Satellite Symposium at ENS:
“What neuromyelitis optica is telling us about multiple sclerosis”
Prague, Czech Republic - 11 June, 2012
General information

Venue
The symposium takes place at the:

**Prague Congress Centre**
5. kvetna 65 - 140 21 Prague 4
Czech Republic

Language
The official language of the symposium is English.

Scientific secretariat
Serono Symposia International Foundation
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Serono Symposia International Foundation
is a Swiss Foundation with headquarters in
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Satellite Symposium at ENS

“What neuromyelitis optica is telling us about multiple sclerosis”

Serono Symposia International Foundation symposium on:

What neuromyelitis optica is telling us about multiple sclerosis
Prague, Czech Republic - 11 June, 2012

Aim of the symposium
The Serono Symposia International Foundation satellite symposium at ENS (European Neurological Society) Meeting will be focused on Neuromyelitis optica (NMO) which has been the subject of intense scientific and clinical interest in the last few years. Although NMO has been recently recognized as a distinct inflammatory and autoimmune disorder, it share many features with multiple sclerosis (MS), thus making the differential diagnosis challenging. This satellite symposium will explore key aspects of NMO and discuss how this condition can enhance our understanding of MS.

Learning objectives
The symposium will provide an extensive overview on:
• Neuropathological aspects of NMO
• NMO pathogenetic mechanisms
• Clinical presentation of NMO and its management

Target audience
Neurologists interested in neurodegenerative diseases.

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Scientific organizer

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

List of speakers and chairmen

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

Hans-Peter Hartung
Department of Neurology
Heinrich-Heine-University
Düsseldorf, Germany

Hans Lassmann
Center for Brain Research
Medical University of Vienna
Vienna, Austria

Angela Vincent
Nuffield Department of Clinical Neurosciences
University of Oxford
John Radcliffe Hospital
Oxford, UK
Monday – 11 June, 2012

11.45 Serono Symposia International Foundation (SSIF) opening
   Giancarlo Comi, Italy

11.55 Welcome and introduction
   Giancarlo Comi, Italy

12.00 L1: Neuropathology
   Hans Lassmann, Austria

12.25 L2: Pathogenesis
   Angela Vincent, UK

12.50 L3: Clinic
   Hans-Peter Hartung, Germany

13.15 Concluding remarks
   Giancarlo Comi, Italy

13.20 End of the symposium
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The following faculty provided information regarding significant commercial relationships and/or discussions of investigational or non-EMEA/FDA approved (off-label) uses of drugs:

<table>
<thead>
<tr>
<th>Faculty Name</th>
<th>Disclosure</th>
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<tbody>
<tr>
<td>Giancarlo Comi</td>
<td>Declared receipt of honoraria or consultation fees from Serono Symposia International Foundation, Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Merck Serono, Bayer Schering, Biogen, and Actelion.</td>
</tr>
<tr>
<td>Hans-Peter Hartung</td>
<td>Declared receipt of honoraria or consultation fees from Biogen Indec, Novartis Pharma, Merck Serono, Genzyme, Sanofi Aventis.</td>
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<tr>
<td>Hans Lassmann</td>
<td>Declared no potential conflict of interest.</td>
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<tr>
<td>Angela Vincent</td>
<td>Declared receipt grants and contracts from: NHS UK to provide AQP4 antibody assays for NHS.</td>
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Abstracts
Neuromyelitis optica (NMO) has originally been defined pathologically as an inflammatory demyelinating disease, related to multiple sclerosis (MS). There are, however, distinct differences in the pathology between these two conditions. Both diseases are based on a chronic inflammatory reaction in the brain, composed of T-lymphocytes, few B-lymphocytes and activated macrophages and microglia cells. In contrast to MS, granulocytes and in particular eosinophils are abundant in active NMO lesions. In both disease lesions are formed in the central nervous system, which show primary demyelination with relative axonal preservation. In NMO, however, in contrast to MS these demyelinating lesions form as a secondary consequence of antibody and complement mediated destruction of astrocytes. Thus profound astrocytic scar formation is a typical feature of MS lesions, while in NMO many lesions are highly destructive, with profound loss of astrocytes, myelin and axons. Lesions in MS brains are randomly distributed in the brain and spinal cord, while in NMO lesions are preferentially present in the spinal cord, the optic nerves and chiasm, as well as in periventricular grey matter, including the hypothalamus, the peri-aqueductal grey matter and the floor of the fourth ventricle. Finally, diffuse injury and cortical demyelination, typical pathological features of MS in the progressive stage of the disease, are sparse or absent in NMO brains. The differences in pathology between NMO and MS suggest fundamentally different mechanisms of inflammation induced tissue injury between these two conditions.
Antibodies to AQP4 (AQP4-Abs) can be measured by several different techniques including indirect immunofluorescence on rodent brain tissue, as originally reported (Lennon et al 2004), immunoprecipitation of labelled AQP4, ELISA or cell-based assays. The latter method is antigen-specific and detects antibodies that bind to the extracellular domain of the AQP4. In addition, the use of the M23 isoform that naturally forms clusters on the cell surface helps improve the detection of the antibodies, and may be the preferred antigen in some patients. The antibody binding can be detected either by direct visualisation of the binding under the microscope, or by use of a fluorescence-activated cell sorter, to obtain quantitative results. Either method can achieve high sensitivity and specificity.

The antibodies have been shown to be pathogenic by in vitro and in vivo experiments. The antibodies are IgG1 subclass and can activate complement on the surface of AQP4 expressing cells. They also cause internalisation of AQP4 with loss of surface expression in transfected HEK cells and cultures astrocytes, and may co-internalise the glutamate transporter EAAT2. The most informative experiments have been done by in vivo injections into mice. Firstly, the systemic injection of IgG purified from the patients, which by itself does not achieve any phenotype or pathology, combined with an encephalotogenic T cell response, that “opens the blood brain barrier”. Alternatively, intracerebral injection of IgG has been combined with human complement. In both situations there are modest clinical signs but the pathology is strikingly similar to the human disease. These models allow one to dissect the different contributions of T cells, antibodies and other cell types such as neutrophils to the pathology of the disease.

So what lessons can be applied to MS? The discovery of antibodies that have the potential to be pathogenic can help to discriminate between diseases with similar presentations. For instance, although isolated optic neuritis or longitudinally-extensive transverse myelitis may not fulfil the clinical criteria for NMO, they are now accepted as related diseases that should be treated in a similar manner. There are beginning to be reports of antibodies in multiple sclerosis that are against neuronal or glial surface proteins, although all the specificities are not yet clear. Better definition of these pathogenic antibodies in patients with MS may allow the distinction of subforms which may be preferably treated by immunotherapies designed to reduce antibody levels rather than conventional disease modifying treatments.

A few selected references:
The classical definition of neuromyelitis optica (NMO) originates from Gault and Devic who in 1894 described 17 cases characterized by acute, monophasic onset of optic neuritis (ON) and acute transverse myelitis (TM) occurring simultaneously or in rapid succession. The definition of NMO developed from the recognition that attacks of ON are more frequently unilateral than bilateral and that attacks of ON and TM usually occur sequentially rather than simultaneously. The discovery of the anti-aquaporin 4 (AQP4) antibody unravelled the NMO clinical and pathogenic complexity, leading to the recognition of a more heterogeneous clinical presentation with peculiar and specific characteristics, different from multiple sclerosis (MS). Typically, transverse myelitis that occurs in NMO cases, affects the cervical and the upper thoracic spinal cord segments, with a longitudinal extension lasting three or more vertebral segments or it could be more limited to cervical spine extending into the brainstem, thus leading to intractable hiccups and vomiting and/or to respiratory failure which is extremely rare finding in MS. Usually ON is unilateral or less often bilateral, associated with ocular pain and visual loss. ON and TM associated with NMO are often severe, and spontaneous and complete recovery of neurological dysfunction is rare. More recently, the NMO spectrum has been enriched by clinical reports of reversible encephalopathy, hypothalamic and cognitive dysfunction in NMO patients with NMO-IgG positivity. Because NMO is a severe central nervous system inflammatory disorder with a less favourable prognosis than MS and with different therapeutic approaches, prompt and early diagnosis based on robust criteria is crucial. Different sets of criteria for NMO have been proposed during the last decade, on the basis of clinical presentation, MRI features, prominent cerebrospinal fluid (CSF) pleocytosis with a high proportion of neutrophils, abd serum AQP4 antibody positivity. Even though they could be helpful in guiding the diagnosis, they need to be validated in large multicentre studies. NMO clinical aspects, epidemiology, differential diagnosis and treatment strategies will be extensively reviewed.
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