MS Preceptorship
“Updating knowledge in multiple sclerosis”
10th edition
Barcelona, Spain - 5-7 June 2013
General information

Venue
The live educational workshop takes place at the:
Centre d’Esclerosis 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 workshop is English.

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www.neurology.seronosymposia.org
Serono Symposia International Foundation live educational workshop on:

MS Preceptorship
“Updating knowledge in multiple sclerosis”
10th edition
Barcelona, Spain - 5-7 June, 2013

Aims
The 2013 Preceptorship in multiple sclerosis (MS) will be hosted in the renewed Cemcat MS center in Barcelona. Since the MS scenario has become even more complex in the last years, an exhaustive mixture of theory and practice will be offered to the learners in order to help them reach more easily MS diagnosis and choose the most appropriate therapeutic intervention. The programme will cover all the main topics related to MS, starting from how to apply the diagnostic tools, addressing to how to assess and monitor cognitive impairment in clinical practice and reviewing the up-to-date data about efficacy and safety profile of the MS treatments. The aim of this live educational event is to guide young neurologists in the MS field, taking advantages of the clinical and research experience of a worldwide reference MS center.

Learning objectives
By attending this live educational event the learners will be able to:
• Select and apply diagnostic algorithm in order to achieve an early MS diagnosis
• Compare the efficacy and safety profile of each drug available for MS treatment
• Plan a long-term clinical and neuroradiological monitoring once MS has been diagnosed
• Review the specific forms of demyelinating disorders and list the most suitable therapeutic approach for each condition

Target audience
Young neurologists involved in MS patient management; neurologists interested in entering the MS field.

Accreditation
Serono Symposia International Foundation [www.seronosymposia.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 MS Preceptorship “Updating knowledge in multiple sclerosis” held in Barcelona, Spain on 5-6-7 June 2013, is designated for a maximum of 12 (twelve) 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.

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We value your opinion!

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

We thank you for participating!

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Scientific organisers

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

Serono Symposia International Foundation designed this programme in partnership with Cemcat (Multiple Sclerosis Centre of Catalonia)

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Scientific programme
5-7 June 2013

Chairpersons: Xavier Montalban and Jaume Sastre-Garriga

Wednesday, 5 June

8.45  Serono Symposia International Foundation (SSIF) opening
      Giancarlo Comi (Italy)

9.00  Introduction to MS Centre of Catalonia (Cemcat)
      Xavier Montalban (Spain)
      Real-time survey

9.30  L1: Epidemiology of MS
      Susana Otero (Spain)

10.00  KNS1: Immunopathogenesis of MS
       Bernard Hemmer (Germany)

10.30 L2: Genetics of MS
        Manuel Comabella (Spain)

11.00 L3: Pathology of MS
         Imke Metz (Germany)

11.30 Coffee break

12.00 PD1: Panel discussion on “New revision of McDonald’s criteria”
         MS diagnosis and differential diagnosis
         Mar Tintoré (Spain)
         MRI in MS: the radiologist perspective
         Alex Rovira (Spain)
         VEPs in MS
         Letizia Leocani (Spain)
         Discussion
         Real-time survey

13.30 Working Lunch

14.30 Cemcat – Nuts and bolts
       Carmen Tur (Spain)

15.00 Cemcat and Vall d’Hebron Hospital premise visits

17.00 End of day 1

Thursday, 6 June

8.45  Specific forms of demyelinating diseases

8.45  L4: Neuromyelitis optica – NMO
      Georgina Arrambide (Spain)
      L5: Primary progressive MS
      Alan J. Thompson (UK)
      L6: Pediatric 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
        Carme Santoyo (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: Alan J. Thompson (UK)
         Diagnosis
         Maria Pia Amato (Italy)
         Treatment
         Bruno Brochet (France)
         Case presentation
         Angela Vidal (Spain)

12.30 KNS2: Injectable therapies in MS
            Eva Havrdová [Czech Republic]

13.00 L8: Role of MS nurses in MS patients’ management
        Rosalía Horno (Spain)
        Real-time survey

13.30 Working lunch

14.30 CS1: Case study session
         Lluís Ramió Torrentà (Spain)
         Lucía Romero (Spain)
         Nuria Solà (Spain)

16.30 End of day 2

Legend:  L: Lecture;  KNS: Key Note Speech;  CS: Case Study;  S: Snapshot;  PD: Panel Discussion
Scientific programme
5-7 June 2013

Friday, 7 June

Real-time survey

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
Xavier Montalban (Spain)
Real-time survey

13.15 Certificate delivery and group picture

13.30 Working lunch and end of the live educational workshop
Disclosure of faculty relationships

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**Georgina Arrambide** Declared receipt of grants and contracts from MAGNIMS Fellowship.

**Bruno Brochet** Declared no potential conflict of interest.

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Letizia Leocani
Abstracts
Epidemiology of MS

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).

References:
Multiple sclerosis (MS) is a commonly occurring inflammatory and demyelinating neurological disease. Based on immunological and genetic studies MS has been considered to be an autoimmune disorder mediated by CD4+ type 1 T helper cells.

Recent studies have challenged this idea by indicating a role for other immune cells such as B cells and Th17 cells. So, T- and B-cell responses in the brain of patients with MS involve the clonal expansion of lymphocytes and the antigen-driven maturation of the B-cell receptors, indicating that the immune response in MS engages a broad range of immune cells that target a limited number of brain antigens. In neuromyelitis optica, Aquaporin-4 was identified as a major target of the autoimmune response. Recent studies have suggested myelin oligodendrocyte glycoprotein as a target in childhood inflammatory demyelinating diseases and the inward rectifying potassium channel KIR4.1 as a target in MS.

Here, I summarize recent advances in our understanding of the pathogenesis of MS, and conclude with an outlook on how to capitalize on this knowledge to develop new therapeutic approaches.
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) pathology is complex and not only involves focal lesions known as MS plaques, but also cortical pathology as well as changes in the normal-appearing white matter. The talk will thus focus on the three topics:

1) Focal MS pathology
2) Cortical pathology
3) Pathology of the normal-appearing white matter.

Focal pathology is characterized by demyelination, inflammation, axonal loss with relative axonal preservation as well as gliosis. However, remyelination as a reparative process may also occur. Remyelinated fibres are characterized by thin and irregular myelin sheaths. Remyelination is extensive in early MS lesions, but limited in chronic MS. Correspondingly, mature oligodendrocytes are abundant in early MS lesions, but lost in chronic MS. In the process of remyelination oligodendrocyte precursor cells (OPCs) differentiate into mature oligodendrocytes that synthesize the new myelin. These OPCs are present in all lesion stages, indicating that a differentiation block of OPCs in chronic MS lesions may be responsible for remyelination failure.

The irreversible axonal damage correlates with the clinical disability and is thus of major importance. The acute axonal damage is most pronounced in early disease stages, but ongoing in chronic MS lesions. Chronic MS lesions thus reveal an axonal reduction of approximately 50%. The extent of axon damage correlates with the severity of inflammation during active demyelination. The second phase of axon degeneration present in chronic demyelinated plaques is also related to inflammation. A range of cellular (e.g. CD8+ T cells), soluble (e.g. nitric oxide, glutamate, perforin) or trophic factors are candidates for mediating the axonal damage.

Cortical lesions are common in MS. Subpial lesions are most frequently observed, followed by leucocortical and intracortical lesions. Cortical lesions occur most often in progressive MS and in patients with long disease duration. They are observed in 90% of autopsy cases with chronic MS but are already present in early disease stages (38%). Cortical lesions are associated with pial inflammation. Remyelination can also be observed in cortical lesions and is more frequent than in white matter lesions.

The “normal-appearing white matter” without demyelination shows numerous pathological changes that are most dominant in chronic disease stages. An inflammation consisting of T cells as well as microglial cells is present. An astrocyte activation is not only found in focal lesions, but also in non-demyelinated white matter. Also, a diffuse axonal damage within the normal-appearing white matter is present. Foci of microglial cells correlate with the axonal damage.

The talk gives insights into some important new aspects of the complex pathology of multiple sclerosis.
PD1. Panel discussion on “New revision of McDonald’s criteria”

Mar Tintoré, Spain
Alex Rovira, Spain
Letizia Leocani, Italy

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 central nervous system disease dissemination in space and time and in reasonable exclusion of other causes. Since McDonald 2001, in patients with a first attack, evidence of dissemination in space and time may be provided by MRI. The recently published 2010 McDonald criteria selected the Magneto 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 cerebro-spinal fluid examination in the diagnosis and differential diagnosis of MS, the presence of oligoclonal bands has not been included in the diagnostic algorithm. These new criteria have been adapted to other populations such as patients with primary progressive MS or patients with paediatric 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

The exact diagnosis of MS still remains challenging in some cases, as there is no single test that can provide a definite diagnosis of this disease, which is based on different diagnostic criteria. The introduction of expensive and not completely free from side effects of different disease modifying treatments that reduce the number and severity of clinical relapses and may slow progression of disability, particularly when administered during the early phases of the disease, makes the accuracy of an early diagnosis 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 (CNS), lesions disseminated in space (DIS) and time (DIT), and to exclude alternative diagnosis that could mimic MS either clinically or radiologically. Although the diagnosis can be made on clinical grounds alone, MRI is usually required 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:
- Fillipi M. Rocca MA. MR Imaging of Multiple Sclerosis. Radiology; 2011; 259: 659-681

VEPs in MS

Letizia Leocani

Abstract not in hand at the time of printing.
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). Over the years, a number of clinical, laboratory, and magnetic resonance imaging studies have provided data to differentiate NMO from MS. More recently, 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. All this information was obtained from adult patients, but now the behavior of NMO is also starting to be better understood in special populations, like children and pregnant women. However, a worldwide consensus regarding NMO-IgG detection is still to be obtained since different methods for antibody identification exist, and the initial described sensitivity of indirect immunofluorescence, the most commonly used assay, has not been reproduced in all centres. This is of utmost importance when considering that such assays fail to detect approximately 20-30% of NMO cases, or that they yield positive results in atypical or MS-like cases, which could delay a proper diagnosis and treatment, especially at disease onset. Each of the abovementioned topics will be reviewed in more detail throughout this talk.
Primary progressive multiple sclerosis (PPMS) has a number of characteristics which make it more challenging to diagnose and manage than relapsing/remitting MS. It does not have acute events or relapses, the hallmark of MS, but rather a slowly progressive course which is often very insidious at onset. However although overall it has a worse prognosis than RRMS it has a variable course with 25% of patients needing assistance to walk at 7.5 years after onset, but with another 25% still walking unaided at 25 years. PPMS comprises approximately 10-15% of MS cases overall. Compared with other forms of MS, PPMS is characterized by a later age of onset (on average 40 years, similar to the age of onset in SPMS) and an equal sex ratio. PPMS has a predominantly motor presentation, tending to present with an asymmetric spastic paraparesis with occasional cerebellar and brainstem, but not usually sensory or visual disorders.

PPMS may be a less inflammatory form of MS but there is some evidence to suggest that both the myelin sheath and nerve axon are more vulnerable to damage than is the case in relapsing/remitting MS. There is continuing discussion as to whether it is a distinct condition or simply one end of a spectrum [1]. The question arises whether disability progression can be predicted so those patients who might be more suitable for therapeutic intervention or enrolment in a clinical trial can be identified. Studies have shown that gender had no impact on clinical features or natural history of PPMS, although the time from onset of MS to death was shorter for men [2]. Clinical presentation, whether brainstem, motor, sensory or cerebellar, had no impact on survival, although presentation with three or more affected systems was associated with worse outcome. A shorter time to reach EDSS 3.0 also had an adverse effect on survival. Koch et al showed that patients who were younger at disease onset took longer to reach EDSS 6.0, but these patients were also younger when reaching EDSS 6.0. [3]. Sensory symptoms at presentation were associated with both a longer time to, and an older age at, EDSS 6.0.

Diagnosis is particularly challenging but has been helped by new criteria which include MRI evidence of dissemination in time and space [4]. PPMS is usually characterized by fewer and smaller lesions on MRI, compared with relapsing MS. A major study evaluated 145 patients with PPMS at 1, 2, 5 and 10 years to determine which MRI abnormalities best predict progression. During this time there was an increase from baseline in average T2 lesion load at years 1 and 2 (14.6% and 23.3% respectively) and a decrease in brain of decrease in grey matter magnetization transfer ratio (MTR; p=0.032), which was also the strongest predictor of the rate of T2 lesion changes are seen in grey matter volume. In early PPM S, progression on the EDSS over 3 years was associated with the mean rate of decrease in grey matter magnetization transfer ratio (MTR; p=0.032), which was also the strongest predictor of the rate of T2 lesion load increase [p=0.024]. The combination of grey matter MTR and focal T2 lesions may therefore prove to be the strongest predictor of disability in PPMS, as well as showing a strong correlation with overall cognitive performance [9].

Despite being progressive from onset, the disease course is quite variable and an active management programme incorporating diet, exercise and a healthy life style is crucial. Although there are currently no effective treatments targeting repair and neuroprotection, a comprehensive rehabilitation programme incorporating management of mobility, bladder function and muscle tone is important. Improved understanding of progression leading to improved treatment for PPMS is a key goal for future MS research and is the focus of a major international collaborative effort [10].

References:
The onset of multiple sclerosis (MS) typically occurs in adults, however the onset in subjects with less than 18 years of age is 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 briefly overview current therapies for symptoms of Multiple Sclerosis.
S1. Symptomatic therapy snapshot #1 on gait rehabilitation

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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:
S2. Symptomatic therapy snapshot #2 on management of dysphagia

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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 happen in moderate to severe dysphagia and/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
Bruno Brochet

Only cognitive impairment is common in MS and affects mainly information processing speed, attention, memory and executive functions. Deficits can have a significant impact on patients’ quality of life and especially have important vocational consequences. Cognitive impairment should be taken into account in the evaluation of the disease. Recently several programmes of neuropsychological rehabilitation have been tested to reduce cognitive deficits and their consequences in daily living. This panel presentation will review several trials recently published. These trials showed preliminary positive results for the effectiveness of neuropsychological rehabilitation in MS to improve memory span, working memory, and immediate visual memory, but the level of evidence remains low and these studies are hampered by many methodological flaws. The overall quality of the studies was low and the interventions were heterogeneous. Therefore well-designed high quality studies are needed on the effects of neuropsychological rehabilitation in MS. Pharmacological approaches using specific drugs acting on the central nervous system will be also reviewed.

Case presentation
Angela Vidal

Abstract not in hand at the time of printing.
Concerning disease modifying drugs (DMDs) in multiple sclerosis (MS), as first line treatment, 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. 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 though systematic 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.

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.
MS nurse has multiple roles within the MS team. We would like to point these different roles and explain how they are developed. Traditionally nurses have had a cooperative role but during the last decades nurses have taken also independent roles which prove a growth of knowledge.

At the end of the 90s is when the idea of having a specialist nurse starts to take shape, mostly because of the introduction of immune modulators. This MS specialist nurse comes with the idea to perform Sanitary Education not only for the manage of the medication but also for the disease. That’s why this type of patient will need a follow up to feel cared for and looked after and if some problem or question comes out, patient can have a direct contact with the nurse by telephone call or by visiting the hospital.

It has been very difficult to start this in the hospital, therefore some sites still have part time nurses. Because in our country doesn’t exist this as a speciality, this nurse has had to self train on her time off.

MS nurse has also taken a Research role being involved in all the clinical research as an important part of the team. On a clinical trial MS nurse may act as a reference for the patient, as a data collector, in takings samples of patients under study.

Other function of MS nurse is to administrate intravenous therapy which can be symptomatic treatment, commercialized medication or IV Clinical Trial study drugs. Some of these medications are getting more and more popular as a second option of treatment, like Natalizumab, for the easy administration and the short period of time the patients have to stay in the Day Hospital.

A Day Hospital allows the MS nurse to observe the patient through the infusion and also check vital signs anytime as per protocol or whenever MS nurse considers on the basis of MS Nurses’ professional criteria. People with MS are treated as outpatients and it doesn’t require hospital admission.

From the traditional cooperative role, MS nurse assist Neurologist when performing a Lumbar Puncture, when filling up a subcutaneous reservoir with Baclophen for an intratecal infusion by internal pump.

The future new oral therapies for MS won’t represent any impairment for the MS nurse to continue being a reference in the management of people with MS. Even though the new oral drugs management will most probably require a multidisciplinary team focus.

In our center we have a very low rate of therapy abandon, partly because of medical and nursing work, together with the multidisciplinary team, making the patients feel cared for. Nevertheless MS is still a disease without a cure so it’s a chronic disease with an high risk of complications and disability progression.
Clinical case

Nuria Solà, Sara Llufriu, 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 hypopalestesia in lower extremities. 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 since 2010 due to the presence of ANA (＞640 U RF), anti-double-stranded DNA (11 U/mL, <10 U/mL) and slightly positive Crithidia lucillae indirect immunofluorescence (IF) determination. At admission, these non-organ-specific antibodies were clearly positive (ANA＞640 U RF, anti-dDNA 91.7 U/mL and Crithidia lucillae 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. A 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 transflect 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 lucillae IF negative) and new serum determination of NMO-IgG was also negative after the immunosuppressive treatment. 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 relapse and development of definite NMO. The improvement of IgG-NMO determination has been crucial in the improvement of the diagnosis and to establish an early treatment.

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

Jordi Río

The objective of the definition of treatment response is to select earlier responders on one hand, and poor- or non-responders on the other hand. Patient response outcomes should be measured taking into consideration the interfering factors related to the disease itself. 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. Several criteria for treatment response to interferon beta have been proposed. Nevertheless, these different criteria have not been validated and there is no consensus among different investigators. Long-term disability data are crucial in order to select the most clinically meaningful definition. 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.). The progression of neurological impairment is another criterion employed to quantify response, however efficacy fluctuations related to depression, fatigue, spasticity, concurrent illness and prolonged relapse need be excluded. Nevertheless, criteria of response to IFNb therapy using disability progression are more clinically relevant than those based only in relapse rate. 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. Moreover, the combination of measures of clinical and MRI disease activity may have a prognostic value for identifying patients with a poor outcome during the next years of therapy. Several factors are related to response from MS heterogeneity to genetic load and IFN response genes to poor healing mechanisms. Other factors related to suboptimal response are: excess disease activity, poor adherence to therapy, misdiagnosis, “pseudo” failure or loss of drug efficacy. In conclusion, in relation with response to therapy in multiple sclerosis patients, the proportion of non-responders varies depending on the definition used, criteria based on relapse measures have poor sensitivity and positive diagnostic value, non-responders have a higher clinical activity at baseline, baseline EDSS predicts long-term disability, 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:
Abstract not in hand at the time of printing.
Gene therapy is a group of techniques that involves 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 differentiate 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 to cells closely related to their organ or tissue of origin, they are multipotent. Recently, researchers have created induced stem cells that 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 damaged tissue, the therapies with stem cells were originally conceived as replacement therapies. However, 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 positive, but they are still controversial and further studies are necessary.
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