MS Preceptorship: Updating knowledge in MS
17 -19 June 2014 - Barcelona, Spain
Dear delegate,

A warm welcome to all attending the course on "MS Preceptorship: Updating knowledge in MS".

I would like to inform you that as of 28 April 2014 the name of our Foundation changed to EXCEMED - Excellence in Medical Education. The name change will not impact your registration status in this or any other Foundation event.

This transition marks an exciting point in the evolution of the Foundation. We are proud to have provided world-class education to thousands of healthcare professionals over the past four decades - as a result, the Foundation has become synonymous with delivery excellence and high-impact CME.

As we further develop our scientific and geographical presence it is important to us that our name accurately reflects the independent nature of the education we provide; EXCEMED symbolises our enduring mission to support the best possible outcomes for patients through the medical education we offer. We take pride in our complete dedication to the provision of CME - it is our sole focus and our passion.

I wish you an inspiring and successful learning experience here in Barcelona.

Yours sincerely,

Rachel Clark
CEO, EXCEMED
General information

Venue
The live educational course will take place at the:

Centre d’Esclerosi Múltiple de Catalunya (Cemcat)
Edifici Cemcat
Hospital Universitari Vall d’Hebron
Pg. Vall d’Hebron, 119-129
08035 Barcelona, Spain

Language
The official language of the live educational course is English.

Scientific secretariat
EXCEMED - Excellence in Medical Education
Salita di San Nicola da Tolentino, 1/b
00187 Rome, Italy
Senior Programme Manager: Alessia Addessi
T: +39 06 420413 591
F: +39 06 420413 677
E-mail: info@excemed.org
Medical Advisor: Doriana Landi
EXCEMED is a Swiss Foundation with headquarters in
14, rue du Rhône, 1204 Geneva, Switzerland

Organising secretariat
Meridiano Congress International
Via Sapri, 6 - 00185 Rome, Italy
Congress coordinator: David H. Slangen
T: +39 06 88 595 250 - F: +39 06 88595 234
E-mail: d.slangen@meridiano.it

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MS Preceptorship:  
Updating knowledge in MS

EXCEMED live educational course:

MS Preceptorship:  
Updating knowledge in MS
17 -19 June 2014 - Barcelona, Spain

Aim
New insights into demyelinating diseases pathogenesis, the development of innovative diagnostic tools and the amount of new  
treatments available in clinical practice demand that neurologists specialising in MS keep abreast of new developments and share  
best practice.
This preceptorship course will provide a comprehensive update on the most important topics in MS in the setting of a centre of  
xcellence.

Learning objectives
By attending this live educational course learners will be able to:
• Apply diagnostic criteria in order to achieve an early diagnosis of MS and to define its clinical course
• Use radiological markers of disease severity in order to project a treatment plan
• Make a differential diagnosis among demyelinating disorders
• List the most suitable therapeutic approach for each condition
• Compare the efficacy and safety profile of each drug available for MS treatment

Target audience
Clinicians recently involved in MS patient management and neurologists interested in entering the MS field.

Accreditation
EXCEMED [www.excemed.org] is accredited by the European Accreditation Council for Continuing Medical Education (EACCME®) to  
provide the following CME activity for medical specialists. The EACCME® is an institution of the European Union of Medical  
Specialists (UEMS), www.uems.net
The CME course “MS Preceptorship: Updating knowledge in MS” held on 17-19 June 2014 in Barcelona, Spain, is designated for a  
maximum of 11 [eleven] hours of European CME credits (ECMEC). Each medical specialist should claim only those credits that  
he/she actually spent in the educational activity. EACCME® credits are recognized by the American Medical Association (AMA)  
towards the Physician’s Recognition Award (PRA). To convert EACCME® credit to AMA PRA category 1 credit, please contact the AMA.

EXCEMED adheres to the principles of the Good CME Practice Group [gCMEp]
We value your opinion!

We are continually trying to develop and improve our educational initiatives to provide you with cutting-edge learning activities. During this course you will be asked to answer a real-time survey and after you will be receiving an online survey to better tailor our future educational initiatives.

We thank you for participating!
Faculty members

Maria Pia Amato
Department of Neurological and
Psychiatric Sciences
University of Florence
Florence, Italy

Maria Jesús Arévalo
Multiple Sclerosis Centre of Catalonia (Cemcat)
Neurology-Neuroimmunology Department
Vall d’Hebron University Hospital
Barcelona, Spain

Georgina Arrambide
Multiple Sclerosis Centre of Catalonia (Cemcat)
Neurology-Neuroimmunology Department
Vall d’Hebron University Hospital
Barcelona, Spain

Wolfgang Brück
Department of Neuropathology
University Medical Center Göttingen
Georg-August University
Göttingen, Germany

Manuel Comabella
Multiple Sclerosis Centre of Catalonia (Cemcat)
Neurology-Neuroimmunology Department
Vall d’Hebron University Hospital
Barcelona, Spain

Giancarlo Comi
Department of Neurology
Institute of Experimental Neurology
Vita-Salute San Raffaele University
Milan, Italy

Carme Costa Riu
Multiple Sclerosis Centre of Catalonia (Cemcat)
Neurology-Neuroimmunology Department
Vall d’Hebron University Hospital
Barcelona, Spain

Herena Eixarch
Multiple Sclerosis Centre of Catalonia (Cemcat)
Neurology-Neuroimmunology Department
Vall d’Hebron University Hospital
Barcelona, Spain

Óscar Fernández
Department of Neurology
Hospital Regional Universitario Carlos Haya
Malaga, Spain

Nicolás Fissolo
Multiple Sclerosis Centre of Catalonia (Cemcat)
Neurology-Neuroimmunology Department
Vall d’Hebron University Hospital
Barcelona, Spain

Angelo Ghezzi
Multiple Sclerosis Centre
Gallarate Hospital
Gallarate, Italy

Eva Havrdová
MS Centre and Neurology Clinic
Charles University
Prague, Czech Republic

Reinhard Hohlfeld
Institute of Clinical Neuroimmunology
Klinikum Grosshadern
Ludwig Maximilians University of Munich
Munich, Germany

Rosalía Horno
Multiple Sclerosis Centre of Catalonia (Cemcat)
Neurology-Neuroimmunology Department
Vall d’Hebron University Hospital
Barcelona, Spain

Letizia Leocani
Institute of Experimental Neurology
University Vita-Salute IRCCS
San Raffaele Hospital
Milan, Italy

Sara Llufriu
Neuroimmunology group
Hospital Clinic Barcelona
IDIBAPS (Institut d’Investigacions Biomèdiques August Pi i Sunyer)
Barcelona, Spain
Xavier Montalban
Multiple Sclerosis Centre of Catalonia (Cemcat)
Neurology-Neuroimmunology Department
Vall d’Hebron University Hospital
Barcelona, Spain

Susana Otero
Multiple Sclerosis Center of Catalonia (Cemcat)
Department of Epidemiology
Vall d’Hebron University Hospital
Barcelona, Spain

Filipe Palavra
Multiple Sclerosis Centre of Catalonia (Cemcat)
Neurology-Neuroimmunology Department
Vall d’Hebron University Hospital
Barcelona, Spain

Lluís Ramió i Torrentá
Department of Neurology
Multiple Sclerosis Unit
“Dr. Josep Trueta” Hospital in Girona
Girona, Spain

Marta Renom Guiteras
Multiple Sclerosis Centre of Catalonia (Cemcat)
Neurology-Neuroimmunology Department
Vall d’Hebron University Hospital
Barcelona, Spain

Jordi Río
Multiple Sclerosis Centre of Catalonia (Cemcat)
Neurology-Neuroimmunology Department
Vall d’Hebron University Hospital
Barcelona, Spain

Lucía Romero
Unit of Multiple Sclerosis
University Hospital of Bellvitge
Barcelona, Spain

Alex Rovira
Unit of Magnetic Resonance
Department of Radiology
Vall d’Hebron University Hospital-IDI
Barcelona, Spain

Samuel Sánchez
Multiple Sclerosis Centre of Catalonia (Cemcat)
Neurorehabilitation Department
Vall d’Hebron University Hospital
Barcelona, Spain

Jaume Sastre-Garriga
Multiple Sclerosis Centre of Catalonia (Cemcat)
Neurology-Neuroimmunology Department
Vall d’Hebron University Hospital
Barcelona, Spain

Mar Tintoré
Multiple Sclerosis Centre of Catalonia (Cemcat)
Neurology-Neuroimmunology Department
Vall d’Hebron University Hospital
Barcelona, Spain

Carmen Tur
Multiple Sclerosis Centre of Catalonia (Cemcat)
Neurology-Neuroimmunology Department
Vall d’Hebron University Hospital
Barcelona, Spain

Ángela Vidal
Multiple Sclerosis Centre of Catalonia (Cemcat)
Neurology-Neuroimmunology Department
Vall d’Hebron University Hospital
Barcelona, Spain
Scientific programme
Scientific programme

Chairpersons: Xavier Montalban and Jaume Sastre-Garriga

Tuesday, 17 June 2014

8.45  EXCEMED opening
      Giancarlo Comi (Italy)

9.00  Introduction to MS Centre of Catalonia (Cemcat)
      Xavier Montalban (Spain)

9.30  Real-time survey

10.00 L1: Epidemiology of MS
      Susana Otero (Spain)

10.30 L2: Genetics of MS
      Manuel Comabella (Spain)

11.00 L3: Pathology of MS
      Wolfgang Brück (Germany)

11.30 Coffee break

12.00 PD1: Panel discussion on “New revision of McDonald’s criteria”
      Chair: Òscar Fernández (Spain)
      MS diagnosis and differential diagnosis
      Mar Tintoré (Spain)
      MRI in MS: the radiologist perspective
      Alex Rovira (Spain)
      EPs and OCT in MS
      Letizia Leocani (Spain)

      Discussion
      Revisiting real-time survey

13.00 Working Lunch

14.30 Cemcat – Nuts and bolts
      Carmen Tur (Spain)

15.00 Visit to Cemcat and Vall d’Hebron Hospital premises

17.00 End of the first day

Wednesday, 18 June 2014

8.45  Specific forms of demyelinating diseases
      L4: Neuromyelitis optica – NMO
      Georgina Arrambide (Spain)
      L5: Primary progressive MS
      Carmen Tur (Spain)
      L6: Paediatric and juvenile MS
      Angelo Ghezzi (Italy)

10.00 L7: Overview on symptomatic therapy and rehabilitation
      Jaume Sastre-Garriga (Spain)

10.30 S1: Symptomatic therapy snapshot #1 on gait rehabilitation
      Samuel Sánchez (Spain)

10.45 S2: Symptomatic therapy snapshot #2 on management of dysphagia
      Marta Renom Guiteras (Spain)

11.00 Coffee break

11.30 PD2: Panel discussion on “Cognition disorders in MS”
      Chair: Maria Pia Amato (Italy)
      Diagnosis
      Maria Pia Amato (Italy)
      Treatment
      María Jesús Arévalo (Spain)
      Case presentation
      Ángela Vidal (Spain)

12.30 KNS2: Injectable therapies in MS
      Eva Havrdovà (Czech Republic)

13.00 L8: Day-to-day patients’ management: nurse and neurologist perspectives
      Rosalía Horno and Filipe Palavra (Spain)

13.30 Working lunch

14.30 CS1: Case study session
      The case study session will involve attendees in an interactive discussion, giving them the chance to share opinions and understanding of different MS related topics. The audience will be divided into three groups for the case presentation and then will discuss all together the cases in the plenary room.
      Sara Llufriu, Lluís Ramió i Torrentá and Lucía Romero (Spain)

16.00 End of the second day

Legend:  L : Lecture;  KNS : Key Note Speech;  CS : Case Study;  S : Snapshot;  PD : Panel Discussion
Thursday, 19 June

8.30  PD3: Panel discussion on “Define treatment success”
      Chair: Mar Tintoré (Spain)
      Define treatment success in present daily practice with clinical and MRI surrogates
      Jordi Río (Spain)
      Define treatment success in the age of pharmacogenomics
      Manuel Comabella (Spain)
      Discussion

9.30  L9: Fostering treatment adherence and compliance: a role-play
      María Jesús Arévalo (Spain)
      Jaume Sastre-Garriga (Spain)

10.30 KNS3: Oral therapies in MS
          Giancarlo Comi (Italy)

11.00 Coffee break

11.30 KNS4: Therapy with monoclonal antibodies
          Xavier Montalban (Spain)

12.00 S3: Snapshot #1 on gene therapy in MS
          Herena Eixarch (Spain)

12.15 S4: Snapshot #2 on DNA vaccines in MS
          Nicolás Fissolo (Spain)

12.30 S5: Snapshot #3 on stem cell therapy in MS
          Carme Costa Riu (Spain)

12.45 Course wrap-up
          Revisiting real-time survey

13.15 Group picture

13.30 End of the course
      Closing lunch
Abstracts
Epidemiology can be defined as the study of the distribution and determinants of disease from a population perspective, using quantitative methods. Descriptive epidemiology pictures the distribution and time trends, using prevalence and incidence data, and analytic epidemiology seeks for possible risk factors related to the disease.

The first descriptive epidemiological studies on multiple sclerosis (MS) used prevalence data to map the distribution of MS around the world. They showed that the disease was not evenly distributed and there was a latitudinal gradient with higher prevalence as we move away from the equator. It should be noted that these studies had certain limitations that have to be considered when comparing data. There were differences between studies regarding methodological aspects such as case definition, sources of information, population size and there was data lacking in certain parts of the world.

Despite the methodological limitations, the characteristic distribution led to genetic and environmental pathogenic hypothesis. Considering that MS has an important genetic component of susceptibility, the distribution could be due to the variation of genetic and ethnic backgrounds of the world’s population. Nevertheless, there are reasons to believe that genetics can not explain all of it. The concordance rates for MS of 24% in monozygotic twins reflect other factors acting in uterine or early life environments. In regions with homogenous population, the latitudinal gradient of MS is still present. According to studies in migrant population, risk of MS can vary when migrating to a different area, particularly when migration occurs early in life. Furthermore, seasonality in the risk of MS has been recently described (“month of birth effect”).

There are several environmental factors that have been postulated. The mirror-image gradient of MS points to a sun related factor such as Vitamin D. On the other hand, an infectious agent acting directly (as a trigger of the disease) or indirectly (protecting if acquired early in life -hygiene hypothesis-) has also been postulated. Epstein-Bar virus (EBV), seems one of the strongest candidates, as MS in unlikely to develop in a EBV negative individual, there is strong evidence that links epidemiology of infectious mononucleosis with MS. Smoking has also been recently linked to MS.

Recent data from prospective studies performed in Europe, America and Asia show that MS incidence and prevalence are increasing during the past 20 years and the classical gradient is disappearing in certain areas. The increase in prevalence could be explained by longer patient survival and increase in incidence (improved case ascertainment thanks to better diagnostic techniques and /or change in causal factors that increase risk of MS).
Autoimmune T and B cell responses to CNS antigen(s) are thought to drive the pathogenesis of MS. New techniques have allowed the precise quantitative analysis of the antigen-receptor repertoire of tissue-infiltrating T and B cells. For example, it is now possible to identify (auto-)aggressive T-cells in affected autopsy or biopsy tissue and to identify paired T-cell receptor (TCR) alpha- and beta-chains from individual tissue-infiltrating T-cells. The matching TCR chains from individual T-cells can then be “resurrected” in hybridoma cells which may be used for antigen searches. Strategies for identification of (auto-)reactive B-cells and immunoglobulin (Ig) molecules are fundamentally different, because Ig molecules are water-soluble and have high affinities. Proteome-based approaches, techniques for analyzing Ig-chains from single B-cells, and repertoire-based methods for comparing Ig-proteomes and Ig-transcriptomes have also been developed.

Novel candidate auto-antigens, including B-cell antigens, have been identified. These include para-nodal antigens such as neurofascin, which are expressed on myelin and/or axons. Several promising immunological “biomarkers” with possible prognostic, diagnostic and therapeutic relevance have been described. One of these markers, antibody to aquaporin-4, has helped to identify “neuromyelitis optica (NMO) spectrum” disease that differs from MS not only in pathogenesis but also clinical course and treatment requirements. Much progress has also been made in understanding the milieu factors that make the CNS a very special and conducive environment for interactions between cells of the immune system and nervous system. Chemokines guide the migration of immune cells into MS lesions, and cytokines foster the long-term persistence of immune cells in the CNS environment. Intriguingly, tissue-infiltrating immune cells secrete neurotrophic factors, which might support the survival of some neuronal and glial cells. Altogether, these discoveries have shed new light on the pathogenesis of MS, and will make a strong impact on the development of novel therapies for this still incurable disease.

Regarding the animal model of human MS, experimental autoimmune encephalomyelitis (EAE), the interplay between MS and EAE research has been very productive over the years. There are many examples of how experimental findings in EAE could be successfully translated to MS, and vice versa. For example, researchers increasingly combine “descriptive” evidence obtained in human MS, e.g. by applying transcriptomics or proteomics techniques, with “functional” experiments in EAE. With ever more sophisticated techniques, including spontaneous and humanized EAE models, MS and EAE research will continue to benefit from each other in the future. Mainly as a consequence of the increasingly better understanding of the pathogenesis, therapy of MS has drastically changed over the last 20 years.
During the last two decades, many research groups have dedicated important efforts to identify the individual genes that confer susceptibility to multiple sclerosis (MS). The main conclusion derived from this work is that the HLA-class II region on chromosome 6p21, specifically the HLA-DRB1*15 haplotype, contributes by far the most to genetic susceptibility in MS, and results from many MS genetic studies support this association. Unfortunately, despite the evidence that MS is a complex genetic trait with multiple genes contributing to disease susceptibility, genetic studies aiming to identify additional risk genes for MS have been rather disappointing, as many of the candidate genes identified in one study were not confirmed in others. It has not been until recently that additional genes located outside the HLA region have been proposed, although with weaker effects, as solid candidates for MS genetic risk. In particular, three single-nucleotide polymorphisms (SNPs), two located within the interleukin-2 receptor α (IL2RA) and one located within the interleukin-7 receptor α (IL7RA), were strongly associated with MS. Other SNPs positioned in attractive genes were also found to be associated with the disease. Most of the genes proposed as risk genes for the disease are related with the immune system. These latest findings have certainly opened new scenarios in MS genetic research.
Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system which leads to focal destruction of myelin, acute axonal damage/loss of axons and reactive astrogliosis. The irreversible axonal loss is thought to be the major correlate of chronic disability in MS. MS has long time been considered a focal white matter disease, however, nowadays it is accepted that MS involves the entire central nervous system (CNS), including the grey matter and the normal-appearing white matter.

The presentation discusses the pathological events occurring in these three compartments:

1. **Focal white matter lesions**: lesion characteristics/heterogeneity in early and chronic disease stages concerning the composition of the inflammatory infiltrate; extent of demyelination and remyelination; oligodendrocyte pathology; acute axonal damage and axonal loss.

2. **Cortical demyelination**: types of cortical lesions; consequences of demyelination for the neuronal compartment; remyelination in the cortex.

3. **Normal appearing white matter**: diffuse inflammation and microglial activation; axonal damage and loss.

The pathology in relation to different disease stages is discussed in detail.
PD1. Panel discussion on “New revision of McDonald’s criteria”

Mar Tintoré, Spain¹
Alex Rovira, Spain²
Letizia Leocani, Spain³

1 - Multiple Sclerosis Centre of Catalonia (Cemcat), Neurology-Neuroimmunology Department, Vall d’Hebron University Hospital, Barcelona, Spain;  
2 - Unit of Magnetic Resonance, Department of Radiology, Vall d’Hebron University Hospital-IDI, Barcelona, Spain;  
3 - Institute of Experimental Neurology, University Vita-Salute IRCCS, San Raffaele Hospital, Milan, Italy

**MS diagnosis and differential diagnosis**

*Mar Tintoré*

Diagnostic criteria for MS rely on the demonstration of CNS disease in space and time and in reasonable exclusion of other causes. Since McDonald 2001, in patients with a first attack, evidence of diagnosis for dissemination in space and time may be provided by MRI. The recently published 2010 McDonald criteria selected the Magnims criteria for dissemination in space (DIS). DIS is defined as the presence of ≥1 asymptomatic T2 lesion(s) in at least two of four locations considered characteristic for MS in previous MRI criteria: juxtacortical, periventricular, infratentorial and spinal cord. These criteria simplify the previous Barkhof criteria and highlight the importance of lesion location for MS diagnosis. Moreover, this new definition relies on T2 lesions only. Non-inclusion of gadolinium enhancing lesions seems appropriate since enhancing lesions per se provide information on disease activity and not on dissemination in space. For demonstration of dissemination in time (DIT), an MRI performed at any time demonstrating DIS and showing at least one or more asymptomatic gadolinium enhancing and non-enhancing lesion(s) (this being used as evidence for DIT) would be sufficient to diagnose MS. Although many studies have already shown the importance of CSF study in the diagnosis and differential diagnosis of MS, the presence of oligoclonal bands has not been included in the diagnosis algorithm. These new criteria have been adapted to other populations such as patients with primary progressive MS or patients with paediatic MS. An overview of the past diagnostic criteria will also be performed as well as new directions for the future will be considered (intracortical lesions, 3 Teslas MRI, other). Clinical cases to illustrate differential diagnoses will be presented.

**MRI in MS: the radiologist perspective**

*Alex Rovira*

Learning objectives of the presentation

- To learn about recognition patterns that might be helpful in suggesting the diagnosis of multiple sclerosis
- To understand the role of spinal cord imaging in the differential diagnosis
- To know the potential value of new MR techniques for the diagnosis of multiple sclerosis

The exact diagnosis of MS still remains challenging in some cases, as there is no single test (including biopsy) that can provide a definite diagnosis of this disease. Due to this fact the neurological community has adopted diagnostic criteria for MS, which have been modified in the last 20 years several times following new evidence and experts recommendations. With the availability of expensive and not completely free from side effects disease modifying treatments, which are particularly effective when administered during the early phases of the disease (Goodin, Bates. MSJ 2009), an early and accurate diagnosis of MS is more imperative than ever. Diagnostic criteria for MS include clinical and paraclinical assessments emphasizing the need to demonstrate demyelinating lesions within the central nervous system disseminated in space (DIS) and time (DIT), and to exclude alternative diagnosis that could mimic MS either clinically or radiologically (Charil et al. Lancet Neurol 2006). Although the diagnosis can be made on clinical grounds alone, MR imaging should be obtained to support the clinical diagnosis and in a significant proportion of patients can even replace some clinical criteria. This possibility has been included in the different versions of the McDonald criteria that for the first time integrated MRI features in the diagnostic scheme, allowing an earlier and more accurate diagnosis of the disease. Nevertheless, we should keep in mind that for optimal application of these MRI criteria, the scans must be technically adequate and neuroradiologist must consider the clinical information to properly interpret the imaging findings, and be expert enough to recognize the full range of brain and spinal cord abnormalities that suggest the diagnosis of MS, as several other disorders can cause white matter lesions with imaging characteristics similar to those seen in MS. Focal white matter T2 hyperintense lesions (T2-HI) mimicking those seen in MS can be detected in a relatively large list of different disorders that may affect middle age and young patients, such as hypoxic-ischemic vasculopathies [CADASIL, Fabry’s disease, Susac’s syndrome], primary and systemic vasculitis, sarcoidosis, adult forms of leukoencephalopathies and even in healthy subjects. While it is recognized that a combination of findings from clinical history, physical examination, and laboratory tests is commonly required to correctly establish a diagnosis of MS, a detailed analysis of different MRI features should also be considered essential: e.g. lesions shape, size, and distribution [both in brain and spinal cord]; pattern of contrast-uptake. In addition to these conventional MRI based
features, non-conventional MR techniques (diffusion-weighted, perfusion-weighted, susceptibility-weighted) may also provide in some cases useful diagnostic information. Knowledge of these features, will assist the diagnostic work-up of patients presenting with T2-HI, and should be considered a first step to take full advantage of the potential of MRI, and in doing so should result in a reduced chance of misdiagnoses and facilitate the correct diagnosis of sometimes treatable disorders.

References:

EPs and OCT in MS
Letizia Leocani

In Multiple Sclerosis (MS), the underlying pathology may precede by years the clinical presentation. Demyelination and neurodegeneration lead to accumulation or progression of disability, although may be countered by functional reorganization, together with some level of remyelination and neuroregeneration. Indeed, early MS disease course is dependent on the balance between demyelination and remyelination, with the clinical manifestation determined by the degree of plasticity offsetting the effect of damage. Although the pathogenesis of demyelination has been well described, the cellular and molecular mechanisms of neurodegeneration are not fully understood. Among the major factors, ion channel expression and redistribution, together with neuroprotective pathways counteracting oxidative stress and mitochondrial dysfunction have been identified 1 Neurophysiological methods, namely evoked potentials (EP), are currently used for the assessment of functional consequences of demyelination, remyelination and axonal loss occurring in the course of the disease, as well as in pre-clinical testing. The functional information provided by evoked potentials accounts for their correlation with disease severity and point to their possible role as paraclinical measure for monitoring disease progression. In particular, they can help assessing the functional impact of the disease on central sensorimotor and cognitive networks affected by MS, and may reveal subclinical lesions. Visual evoked potential (VEP), combined with OCT, provide a complete evaluation of structural and functional damage of the optic pathway, representing a sensitive surrogate measure of neurodegeneration e demyelination. 2,3. Furthermore, EP also provide some prediction on the future evolution of disability, consistently with the hypothesis that early demyelination may prompt future neuronal loss, as shown in longitudinal studies. 3 If further validated, neurophysiological methods may have a role in the early identification of patients who are more likely to develop future disability and for whom a closer clinical monitoring of treatment response is necessary. Finally, the possibility to demonstrate improved conduction through evoked potentials can represent a key feature in the assessment of efficacy of novel therapeutic approaches targeting demyelination.

References:
In this talk we will give a practical view of the Cemcat, which is a strategic alliance between the Catalan Health Institute, through the University Hospital Vall d’Hebron, the Catalan Health Service and the Multiple Sclerosis Foundation. Functionally, Cemcat is the integration and fusion of two professional teams dedicated to the comprehensive care of people with multiple sclerosis. All Cemcat activities are carried out in a new building located within the Vall d’Hebron University Hospital. In this talk, we will discuss the main points related to the clinical, research, and teaching activities that are carried out at Cemcat.
Neuromyelitis optica (NMO) is a rare and severe inflammatory demyelinating disease with predominant involvement of the optic nerves and the spinal cord, previously considered to be a variant of multiple sclerosis (MS). The main objective of this talk is to provide a general update on this disease and on NMO spectrum disorders (NMOsd). Over the years, a number of clinical, laboratory, and magnetic resonance imaging studies have provided data to differentiate NMO from MS. The discovery of serum IgG antibodies targeting the water channel aquaporin-4 has not only helped categorize NMO as an independent entity from MS, but has also broadened the disease spectrum. The discovery of these highly specific antibodies, in turn, could potentially aid in finding a more specific treatment aimed at the prevention of recurrences than those drugs currently supported by clinical guidelines, like rituximab or mofetil mycophenolate. However, a worldwide consensus regarding NMO-IgG detection is still to be obtained since different methods for antibody identification exist. Recent data points to a combination of improved immunohistochemistry tissue-based assays and cell-based assays as the most sensitive methods to detect this antibody. Nevertheless, 20-30% of results are still negative and, in these instances, other antibodies have been identified in a proportion of cases. The most relevant to date is the anti-MOG antibody since its presence appears to indicate a more benign disease course. Despite these improvements, atypical cases with intermediate MS and NMO features exist and they are still difficult to differentiate early in the disease course.
About 15-20% of all people with MS have primary progressive multiple sclerosis, which is characterised by the presence of progression since symptom onset. This progression may vary widely amongst patients, but, at present, only a few tools provide modest prediction of clinical outcome. Importantly, up to now, no treatment has proved effective in slowing down disability progression. In this talk we will give an overview of this form of the disease, emphasising some novel aspects of their diagnostic criteria, the most recent perspectives of the available tools to predict progression, and the most relevant clinical trials carried out.
The onset of multiple sclerosis (MS) typically occurs in adults, however the onset in subjects with less than 18 years of age is being increasingly recognized, in about 3-10% of all patients with MS (1). The diagnostic criteria of this form have been reviewed and defined in a recent paper (2), and, in cases with a typical MS onset and excluding the ADEM-like onset, diagnosis of definite MS can be made if the new revised MS diagnostic criteria are fulfilled (3).

Some clinical findings seem to be peculiar of pediatric-MS (Ped-MS):
- the onset with cerebellar and brainstem dysfunction (1, 4), specially in subjects with less than 12 years,
- the polysymptomatic presentation, with fever, headache, letargy, meningism, seizures (ADEM-like onset), specially in very young patients (1),
- the evolution with a high relapse rate, specially in the first years of the disease, resulting in an annualized relapse rate higher than observed in adult MS [4-7],
- the evolution with a relapsing-remitting (RR) course in more than 90% of cases [1].
- the progression with a longer interval but a lower age to reach the end-points of mild (EDSS score of 3-4) and severe (EDSS score of 6) disability, compared to adult onset MS (5, 8). So, at a given age, patients with onset in childhood are more disabled than those with a later onset.

The frequency of relapses (or the inter-attack interval) in the first few years after disease onset is a negative prognostic factor as it correlates with an increased disease severity and with an earlier entry into the secondary progressive phase of MS (1). Moreover, this finding suggests that probably the inflammatory process is more pronounced in children with MS compared to adults. The frequent pleocytosis in the CSF (9) and the aspect of MRI lesions seem to confirm this conclusion (10, 11). Recent studies have demonstrated that about 30% of children and adolescents with MS develop cognitive dysfunction early, with a negative impact on academic functioning and on social relationships (12-14).

The objective of MS treatment is to prevent the occurrence of relapses, to delay the accumulation of disability, and to reduce irreversible brain damage. What is the best treatment of ped-MS? The use of drugs for MS in children and adolescents has not been studied in randomised controlled clinical trials, so their use is mainly based on results from trials in adults and on observational class 3 and 4 studies: however, in spite of methodological limitations, these studies (15, 16) have shown that immunomodulators, namely Interferon-Beta and Glatiramer acetate:
- are safe and well tolerated in children and adolescents with MS,
- significantly reduce relapse rate and disease progression in this population.

A panel of European experts (15) has recommend to start early the therapy with IAs in children and adolescents with relapsing MS; subjects at the first demyelinating episode must be monitored clinically and with MRI study, offering the treatment if a new clinical or subclinical (new T2 or Gadolinium enhancing lesions) episode occurs; moreover the treatment could also be considered in selected cases with an aggressive onset at their first episode.

A similar position has been taken by the International pediatric MS Study Group with the following statement "Use of first-line therapies in pediatric MS [where available] is generally accepted as the standard care. Based on these findings, the IPMSSG recommends that all pediatric patients with MS, as defined by Krupp et al., should be considered for treatment with either a beta-interferon or glatiramer acetate as first line therapy.

However, in spite of IA treatment about 30% of cases continue to progress and develop relapses. There are no accepted criteria to define treatment failure, and the decision is made on a clinical basis, taking into account the occurrence of relapses, the increase of EDSS score, MRI activity (new T2 lesions, Gadolinium-enhancing lesions) (15, 16). For patients with poor tolerability, severe side effects, evidence of clinical activity there are two options:
- to shift from IFNB (in particular if neutralising antibodies to IFNB are present) to GA or vice-versa
- to shift to second line treatments: this option should be considered in particular for cases with a very active form of MS.

Natalizumab was demonstrated to be safe and effective in a few case reports and in two studies which have included 19 and 24 patients (see ref. 15 and 16), with a mean follow up of 15 and 18 months, respectively (17, 18); in all this studies a strong suppression of disease activity was found. The risk of PML must be carefully considered, but this risk can now be predicted by the test to detect anti-JCV antibodies (19).

Cyclophosphamide has shown to reduce disease activity in a retrospective study of 17 ped-MS subjects with a mean age of 15 year and a mean disease duration of 3.1 years, but many adverse events were recorded. (20).
Mitoxantrone has shown a beneficial effect in 4 ped-MS cases with severe evolution (21), but the safety profile, particularly the of leukaemia and cardiomyopathy, discourages its use (15, 16). Daclizumab has been proposed as a possible second-line treatment for pediatric cases with an active MS evolution in a study where 6 cases were included (22).

Further studies are necessary to better define the efficacy and safety profile of new medications in ped-MS, a registry on an international basis could contribute to clarify this issues. The International Pediatric MS Study Group (www.ipmssg.org) has been created to promote and coordinate international studies in the field of research, treatment and clinical care of ped-MS.

References:
Multiple Sclerosis (MS) may cause a variety of symptoms: fatigue, cognitive dysfunction, bladder and bowel problems, sexual problems, tremor, spasticity, speech and swallowing disorders, sensory symptoms including pain, among others. Motor and coordination symptoms causing gait problems and upper limb dysfunction also need to be considered. These symptoms, in isolation, or more commonly in association, are the ultimate cause of worsening quality of life and therefore must be treated with the same emphasis as the condition itself. There is a need for an interdisciplinary management of symptoms in MS; this management is the focus of neurorehabilitation. Neurorehabilitation approaches emphasize education of patients and self-management of symptoms; this approach is ideally suited to meet the evolving needs of people with MS. Thus, symptom management should be performed on a neurorehabilitation setting using an interdisciplinary approach. According to this, clinical trials evaluating the efficacy and safety of a drug intervention to treat a given symptom lack the added value of interdisciplinary interventions (e.g. drug A may be useful for spasticity, but its combined efficacy together with physiotherapy and occupational therapy has not been investigated; in combination they are likely to have a greater impact on quality of life, the final goal of any symptomatic therapy). Clinical trials evaluating the effectiveness of neurorehabilitation approaches in people with MS have shown that improvements in activities and participation are to be expected. However, modalities of intervention have been usually ill-defined (rehabilitation black box) and clinical trial methodologies suboptimal. Therefore, further research is needed to improve clinical trial methodology and our ways of evaluating the impact of neurorehabilitation by means of goal achievement frameworks and through the use of clinically appropriate and scientifically sound outcome measure tools. In this lecture we will provide an overview of the evidence in favor of neurorehabilitation in MS; current therapies for fatigue and bladder disturbances due to Multiple Sclerosis will be specifically discussed.
One of the most pronounced incapacitating manifestations of MS are gait abnormalities, resulting from the combined effect of decrease in muscle strength, spasticity, cerebellar ataxia, sensory disorders and reduction in aerobic capacity. Pathological gait patterns are less functional, secure, and effective which contribute to secondary problems such as increased risk of falls and increased energy expenditure and affect activity, participation and quality of life.

Physical therapy interventions firstly aim to develop motor recovery and secondly to train compensatory strategies in order to improve or maintain functional independence and efficacy in deambulation.

In this speech we’ll revise the main rehabilitation strategies for gait impairment in MS: from conventional rehabilitation to the latest robotic biofeedback devices.

References:
The reported prevalence of dysphagia in MS ranges between 33% and 43%. It is clearly more frequent in advanced stages of the disease but can also appear in early stages. It is associated to brainstem and cerebellar impairment. Dysphagia can lead to serious complications such as bronchopneumonitis, bad nutritional state and decrease of the quality of life. It can affect swallowing of liquids and/or solids, the later being more frequent in severe dysphagia.

The intervention is interdisciplinary and can involve neurologists, speech and language pathologists, physiotherapists, nurses, radiologists and dieticians among others.

Assessment: the presence of altered feeding habits and of cough and/or choking during or after meals are the two most commonly reported symptoms. A questionnaire is currently available to detect dysphagia (DYMUS). Clinical assessment should include observation of the oral anatomy and examination of the cranial nerves involved in swallowing and of the muscular tone, oral reflexes and movement execution pattern. A functional assessment of chewing, swallowing, phonation and articulation should also be performed. The volume-viscosity swallow test (V-VST, Clavé et al. 2008) is a bedside method to screen patients for dysphagia. Referral to instrumental examination should be done in moderate to severe dysphagia or when specific objectives of examination can be identified. Videofluoroscopy and fiberoptic laryngoscopy are the two most commonly used instrumental procedures.

Treatment of dysphagia should begin soon after appearance of the first symptoms. Its goal is to improve security and efficacy of swallowing and to improve quality of life and social participation. It can include rehabilitation, pharmacological treatment and eventually implementation of enteral feeding. Rehabilitation includes restorative, compensatory and adaptive approaches and also education on security manoeuvres. The restorative approach includes neuromuscular exercises without food, directed to improve the sensoriomotor and praxic-cognitive control of the swallowing mechanisms and can also include neuromuscular electrostimulation. The compensatory approach consists of general advice, strategies and manoeuvres to be taken into account while eating and drinking. The adaptive approach includes measures involving adaptation of the food consistency. Family and caregivers should be involved in rehabilitation. Pharmacological treatment includes use of botulinum toxin, especially for the treatment of drooling.

References:
Diagnosis

Maria Pia Amato

Only during the past 20 years clinicians have become aware of the prevalence and functional impact of MS-related cognitive impairment and its profound functional impact. Cognitive dysfunction is highly variable and estimates of its frequency range from 43% to 65% of the cases. The domains most commonly impaired are episodic memory, complex attention and information processing speed, executive functions and verbal fluency. Language, semantic memory and attention span are less frequently involved. Cognitive dysfunction can have a dramatic impact on several aspects of quality of life, independently on degree of physical disability and is one of the most important predictors of the patient work status. Current therapeutic approaches include the use of disease-modifying drugs, symptomatic drugs for fatigue and donepezil, as well as different rehabilitative programmes. Recent data on the use of interferon-beta in patients with clinically isolated syndromes and early relapsing-remitting MS have suggested a better preservation of cognitive functioning in subjects treated at the very beginning of the disease. Due to the high prevalence and great functional impact of MS-related cognitive impairment, the search for effective therapeutic strategies is an urgent priority for future research.

Treatment

María Jesús Arévalo

Multiple sclerosis (MS) is a chronic inflammatory disease of central nervous system. The main physiopathological feature of MS is demyelination. MS is one of three most common causes of severe disability in youngest people. In patients with MS (PwMS), apart from complete psychophysical status and objective neurologic status, a subjective perception of symptoms and signs, known as quality of life, must be considered, too.

PwMS have a substantial risk of cognitive dysfunction, even in the earliest stages of the disease, where there is minimum physical disability. Despite the high prevalence rates and the significant impact of cognitive dysfunction on quality of life in this population, cognitive functions are not routinely assessed due to the high cost and time consumption. Studies of the cognitive profile of PwMS suggest that some cognitive abilities are more likely to decline than others (e.g. disturbances in memory, attention, concentration, speed of information processing and executive functions). Although some reduction in self-awareness of cognitive decline occurs, metacognitive skills and awareness of more concrete impairments appear preserved. Cognitive impairments can be extremely disruptive and interfere with PwMS ability to work, engage in social activities, and maintain a household and drive. Since the onset and progression of MS typically occurs when PwMS are attempting to establish and maintain cognitively demanding life roles (e.g. parent and worker), their cognitive symptoms can further accentuate the need to successfully maintain functioning.

The available immune-modulating agents may reduce the development of new lesions and therefore prevent or minimize the progression of cognitive decline. There is currently insufficient evidence concerning the efficiency of symptomatic treatment in MS. Donepezil and rivastigmine (AChEIs) have demonstrated some specific benefits in PwMS cognitively impaired, but the studies were small. There is also currently no optimal non-pharmacological treatment strategy for cognitive decline in MS, as the studies published to date report heterogeneous results. Nevertheless, non-pharmacological treatments such as cognitive rehabilitation may benefit some MS patients.

In the present talk, we will briefly review recent research on non-pharmacological and pharmacological approaches to improve cognitive function in our patients.
Disease modifying drugs (DMDs) in MS: First line drugs: Three recombinant interferon beta (IFNb) preparations and glatiramer acetate (GA) are currently approved for relapsing-remitting multiple sclerosis (RR MS). Their efficacy is very similar and was proven even in head-to-head trials conducted recently. Also 3T MRI confirmed similar efficacy on MR measures. All of them are approved for patients with clinically isolated syndrome (CIS) and in high risk for clinically definite MS. In some countries there is extended approval for RR MS under age of 18. There is no proven effect of these drugs for chronic progression of MS without the presence of relapses. There is not enough publications supporting the idea of combination therapies to start with; and there is not enough publications on sequential therapy. Long-term follow-ups of clinical trials have many limitations: no control groups any more, no blinding, and selection bias due to drop-outs. They may be useful in trying to define some prognostic markers. Post marketing follow-ups on long-term efficacy of these drugs show the importance of early treatment as the only tool to slow down the development of disability in MS. 21-year data from the original trial with IFNB-1b show that delaying the treatment by 5yrs shortens life expectancy by 10 years. 8-year follow up from BENEFIT trial (IFNB-1b in CIS) shows that with early treatment long term stability measured by EDSS may be achieved in a substantial number of patients. Long-term side effect profile and tolerability of above mentioned drugs is very good, the adherence to injectable treatments decreases over time, and seems to be a challenge for both the patient and treating physician. New formulations (pegylated interferon beta 1a administered every other week, double dose of GA administered every other day) may increase the persistence of patients.

As the new goal for treatment in MS has been proposed being freedom from measurable disease activity, it is of great importance not only to start treatment early but also to check regularly the effect of treatment not to miss the window of opportunity for escalating treatment in patients with suboptimal response.
In recent years significant progress has been made in the field of multiple sclerosis (MS), not only considering the diagnosis (done at progressively earlier stages of the disease), but also with regard to therapy. The number of drugs available for clinical usage has increased (and there are still several molecules in research) as the challenges faced by health professionals regarding the management of the disease itself, in daily life. Since the communication of the diagnosis to choosing a treatment, passing through the approach of the symptoms associated with the disease that can greatly contribute to an impaired quality of life, several sensitive points of interaction with the patient require from health professionals a dynamic organization and a very large availability. Indeed, the binomial neurologist-specialist nurse is key for an effective management of the disease in the individual patient, ensuring the success of the therapeutic approach in all of its dimensions. In this presentation, some very practical aspects of the contact with patients in a day-to-day approach will be reviewed, highlighting the benefits that neurologists and specialist nurses can provide, as a team, to people with MS.
Clinical case

Sara Llufriu, Nuria Solà, Maria Sepúlveda, Yolanda Blanco, Albert Saiz

Summary of the presentation: A 32 year-old woman was admitted to our Hospital because of an acute urinary retention. Neurological examination revealed muscular weakness in her right arm with a global muscle balance 4 out of 5, impairment of sensation to temperature and pain below thoracic T4 level and reduced proprioception in legs. Deep tendon reflexes were globally hyperactive and right plantar response was extensor. The spinal MRI showed T2 signal alteration between C4-C7, T4-T6 and T8-T9 with diffuse contrast enhancement. CSF showed pleocytosis (10 cells/mm3) and absence of oligoclonal bands. MRI brain, visual evoked potentials and coherence optical tomography were normal. She had been controlled by Internal medicine department for three years due to the presence of ANA (>640 URF), anti-double-stranded DNA (11 U/mL, n<10 U/mL) and slightly positive Crithidia lucilae indirect immunofluorescence (IF) determination. At admission, these non-organ specific antibodies were clearly positive (ANA>640 URF, anti-dDNA 91.7 U/mL and Crithidia lucilae IF positive) but NMO-IgG were negative by immunohistochemistry and cell-based assay. The diagnosis of longitudinal extensive transverse myelitis (LETM) associated with a probable systemic lupus erythematosus disease (SLE) was established. 3-days cycle of high dose of methylprednisolone and 6 cycles of cyclophosphamide (CFM) were done. Retrospectively, the serum was reanalyzed by an assay of transfect cells with the isoform M23 of AQP-4 and NMO-IgG resulted positive. This led to the final diagnosis of NMO spectrum disorder. The patient’s clinical status and spinal MRI lesions improved after the established treatment. The titer of serologic non-organ specific Ab decreased (anti-dDNA 39.4 U/mL and Crithidia lucilae IF negative) and new serum determination of NMO-IgG was also negative after the immunosuppressive treatment. The patient is currently treated with azathioprine and prednisone and has not presented new neurological symptoms.

LETM is a heterogeneous syndrome defined by the existence of more than a three-vertebral-segment spinal cord lesion seen in MRI and produced by an inflammatory process that may occur in the context of multiple sclerosis, NMO or as an uncommon manifestation of systemic autoimmune diseases, such as SLE. NMO often leads to severe disability and its diagnosis is crucial due to its worse prognosis. Although the coexistence of clinical and/or serological markers of non organ-specific disease is well established, IgG autoantibody recognizing the water channel aquaporin-4 represents a highly specific biomarker for NMO. Its existence predicts future relapses and development of definite NMO. The improvement of IgG-NMO testing has been crucial in the improvement of the diagnosis reliability and to establish an early treatment.

References:
Define treatment success in present daily practice with clinical and MRI surrogates

Jordi Río

The objective of the definition of treatment response is to select responders on one hand, and poor- or non-responders on the other hand. Several criteria for treatment response to treatment have been proposed. Nevertheless, these different criteria have not been validated and there is no consensus among different investigators. These criteria are based on relapses, disability progression or both. Several factors make difficult the employment of relapse outcomes to determine therapeutic response (low predictive value, regression to the mean, etc.). whilst long-term disability data are crucial in order to select the most clinically meaningful definition. Relatively to the progression of neurological impairment, efficacy fluctuations related to depression, fatigue, spasticity, concurrent illness and prolonged relapse need to be excluded. Nevertheless, criteria of response to IFNb therapy using disability progression are more clinically relevant than those based only in relapse rate. MRI offers an advantage in the response evaluation as it produces objective data, however the frequency of evaluation is limited and low frequency of MRI evaluations leads to poor perspective data. On the other hand, there are limited prospective data to validate MRI measures of disease activity as reliable prognostic factors of suboptimal response to therapy, but MRI changes which occurred during the first months of IFN may have a prognostic value for identifying patients with a confirmed increase of disability in the next years of therapy. A suboptimal response may be due to several individual features from MS heterogeneity to genetic load and IFN response genes to poor healing mechanisms. Other factors may play a role, such as excess disease activity, poor adherence to therapy, misdiagnosis, “pseudo” failure” or loss of drug efficacy. In conclusion, the proportion of non-responders varies depending on the definition used. Criteria based on relapse measures have poor sensitivity and positive diagnostic value; there are limited prospective MRI data as predictors of therapeutic response and the combination of clinical and MRI measures of disease activity may have a prognostic value for identifying patients with a poor response.

Define treatment success in the age of pharmacogenomics

Manuel Comabella

The mechanisms underlying heterogeneity in the response to treatment in multiple sclerosis (MS) are not completely understood, although genetic factors are most likely to be playing important roles. Moreover, given the complex nature of the disease, this heterogeneity is probably explained by the contribution of multiple genes. Disease Modifying Therapies (DMTs) are the mainstay of treatment in relapsing-remitting MS and have demonstrated a beneficial effect on disease activity. However, DMTs are partially effective, and their long-term impact on disease progression remains elusive. In addition, not all patients respond to current DMTs. The increasing number of new therapies for MS and the potential risk for a lack of response and/or serious adverse reactions make individualized therapy a high-priority for MS. Pharmacogenomics applies technologies such as gene expression profiling, single nucleotide polymorphisms (SNP) screens, and proteomics in order to predict response to treatment and toxicity to drugs. Although pharmacogenomics holds great promise for individualized therapy in MS, big efforts should first be made to identify markers for treatment efficacy. This talk will focus on the current status and future directions of pharmacogenomic studies in MS, mainly in relation with interferonbeta treatment.
Evidence coming from the pivotal clinical trials and from some other well-performed clinical trials has clearly demonstrated the benefit of immunomodulatory therapies in MS. It is also clear that present therapies are not without side effects and mode of administration is still cumbersome for a number of patients; these factors impact on adherence to treatment, which may render the therapeutic efforts futile. Several studies have shown that most drop-outs occur in the early phases of therapy so especial care needs to be taken when patients start their immunomodulating therapy in order to avoid treatment discontinuation. Available evidence suggests that individualized care is an important factor to keep drop-out rates low; in this regard, management of side effects of therapies is crucial, as it is responsible for almost a half of all discontinuations. Another important factor related to treatment discontinuation seems to be perceived lack of efficacy as a consequence of wrong expectations about treatment effects; therefore, adequate setting of expectations about therapy is crucial from outset of treatment with disease-modifying drugs. Side effects profile of IFNbeta preparations and GA are not entirely overlapping. In the case of IFNbeta preparations, it is especially important to manage flu-like symptoms at onset of therapy. Several strategies can be implemented to diminish patient discomfort, such as gradual dose increase and anti-inflammatory therapy administration schemes. Other side effects such as injection site reactions, flushing and laboratory abnormalities also need to be closely monitored. Nurse-led patient education at onset of therapy may be helpful to manage patients’ expectations from therapy and to anticipate and diminish the impact of side effects on adherence to treatment. Finally, even though results from clinical trials are the keystone to our clinical practice, measuring efficacy of therapy in clinical practice in an appropriate manner is crucial to obtain the most from available therapies. Clinical daily practice individualized monitoring of treatment response, treatment adherence, and side effects profile is therefore highly recommended if clinical trials efficacy results are to be met in our clinics.

In the present talk, we will briefly review these issues and in the role playing that will ensue, we will put into practice our interpersonal skills so as to maximize patients’ adherence to treatment in order to make the most of the available therapies.
Actually approved disease modifying drugs (DMDs) for relapsing-remitting multiple sclerosis include recombinant interferon (IFN-beta) and glatiramer acetate (GA). All these immunomodulatory treatments have been shown to reduce the frequency and severity of relapses, as well as reducing progression of neurological disability. However all DMDs are administered parenterally and need frequent injections which may be inconvenient and uncomfortable for patients. In addition, not all patients respond adequately and common side effects associated with these therapies may reduce adherence. The development of drugs with easier administration, such as oral agents, would further promote adherence, increase patient satisfaction and thereby improve efficacy. Two phase III clinical trials CLARITY and TRANSFORM have provided promising results for Cladribine and fingolimod respectively.

The results of the CLARITY study show that annual short-course treatment with both doses (3.5 mg/kg and 5.25 mg/kg) of cladribine tablets led to a significant reduction in the rate of clinical relapses, disability progression and brain lesions, as well as a significant increase in the proportion of patients who remained relapse-free. Overall, the frequencies of adverse events in both Cladribine treatment groups were comparable to those observed in the placebo group dose.

The results of TRANSFORM study, also show a significant reduction in annualized relapses rate and MRI activity. During this study, two fatal viral infections occurred. Moreover, the FREEDOMS study demonstrated a significant reduction of disease activity of both doses of Fingolimod against Interferon beta 1a. The safety profile of the drug open some concern for the risk of herpes infections and cardiovascular problems.

Other oral drugs in earlier phase of the development include BG12, Teriflunomide and Laquinimod. For all these three drugs, a preliminary efficacy emerged from Phase II studies and phase III studies are ongoing.

References:
Gene therapy is a group of techniques that involve an individual’s modification of genetic makeup to treat acquired and hereditary diseases. Among all the different vehicles used to deliver genes into an individual’s cells, viral vectors are the most used due to the innate capability of viruses to introduce their genetic material into a host cell. Gene therapy is a relatively new field in biomedicine since the first clinical trial was approved in 1989. From then on, the amount of trials increased exponentially, indeed, from the late 90’s until now approximately 100 clinical trials are approved each year worldwide.

Several approaches to treat multiple sclerosis have been made in its animal model [experimental autoimmune encephalomyelitis, EAE], including delivery of immunomodulatory molecules in the CNS, enhancement of neuroprotection or induction of antigen-specific immune tolerance. The different strategies developed to treat EAE are going to be discussed, as well as the new tools that are being developed in the field of gene therapy that in the future could be useful to overcome the neurodegenerative processes that take place in MS patients.
Since the discovery, over a decade and a half ago, that genetically engineered DNA can be delivered in vaccine form and elicit an immune response, there has been much progress in understanding the basic biology of this technology. DNA vaccination is a strategy of immunization based on the injection of a gene encoding a target protein with the goal of eliciting a potentially protective immune response in the host. Classically, DNA vaccines have been successful at generating protective immune responses in various cancer models and infectious diseases, due to an activation of the immune system. Although, in the last years different studies have shown the potential use of DNA vaccines to modulate autoimmune diseases, like multiple sclerosis (MS), inducing tolerance rather than stimulation of an immune response.

Compared to traditional immunization procedures, DNA vaccination offers several advantages: for instance, expression of native antigens in situ, prolonged in vivo antigen production, increased availability of antigenic peptides because of the endogenous and long-term synthesis of the gene product and the modification of the vaccination protocol that could induce either Th1 or Th2 immune responses.

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system, probably of autoimmune aetiology, in which auto-reactive T cells play an essential role in the pathogenesis of the disease through the attack of myelin components. At present, there is not an effective treatment for the disease. Most of the currently used drugs for the treatment of MS target the immune response, but are not selective for the auto-reactive T cells.

The application of DNA vaccination to the treatment of the animal model of MS, experimental autoimmune encephalomyelitis (EAE), has demonstrated the great potential of this procedure for therapeutic purposes. The protection appears to be highly influenced by the capacity of DNA vaccination to modulate immune responses affecting the Th1, Th2 and, importantly, the T cell immunoregulatory arms.

So far, two clinical trials of DNA vaccines have been reported in MS. From these studies, it can be concluded that the vaccine was safe, well-tolerated, and caused antigen-specific immune tolerance.
Stem cells are found in all multicellular organisms. They are characterized by the ability to renew themselves through mitotic cell division and differentiated into a diverse range of specialized cell types.

There are different kinds of stem cells. The embryonic stem cells are obtained from embryos and can differentiate into whatever cell of the organism, they are pluripotent. The adults also have stem cells, which can only give rise cells closely related to their organ or tissue of origin, they are multipotent. Recently, researchers have created induced stem cells, they are a type of pluripotent stem cells artificially derived from an adult somatic cell by inducing a forced expression of certain genes.

Since the stem cells have the ability to repair and regenerate the damage tissue, the therapies with stem cells were originally conceived as replacement therapies. But it has been shown that stem cells affect the recovery by an additional mechanism, they also have the ability to regulate the immune system.

Several studies with stem cells have been undertaken in animal models of multiple sclerosis with encouraging results. They have shown that stem cells can contribute to repair the tissue damage, but they play a more important role in modulating the immune system.

Treatments with haematopoietic or mesenchymal stem cells have been used to treat multiple sclerosis patients. The results have been apparently positives, but there still are controversial and further studies are necessary.
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