Preceptorship on MRI in multiple sclerosis
29-30 October 2015 - Milan, Italy
General information

Venue
This live educational course takes place at the:
San Raffaele Scientific Institute
Caravella Nina Meeting room
San Raffaele Congress Centre
Via Olgettina, 58
20132 Milan, Italy

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

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Preceptorship on MRI in multiple sclerosis

EXCEMED live educational course:

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Aim
Applying imaging technologies in clinical neurology has been pioneered by the field of multiple sclerosis (MS). Today, technical advances make central nervous system MRI essential to diagnosing MS, ruling out mimicking conditions, unveiling the histopathological bases of tissue damage and monitoring side effects of new drugs. Quantitative MRI helps to provide prognostic data and drive treatment choices. MRI markers are also increasingly used as end points of clinical trials exploring the efficacy of new drugs, both in relapsing-remitting and in progressive MS. So, it is mandatory for clinical neurologists involved in MS to be aware of the basics of MRI in order to use imaging markers in the everyday management of MS patients. World-renowned MR experts in the MS field will comprehensively illustrate these issues in the preceptoship. Participants will also benefit from hands-on training held at the Neuroimaging and Neuroimmunology Research Unit.

Learning objectives
By attending this live educational course, participants will be able to:
• Describe the clinical work up of patients suspected of having MS and rule out clinical conditions that can mimic MS in the MR scan
• Summarise the novel functional and structural markers of disease severity obtained by advanced MRI techniques
• Illustrate the main MR techniques used to explore the spinal cord and optic nerve
• Define the role of MRI in clinical trials

Target audience
Young clinicians and scientists currently involved in MS management and radiologists interested in MS.

Accreditation
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EXCEMED designed this programme in partnership with the Scientific Institute and University Vita-Salute San Raffaele.

Share your opinion with us

We are always looking for ways to bring our educational activities to the next level and meet your needs as a healthcare practitioner.

You will be asked to answer a real-time survey during this event, followed by a post-event online survey to find out if the experience met your educational expectations. Your views also help us tailor future initiatives.

Thank you for taking the time to participate.
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Milan, Italy
Scientific programme
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**Thursday, 29 October 2015**

9.00  **EXCEMED opening and introduction**  
G. Comi (Italy) and M. Filippi (Italy)

9.15  **Real-time survey**

9.30  **L1: The role of imaging techniques in clinical neurology**  
M. Filippi (Italy)

10.00  **L2: The clinical work up of patients suspected of having MS**  
L. Kappos (Switzerland)

10.30  **L3: Individualised treatment in patients with MS**  
G. Comi (Italy)

11.00  **Coffee break**

11.30  **L4: The MRI criteria for diagnosing MS**  
J. Sastre-Garriga (Spain)

12.00  **L5: MRI and differential diagnosis in patients suspected of having MS**  
A. Falini (Italy)

12.30  **Revisiting real-time survey**

12.45  **Lunch**

13.45  **CS1: Case studies on diagnosis/differential diagnosis**  
There will be two case study sessions and different cases will be presented and discussed. These sessions will involve attendees in an interactive discussion, giving them the chance to share opinions and understanding of different MS related topics.  
S. Gerevini (Italy)

15.15  **Guided visit to the Neuroimaging Research Unit and Neuroimmunology Unit**

16.15  **End of the first day**

**Friday, 30 October 2015**

8.45  **Real-time survey**

9.00  **L6: Understanding MS evolution using structural MR techniques**  
M.M. Schoonheim (The Netherlands)

9.30  **L7: Understanding MS evolution using functional MR techniques**  
M.A. Rocca (Italy)

10.00  **L8: Optic nerve MRI**  
D. Chard (UK)

10.30  **L9: Spinal cord MRI**  
P. Valsasina (Italy)

11.00  **Coffee break**

11.30  **L10: MRI and cognition**  
P. Preziosa (Italy)

12.00  **L11: Future MR markers to monitor MS**  
N. De Stefano (Italy)

12.30  **L12: MRI and clinical trials**  
G. Edan (France)

13.00  **Revisiting real-time survey**

13.10  **Lunch**

14.10  **CS2: Case studies on treatment decision making: the role of MRI**  
M.A. Rocca (Italy)

15.40  **Concluding remarks**

15.50  **Guided visit to the Neuroimaging Research Unit**

16.20  **End of the live educational course**

**Legend:**  
L: Lecture;  
CS: Case studies;
Disclosure of faculty relationships

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  Declared receipt of grants and contracts from MS Society of Great Britain and Northern Ireland, and the National Institute for Health Research University College London Hospitals Biomedical Research Centre. He declared also receipt of honoraria or consultation fees from Bayer, Teva and to be member of a company advisory board, board of directors or other similar group: Teva for advisory board work. He declared to be stakeholder in a company: Teva and Novartis.

- **Giancarlo Comi**
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- **Nicola De Stefano**
  Declared receipt of honoraria or consultation fees from Biogen Idec, Novartis, Merck Serono. He declared also to be member of a company advisory board, board of directors or other similar group: Biogen Idec, Novartis, Merck Serono. He declared participation in a company sponsored speakers’ bureau: Biogen Idec, Novartis, Merck Serono.

- **Gilles Edan**
  Declared no potential conflict of interest.

- **Andrea Falini**
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- **Menno Schoonheim**
  Declared no potential conflict of interest.

- **Paola Valsasina**
  Declared no potential conflict of interest.
Abstracts
Over the past decade, conventional and modern structural magnetic resonance imaging (MRI) techniques have been extensively used to study patients with neurological diseases, with the ultimate goal to contribute to the diagnostic work-up and increase the understanding of the mechanisms responsible for the accumulation of irreversible disability and cognitive impairment in these conditions. Despite this, the magnitude of the correlation between structural MRI and clinical findings remains suboptimal. Among the reasons for such a discrepancy, the limited ability of conventional MRI to grade the extent of tissue injury as well as the variable effectiveness of reparative and recovery mechanisms following central nervous system damage have been suggested to play a role. In the last 10-15 years, we have witnessed an unprecedented application of new strategies to obtain hidden pieces of information from conventional MRI images as well as the development of new MR-based techniques to quantify the extent and define the nature of focal and diffuse abnormalities associated with demyelinating and neurodegenerative diseases. More recently, functional MRI has also been used to study patients with different neurological disorders in an attempt to measure the ability of the damaged brain to respond to tissue injury. There are several pieces of evidence indicating that a multiparametric approach, combining aggregates of different MR quantities, might improve our ability to understand the pathophysiology of the different neurological conditions and provide new objective metrics that might be useful to monitor disease evolution.
The diagnostic process aims at establishing diagnosis and excluding other, better or differently treatable diseases. In addition we need a valid sub-classification with implications for prognosis, and individualized therapeutic decisions. In this presentation we will discuss the current criteria for the clinical diagnosis of MS (McDonald Criteria) and the new classification of clinical phenotypes as described by F. Lublin et al. 2014 and diagnostic challenges around CIS and RIS. The key diagnostic criteria remain unchanged in the last 40 years: 2 or more lesions inside CNS; 2 or more episodes of CNS dysfunction (relapses) or (chronic) progression for defined observation time (> 6 or 12 mths); Exclusion of other diagnoses. No single diagnostic test is definitive proof - always synthesis of history, neurological findings and results of additional investigations. McDonald Criteria 1999: Three diagnostic groups: “MS”, “possible MS”, “no MS”. The focus remains on the objective demonstration of dissemination of lesions in both time and space. Magnetic resonance imaging is integrated with clinical and other paraclinical diagnostic methods. MRI can substitute for clinical observation; MRI-criteria well defined and “conservative” - high specificity rather than high sensitivity.

Revised McDonald Criteria 2005: Concept fundamentally unchanged; Definitions changed: Demonstration of dissemination in time more liberal: (i) A Gd-enhancing lesion at least 3 months after CIS onset or (ii) A new T2 lesion at any time compared to a reference scan done at least 30 days after onset of clinical event; use of spinal cord imaging better defined: Useful in showing DIS if brain lesions not informative: No cord swelling; unequivocal hyperintense T2 or Gd-enhancing; focal lesions (not diffuse) ≥ 3mm in size; < 2 vertebral segments long; occupying only part of cord cross-section; Equivalent to a brain infratentorial lesion; can contribute along with individual brain lesions to reach required lesion number.

Revised McDonald Criteria 2011: Definitions changed: Dissemination in Space: MAGNIMS criteria; Dissemination in Time: timing more liberal, one scan can be enough: (i) A new T2 on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI; (ii) Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time. Diagnosis of PP MS: One year of disease progression [Retrospective or prospective] plus 2/3 of the following: (i) + brain MRI, by ≥9 T2 lesions or ≥4 T2 lesions with +VEP; (ii) +spinal cord MRI, by ≥2 focal T2 lesions; (iii) +CSF, by OCB by isoelectric focusing and/or elevated IgG index.
Current disease-modifying therapies for multiple sclerosis (MS) include interferon (IFN) beta (subcutaneous [sc] and intramuscular [im]) glatiramer acetate, mitoxantrone, and natalizumab that are characterized by specific safety and efficacy profile.

These therapies have demonstrated clear efficacy in clinical trials and in postmarketing studies, however the full response on long term is rare, thus requiring the development of alternative therapies in order to achieve a full control of the disease. Some alternative treatments, such as Fingolimod, are currently a therapeutic option for second line therapy and other potential new treatments are in different phases of development. The availability of several therapeutic options may give the opportunity to achieve the ambitious target of a full control of disease activity in multiple sclerosis. Since MS evolution is quite variable from patient to patient with possibility of a very aggressive course from the onset, an early and accurate clinical and radiological assessments may help to identify patients who require more aggressive therapeutic options. The definition of individual prognostic factors with the history of previous treatments will contribute to define the best candidate therapy for a given patient at a specific time of disease evolution. In the future, it may become possible to apply also pharmacogenomic informations in order to individualize treatment as suggested by the scientific discovery of the association between glypican 5 gene polymorphisms and response to IFN-beta treatment. Close monitoring of the response to treatment with clinical biomarkers will be fundamental in order to allow rapid shift from a treatment to another.

Patient adherence to prescribed treatment is hugely variable and can influence decision-making. An assessment of each patient’s benefit-to-risk preferences may also help to identify those patients who are willing to accept additional risks in exchange for potentially greater clinical efficacy.
Differential as well as positive diagnoses of Multiple Sclerosis (MS) mostly rely on Magnetic Resonance Imaging (MRI). Differential diagnosis of MS will be covered in a separate talk, while in this part of the course we will be focusing on the fulfillment of diagnostic criteria for MS once other alternative causes for the clinical picture have been excluded. In the last thirty years, and mostly so in the last ten, as diagnostic criteria for MS have evolved, MRI has taken the spotlight and have become the crucial tool to demonstrate dissemination in space (DIS) and time (DIT) the two main pillars to establish a diagnosis of MS. In relapsing-remitting MS (RRMS) MRI is now the only test allowed to support DIS and DIT, as no other paraclinical tool can be used to satisfy diagnostic criteria, once the study of cerebrospinal fluid (CSF) and visual evoked potentials (VEP) have been taken out of the diagnostic algorithms. As for primary progressive MS (PPMS), CSF can also be of use to complement MRI findings. Across different releases of RRMS diagnostic criteria, these have been evolving aiming to:

1. Simplify the diagnostic algorithms;
2. Increase sensitivity while maintaining specificity;
3. Becoming more operational in its application;
4. Introducing spinal cord MRI.

As for PPMS, the aims have been:

1. Reduce the gap between RRMS and PPMS in criteria content;
2. Simplify the criteria;
3. Reduce the need for CSF studies from mandatory to simply useful.

In this talk we will discuss the evolution of the MRI role in the MS diagnostic criteria, and the pros and cons of the present release of the diagnostic criteria. Clues for future advances of the criteria will be provided.
Although MR imaging is the most sensitive investigational technique for MS, it is important to keep in mind that the appearance of multiple lesions on MR imaging is not specific for MS. Various pathological conditions can mimic multiple sclerosis both clinically and radiologically. The inflammatory, vascular, neoplastic and metabolic conditions which show features similar to those of MS on magnetic resonance imaging (MRI) will be reviewed. Behcet’s disease, Lyme disease, progressive multifocal leukoencephalopathy, neurosarcoïdosis, Whipple’s disease, listeria rhombencephalitis, Bickerstaff’s brainstem encephalitis, vasculitis due to systemic lupus erythematosus, and acute disseminated encephalomyelitis produce inflammatory lesions similar to those of MS. Neoplastic diseases, in particular gliomas and lymphomas, can mimic MS. Vascular ischaemic lesions, either due to infarction produced by occlusion of a major circulation artery or due to small vessel vasculopathy, can lead to posterior fossa or supratentorial lesions. The MRI changes of central pontine and extrapontine myelinolysis can also mimic MS. Diffuse axonal injury, radiation and chemotherapy induce lesions that resemble MS, however the clinical history will exclude these possibilities. Analysis of the MRI findings with clinical history and laboratory data helps to narrow down the diagnosis of demyelinating pathology.
In this session clinical cases with challenging radiological diagnosis will be shown. Clinical conditions that can mimic MS at the MRI imaging will be illustrated and discussed, focusing on differential diagnosis of focal T2 hyperintense lesions of white matter.

Typical and atypical MRI patterns of white matter hyperintensities will be explained considering the distribution, signal modification and/or evolution of white matter lesions. Initial and follow up studies of patients will be shown both on conventional and advanced MRI techniques.
Multiple sclerosis (MS) is a complex disease involving both the white matter (WM) and the grey matter (GM) of the central nervous system. In the early phases of the disease, its pathology is characterized by prototypical inflammatory demyelination around the ventricles, whereas in later stages, demyelination and inflammation spread throughout the WM and become more diffuse of character. With developing disease, involvement of the GM also becomes more prominent, which was shown to be relevant in understanding e.g. cognitive decline in MS. This presentation will highlight several structural MR imaging techniques that can be used to visualize different aspects of MS pathology, in different phases of the disease. These methods include conventional lesion load measurements of the WM and GM of brain and spinal cord, but also more quantitative techniques such as magnetization transfer ratio, diffusion tensor imaging, relaxation time measurements, and brain atrophy. This will be complemented with a brief digression through the highly exciting and emerging field of “connectomics”. Clinical relevance of the techniques will be discussed, as well as their sensitivity to damage and their pathological specificity. Then, finally, the question will be asked whether measuring structural damage is sufficient to understand the evolution of MS, or whether we need additional information.
There is increasing evidence that the severity of the clinical manifestations of MS does not simply result from the extent of tissue destruction, but it rather represents a complex balance between tissue damage, tissue repair and cortical reorganization. Functional magnetic resonance imaging (fMRI) provides information about the plasticity of the human brain and, therefore, has the potential to provide important pieces of information about cortical reorganization following MS-related structural damage, which should improve our understanding of the factors associated to the accumulation of progressive disability in this disease. fMRI changes have been described in virtually all patients with MS and different clinical phenotypes when investigating the visual, cognitive, and motor systems. These functional changes have been related to the extent of brain damage within and outside T2-visible lesions as well as to the involvement of specific central nervous system structures. In addition, it has also been suggested that a maladaptive recruitment of specific brain regions might be associated to the appearance of clinical symptoms in MS, such as fatigue and cognitive impairment. Brain functional changes have been shown to be dynamic over time, not only after an acute relapse, but also in clinically stable patients or after drug administration, thus providing an additional paraclinical tool to monitor treatments. fMRI studies from clinically impaired MS patients may be influenced by different task performance between patients and controls. As a consequence, new strategies have been introduced to assess the role, if any, of brain reorganization in severely impaired patients, including the analysis of resting state networks. The enhancement of any beneficial effects of this cortical adaptive plasticity should be considered as a potential target of therapy for MS.
Optic nerve involvement is common in people with MS, however observing this using MRI remains challenging. While the optic nerve is a relatively simple structure when compared with the brain, its small size and surrounding bone, fat and cerebrospinal fluid, make it more difficult to obtain scans with high signal to noise, adequate resolution, and free from artefacts. However, it is a structure of significant interest in MS research, as lesions within the optic nerve can provide valuable insights into the relationship between evolving pathology and neurological disability. In this session we will review optic nerve involvement in MS, how MRI can be used to image this, and what MRI studies of the optic nerve have told us about the relationship between MS pathology and neurological impairments.
The spinal cord is a clinically eloquent region of the central nervous system, whose damage can affect dramatically the functional outcome of patients with multiple sclerosis (MS). Acquiring good quality spinal cord MRI scans is of paramount importance; however, cord imaging presents inherent difficulties that make cord acquisition technically challenging. Nevertheless, in the last decade, advances in MR technology and post-processing are improving conventional and quantitative MRI techniques, making cord sequences more sensitive to MS-related pathology and allowing a better definition not only of global, but also of regional cord involvement.

Cervical cord lesions in MS are usually limited to two vertebral segments in length and occupy less than half the cross-sectional area. Diffuse hyperintense signal abnormalities, a pathological feature particularly frequent in primary progressive (PP) MS, are usually seen in the whole cord cross-section, while contrast-enhancing lesions are less frequently seen in the spinal cord than in the brain. Spinal cord lesions have been traditionally described as rarely T1 hypointense, but the recent introduction of high-field scanners and the use of optimized high-resolution sequences is significantly improving our ability to detect T1 hypointensities both in the cervical and in the thoracic cord segments.

As a consequence of the extensive presence of demyelination and axonal loss, MS patients usually develop cord atrophy. Although a significant reduction of cord area can be seen in the early phases of MS, cord atrophy is more severe and correlated with disability in the progressive forms of the disease. Recently, a new semi-automatic method based on an active surface (AS) model allowed segmentation of large portions of the cord and voxel-wise analysis of the regional distribution of cord atrophy. Another recent study used phase-sensitive inversion recovery (PSIR) sequences to assess atrophy of cord GM and WM compartments, separately, and found that cord GM atrophy was the strongest correlate of disability.

Using non-conventional MRI techniques, extensive microstructural abnormalities have been shown in the cervical cord of patients with MS. Magnetization transfer (MT) MRI abnormalities seem to occur relatively late in the course of the disease, especially in progressive MS phenotypes, while diffusion tensor (DT) MRI changes can be detected also in RRMS and BMS patients. At present, only one 2-year follow-up study assessed longitudinal cord DT-MRI changes in a large cohort of MS patients with different phenotypes and found significantly reduced fractional anisotropy (FA) and increased mean diffusivity (MD) over time. As it was the case for lesion and atrophy studies, the most recent advances of non-conventional MRI studies consisted in the regional quantification of cord microstructural abnormalities. For instance, MT MRI abnormalities were recently measured in an area corresponding to the expected location of pia mater and subpial regions in the outer cervical spinal cord. Contrary to what happened with global cord MT MRI measurement, outer spinal cord abnormalities could be seen early in the course of MS before cord atrophy was evident. Several reports using either regions of interest or DTI tractography approaches have quantified damage within different compartments over short portions of cervical cord.

References:
Cognitive impairment affects a large proportion of patients with multiple sclerosis (MS) and has a profound impact on their daily-life activities. Improving the knowledge of the pathophysiology of cognitive impairment in MS and of the mechanisms responsible for its evolution over time might contribute to development of better outcome measures and targets for innovative treatment strategies.

Magnetic resonance imaging (MRI) techniques have contributed to ameliorate the understanding of the mechanisms responsible for the accumulation of cognitive impairment in MS patients. Earlier studies demonstrated a relationship of the location of T2-visible lesions in critical brain regions and atrophy of several brain compartments with the severity of cognitive impairment in these patients. More recently, the development of new postprocessing approaches and the application of quantitative MR techniques for the assessment of structural disease-related damage in the brain normal-appearing white matter and gray matter resulted in a better understanding of the factors associated to the onset and development of deficits of several cognitive domains. The development of clinical and imaging biomarkers that can monitor disease development and treatment response is crucial to allow early identification of patients with MS who are at risk of cognitive impairment.
Several modern MR techniques have been developed and applied during the last couple of decades, providing a number of imaging biomarkers that, compared with conventional MRI measures, are able to better capture the complexity of the pathological process occurring in the MS brain. Among such quantitative techniques, magnetization transfer (MT) MRI has shown in several studies to be superior to conventional MRI in the detection and quantitation of subtle brain tissue changes.

Also diffusion Tensor imaging (DTI) has provided useful measures in MS, both within and outside lesions and longitudinal studies have demonstrated that DTI is sensitive to the evolution of tissue damage within MS lesions. Among the number of new magnetic resonance (MR) techniques that have found application on clinical ground, proton MR spectroscopy (1H-MRS) has the unique propriety to provide chemical-pathological characterization of MR-visible lesions and normal-appearing brain tissues by providing evidence of neurodegeneration (based on levels of N-acetylaspartate, a putative marker of axonal integrity) and by measuring brain changes of metabolites such as choline and myoinositol (good markers of myelin damage and repair). Since all the MR-derived measures described above can be routinely obtained from any MR clinical scanner, their use in large, multicentre clinical research studies to monitor MS evolution and progression is feasible when the inherent technical complexities are carefully taken into account.
Clinical trials of any new therapeutic agent depend on sensitive indices of disease activity to detect benefit. In multiple sclerosis clinical trials, MRI markers of inflammatory disease activity have been crucial to rapid acceleration in development of MS therapeutic. MRI measures will likely be central to development of drugs for primary neuroprotection and repair as well.

The principal impetus for utilization of MRI as an outcome measure in MS clinical trials is the potential for increased sensitivity to change and treatments effects compared to clinical measures. MRI lesion activity in MS exceeds the rate of relapses 5-10 fold, providing a much more sensitive measure of the disease process. When analysed by a blinded “central reading center” within a clinical trial, MRI data provide an independent, quantitative means to supplement potentially subjective clinical ratings.

Standard MRI assessment in MS clinical trials includes measures of lesion activity (gadolinium enhancing lesions, new or enlarged T2-hyperintense lesions) and measures of disease severity or burden (total T2-hyperintense lesion volume, total T1hypointense lesion volume, and whole-brain atrophy). Newer MRI parameters potentially provides additional sensitivity or pathologic specificity (magnetization transfer imaging, MTI, diffusion tensor imaging, DTI, gray matter atrophy measures, lobar atrophy, spinal cord atrophy, proton magnetic resonance spectroscopy and functional MRI).

In clinical trials, MRI can be use for subject selection, assessment of efficacy, monitoring safety and can serve different purposes in phase 1, phase 2 and phase 3 studies.

MRI is an integral part of MS clinical trials. Its provides the primary efficacy outcome of preliminary proof-of-concept studies and important corroborating data as secondary and exploratory outcomes in pivotal trials. At all stages of drug development, MRI provides important information on the kinetics and magnitude of treatment effect and insight into potential mechanisms of action. Attention to issues in scan acquisition, quantitative image processing and statistical analysis are critical to generate high quality data. Though it is unlikely that one single outcome measure will capture all aspects of MS disease process, there is potential for MRI outcomes to evaluate both inflammatory and degenerative components within clinical trials.
Conventional MR sequences (dual-echo and post-contrast T1-weighted scans) are the “reference standard” for diagnosis and monitoring disease progression in patients who present with clinically isolated syndromes suggestive of MS. In patients with established MS, and in those participating in treatment trials, these sequences provide objective measures for monitoring disease activity and progression; however, they have a limited prognostic role. Although MR imaging has improved the understanding of the pathophysiology of the disease and of the mechanisms responsible for the accumulation of irreversible neurological disability, its use in routine clinical practice for monitoring individual patients and response to treatment is, currently, not recommended.

Three clinical cases will be presented to help the clinicians in the application of MRI in treatment decision making in clinical practice. The first will focus on the utility of MRI for early treatment initiation. The second, will face the definition of non response to a specific treatment, based on an integrated clinical and MRI algorithm. The last one, will help for an early identification of incipient signs of side effects associated with second-line treatments.
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