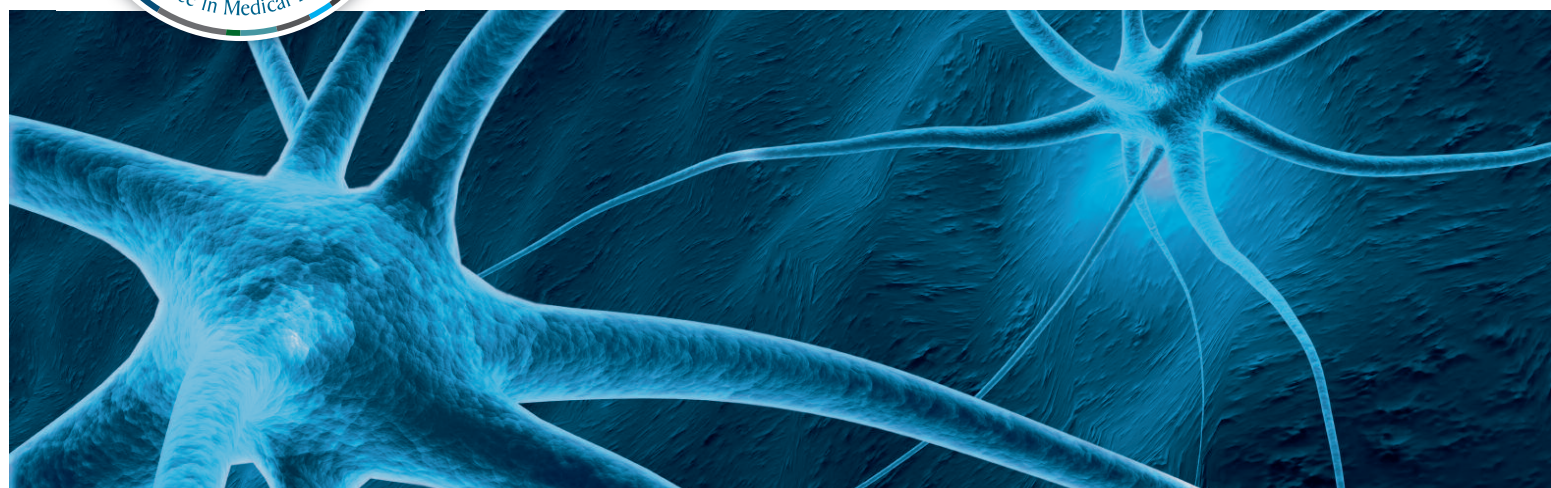




In-depth MRI techniques and analysis in multiple sclerosis

13-14 October 2016 - Milan, Italy



In-depth MRI techniques and analysis in multiple sclerosis

Overview

Basic knowledge of MRI imaging is an undeniable skill for all neurologists involved in multiple sclerosis (MS) management. Brain and spinal MRI are required to diagnose MS and to monitor efficacy and safety of all MS drugs. Nevertheless, neurologists willing to understand the disease's mechanisms and functional consequences of MS cannot miss information coming from advanced MRI techniques, which will be provided during the course. While numerical quantification of white and grey matter structural damage are part of everyday clinical practice when understanding MS impact at the individual level, it is essential to grasp post-processing of imaging, and volumetric estimates. Therefore, participants will benefit from hands-on training at the Neuroimaging Research Unit and they will have the opportunity to challenge themselves with analysis of imaging after processing. Applications of conventional and unconventional MRI techniques will be comprehensively illustrated during the course by world-renowned MRI experts.

What's new

This year the course features a new practical training session on lesion and atrophy quantification in MRI. Attendees will be supplied with a laptop containing softwares to aid their practical understanding and exploration of quantitative MRI analysis. The softwares work as an analytical videogame where users submit MRI scans from which they can extract important numerical data concerning lesions, white matter and more.

Learning objectives

By attending this live educational course, participants will be able to:

- Describe the present MRI diagnostic criteria for MS
- Summarize the novel functional and structural markers of disease severity obtained by advanced MRI techniques
- Illustrate the main findings of functional MRI techniques
- Describe the main software for imaging post-processing and basic principles of quantitative analysis of MRI imaging

Target audience

Young clinicians and scientists currently involved in MS management as well as radiologists interested in MS.

Chair

Massimo Filippi

Neuroimaging Research Unit
Institute of Experimental Neurology
Division of Neuroscience
San Raffaele Scientific Institute
Vita-Salute San Raffaele University
Milan, Italy

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General information

This live educational course takes place at:

San Raffaele Scientific Institute

Caravella Niña Meeting room

San Raffaele Congress Centre

Via Olgettina, 58

20132 Milan, Italy

Language

The official language of this live educational course is English.

CME Provider

EXCEMED - Excellence in Medical Education

Senior Programme Manager: Alessia Addressi

T +39 06 420413 591 - F +39 06 420413 677

alessia.addressi@excemed.org

Medical Advisor: Doriana Landi

doriana.landi@gmail.com

For any logistic support please contact:

Meridiano Congress International

Congress Coordinator: David H. Slangen

T +39 06 88 595 250 - F +39 06 88595 234

david.slangen@meridiano.it

Faculty

Declan Chard

Institute of Neurology
Faculty of Brain Sciences
University College of London
London, UK

Giancarlo Comi

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

Nicola De Stefano

Neurology and Neurometabolic Unit
Department of Neurological and Behavioral Sciences
University of Siena
Siena, Italy

Andrea Falini

Department of Neuroradiology
San Raffaele Scientific Institute
Vita-Salute San Raffaele University
Milan, Italy

Massimo Filippi

Neuroimaging Research Unit
Institute of Experimental Neurology
Division of Neuroscience
San Raffaele Scientific Institute
Vita-Salute San Raffaele University
Milan, Italy

Simonetta Gerevini

Department of Neuroradiology
San Raffaele Scientific Institute
Vita-Salute San Raffaele University
Milan, Italy

Mark A. Horsfield

Xinapse Systems Ltd
West Bergholt, UK

Ludwig Kappos

Department of Biomedicine
University Hospital Basel
Basel, Switzerland

Elisabetta Pagani

Neuroimaging Research Unit
Institute of Experimental Neurology
Division of Neuroscience
San Raffaele Scientific Institute
Vita-Salute San Raffaele University
Milan, Italy

Paolo Preziosa

Neuroimaging Research Unit
Institute of Experimental Neurology
San Raffaele Scientific Institute
Vita-Salute San Raffaele University
Milan, Italy

Maria Assunta Rocca

Neuroimaging Research Unit
Institute of Experimental Neurology
Division of Neuroscience
San Raffaele Scientific Institute
Vita-Salute San Raffaele University
Milan, Italy

Menno M. Schoonheim

Department of Anatomy & Neurosciences
Section of Clinical Neuroscience
VU University Medical Center
Amsterdam, The Netherlands

Gioacchino Tedeschi

Second University of Naples
Naples, Italy

Paola Valsasina

Neuroimaging Research Unit
Institute of Experimental Neurology
Division of Neuroscience
San Raffaele Scientific Institute
Vita-Salute San Raffaele University
Milan, Italy

Programme

Programme

Thursday, 13 October 2016

- 9.00 **Opening and introduction**
G. Comi (Italy) and M. Filippi (Italy)
- 9.15  **Real-time survey**
- 9.30 **L1: The clinical work up of patients suspected of having MS**
L. Kappos (Switzerland)
- 10.00 **L2: The MRI criteria for diagnosing MS**
M. Filippi (Italy)
- 10.30 **L3: MRI and differential diagnosis in patients suspected of having MS**
A. Falini (Italy)
- 11.00 **Coffee break**
- 11.30 **L4: Monitoring treatment response with MRI (from NEDA-3 to NEDA-4)**
N. De Stefano (Italy)
- 12.00 **L5: Individualised treatment in patients with MS**
G. Comi (Italy)
- 12.30  **Revisiting real-time survey**
- 12.45 **Lunch**
- 13.45  **Case studies on diagnosis/differential diagnosis and treatment decision making**
S. Gerevini (Italy) and M.A. Rocca (Italy)
- 16.15  **Guided visit to the Neuroimaging Research Unit**
- 17.00 **End of the first day**

Friday, 14 October 2016

- 8.45  **Real-time survey**
- 9.00 **L6: Advanced imaging techniques: basic principles**
E. Pagani (Italy)
- 9.30 **L7: Understanding MS evolution using structural MR techniques**
M. Schoonheim (The Netherlands)
- 10.00 **L8: Understanding MS evolution using functional MR techniques**
M.A. Rocca (Italy)
- 10.30 **L9: MRI and cognition**
P. Preziosa (Italy)
- 11.00 **Coffee break**
- 11.30 **L10: Optic nerve MRI**
D. Chard (UK)
- 12.00 **L11: Spinal cord MRI**
P. Valsasina (Italy)
- 12.30 **L12: Atrophy: from clinical trials to single patient**
G. Tedeschi (Italy)
- 13.00  **Revisiting real time survey**
- 13.10 **Lunch**
- 14.10  **Practical session: training on lesion and atrophy quantification**
M.A. Horsfield (UK), E. Pagani (Italy), P. Preziosa (Italy), M.A. Rocca (Italy)
- 16.10 **Concluding remarks**
M. Filippi (Italy)
- 16.20 **End of the live educational course**

Legend: L : Lecture  Real-time survey  Clinical cases  Site visit  Practical session

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Andrea Falini	Declared no potential conflict of interests.
Massimo Filippi	Declared receipt of grants and contracts from Biogen Idec, Teva, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla and receipt of honoraria or consultation fees from Biogen Idec, Novartis, Teva. He declared to be member of a company advisory board, board of directors or other similar groups: Teva.
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Elisabetta Pagani	Declared no potential conflict of interests.
Paolo Preziosa	Declared no potential conflict of interests.
Maria Assunta Rocca	Declared receipt of grants and contracts from Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla and receipt of honoraria or consultation fees from Biogen Idec, Novartis, Teva, Genzyme.
Menno M. Schoonheim	Declared no potential conflict of interests.
Gioacchino Tedeschi	Declared receipt of grants and contracts from Biogen Idec, Merck, FISM. He declared receipt of honoraria or consultation fees from Bayer Schering, Biogen Idec, Merck, Teva, Novartis. He declared participation in a company sponsored speakers' bureau: Bayer, Biogen Idec, Merck, Teva, Genzyme, Novartis.
Paola Valsasina	Declared no potential conflict of interests.

Abstracts

L1. The clinical work up of patients suspected of having MS

Ludwig Kappos

Department of Biomedicine, University Hospital Basel, Basel, Switzerland

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 (Mc Donald 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. **Mc Donald Criteria 2001:** 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 Mc Donald 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) $\geq 3\text{mm}$ 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 Mc Donald 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.

L2. The MRI criteria for diagnosing MS

Massimo Filippi

Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience
San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Magnetic resonance imaging (MRI) has been formally included in the diagnostic work-up of patients presenting with a clinically isolated syndrome (CIS) suggestive of multiple sclerosis (MS) in 2001 by an International Panel of experts.¹ MS diagnosis requires the demonstration of disease dissemination in space (DIS) and time (DIT) and the exclusion of other conditions that can mimic MS by their clinical and laboratory profile. MRI can support and substitute clinical information for MS diagnosis, allowing an earlier and accurate diagnosis and, consequently, earlier treatment.

MRI criteria for MS are based on the presence of focal lesions in the white matter (WM) of the central nervous system (CNS), which are considered typical for this condition in terms of distribution, morphology, evolution and signal abnormalities on conventional MRI sequences (e.g., T2-weighted, T2-FLAIR, pre- and post-contrast T1-weighted scans).²⁻⁴ Several modifications of MRI diagnostic criteria have been proposed over the years. These revisions have simplified the lesion count models for demonstrating DIS, changed the timing of MRI scan for demonstrating DIT, and increased the value of spinal cord imaging.⁵⁻⁸ In 2007 the European collaborative research network that studies MRI in MS (MAGNIMS) has reviewed the findings of studies that addressed these issues and proposed new MRI criteria to be applied in MS.⁹ Those MAGNIMS criteria are currently included in the most recent of the MS diagnostic criteria, known as the 2010 McDonald criteria.¹⁰

Since the last update of these criteria, new data regarding the application of MRI for demonstrating DIS and DIT have become available and improvement in MRI technology has occurred. State-of-the-art MRI findings in these patients have been recently revised by MAGNIMS experts and evidence-based and expert-opinion consensus on diagnostic MRI criteria modifications have been proposed, which should be included in future revisions of MS diagnostic criteria.¹¹

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L3. MRI and differential diagnosis in patients suspected of having MS

Andrea Falini

Department of Neuroradiology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

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.

L4. Monitoring treatment response with MRI (from NEDA-3 to NEDA-4)

Nicola De Stefano

Neurology and Neurometabolic Unit, Department of Neurological and Behavioral Sciences, University of Siena, Siena, Italy

The advent of a large number of new therapies in multiple sclerosis (MS) warrants the development of tools able to select the best treatment option for each new MS patient. Evidence from clinical trials clearly supports the efficacy of a number of drugs for the treatment of MS but only a small number of factors predicting a response to treatment on individual patient-basis have emerged. This might be due, at least in part, to the lack of a standardized definition of the clinical outcome used to assess improvement/worsening of the disease. Magnetic Resonance Imaging (MRI) markers and clinical relapses have been the most widely studied short-term factors to predict long-term response to therapies, although results are conflicting. Recently, integrated strategies combining MRI and clinical markers in scoring systems provided a potentially useful approach for the management of MS patients. We will review the many definitions of response to therapy, including the emerging and evolving concept of no evidence of disease activity (NEDA). Furthermore, we will explore the MRI markers able to predict such response. Finally, we will highlight advantages and limitations of the existing scoring systems to predict the response to interferon in the light of a future expansion of these models to biological markers and to other classes of new emerging therapies for MS.

L5. Individualised treatment in patients with MS

Giancarlo Comi

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

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.

L6. Advanced imaging techniques: basic principles

Elisabetta Pagani

Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience
San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

To the main objective of this lecture will be to introduce advanced MRI methods that can be applied in the field of multiple sclerosis. Several techniques will be touched upon, giving an overview of the basic principles of MR acquisition, the steps of post-processing and the metrics that can be derived. In particular, the lecture will focus on methods for measuring atrophy, characterizing white matter micro-structure in terms of architecture and myelin content, detecting the presence of lesions in gray matter and for studying the function of the brain.

The description of the MR acquisition will make participants aware of the mechanisms involved in obtaining a particular measure, with reference to recognized gold standard methods, as well as a discussion about applicability of techniques in the clinical setting. Methods of analysis for extracting the relevant metrics during post-processing will be described. For each technique, limitations and critical issues will also be reviewed.

L7. Understanding MS evolution using structural MR techniques

Menno M. Schoonheim

Department of Anatomy & Neurosciences, Section of Clinical Neuroscience, VU University Medical Center
Amsterdam, The Netherlands

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.

L8. Understanding MS evolution using functional MR techniques

Maria Assunta Rocca

Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience
San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

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.

L9. MRI and cognition

Paolo Preziosa

Neuroimaging Research Unit, Institute of Experimental Neurology, San Raffaele Scientific Institute,
Vita-Salute San Raffaele University, Milan, Italy

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 between the location of T2-visible lesions and atrophy and the severity of cognitive impairment in MS. More recently, the development of new post-processing approaches and the application of quantitative MR techniques for the assessment of structural disease-related damage in the normal-appearing white matter and gray matter have led to a better understanding of the factors associated to the onset and evolution of deficits of several cognitive domains. The development of clinical and imaging biomarkers that can monitor disease course and treatment response is crucial to allow early identification of patients with MS who are at risk of cognitive impairment.

L10. Optic nerve MRI

Declan Chard

Institute of Neurology, Faculty of Brain Sciences, University College of London, London, UK

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.

L11. Spinal cord MRI

Paola Valsasina

Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience
San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

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.¹ Diffuse hyperintense signal abnormalities, a pathological feature particularly frequent in primary progressive (PP) MS, are usually seen in the whole cord cross-section,¹ while contrast-enhancing lesions are less frequently seen in the spinal cord than in the brain.² Spinal cord lesions have been traditionally described as rarely T1 hypointense,¹ 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.³

As a consequence of the extensive presence of demyelination and axonal loss, MS patients usually develop cord atrophy.⁴ Although a significant reduction of cord area can be seen in the early phases of MS,⁵ cord atrophy is more severe and correlated with disability in the progressive forms of the disease.^{4,6} Recently, a new semi-automatic method based on an active surface (AS) model allowed segmentation of large portions of the cord⁷ and voxel-wise analysis of the regional distribution of cord atrophy.⁸ 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.⁹

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,⁶ while diffusion tensor (DT) MRI changes can be detected also in RRMS and BMS patients.⁶ At present, only one 2-year follow-up study assessed longitudinal cord DT-MRI changes in a large cohort of MS patients with different phenotypes¹⁰ 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.¹¹ 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,¹² voxel-wise,¹³ or DTI tractography¹⁴ approaches have quantified damage within different compartments over short portions of cervical cord.

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L12. Atrophy: from clinical trials to single patient

Gioacchino Tedeschi

Second University of Naples, Naples, Italy

Axonal loss and neuro-degeneration occur early in multiple sclerosis (MS) and may lead to irreversible neurological impairment. Indeed, reduction of brain volume can be observed from the earliest stage of MS. In untreated MS patients, the rate of atrophy is about 0.5%-1.35% of brain volume per year. Brain volume loss can be non-invasively and reproducibly detected and quantified by magnetic resonance imaging (MRI). For this reason, whole brain atrophy has recently emerged as an attractive measure of tissue loss and as a substrate for clinical disability and therapy effectiveness. There are a number of cross-sectional and longitudinal MRI-based methods for determining global or regional brain volume. As the majority of disease modifying therapies (DMTs) predominantly act on the inflammatory component of the disease mechanism, clinical trials are typically powered to establish the effect on relapses, disability progression, T1/T2 lesion burden/activity and occurrence of gadolinium enhancing lesions. In those trials investigating also brain volume changes, DMTs appear to attenuate brain atrophy over time when compared with placebo. Moreover, their efficacy appears to be greater during the second year of treatment (in comparison to the first year) and linearly increases with longer treatment duration. This behavior may limit the ability of these DMTs to control early loss of brain volume. The delayed effect of DMTs may be explained by the complex biological phenomena underlying the measured brain volume. Recently, brain volume loss was added to the new concept of “no evidence of disease activity” (NEDA)-3 (relapses, new/enlarged MRI lesions/gadolinium enhanced lesions and disability progression) to provide a more comprehensive assessment of disease activity and progression.

Although it is difficult to extend the use of brain volume measurements to single-patient clinical practice, preventing brain volume loss may have important clinical implications.

Brain atrophy measurement methods are sensitive and reproducible, but caution must be exercised when interpreting brain volume data, as numerous factors (e.g. pseudoatrophy) may have a confounding effect on measurements, especially in a disease with complex pathological substrates such as MS. Several factors potentially impact on the precision of brain atrophy measurements (MS heterogeneous pathological substrates, physiological variability, measurement errors, presence of concomitant pathophysiological conditions etc.). While this is not a major issue in clinical trials, brain volume measurements should be improved in a real-world setting, taking into account these confounding factors. Furthermore, future studies are needed to establish normative values for brain volume changes both for healthy individuals and MS patients.

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Headquarters

14, Rue du Rhône - 1204 Geneva, Switzerland

Representative Office

Salita di San Nicola da Tolentino 1/b - 00187 Rome, Italy

T +39 06 420413 1 - F +39 06 420413 677

