Preceptorship on MRI in multiple sclerosis
24-25 October 2013 - Milan, Italy
General information

Venue
The live educational workshop takes place at the:
**Aula Caravella Nina**
**San Raffaele Congress Centre**
Via Olgettina 48
20132 Milan, Italy

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

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Preceptorship on MRI in multiple sclerosis

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Aim
Magnetic resonance imaging (MRI) techniques are central to making a diagnosis of multiple sclerosis (MS) even at the very early stages of the disease - allowing a prompt therapeutic intervention. The MRI role in disease monitoring and in clinical trials is also well established. In recent years, innovative imaging techniques have been developed, enabling new insights into MS pathogenesis and evolution. Only expert and trained health professionals can analyze and interpret the MRI results and only a few worldwide reference centers with advanced biosignal analysis technology are recognized. In this context, the preceptorship on MRI will provide learners with plenary lectures given by world recognized experts in the use of MRI in MS. In addition, guided tours of the Neuroimaging Research Unit and at the Departments of Neuroradiology and Neurology, aim to improve understanding and experience on MRI techniques applied to the MS field.

Learning objectives
By attending this live educational workshop the learners will be able to:
• Describe the clinical workout of a patient suspected of having MS
• Illustrate the clinical conditions that mimic MS at the MRI scan
• Summarize the updated findings on MS pathophysiology and evolution obtained by structural and advanced MRI techniques

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

Accreditation
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Scientific programme
24-25 October 2013

Thursday, 24 October

9.00  Serono Symposia International Foundation (SSIF) opening and introduction
G. Comi (Italy), 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
P.S. Sørensen (Denmark)

10.30  L3: Individualized 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 the differential diagnosis in patients suspected of having MS
A. Falini (Italy)

12.30  Real time survey

12.45  Lunch

13.45  CS1: Case studies on diagnosis/differential diagnosis
S. Gerevini (Italy)

15.15  Guided visit to the Neuroimaging Research Unit and Neuroimmunology Unit

16.15  End of the first day

Friday, 25 October

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

11.20  L10: MRI and cognition
F. Agosta (Italy)

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

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

12.50  Real time survey

13.00  Lunch

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

15.30  Concluding remarks

15.40  Guided visit to the Neuroimaging Research Unit and Neuroimmunology Unit

16.10  End of the live educational workshop

Legend:  L : Lecture;  CS : Case Study;
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**Declan Chard**
Declared receipt of grants and contracts from MS Society of Great Britain and Northern Ireland, UCLH/UCL NIHR Biomedical Research Centre. He declared also receipt of honoraria or consultation fees from Bayer, Teva. He is member of a company advisory board, board of directors or other similar group: Teva. He is stakeholder in GlaxoSmithKline.

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**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.

References:
The diagnosis of multiple sclerosis has been increasingly standardized over the years and has evolved to incorporate new diagnostic modalities. There is no single test that is diagnostic of MS, including MRI. The gold standard for diagnosing multiple sclerosis remains clinical, with dissemination of typical white matter symptoms and signs in time and space. There is no single test that is diagnostic of MS, including MRI.

Diagnostic criteria
The diagnostic criteria for MS have been revised several times over the years, most recently giving rise to the McDonald 2010 criteria that allow MRI changes to account for both dissemination in space and time. The diagnosis of MS begins with a patient who presents with symptoms typical for the disease, and if also the imaging is typical for MS, the clinician can then apply the appropriate diagnostic criteria. In case of atypical clinical or imaging findings, alternative aetiologies must be pursued as appropriate.

Clinical presentation
In the majority of cases the patient presents with symptoms typical for the disease, most commonly affecting the optic nerves (visual loss), brainstem (diplopia or vertigo), or spinal cord (paraesthesias or limb weakness), and this presentation is termed a clinically isolated syndrome. This is the first manifestation of a relapsing-remitting course, and with the next demyelinating episode the patient has clinical definite MS. In 10-15% the presentation is a gradual deterioration of symptoms, usually insidious development of paraplegia, indicative of a primary progressive course.

MRI
MRI is the most important paraclinical examination that may both contribute to the diagnosis and exclude alternative diagnoses. MRI is the most sensitive method for revealing asymptomatic dissemination of lesions in space and time, and MRI demonstration of dissemination of the disease in space and in time is now integrated in the diagnosis of McDonald MS.

CSF oligoclonal bands
With typical clinical and MRI presentations the diagnosis of MS can be established without examination of oligoclonal bands in the CSF, but in many countries a routine lumbar puncture is recommended to demonstrate the CNS inflammation. However, in clinically uncharacteristic cases, and in particular with negative or atypical MRI findings, CSF examination for oligoclonal bands is highly recommended.

Evoked potentials (EPs)
With the refinement of MRI diagnosis the importance of EPs has decreased, but they are still of value, in particular VEP, to clarify the demyelinating nature of the lesion. If atypical clinical or imaging findings are present, and sometimes they may contribute to establish dissemination in space of the disease.

Differential diagnosis
Symptoms may be difficult for patients to characterize and for clinicians to interpret; findings on examination may be subtle; imaging is not always specific; and the differential diagnosis of possible demyelinating disease is quite broad. Among the most important differential diagnoses are: Stroke, neoplasm, subacute combined degeneration, spinal neoplasm, cervical spondylosis, vertebral disc herniation, hereditary spastic paraparesis, adrenoleukodystrophy, mitochondrial disease (Lebers optic atrophy), hereditary ataxias, neuro-sarcoidosis, neuro-Bechet syndrome, phospholipid [anticardiolipin] antibody syndrome, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukodystrophy), paraneoplastic syndromes (encephalopathy) and CNS lymphoma. There are some manifestations or findings that might lead to doubt concerning a diagnosis of MS, so-called red flags, including: Strong family history, weight loss, arthropathy, rash, ulcers, persistent headache, fits, encephalopathy, movement disorders, stroke-like events, signs of peripheral neuropathy, raised ESR and/or CRP, abnormal chest x ray, absent oligoclonal bands, persistent CSF pleocytosis, normal MRI or pronounced meningeal enhancement on MRI.

Laboratory work-up
The basic laboratory work-up includes Routine haematological study, blood chemical studies including sodium, potassium, creatinine, albumin, urea, liver function tests, glucose, cholesterol, CPK, ESR / CRP, Thyroid function test, i, ANA titer and staining, B-12, methyl malonate, and urinalysis. In special patients measurements of angiotensin converting enzyme activity, anti-cardiolipin antibodies, partial thromboplastin time / prothrombin time, Sjögren’s syndrome antigens, Borrelia serology, HTLV-1, HIV, WR, paraneoplastic antibodies and plasma very long chain fatty acids might be appropriate.
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.
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, neurosarcoidosis, 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.
3 different cases focused on differential diagnosis between MRI of patients with focal T2 hyperintense lesions of white matter and patients with defined MS will be discussed.

The typical and atypical MRI pattern of these lesions will be explained.
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, for example, the brain, its small size and surrounding bone, fat and CSF, make it difficult to obtain scans with high signal to noise, adequate resolution, and free from artefacts. However, it remains a structure of interest in MS research, as lesions within the optic nerve have the potential to provide valuable insight into the relationship between evolving pathology and neurological function. In this session we will review optic nerve involvement in MS, how MRI can be used to image this, and what insight this has provided into the relationship between MS lesion 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). Imaging of the spinal cord in vivo using magnetic resonance (MR) techniques is still suboptimal due to the many challenges that such an approach still poses, which include the small size of the target organ and the presence of motion artefacts. Dual-echo spin echo MRI can detect spinal cord abnormalities in MS patients with a high sensitivity [1]. Cord MS lesions, which are more frequently observed in the cervical than in other regions, are usually in the peripheral white matter (WM), limited to two vertebral segments in length or less, occupy less than half the cross-sectional area of the cord, and typically are not T1-hypointense [1].

Although significant reduction of cervical cord size can be observed in the early phase of MS (2), cord atrophy is more severe in the progressive forms of MS [1]. Changes in cord cross-sectional area, both at a given time point and over time, correlate better with clinical disability than do changes of T2 lesion burden [3]. A recently developed method based on active surfaces (AS) [4] made possible the measurement of cord atrophy throughout large portions of the cord. This method allowed a precise characterization of cord tissue loss in a large cohort of MS patients with different clinical phenotypes [5].

The development of phased-array receiver coils and fast imaging techniques has improved the quality of quantitative data. Studies based on magnetization transfer ratio (MTR) have shown that cord MTR ratio (MTR) changes are occurring relatively late in the course of the disease, since significant reductions of MTR were observed principally in primary progressive (PP) MS patients and in secondary progressive (SP) MS patients rather than in relapsing remitting (RR) MS and patients with clinically isolated syndromes (CIS) [6-8]. Cord MTR was found to be significantly more altered in patients with locomotor disability than in those without [9].

Diffusion MRI of the spinal cord is technically more challenging than that of the brain, and diffusivity studies of this structure are, therefore, scanty. Nevertheless, the development of novel diffusion tensor (DT) MRI sequences has made possible to obtain accurate estimates of the extent of damage to this CNS region. Abnormal diffusivity and anisotropy of the cervical cord have been shown in RRMS, SPMS and PPMS patients [10,11]. DT abnormalities are worsening over time in all these MS phenotypes [12], while a relative sparing of cord tissue was shown in benign MS compared with SPMS [13].

Functional MRI (fMRI) has also been applied to assess functional abnormalities in the spinal cord of MS patients. Studies assessing neuronal activity in the cervical cord during a tactile stimulation of the right upper limb found that MS patients experienced a higher tactile-associated functional MR activity in the cervical spinal cord. 

References:
Conventional and quantitative MRI contributed to improve the understanding of the development of cognitive and neuropsychiatric disturbances in MS [1]. Available data suggest that focal white matter (WM) lesions play a role, but the overall burden of T2 lesions on MS-related cognitive and behavioural abnormalities is limited. On the contrary, the location of WM lesions in critical brain areas appears to be important. In addition, our recently improved capability to detect cortical lesions is likely to provide additional pieces of information central to this field [2]. Irreversible tissue loss, measured in terms of global and regional atrophy, is also substantially associated with cognitive deficits [3]. In addition, quantitative MRI studies pointed to the fact that brain tissue damage beyond the resolution of conventional MRI is also likely to contribute to the neuropsychological/behavioural impairment of these patients. Many of these studies emphasized the relevance of “diffuse” grey matter pathology as well as critical WM tracts injury, which can contribute to cortical disconnections. In addition, the application of functional MRI demonstrated different patterns of cortical activations associated with cognitive tasks or at rest, which are likely to have an adaptive role, at least at some stages of the disease. Improving the knowledge of the pathophysiology of cognitive impairment and behavioural changes in MS and of the mechanisms responsible for their evolution over time might contribute to the development of better outcome measures, which might be useful to screen rapidly innovative treatment strategies.

References:

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 agents. 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 T1-hypointense lesion volume, and whole-brain atrophy). Newer MRI parameters potentially provide 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 used 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. It 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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