity to change, insofar as the progression of volume loss is associated with the onset and advancement of disability. These results are likely to strengthen upon the analysis of grey matter atrophy [26] because, although it occurs at a later stage, the appearance of these lesions is not constant but increases as a function of the stage of the disease. Their use as a marker of neurodegeneration may be limited by the expected effect of chemotoxicity in cases of drugs with potent anti-inflammatory effects or the healing of any inflammation, as reflected by the results obtained in patients undergoing immunoablation and autologous transplant of hematopoietic stem cells, in which, after a month of treatment, atrophy has been shown to increase 10-fold [27]. A study using ibudilast has shown probable neuroprotective effects, thereby demonstrating its impact on atrophy, although there was no drug effect on inflammation [28].

Advanced MRI is much more specific to the underlying disease process, and it quantifies pathophysiological phenomena. MR spectroscopy studies have reflected defects in terms of neuroaxonal mitochondrial loss or dysfunction, as determined by a decrease in N-acetyl-aspartate. However, its specificity may be limited by technical or reproducibility difficulties, affecting the results of multicentre studies of neuroprotection, as occurred in the study with glatiramer acetate, in which each centre considered a different region as the area of interest for quantification [29].

Diffusion tensor imaging (DTI) allows obtaining values of fractional anisotropy or mean diffusivity, reflecting impaired tissue integrity due to demyelination, axonal injury or gliosis, and values of axial and radial diffusivities, which in experimental models correlate with axonal injury and demyelination, respectively [30,31]. A recent study using DTI has shown that in MS patients with a few years of progression and very little disability, there is impaired microstructural integrity that affects virtually the entire brain. Furthermore, the most widely altered measures were those reflecting predominant demyelinating damage, whereas those associated with axonal injury were only altered in very confined grey matter regions, a finding coincident with the fact that these patients had very little cortical atrophy [32].

The growing interest in the study of abnormal iron accumulation by neuroimaging as an MRI potential biomarker is based on its relationship with oxidative stress and resulting mechanisms leading to neuronal death [33], combined with pathological findings showing iron deposition within the lesions and on their edges and iron accumulation in perivascular spaces and in deep grey matter [34]. The proposed techniques to assess iron accumulation in-

Table I. Practical recommendations in cranial and spinal magnetic resonance imaging (MRI).

Cranial MRI	3 T > 1.5 T	
	Thickness of 3 mm	
	Contrast: 0.1 nmol Gd/kg	
	Sequences	Axial PD/T_2, sagittal FLAIR and axial T_1 post-Gd
		Optional: DIR, T_1 pre-Gd, SWI, DTI, MTR and MRS
Spinal MRI	After cranial MRI	
	≥ 1 T	
	Thickness of 3 mm	
	Contrast: 0.1 nmol Gd/kg	
	Sequences	Axial PD/T_2, axial T_1 post-Gd
		Optional: Axial T_1 + T_2, FSE and STIR
Other recommendations	Importance of MRI in preclinical states (radiologically isolated syndrome)	
	One single MRI may be diagnostic of multiple sclerosis	
	It is important to have cranial and spinal MRI performed at baseline, especially at the cervical level	
	Spinal cord MRI is important in the differential diagnosis of other diseases with cranial lesions	
	Spinal cord MRI is more useful early in the disease than in the follow-up phase	
	Control cranial and spinal MRI in a patient with clinically isolated syndrome: Gd is not always necessary for the diagnosis of multiple sclerosis	
	Control cranial MRI with Gd is important to monitor treatment and/or the disease	

Table II. Biomarkers of neurodegeneration in brain and spinal cord imaging.

	Reproducibility	Neural specificity	Sensitivity to change	Current applicability in clinical trials
Brain MRI				
Hypointense lesions	Good	Moderate	Good	Yes
Atrophy	Very good	Weak	Good	Yes
Spectroscopy: NAA	Good	Strong	Unknown	Yes
DTI: axial diffusivity	Moderate	Strong	Unknown	No
	Pathophysiology	**Clinical value**	**Sensitivity**	**Applicability**
Spinal MRI				
Atrophy	Good	Good	Good	Good
T_2 lesions	Weak	Weak	Moderate	Good
Diffuse damage	Moderate	Good	Moderate	Weak
Functional changes	Weak	Moderate	Weak	Weak

DTI: diffusion tensor imaging; MRI: magnetic resonance imaging; NAA: N-acetyl aspartate.

clude T_1, T_2 and T_2^* (R_2^*) relaxation time maps, correlation magnetic field, quantitative phase imaging, direct saturation imaging (DSI), and diffusion-weighted imaging (DWI), with the R_2^* relaxation rate constant likely being the most important.

To date, the vast majority of studies exploring the clinical implications of iron deposits in MS have used T_2-weighted MRI sequences to indirectly estimate brain iron levels via hypointense signals and have shown more pronounced iron accumulation in deep grey matter structures, such as the basal ganglia. Iron accumulation in these areas appears to be associated with the severity of the disease, as measured by the duration of the disease and brain atrophy, as well as with cognitive performance, findings that have been largely confirmed by the application of new and more advanced techniques for mapping iron. However, we are still far from validating the R_2^* relaxation map as a marker of neurodegeneration, whose data of reproducibility and sensitivity to change must be confirmed over the long term.

The intactness of the corpus callosum has been evaluated as a progression biomarker in secondary progressive (SP) forms [35]. Its relatively easy determination and previous evidence of atrophy measurements form the basis on which its possible utility in detecting biologically significant changes at one year has been established. Should this marker be robust, it would help the design of clinical trials with fewer patients and shorter exposure times. This is especially important in the SP forms, considering that only 30% of patients were progressing after two years. This study examined a total of 348 patients with SPMS in the multi-centre dirucotide (MBP8289) trial and evaluated corpus callosum atrophy and its relationship with the Paced Auditory Serial Addition Test (PASAT). The results showed that the area of the corpus callosum was reduced by 1.2% the first year and 2.1% in the first two years. There was a correlation between the area of the corpus callosum and the PASAT but not between the change or reduction of the corpus callosum area and the PASAT at a two-year follow-up.

Biomarkers of neurodegeneration in the spinal cord

The clinical relevance of spinal cord atrophy has been confirmed in studies showing correlation with the degree of disability in the RR and progressive forms but not in the clinically isolated syndrome or benign forms [36]. Voxel-based analysis allows the visualisation of the three-dimensional area of the spinal cord, which is not accessible to cross-section, and shows a non-uniform distribution of cervical spinal atrophy mainly affecting the posterior and lateral zones [37]. Nevertheless, clinical and radiological dissociation is still present, as evidenced by the lack of correlation between the number of lesions and atrophy.

Compared to non-conventional techniques, magnetisation transfer imaging (MTR) shows a decrease in the magnetisation transfer ratio, which is more pronounced in progressive forms [38]. Meanwhile, DTI of the spinal cord illuminates a decrease in the values of fractional anisotropy and an increase in mean diffusivity, yielding stronger correlations with the EDSS (r = 0.7) than parallel correlations yielded using the brain.

As future measures of spinal cord atrophy, Kearney et al. [39] have proposed the evaluation of pial and subpial regions, previously not analysed *in vivo*. Using MTR, they studied patients with clinically isolated syndrome and MS in all its forms, with results showing a decrease in MTR measures in MS patients but not in those with clinically isolated syndrome. Additionally, the MTR measure was even more reduced in patients with SPMS compared to those with RRMS, and a correlation between the measurements of MTR and EDSS was found. No differences were found between the cervical area of patients with clinically isolated syndrome and RRMS compared to controls, although

these were found between the SP and primary progressive (PP) forms ($p < 0.01$). The decrease in MTR in this region in MS patients may reflect meningeal inflammation and/or subpial demyelination.

Along with the spinal cord, the retina is commonly affected in MS. These are, therefore, two optimal regions in which to study possible relationships between structure and function and to identify disturbances that would provide a more complete picture of disability-related phenomena in MS. This hypothesis justified the original study led by Oh [40], which had the aim of examining correlations between the spinal cord and retinal involvement in MS. To accomplish this, they used quantitative MR with DTI and MTR, in addition to OCT and clinical measures. The results showed significant correlations between the transverse area, fractional anisotropy, perpendicular diffusivity and the retinal nerve fibre layer ($p = 0.01$, $p = 0.002$, $p = 0.001$, respectively) and the ganglion cell and internal plexiform layer ($p = 0.003$, $p = 0.003$, $p = 0.01$, respectively). Multivariate models of clinical dysfunction, with measures of brain, spinal cord and retinal atrophy, showed that the transverse area and the thickness of the retinal nerve fibre layer had an independent relationship with visual acuity ($p = 0.04$, $p = 0.002$, respectively) and vibratory sensation ($p = 0.01$, $p = 0.05$). The area of the cervical cord was associated with the EDSS (the score on the Multiple Sclerosis Functional Composite scale) and proximal lower extremity strength. The brain parenchymal fraction was associated only with the Multiple Sclerosis Functional Composite scale. These findings suggest that the spinal cord and retina independently reflect pathological processes related to disability that are not evident in measures of brain atrophy and highlight the importance of combining measures of unique compartments of the central nervous system to provide a more complete picture of both the regional and global phenomena that lead to patient disability.

New approaches to early inflammation and neuronal involvement

The onset and progression of the disease during the course of MS is partially explained by current imaging studies. Doubts remain about the beginning of axonal degeneration and the existence of a relationship between white matter and grey matter and between atrophy and neuronal integrity. Positron emission tomography (PET) is shown to be a promising tool to obtain a different view of the pathophysiology of the disease through the use of markers at the cellular or molecular level. Some studies have shown an inverse correlation between the binding of ^{11}C-flumazenil, a benzodiazepine receptor antagonist that is a marker of neuronal integrity, and cortical thickness in the sensorimotor cortex; conversely, they have shown a lack of correlation with cortical thickness in the associative frontal or parietal cortex. These findings suggest that cortex disruption exists prior to cortical atrophy and that they are most likely not related. Additionally, the absence of any relationship between axonal destruction, as measured by ^{11}C-flumazenil, and disruption of the various tracts implicates a cortical neuronal disorder, which is different from white matter pathology. Early neuronal impairment is reflected by a reduction in ^{11}C-flumazenil binding in cortical lesions and in the area where there are no lesions in very early stages of the disease. Furthermore, ^{11}C-flumazenil binding serves as a marker for microglia; this property has been used to elucidate the relationship between inflammation by microglial activation and disability [41]. In line with the findings above, Freeman et al. [42] have quantified and mapped neuronal damage in patients with clinically isolated syndrome and RRMS using PET with ^{11}C-flumazenil. The results have shown that there is a cortical decrease of diffuse benzodiazepine receptors, predominating in the frontal, parietal and temporal lobes, which is not correlated with the atrophic areas visualised by the Freesurfer image analysis program. Their study concludes that ^{11}C-flumazenil could be a marker of neuronal involvement and that cortical involvement occurs at an early stage, before atrophy begins to be detectable.

The mitochondrial translocator protein (TSPO) is upregulated in activated microglia. Previous studies using the PET tracer for ^{11}C-PK11195 TSPO have shown a relationship between microglia-mediated inflammation and disability [41], findings that again show microglial impairment prior to the appearance of white matter lesions, based on studies of animal models that have shown increased reuptake of ^{18}F-PRB111 in areas of activated microglia [43]. Colasanti et al. [44] have tested the specific binding of the ^{18}F-PBR111 marker to the TSPO receptor as a measure of the cerebral state around the injuries. In MS patients who should be homozygous for the *TSPO* gene, based upon differences in uptake affinity found in previous studies due to the *TSPO* gene rs6971SNP polymorphism [45], Colasanti and colleagues measured T_2 lesions, the perilesional volume and non-lesional area with normal or reduced MTR measures. The results showed greater microglial impairment in lesional, perilesional

and non-lesional regions, with reduced MTR involvement, compared to non-lesional regions with normal MTR. In conclusion, microglial activity can be evaluated quantitatively in the human brain *in vivo* using TSPO-PET. This technique shows increased uptake in white matter lesions and perilesional areas and increased uptake in white matter lesions and perilesional areas with low MTR. The TSPO-PET technique may be useful for measuring innate immunity.

The potential impact of macrophage activity in tissue disruption has been studied by Maarouf's team [46] on the basis of the known involvement of macrophage infiltration in the inflammatory disease processes. They determined the uptake prevalence of a new contrast agent, ultrasmall superparamagnetic particles of iron oxide (USPIO), which is specific to macrophages, in patients with clinically isolated syndrome. The results show that USPIO (+) lesions have a degree of tissue damage at 12 months greater than that of Gd (+) lesions; i.e., there is greater tissue destruction in lesions with macrophages.

Functional imaging and neural connectivity in multiple sclerosis

Adaptive cortical reorganisation

Conventional MRI measures show poor correlation with disability, and one of the causes is functional cortical reorganisation that occurs in the isolated neurological syndrome or the RR form, limiting the consequences of structural damage. Functional MRI (fMRI) studies in patients with multiple sclerosis show how minimal tissue damage in early stages of the disease induces the activation of cognitive neural networks, i.e., compensatory cortical activation, in relation to certain cognitive tasks.

This was demonstrated in a study using 10 patients with clinically isolated syndrome. PASAT performance yielded greater fMRI activation than controls in regions related to executive functions: right frontal cortex, bilateral prefrontal cortex and right hemi-cerebellum. This brain neuroplasticity may mask clinical signs of cognitive impairment in the early stages of the disease [47].

This reorganisation in cognitive neural networks or this compensatory cortical activation would be initially more evident in patients with higher cognitive impairment in RR forms and even more in patients with SP forms. However, in more advanced phases, with disease progression, this reorganisational capacity would expire, decreasing the compensatory activity. Several studies have attempted to prove this theory, suggesting that early in the course of the disease, recruitment of areas involved in a particular task occurs. As the disease progresses, with the accumulation of structural damage and reduced neuronal reserve, the same tasks will recruit cortical areas that are not ordinarily involved [48,49]. In this regard, benign MS has a similar pattern to the clinically isolated syndrome, without recruitment of contralateral areas, as occurs in long-lasting MS, in conjunction with the accumulation of clinical disability [49]. The same occurs in paediatric MS with RR progression; when there is no accumulation of disability, the functions are preserved, which most likely explains in part the favourable clinical evolution over the short and medium terms [50].

Maladaptive plasticity

Maladaptive connectivity, i.e., an abnormal recruitment of areas not involved in a specific task, may be partly responsible for disability. One study observed an abnormal recruitment of frontal thalamic circuits that could be related to fatigue induced by interferon β-1a [51]; in PPMS, unusual areas are recruited, such as the insula [52], and in the SP form, a decrease in the activity of classical areas of the motor system, such as the sensorimotor area and the cerebellum, is observed [53].

Impaired functional reserve and altered functional connectivity

Functional reserve impairment is the inability to recruit the typical areas involved in a particular task upon increases in the task's complexity. In early MS, with low activation requirements, functional reserve is high; however, when the task is more complex and has higher needs, this functional reserve fails [54]. Thus, activation patterns change in MS in motor and cognitive networks compared to controls [55,56]. Interventions that promote adaptive neuroplasticity may contribute to functional recovery of the affected areas [56,57].

In cases of RIS, defined as asymptomatic subjects with characteristic MS MRIs, it had not yet been explored whether tissue damage would be associated with altered functional connectivity, this being the objective of the study presented by Giorgio et al. [58]. The results showed macroscopic damage with conventional MRI measures, similar to those seen in patients with RIS and RRMS, and

damage to the white matter tracts by fractional anisotropy, similar in RIS and RRMS. However, using fMRI, RIS patients show co-activation of the sensorimotor circuit similar to controls and lower than that observed in RRMS patients. The authors offer two possible explanations: they are compensatory mechanisms not yet required in RIS, or there is no maladaptation in RIS that can contribute to the onset of symptoms.

The image of overall connectivity by DTI offers advantages over conventional techniques. In MS, it is sensitive to microstructural changes in normal-appearing white matter [59], although it is not specific for brain tracts, information that is instead provided by DTI tractography by showing brain connectivity via tracts. Among the promising techniques to detect changes in brain connectivity is anatomical connectivity mapping, which is based on global brain tractography and provides indexes and connectivity maps between voxels and the rest of the brain. Its application in patients with RR and SP forms has yielded stronger correlations between changes in anatomical connectivity mapping in the motor tracts and motor impairment based on the EDSS compared with DTI (unpublished data).

Networks and cognitive impairment

It has been proposed that the 'disconnection' between regions, functional nodes or brain areas produced by white matter lesions is one of the mechanisms by which cognitive impairment occurs in MS. In a study performed with DTI in MS patients, a correlation was found between the degree of impairment in neuropsychological batteries and the reduction of fractional anisotropy in white matter tracts connecting the cortical areas involved in the realisation of the tests to the compensatory activation of other areas [60]. Another similar study, also using tractography, proposed that damage assessment in strategic white matter tracts, such as the cingulate region, would better explain the cognitive state of patients than other parameters, such as the global involvement of tracts, cerebral atrophy or T_2 lesion load. Injury to these strategic tracts produces a disconnection syndrome that would contribute decisively to cognitive decline [61].

Cognitive impairment is common in MS and affects approximately 45-60% of patients, hence its relevance and the increased interest paid to it in recent years. There are assessment and measurement tools for cognitive impairment, some widely validated, such as the Rao Brief Repeatable Neuropsychological Battery and Minimal Assessment of Cognitive Function in Multiple Sclerosis, which, although composed of different subtests exploring different domains, has been shown to have similar sensitivity to diagnose cognitive impairment in MS. The Symbol Digit Modality Test (SDMT) is the subtest that has demonstrated greater sensitivity [62]. These two scales facilitate the early detection of cognitive decline and the development of treatment and management strategies during patient follow-up. Nonetheless, these scales are large and difficult to apply, so in clinical practice, they are replaced by screening scales such as the SDMT or the Multiple Sclerosis Neuropsychological Screening Questionnaire, which, besides being used as screening instruments, have proven to be reliable for monitoring long-term cognitive impairment, regardless of the language used and the region of the world where they are applied (the study was conducted in 21 countries in 14 different languages) –although the SDMT showed some learning effect [63]– and are proposed as promising alternatives. In fact, one study even raised the possibility of replacing the PASAT with the SDMT in the functional composite scale, demonstrating the latter's higher diagnostic power and simplicity of administration [64]. Benedict's team [65] introduced a new neuropsychological battery called the Brief International Cognitive Assessment for Multiple Sclerosis, consisting of the SDMT, version 2 of the California Verbal Learning Test and the revised test of visual and spatial memory, which is being validated for use in consultation with a small staff, few resources and no specific training in neuropsychology.

Conclusions

Conventional MS sequences remain central to the diagnosis, differential diagnosis and disease follow-up processes. Cervical MRI is especially informative at baseline, MRI does not predict good response to treatment, and the control MRI during the first two years of treatment predicts medium- and long-term prognosis.

New MRI techniques can help to assess the neurodegenerative process, and some of the new sequences are more specific to neuroaxonal [66] damage. However, an improvement in the sensitivity to changes and their applicability is necessary for them to be used as surrogate markers of neurodegeneration. Very high field MRI provides better understanding of the lesion load in terms of lesions, their distribution and their heterogeneity, allowing the measurement of subpial involvement in vivo.

PET studies offer a different view of the pathophysiology of the disease, showing that the involvement of tissue microstructure is more important than measures of atrophy. The behaviour of lesions with PET, coupled with the possibility of assessing microglial involvement, links, perhaps for the first time, pathophysiology and imaging studies. The relationship between retinal involvement by OCT and spinal cord involvement on MRI reflects independently disability-associated conditions, which are not apparent in measures of brain atrophy.

Functional imaging and neural connectivity studies in MS show that there is cortical reorganisation whose balance with structural damage is responsible for the disability. Neuroplasticity also occurs in cognitive neural networks, and its activity and connections in fMRI measures could be used as a marker of the cognitive status of a patient. Interventions that promote neuroplasticity may contribute to functional recovery.

Numerous drugs are on the horizon for MS treatment, with different mechanisms of action [67], although there is a need for new strategies, new treatment algorithms, new biomarkers new assessment measures of secondary progression, and long-term records to assess safety.

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

Resumen. Los datos más relevantes presentados en la XXIX edición del Congreso del Comité Europeo para el Tratamiento e Investigación en Esclerosis Múltiple (ECTRIMS), celebrado en octubre de 2013 en Dinamarca, se han resumido en la sexta edición de la Reunión de Expertos Post-ECTRIMS celebrada en Madrid en octubre de 2013, fruto de la cual nace esta revisión, que se publica en tres partes. Esta segunda parte de la revisión Post-ECTRIMS se centra en la imagen del diagnóstico y diagnóstico diferencial, en la monitorización clínica y paraclínica de la neurodegeneración, progresión y discapacidad, y en la imagen funcional y conectividad neural. Queda patente que las secuencias convencionales de esclerosis múltiple siguen siendo básicas para el diagnóstico, el diagnóstico diferencial y el seguimiento de la enfermedad, que las nuevas técnicas de resonancia magnética ayudan a evaluar el proceso de neurodegeneración, y algunas de las nuevas secuencias son más específicas del daño neuronal-axonal. La resonancia magnética de campo muy alto permite un mejor conocimiento de la carga lesional, distribución y heterogeneidad de las lesiones, y los estudios con tomografía por emisión de positrones ofrecen una nueva visión de la fisiopatología de la enfermedad. Los estudios de imagen funcional y conectividad neural muestran que en la esclerosis múltiple existe una reorganización cortical cuyo equilibrio con el daño estructural es responsable de la discapacidad.

Palabras clave. Conectividad neural. Esclerosis múltiple. Imagen funcional. Resonancia magnética. Tomografía de coherencia óptica. Tomografía por emisión de positrones.