INTRODUCTION

It is a pleasure to present the annual report from Copenhagen Multiple Sclerosis Centre, Department of Neurology, Neuroscience Centre, Copenhagen University Hospital, Rigshospitalet.
Copenhagen Multiple Sclerosis Centre is composed of Copenhagen MS Clinic and MS Research Unit.
Copenhagen Multiple Sclerosis Centre constitutes one of the "European MS Centres of Excellence".

Copenhagen MS Clinic is the largest in the country with responsibility for the care of more than 1000 patients with multiple sclerosis. The MS Clinic is a multidisciplinary MS Clinic with the mission of providing total care for patients with multiple sclerosis. An important activity is clinical research with emphasis on development of new therapies. A number of clinical trials, both national and international have been initiated and managed from the Copenhagen MS Centre, and, in addition, the clinic offers the possibility for patients to take part in clinical controlled trials sponsored by pharmaceutical companies.

The MS Research Unit including the Neuroimmunology Laboratory has had a busy year with initiation of new activities and continuation of former initiated research projects. The research embraces 3 major areas: Research in the neurogenetics of multiple sclerosis, research in the immunology of multiple sclerosis, and experimental studies.

We hope that you will enjoy reading the annual report for the year 2003.

On behalf of the Copenhagen Multiple Sclerosis Centre

Mads Ravnborg Poul Erik Hyldgaard Jensen Per Soelberg Sørensen

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1. ORGANISATION AND STAFF

1.1. Personnel at Copenhagen MS Clinic

Head of the MS Group:
Professor Per Soelberg Sørensen, MD, DMSc

Executive manager of the MS Clinic:
Mads Ravnborg, MD, DMSc, chief consultant

Senior physicians:
Susanne Helweg-Larsen, MD, DMSc, consultant
Morten Blinkenberg, MD, PhD, consultant
Jesper Rønager, MD, senior registrar

Junior physicians:
Annette Oturai, MD, PhD
Jens Christian Faber-Rod, MD
Finn Sellebjerg, MD, PhD, DMSc
Pameli Datta, MD

Psychologist:
Agnete Jønsson, chief psychologist

MS-nurses:
Anne Hansen
Merete Mogensen
Rikke Lønborg

Physiotherapist:
Lis Albrechtsen

Medical social counsellor:
Merete Møller Olsen

Secretaries:
Kristina Kristensen
Annette Larsen

1.2. MS Clinic

Near to a thousand MS patients are treated regularly in the MS Clinic. Most of these (70%) are from the H:S area. The rest comes from all over Denmark, often referred for specialised immunosuppressive treatment.
The MS Clinic is a subunit of the Neuroscience Centre that was established in 1994. The clinical work is taken care of by a professor, a chief consultant, two consultants, a number of junior physicians, three MS nurses and two secretaries. Apart from these a neuropsychologist, a physiotherapist and a social worker are members of the MS team. Working in close relationship to these are two project nurses and a scientific secretary whose appointments are based on external funding.
The MS Clinic is located at departments N2082 and N2084 and comprises a secretariat, a chief consultant office, two nurses offices, two consultation rooms, a nurse consultation room, a room for intravenous infusions, and a procedure room for baclofen pump refilling and lumbar punctures.
The yearly number of visits to the clinic is about 2500. For the regular visits the schedule allows 45 minutes. The consultation comprises a thorough and goal directed interview, a quantitative neurological examination, and a conclusion in terms of goals and efforts. The visit frequency varies from 1 - 4 times a year depending on disease activity and treatment regimen. In addition to the scheduled visits, the patients are encouraged to show up spontaneously if acute needs arise.
The primary goal of the MS clinic is to offer the best possible treatment of multiple sclerosis, disease modifying as well as symptomatic treatments, while considering the overall impact of the disease on the patients´ lives. The disease modifying treatments used currently are interferon beta, glatiramer acetate, methotrexate, azathioprin, and mitoxantron. More than 300 patients are treated with one or more of these drugs.
Other specialist tasks are the treatment of bladder and bowel dysfunction, neurogenic pain and spasticity. About 80 patients with severe spasticity are treated with intrathecal baclofen pumps. This treatment implies 4-6 controls per year for refilling and adjustments.
A secondary goal of the MS clinic is to involve as many patients as possible in clinical trials. A number of multicentre investigator driven randomised trials are organised and directed by the Copenhagen MS Centre (see below). In addition, the MS Clinic is enrolling patients in a number of clinical trials sponsored by the pharmaceutical industries. In 2003 patients from the MS Clinic have been participating in trials comparing a new immunomodulatory product, natalizumab (antegren), both in a placebo-controlled trial and in a trial in which natalizumab has been used as add-on therapy to patients already treated with interferon-beta 1a. Natalizumab is a monoclonal antibody against adhesion molecules and prevents leucocytes from entering the central nervous system. It is administered as an intravenous infusion once monthly. In another large multicenter randomised trial a new compound given orally, FTY720 (Novartis) is tested against placebo.

All documentation, ordering and planning related to clinical activities are executed in the context of the MS clinic database, a multi-user on-line facility to which all members of the MS team have access.
The MS nurses are working increasingly independent of the doctors. The nurses instruct patients and relatives in injection techniques, give infusions of immunosuppressive drugs, make ultra-sound bladder scans, instruct patients in clean intermittent self-catheterisations, and guide patients through daily life obstacles. A nurse line is open for patient counselling weekdays from 9 to 11 a.m.

1.3. Personnel at MS Research Unit and Neuroimmunology Laboratory

Head of the MS Research Group:
Professor Per Soelberg Sørensen, MD, DMSc

Senior research fellows:
Mads Ravnborg, MD, DMSc, chief consultant
Poul Erik Hyldgaard Jensen, MSc, DMSc, Head of Neuroimmunology Laboratory
Signe Humle Jørgensen, MSc, PhD
Agnete Jønsson, chief neuropsychologist

PhD-students:
Thomas Tscherning, MD
Lars Storr, MD
Pameli Datta, MD
Bodil Petersen, MD
Martin Krakauer, MD

Stipendiary scholar
Nicolas Storm

Part-time research fellows:
Morten Blinkenberg, MD, PhD
Annette Oturai, MD, PhD
Susanne Helweg-Larsen, MD, DMSc
Jens Christian Faber-Rod, MD
Finn Sellebjerg, MD, PhD, DMSc

Technical staff:
Susanne Velgaard, laboratory technician
Henriette Egeblad, laboratory technician
Gunvor Helt, laboratory technician
Vibeke Jespersen, project nurse
Joan Pietraszek, project nurse
Annette Larsen, scientific secretary

1.4. MS Research Unit

The MS Research Unit is located at Juliane Maries Vej 24 in an old villa named building 92 at the Rigshospitalet campus.
The MS Research Unit Neuroimmunology Laboratory resides in building 93, Juliane Maries Vej 20, just opposite building 92. The ground floor is shared with the Neurobiology Research Unit Experimental Laboratory and the Cardiovascular Laboratory. One room is allocated to the Neuroimmunology Laboratory and it shares another 3 rooms with the other groups mentioned above. The head of the Neuroimmunology Laboratory is Poul Erik Hyldgaard Jensen, MSc, DMSc. In the Neuroimmunology Laboratory the MS Research Unit conducts research on the neuroimmunology and biochemistry of multiple sclerosis and experimental studies using the experimental autoimmune encephalomyelitis (EAE) as a model of MS. Further, the Neuroimmunology Laboratory offers examination of cerebrospinal fluid for oligoclonal bands employing isoelectric focusing electrophoresis. In addition the laboratory carries out measurements of antibodies against acethylcoline receptors. The laboratory also contains a biobank of plasma, CSF and DNA for experimental use.

Research areas
The main research areas are:
- Clinical research
- Pathogenesis of MS
- Genetics in MS
- Experimental model of MS

2. RESEARCH PROJECTS

2.1. Clinical research

2.1.1. Clinical randomised trials

Treatment of acute relapses with intravenous immunoglobulin in multiple sclerosis (TARIMS)
An investigator driven international, multicentre study initiated and organised by Copenhagen MS Centre. Principal investigator is professor Per Soelberg Sørensen.

Objectives: The main objective of this study was to test the hypothesis that treatment with IVIG 1 g/kg bodyweight i.v. followed by 1 g methylprednisolone i.v. daily for 3 three days resulted in a better recovery of targeted deficits in MS-relapses compared to methylprednisolone alone.
Study design and patients: The study was a multicentre, double-blind, placebo-controlled prospective trial with parallel groups. Seventy-six patients were enrolled.
Results: The study gave only hints for a slightly better remission of acute relapses by a combined treatment of a single dose IVIG and standard therapy with methylprednisolone compared with placebo and methylprednisolone, but did not provide a statistical proof for this hypothesis. However, the relapse-rate in IVIG treated patients was reduced by more than 10%, and also the time to first relapse appeared to be prolonged when compared to placebo.
Financial support: Bayer Vital
Principal investigator: Per Soelberg Sørensen
Project group: Per Soelberg Sørensen, Mads Ravnborg, Vibeke Jespersen, Joan Pietraszek

Nordic trial of methylprednisolone as add-on therapy to interferon-beta for treatment of relapsing-remitting multiple sclerosis (NORMIMS)
An investigator driven international, multicentre study initiated and organised by Copenhagen MS Centre. Principal investigator is professor Per Soelberg Sørensen.
Objectives: The main objective is to compare the effect of methylprednisolon given at 4 weeks intervals with the effect of placebo in patients treated with interferon-beta 1a (Rebif) who during therapy have shown clinical activity.
Study design and patients: Patients with relapsing-remitting multiple sclerosis treated with interferon-beta 1a (Rebif) for at least 1 year are eligible if they have shown clinical activity defined as at least one relapse during the last 12 months. Two treatment groups with 150 patients in each as planned. Eligible patients are randomized to treatment with methylprednisolone 200 mg daily for 5 days at 4 weeks intervals in combination with interferon-beta 1a (Rebif) or placebo in combination with interferon-beta 1a (Rebif) for 24 months. The patients will be examined clinically at six months intervals. MRI is performed before start of treatment and after 24 months.
Outcome measures: The primary outcome measure is the number of documented relapses per year, and the secondary outcome measures include the occurrence of neutralizing antibodies at 24 months, the time to a permanent increase in disability of 1 point on the EDSS, and the number of active lesions on T2 weighted MRI.
Timelines:
Start of patient enrolment: January 2004
End of patient enrolment: February 2005
End of study: February 2007
Financial support: Serono
Principal investigator: Per Soelberg Sørensen
Project group: Thomas Tscherning, Bodil Petersen, Pameli Datta, Jens Christian Faber-Rod, Anne Hansen, Per Soelberg Sørensen

A prospective multicentre, double-blind, randomized placebo-controlled parallel group trial investigating immunoglobulin G intravenously as add-on therapy to interferon-beta 1a for the treatment of relapsing-remitting multiple sclerosis (IVIMS)
An investigator driven international, multicentre study initiated and organised by Copenhagen MS Centre. Principal investigator is professor Per Soelberg Sørensen.
Objectives: The primary objectives is to assess the add-on effect on intravenous immunologbulin G (IVIG) given at 30 days intervals versus placebo on the mean number of documented relapses per year in patients who prior to study entry shown clinical activity during treatment with interferon-beta 1a (Avonex).
Study design and patients: Patients with definite relapsing-remitting multiple sclerosis who during therapy for at least one year with interferon-beta 1a (Avonex) have shown clinical activity during the last year on therapy.
The study design is a placebo-controlled, randomized, parallel group trial, comprising two treatment groups with 140 subjects in each group. Eligible patients on treatment with interferon-beta 1a (Avonex) are randomized to treatment with either 0.2 g/kg intravenous immunoglobulin G as add-on therapy at 30 thirty days intervals or placebo for 24 months.
Outcome measures: The primary outcome measure is the number of documented relapses per year. Secondary outcome measures include time to confirmed progression of 1 point on the EDSS, and brain atrophy measured as the brain parenchymal fraction.
Timelines:
Start of patient enrollment: January 2004
End of patient enrollment: January 2005
End of study: January 2007
Financial support: Baxter and Biogen Idec
Principal investigator: Per Soelberg Sørensen
Study group: Per Soelberg Sørensen, Mads Ravnborg, Jens Christian Faber-Rod, Pameli Datta, Joan Pietraszek

A prospective multicentre, double-blind, randomised, parallel-group trial investigating the combination of interferon-beta 1a and monthly methylprednisolone versus interferon-beta 1a and placebo for treatment of relapsing-remitting multiple sclerosis (MECOMBIN)
An investigator driven international, multicentre study initiated and organised by Copenhagen MS Centre. The study was initiated by professor Per Soelberg Sørensen and chief physician Mads Ravnborg. Principal investigator is Mads Ravnborg.
Objectives: The primary objectives is to assess the effect of interferon-beta 1a (Avonex) in combination with mehylprednisolone given at 4 weeks intervals compared to interferon-beta 1a (Avonex) and placebo on progression of disability in patients with relapsing-remitting multiple sclerosis.

Study design and patients: Patients with definite relapsing-remitting multiple sclerosis who have not previously been treated with immunomodulatory therapy. The study is a prospective multicentre, double-blind, placebo-controlled, randomised, parallel-group trial comprising 2 treatment groups of 150 subjects in each group. Eligible patients are randomised to treatment with either interferon-beta 1a (Avonex) 30 micrograms weekly and monthly methylprednisolone 500 mg orally on 3 consecutive days for 36 months.
Outcome measures: The primary outcome measure is confirmed progression of 1 step on EDSS. Secondary outcome measures include the annual relapse rate and the lesion load on T2-weighed MRI.
Time lines:
Start of patient enrolment: January 2003
End of patient enrolment: December 2004
End of study: December 2007
Financial support: Biogen Idec
Principal investigator: Mads Ravnborg
Study group: Mads Ravnborg, Per Soelberg Sørensen, Morten Blinkenberg, Bodil Petersen, Joan Pietraszek
For further information visit www.mecombin.dk

A double –blind, placebo controlled, randomised cross over clinical trial of tetrahydrocanabinol in the treatment of ataxia and spasticity in patients with multiple sclerosis
The study was initiated by professor Per Soelberg Sørensen and chief physician Mads Ravnborg. Principal investigator is Mads Ravnborg
Objectives: The primary objective is to evaluate the effect of tetrahydrocanabinol (THC) on ataxia and spasticity in patients with multiple sclerosis.
Study design and patients: Patients with clinically and functionally significant spasticity entered the A-study, while patients with clinically and functionally significant ataxia were included in the B study.
The study is a prospective, double-blind, placebo-controlled, randomised, cross-over trial comprising 2 sub-studies with 24 subjects in each group. Eligible patients were randomised to treatment with THC/placebo a treatment period of 3 weeks followed by a 3 week wash out and finally 3 weeks treatment with placebo/THC.
Time lines:
Start of patient enrolment: August 2001
End of patient enrolment: August-2003
End of study: October 2003. The recruitment failed and only 18 patients entered study B and 11 patients study A. Database locking is pending
Financial support: Solvay
Responsible investigator: Mads Ravnborg
Study group: Mads Ravnborg, Per Soelberg Sørensen, Vibeke Jespersen, Joan Pietraszek

2.1.2. Other clinical studies of immunomodulatory therapy

Long-term effect on disability of interferon-beta therapy in relapsing-remitting multiple sclerosis
A Danish Multiple Sclerosis Group (DMSG) project initiated and organised by Copenhagen MS Centre.
Objectives: The main objective is to investigate whether interferon-beta treatment in relapsing-remitting patients for more than 5 years results in a delay of disease progression when compared to untreated controls.
Study design and patients: A cohort of 940 patients with relapsing-remitting multiple sclerosis who between June 1996 and June 1999 started on treatment with interferon-beta. The cohort is compared with a historical control cohort from the London Ontario Multiple Sclerosis Registry.
Outcome measures: The primary efficacy outcome measure is time to EDSS 6 and 7 respectively.
Financial support: Danish Multiple Sclerosis Society, Warwara Larsen Foundation
Responsible investigator: Bodil Petersen
Project group: Bodil Petersen, Nils Koch-Henriksen, Jette Frederiksen, Henrik Brønnum Hansen, Mads Ravnborg, George Ebers, Per Soelberg Sørensen

Rebound effect of the discontinuation of interferon-beta therapy in patients with relapsing-remitting MS
A Danish Multiple Sclerosis Group (DMSG) project initiated and organised by Copenhagen MS Centre.
Objectives: The main objective is to investigate whether the annual relapse rate increases in patients who discontinue therapy after at least 1 years treatment with interferon-beta.
Study design and patients: Clinical information on relapses and disability is gathered for at least 6 months following secession of interferon-beta therapy.
Outcome measures: The primary efficacy outcome is the annualised relapse rate.
Financial support: Danish Multiple Sclerosis Society, Warwara Larsen Foundation
Responsible investigator: Bodil Petersen
Project group: Bodil Petersen, Nils Koch-Henriksen, Mads Ravnborg, Per Soelberg Sørensen

2.1.3. Clinical immunology

Neutralizing antibodies against interferon-beta

Clinical importance of neutralizing antibodies
A Danish Multiple Sclerosis Group (DMSG) project initiated and organised by Copenhagen MS Centre.

Objectives: The main objective of this study was to follow the development of neutralizing antibodies (NAb) during treatment with interferon-beta and to evaluate the clinical impact of NAb.
Study design and patients: We measured NAb every 12 months for up to 60 months in 541 MS patients using an anti-viral neutralization assay.
Results: During NAb-positive periods patients had significantly higher relapse rates compared to NAb-negative periods, yielding an odds ratio for relapses of 1.5. The time to first relapse was significantly increased by 244 days in NAb-negative patients. A trend was found towards faster progression in NAb-positive patients.
Financial support: Danish Multiple Sclerosis Society
Principal investigator: Per Soelberg Sørensen
Project group: Per Soelberg Sørensen, Mads Ravnborg
Publications: Ross C, Clemmesen KM, Svenson M, Sorensen PS, Koch-Henriksen N, Skovgaard GL, Bendtzen K. Immunogenicity of interferon-beta in multiple sclerosis patients: influence of preparation, dosage, dose frequency, and route of administration. Danish Multiple Sclerosis Study Group. Ann. Neurol. 2003; 48,5:706-12
Sorensen PS, Ross C, Clemmesen KM, Bendtzen K, Frederiksen JL, Jensen K, Kristensen O, Petersen T, Rasmussen S, Ravnborg M, Stenager E, Koch-Henriksen N, and the Danish Multiple Sclerosis Study Group. Clinical importance of neutralizing antibodies against interferon beta in patients with relapsing-remitting multiple sclerosis. Lancet. 2003;362:1184-91

Biologic response to interferon-beta in patients with and without neutralizing antibodies
Objectives: The main objective of this study is to assess the in vivo biologic response to an interferon-beta injection by measuring changes in neopterin, beta2-microglobulin and MxA protein.
Study design and patients: Thirty-two patients have been included in the study. Neutralizing antibodies are measured using an anti-viral neutralization assay. Neopterin and beta2-microglobulin are measured with in-house assays. MxA protein measured by professor F. Deisenhammer, Austria. Four MRI with gadolinium contrast are performed at monthly intervals.
Outcome measures: The primary outcome measure is the response to interferon-beta injection documented as an increase in neopterin, beta2-microglobuline and MxA protein blood levels. The secondary measure is the number of gadolinium enhancing lesions per scan in patients with a biologic response compared to patients without a biologic response.
Timelines: The study has been terminated and data are currently reviewed.
Principal investigator: Per Soelberg Sørensen
Project group: Per Soelberg Sørensen, Thomas Tscherning, Mads Ravnborg

The reversibility of neutralizing antibodies against interferon-beta
Objectives: The main objective of this study is to assess if neutralizing antibodies against interferon-beta developed during therapy can be reduced or removed by treatment with azathioprine and cyclic methylprednisolone.
Study design and patients: Ten patients with high concentration of neutralizing antibodies and no in vivo biologic response to interferon-beta injection are treated with azathioprine 2.5 mg/kg daily and cyclic methylprednisolone 1 g monthly for 6 months. After 6 months the NAb concentration is measured and the biologic in vivo response to interferon-beta injection is assessed by measuring the increase in blood levels of neopterin, beta2-microglobulin and MxA protein after an interferon-beta injection.
Outcome measure: The primary outcome measure is the proportion of patients with reestablishment of a biologic response to interferon-beta and a decrease in NAb concentration.
Timelines:
Start of enrolment of patients: March 2004
End of patient enrolment: June 2004
End of study: November 2004
Principal investigator: Per Soelberg Sørensen
Project group: Per Soelberg Sørensen, Mads Ravnborg

Persistence of neutralising antibodies against interferon-beta after discontinuation of therapy
A Danish Multiple Sclerosis Group (DMSG) project initiated and organised by Copenhagen MS Centre.
Objectives: The main objective is to follow concentrations of neutralising antibodies against interferon-beta after discontinuation of interferon-beta therapy.
Study design and patients: Concentrations of neutralising antibodies (NAb) against interferon-beta are measured using an antiviral neutralisation assay. The concentration of neutralising antibodies (neutralising capacity) is followed in patients who have been treated with interferon-beta for more than 1 year, and thereafter have discontinued therapy or switched therapy to glatiramer acetate (Copaxone).
Outcome measure: The primary outcome measure is change in neutralising capacity.
Timelines:
Patient enrolment ends by March 31, 2004
Financial support: Danish Multiple Sclerosis Society, Warwara Larsen Foundation
Responsible investigator: Bodil Petersen
Project group: Bodil Petersen, Nils Koch-Henriksen, Mads Ravnborg, Per Soelberg Sørensen

2.1.4. Neuro-imaging

Positron Emission Tomography (PET), MRI and cognitive dysfunction in patients with newly diagnosed relapsing-remitting multiple sclerosis (MS)
Objectives: The aim of the study is to examine the cross-sectional and longitudinal changes in positron emission tomography (PET) measurements of cerebral glucose metabolism, in patients with newly diagnosed MS. The results are compared with pathological changes in magnetic resonance imaging (MRI), and a selected panel of neuropsychological tests evaluating cognitive dysfunction.
Study design and patients: 21 patients were included in the initial evaluation with PET, MRI and neuropsychological evaluation, and the results of this initial cross-sectional study have been presented elsewhere. Currently, the studied population is undergoing final MRI, PET and neuropsychological evaluation after a two year time period, in order to evaluate the longitudinal pathological changes in the early course of MS.
Timelines:
Time of enrolment of patients: August 2000 and following
End of study: December 2004
Financial support: Copenhagen University
Responsible investigator: Thomas Tscherning
Project group: Thomas Tscherning, Agnete Jønsson, Henrik Kahr Mathiesen, Per Soelberg Sørensen, Morten Blinkenberg, Lars Hanson, Egill Rostrup, Olaf B. Paulson

2.1.5. Rehabilitation and neuropsychology

Cognitive dysfunction in MS
A longitudinal study of cognitive dysfunctions in newly diagnosed multiple sclerosis patients
Objectives: The aims of the study are 1) to examine frequency, type and severity of cognitive dysfunctions in newly diagnosed MS, 2) to follow the development of cognitive dysfunctions over a period of 5 years with re-examination once a year and 3) to correlate cognitive dysfunctions with neurological impairment and psychosocial factors in order to optimize relevant advise and rehabilitation.
Study design and patients: Eighty consecutive patients diagnosed with MS within one year have been included. The last patient was included in the middle of 2001. Seventy-one of 80 patients have passed the second examination and 68 patients passed the third examination. These data are being analyzed. Forty-seven patients have passed the forth examination, 28 patients the fifth examination and 7 patients have passed the sixth and last examination.
Timelines:
Time of enrolment of patients: March 1997
End of study: August 2006
Financial support: Rigshospitalets Forskningsudvalg, Fonden for Neurologisk Forskning
Responsible investigator: Agnete Jønsson
Project group: Agnete Jønsson, Mads Ravnborg, Lars Storr, Thomas Tscherning, Per Soelberg Sørensen.

2.1.6. Rehabilitation in MS

Rehabilitation of patients with multiple sclerosis: a population based analysis of needs, ressources and efficacy of rehabilitation.
Mads Ravnborg took the initiative to this study, which was performed by Lars Storr. The primary objective was to evaluate the effect of multidisciplinary rehabilitation as it is practiced in the MS-rehabilitation centre in Haslev.
Study design and patients: double blind, controlled, wait-list randomised, parallel group design.
Inclusion: A total of 223 patients (treatment, n = 106; control, n = 117) were contacted by telephone. Of these, 106 (treatment, n = 41; control, n = 65) consented to join the project.
The results will be published in due course.
Responsible investigator: Lars Storr
Project group: Lars Storr, Per Soelberg Sørensen, Mads Ravnborg

2.2. Pathogenesis of MS

Examination of complement factor C3 activation in MS-patients
Background: The complement system is an important part of the human immune defense system. It involves a cascade of proteins, which activate and start an inflammatory event in the body, whereby other parts of the immune system become activated. The central protein in this cascade is C3, which is produced in large amounts and circulate in the whole body. When C3 is activated, a structural change in the molecule occurs, and it becomes reactive towards surfaces of biologic structures, which thereby becomes neutralized. It is known that the complement system in some MS patients is involved in the demyelination process. High complement activity can be connected to an antibody-controlled disease course. However, at present no biological markers have been identified, which can distinguish such a course from others.
Objectives: Objectives are to determine changes in the activation of complement factor C3 in blood and cerebrospinal fluids of patients with MS, and to relate these to the disease course and pathogenetic subgroups of patients.
Methods: By use of an ELISA-method, the concentrations of the final C3-activation product can be measured in cerebrospinal fluid and blood samples. This has been done for a group of MS patients in comparison to a control group. Furthermore have the measurements of the concentrations of total C3 in CSF and in blood samples been performed by use of ELISA and radial immunodiffusion respectively. Fractions of

activated to total C3 have been calculated for each individual in both MS-patients and controls.
Financial support: Direktør Ib Henriksens Fond, Hestehandler Ole Jakobsens Mindelegat
Responsible: Poul Erik Hyldgaard Jensen
Project group: Signe Humle Jørgensen, Per Soelberg Sørensen, Susanne Velgaard and Poul Erik Hyldgaard Jensen

Conformational changed α2-Macroglobulin in patients with MS
Background: Many proteinases have been suggested to play roles in the demyelination process of MS, and human α_2-Macroglobulin (α_2M) inhibits most of the proteinases in vitro. α_2M is present at high concentrations (about 2 mg/ml) in the blood, and is found in the CSF in approx. a five hundred-fold lower concentration than in plasma. It is produced and secreted by macrophages and probably by astrocytes in CSF. The main source of α_2M in blood is the liver. A cleavage activates the inhibitor and conformational changes occur whereby the proteinase is bound in α_2M. The proteinase-complex form of α_2M (termed transformed α_2M) is recognized by the α_2M-receptor/LRP, which removes it from the circulation. α_2M can furthermore complex with several cytokines and growth factors (such as NGF, TNF-α, TGF-β, Il-10, Il-6, Il-1). The role as an inhibitor of proteinases in MS has not been studied even though some interesting results on α_2M in MS-patients has been presented, i.e. abnormality ofα_2M in MS-patients has been observed by electrophoretic and isoelectric focusing methods.
Objectives: Objectives are 1) to demonstrate correlation between the proteinases MMP-1, -2, -3, -9 and α_2 M of MS-patients in both plasma and CSF, 2) to identify the abnormality in α_2M, if any, and 3) to identify the influence of α_2M on oligodendroglial cell responses, induced by the cytokines TNF-α, interferon-γ, Il-6, Il-10, and TGF-β.
In 2003 we have measured the concentrations of α_2M and of MMP-9 in plasma from 95 MS-patients and 132 controls. In controls there is a correlation between MMP-9 and α_2M concentrations, but this disappears in the MS-patients. We believe this could be due to the inhibition of more various proteinases, whereby the MMP-9 amounts bound to α_2M are relatively decreased.
In 2003 we have measured α_2M concentrations and identified significantly increased concentrations of transformed α_2M in plasma of RR/SP MS-patients. In contrary the native α_2M demonstrated decreased concentrations in the same samples.
Financial support: Fonden til Lægevidenskabens Fremme, A.P. Møller og Hustru Chastine McKinney Møllers Fond til Almene Formål, Oda og Hans Svenningsens Fond, Jacob Madsens og Hustru Olga Madsens Fond
Responsible: Poul Erik Hyldgaard Jensen
Project group: Signe Humle Jørgensen, Per Soelberg Sørensen, Susanne Velgaard and Poul Erik Hyldgaard Jensen

Determination of concentrations of the soluble receptor CD163 in cerebrospinal and serum samples from MS-patients
By use of a developed ELISA-system the concentrations of the soluble receptor CD163 were measured in serum and CSF from control groups and MS-patients.
Financial support: None
Responsible: Poul Erik Hyldgaard Jensen
Project group: Poul Erik Hyldgaard Jensen, Per Soelberg Sørensen, Søren Moestrup, Holger Jon Møller

Immune activation in subsets of blood mononuclear cells in MS patients before and during immunomodulatory treatment
Background: The mechanisms of action of the immunomodulatory drugs currently used in the treatment of MS are still unclear. Better understanding of these mechanisms is required in order to devise future treatment regimens and rational drug combination treatment.
Objectives: We aim to assess the cellular effects of immunomodulatory treatment (interferon-β, glatiramer acetate, methylprednisolone, intravenous immunoglobulin, and mitoxantrone) on peripheral blood mononuclear cells.
Methods: Blood samples are collected from MS patients beginning an immunomodulatory drug treatment. Patients are re-sampled after 3 months and 6 months of treatment. Inflammatory activity is monitored by means of serial MRI scans and clinical parameters and is correlated to the immunological findings. Mononuclear cells are stained for flow cytometry with an extensive panel of surface and intracellular antigens. In addition, production of specific mRNA in response to treatment is assessed by microarray analysis and real time reverse transcriptase PCR (quantitative PCR).
In vitro cell culture experiments are employed to verify results obtained *in vivo*. In addition, basic immunological regulatory mechanisms are studied, including the CD4+CD25+ T-cell population as well as inter- and subcellular signalling pathways.
Financial support: University of Copenhagen, Faculty of Health Sciences, Danish Multiple Sclerosis Society, Rigshospitalet, Lily Benthine Lund Foundation, Dagmar Marshall Foundation
Responsible: Martin Krakauer
Project group: Martin Krakauer, Finn Sellebjerg, Henriette Egeblad, Susanne Velgaard, Pameli Datta, Annette Oturai, Per Soelberg Sørensen

Monitoring in vivo interferon-β responses in MS
Background: There are marked individual differences in clinical interferon-β responses in MS patients. Some can be explained by the long-term development of neutralizing antibodies to interferon-β (NAb). There is, however, also a subgroup of patients with little or no initial response to interferon-β, which can not be explained by NAb's. These patients probably have a defective cellular response to interferon-β.

Present assays for NAb (cytopathic bioassays) are laborious and difficult to standardise. Moreover, these assays do not identify NAb-negative non-responders.
Methods: We plan to investigate the cellular mechanism responsible for NAb-negative non-responders. We are currently developing a real time reverse transcriptase PCR method to quantify *in vivo* interferon-β induced MxA protein mRNA in blood mononuclear cells. MxA protein is exclusively induced by type 1 interferons and serves as a marker of interferon-β response. MxA mRNA will be correlated to the presence of Nab's and clinical and paraclinical markers of interferon-β response. Mechanisms conferring interferon-β non-responsiveness on a cellular level are also studied.
Financial support: University of Copenhagen, Faculty of Health Sciences, Danish Multiple Sclerosis Society, Rigshospitalet
Responsible: Per Soelberg Sørensen
Project group: Per Soelberg Sørensen, Martin Krakauer, Henriette Egeblad, Finn Sellebjerg

Identifying immunopathogenetic subtypes of MS
Objectives: The aims of the study are 1) to perform a detailed basic comparison of spinal cord pathology between cases of primary and secondary progressive MS. Preparing lesion maps of spinal cord pathology and analyse the distribution of inflammatory infiltrates, the size and location of demyelinated plaques, the extent of axonal loss and atrophy and the extent of Wallerian tract degeneration. 2) When this is established we will procede with further investigations.
Study design and patients: Histopathological evaluation of autopsy lesions of 46 patients (225 blocks) with RR and PP MS. 39 patients have not been treated with any immunosuppresives and the mean disease duration is 23 years.
Outcome measures: Systematic investigation of spinal cord lesions of MS patients may solve open questions regarding pathological heterogeneity between patients with PP and RR MS. This can have implications for treatment of pathologically defined subtypes of MS.
Responsible: Jens Christian Faber-Rod
Project group: Jens Christian Faber-Rod, Per Soelberg Sørensen
This project is done in collaboration with department of neuropathology, Rigshospitalet (Henning Laursen), The Danish MS Registry (Nils Koch-Henriksen) and Institute of neuropathology, Vienna, Austria (prof. Hans Lassmann)

2.3. Genetics

Identification of risk factors in Multiple Sclerosis
Background: Worldwide, eight genome screens have been published without identification of any major gene(s). From these studies it seems more likely that about 20 genes with moderate genetic effects are interacting. Today more than 10.000 micro-satellites are known. The Nordic countries have participated in a large European collaboration doing genome screens, using 6000 micro-satellites in two sets of Nordic populations. Results have been published, and a European meta-analysis is ongoing. The Nordic group has been collaborating since 1994.
Methods: The aim of this study is to identify susceptibility and disease modifying genes in MS.
Financial support: The Danish Multiple Sclerosis Society, Johnsen og hustrus mindelegat, Warwara Larsen Fond
Responsible: Annette Oturai
Project group: Annette Oturai, Pameli Datta, Per Soelberg Sørensen
This project is done in collaboration with department of Clinical Immunology, Rigshospitalet Denmark (Lars P. Ryder, Hans O. Madsen, Arne Sveigaard)

Two genome-wide linkage disequilibrium screens in Scandinavian multiple sclerosis patients
Background: The aetiology of MS is complex and includes a complicated interplay between unknown genetic and environmental factors. Worldwide, eight genome screens have been published without identification of any major gene(s). From these studies it seems more likely that about 20 genes with moderate genetic effects are interacting. The Nordic countries have participated in a large European collaboration doing genome screens, using 6000 micro-satellites in two sets of Nordic populations. Results have been published, and a European meta-analysis is ongoing. The Nordic group has been collaborating since 1994.
Objectives: The objective of this study was to perform genome-wide linkage disequilibria screens in Scandinavian MS patients to identify regions encompassing putative susceptibility genes.
Study design and patients: 400 Scandinavian MS patients and unrelated control individuals were included in two independent screens. A set of 6000 micro satellite markers were typed on pooled DNA as described by Barcellos et al. 1997.
Outcome measures: 3331 markers were analysed in both screens, and a comparison between them revealed 31 markers associated to MS. Among these several markers confirmed the well-established association of MS to the HLA-region on chromosome 6. The most promising regions were located on 19q13 and 11q23.
Future perspectives: To confirm the results in a new patient material by individual typing.
Financial support: The Danish Multiple Sclerosis Society, Warwara Larsens Fond, Ejner Jonasson og Hustrus mindelegat, Christenson - Cesons Familiefond
Responsible: Pameli Datta
Project group: Pameli Datta, Annette Oturai, Per Soelberg Sørensen
This project is done in collaboration with Department of Clinical Immunology, Rigshospitalet Denmark (Lars P. Ryder, Arne Svejgaard); Department of Neurology, Huddinge University Hospital, Karolinska Institute, Huddinge, Sweden (Jan Hillert, Eva Aakesson); Department of Neurology, Göteborg University Hospital, Göteborg, Sweden (Oluf Andersen); Department of

Neurology, Ullevål University Hospital, Oslo, Norway (Hanne Harbo); Institute of Immunology, The National Hospital, Oslo, Norway (Anne Spurkland); The Multiple Sclerosis National Competence Center, Department of Neurology, Haukeland University Hospital, Bergen, Norway (Kjell-Morten Myhr); Department of Neurology, Gothenburg University hospital, Gothenburg, Sweden (Magnhild Sandberg-Wollheim); Neurology Unit, Addenbrooke's Hospital, University of Cambridge, Cambrige, UK (Stephen Sawcer, Alastair Compston)

Publication: Datta P, Harbo HF, Oturai A, Ryder LP, Sawcer S, Setakis E, Akesson E, Celius EG, Modin H, Sandberg-Wollheim M, Myhr KM, Andersen O, Hillert J, Sorensen PS, Svejgaard A, Compston A, Vartdal F, Spurkland A. Two genome-wide linkage disequilibrium screens in Scandinavian multiple sclerosis patients. J Neuroimmunol. 2003 Oct;143(1-2):101-6

Confirmation of genome-wide screen candidate regions in Nordic MS patients

Objectives: Several association genome-wide screens, based on pooled DNA, have been performed to determine genetic factors involved in MS. These results need to be confirmed with individual genotyping in new patient materials. The aim of this study was to confirm the results from three independent Nordic screens by individual typing.

Methods and patients: We collected 328 Caucasian Nordic trio families and 372 unrelated control individuals from Denmark, Norway, Sweden and Iceland. The best thirty-three micro satellite markers from three Nordic LD genome screens were investigated by individual typing. Two comparisons were made; Fisher's exact test for cases and controls and TDT for testing the trio families.

Results: Fourten and eleven regions were found associated to MS by Fisher's exact test and TDT respectively.

Conclusion: Seven regions were significantly ($p<0.05$) associated to MS in both Fisher's test and TDT. Of these regions 11q23 and 1p34 were the supported with the strongest evidence, apart from the HLA-region.

Future perspectives: To finemap these regions with a dense panel of SNP markers, in order to identify the causative genes.

Financial support: The Danish Multiple Sclerosis Society, Warwara Larsens Fond, Ejner Jonasson og Hustrus mindelegat, Fonden for Neurologisk forskning, Emmy Langes, født Kramps Legat

Responsible: Pameli Datta

Project group: Pameli Datta, Annette Oturai, Per Soelberg Sørensen

This project is done in collaboration with Department of Clinical Immunology, Rigshospitalet Denmark (Lars P. Ryder, Arne Svejgaard); Department of Neurology, Huddinge University Hospital, Karolinska Institute, Huddinge, Sweden (Jan Hillert, Eva Aakesson); Department of Neurology, Göteborg University Hospital, Göteborg, Sweden (Oluf Andersen); Department of Neurology, Ullevål University Hospital, Oslo, Norway (Hanne Harbo); Institute of Immunology, The National Hospital, Oslo, Norway (Anne Spurkland); The Multiple Sclerosis National Competence Center, Department of Neurology, Haukeland University Hospital, Bergen, Norway (Kjell-Morten Myhr); Department of Neurology, Gothenburg University Hospital; Gothenburg, Sweden (Magnhild Sandberg-Wollheim); Neurology Unit, Addenbrooke's Hospital, University of Cambridge, Cambrige, UK (Stephen Sawcer, Alastair Compston); deCODE Genetics, Reykjavik, Iceland (Ragnheidur Fosdal, Jeffrey Gulcher)

2.4. Experimental models of MS

Treatment of experimental autoimmune encephalomyelitis (EAE) with intravenous immunoglobulin

Background: Clinical trials have shown that intravenous administration of polyclonal immunoglobulin (IVIG) has the potential to reduce the disease activity in multiple sclerosis (MS). However, the mechanisms by which IVIG may interfere with the pathophysiology of MS are not yet fully understood. In the present study we evaluate IVIG treatment of experimental autoimmune encephalomyelitis (EAE), the primary animal model for human MS.

Objectives: The objectives of the study are to assess the effects of IVIG on: 1) the incidence, time course and severity of active EAE in the Dark Agouti rat, 2) the EAE pathology in the brain and spinal cord, and 3) the expression of the inflammatory cytokines and growth factors that contribute to demyelination and inflammation in the central nervous system.

Methods: In the Dark Agouti rat, a protracted and relapsing form of EAE is induced by inoculating animals with spinal cord homogenate obtained from syngenic donors. The EAE disease course involves repeated incidents of neurological deficits, thus resembling the disease course in relapsing-remitting MS. After the induction of EAE, animals receive treatment with intravenous infusions of IVIG or placebo. It is assessed if the IVIG treatment protocol reduces the incidence or duration of active EAE, or if treatment with IVIG may influence the severity of neurological symptoms. The outcome of IVIG treatment is also evaluated by histological investigations, where the pathological changes in the central nervous system are studied. Moreover, the production of inflammatory mediators and growth factors is studied in tissue from the CNS during the development of active EAE disease and during the remission of symptoms.

Results: In 2003, two 4-week studies have been performed using IVIG infusions in either a prophylactic or a therapeutic treatment protocol. Neurological symptoms and the loss of body weight due to EAE were significantly reduced by the early treatment. The prophylactic immunoglobulin infusions also significantly attenuated the inflammatory response in brain and spinal cord tissue. Further experiments include TaqMan analysis (real-time PCR) of cytokines and growth factors in the CNS tissue samples.

Financial support: Hørslev Foundation, Danish MS Society, Warwara Larsen Foundation, Augustinus Foundation, Aase and Ejnar Danielsen Foundation, Karen A. Tolstrup Foundation, Dir. Ejnar Johnsen Foundation, Bayer vital

Responsible: Signe Humle Jørgensen

Project group: Signe Humle Jørgensen, Poul Erik Hyldgaard Jensen, Per Soelberg Sørensen
This project is done in collaboration with Department of Neuropathology, Copenhagen University Hospital, Rigshospitalet (Henning Laursen)

Blood-brain barrier passage of ^{99}Tc-labelled IVIG during the acute attack in EAE
Background: Treatment with intravenously administered immunoglobulin G (IVIG) may reduce the disease activity in multiple sclerosis (MS). The preparations of IVIG are produced by purification from large pools consisting of plasma from thousands of donors, and IVIG thus contains a variety of antibody specificities. IVIG may, therefore, accumulate non-specifically in areas of inflammation, also making IVIG a valuable tool in imaging and radioimmunodetection of infections and inflammatory foci.
Objectives: In the present project we study if IVIG enters the central nervous system by passing through the blood-brain barrier.
Methods: The experiments are carried out in the MS animal model, experimental autoimmune encephalomyelitis (EAE). After inducing EAE in rats, the animals are treated with IVIG infusions during the acute attack of the disease. It is then evaluated, if IVIG accumulates in the inflammatory infiltrates found in the brain and spinal cord. The immunoglobulin is conjugated to hydrazine nicotinamide (HYNIC) for labelling with radioactive ^{99m}Tc-pertechnetate, and the radiochemical purity of the preparation is measured using instant thin layer chromatography (iTLC). After in vivo administration, the ^{99m}Tc-IVIG may be localised and visualised in CNS tissue sections by means of autoradiography. Studies evaluating the ^{99m}Tc-IVIG biodistribution and plasma half-life are also performed. The experiments described above have been carried out during 2003, and the project now awaits the final working on data and publication of the results.
Financial support: Hørslev Foundation, Danish MS Society, Warwara Larsens Foundation, Augustinus Foundation, Aase and Ejnar Danielsen Foundation, Karen A. Tolstrup Foundation, Dir. Ejnar Johnsen Foundation, Bayer Vital
Responsible: Signe Humle Jørgensen
Project group: Signe Humle Jørgensen, Nicolas Storm, Poul Erik Hyldgaard Jensen, Per Soelberg Sørensen
This project is done in collaboration with Department of Neuropathology, Copenhagen University Hospital, Rigshospitalet (Henning Laursen)

Micro-array analysis of the gene expression profile in EAE
Project outline: In multiple sclerosis (MS), the autoimmune disease processes are driven by immune cells that are first activated, then pass through the blood-brain barrier into the central nervous system, where re-activation takes place. For all of these processes to occur, changes in the cellular expression of proteins are required, e.g. proteins which are involved in cell signalling, cell adhesion, ligand binding, second messenger systems etc. Recently, development of the micro-array technology has made it possible to screen thousands of gene transcripts simultaneously from small amounts of tissue. In 2003, we used the Affymetrix Genechip to evaluate the differential regulation of genes after induction of the MS animal model 'experimental autoimmune encephalomyelitis' (EAE) in susceptible rats. By analysing approximately 9,000 genes, more than 500 genes were found differentially expressed after the induction of EAE. The results from analysing the EAE gene expression profile will be related to the presence of the different classes of immune cells within the CNS, as evaluated by immunohistochemistry.
Financial support: Hørslev Foundation, Danish MS Society, Warwara Larsens Foundation, Augustinus Foundation, Aase and Ejnar Danielsen Foundation, Karen A. Tolstrup Foundation, Dir. Ejnar Johnsen Foundation
Responsible: Signe Humle Jørgensen
Project group: Signe Humle Jørgensen, Annette Oturai, Per Soelberg Sørensen
This project is done in collaboration with Department of Clinical Immunology, Copenhagen University Hospital, Rigshospitalet (Jacob Larsen, Lars Ryder)

3. SCIENTIFIC PUBLICATIONS 2002 - 2003

3.1. Peer-reviewed original papers

Schreiber K, **Oturai A**, Ryder LP, Madsen, HO, Jørgensen OS, Svejgaard A, **Sorensen PS**. Disease severity in Danish multiple sclerosis patients evaluated by MRI and three genetic markers (HLA-DRB1*1501, CCR5 deletion mutation, Apolipoprotein E). Multiple sclerosis 2002;8:295-8

Akesson E, **Oturai A**, Berg J, Fredrikson S, Andersen O, Harbo HF, Laaksonen M, Myhr KM, Nyland HI, Ryder LP, Sandberg-Wollheim, **Sorensen PS**, Spurkland A, Svejgaard A, Holmans P, Compston A, Sawcer S. A genome-wide screen for linkage in Nordic sib-pairs with multiple sclerosis. Genes Immun 2002;3:279-85
Sørensen PS, Fazekas F, Lee M. Intravenous immunoglobulin G for the treatment of relapsing-remitting multiple sclerosis: A meta-analysis. Eur J Neurol 2002;9:557-63

Gunnarsson, M, Frängsmyr, L, Stigbrand, T, **Jensen, PEH**. Stimulation of peripheral blood mononuclear cells with lipopolysaccharide induces expression of the plasma protein α_2-macroglobulin. Protein Expression and Purification 2003;27(2):238-43

Gunnarsson, M, Sundström, P, Stigbrand, T, **Jensen, PEH**. Native and transformed α_2-macroglobulin in plasma from patients with multiple sclerosis. Acta Neurol Scand 2003;108:16-21

Åkesson E, Coraddu F, Marrosu M, Massacesi L, Hensiek A, Harbo HF, **Oturai A**, Hillert J, Compston A, Sawcer S. Refining the linkage analysis on chromosome 10 in 449 sib-pairs with multiple sclerosis. J Neuroimmunol 2003;143(1-2):31-8

Barkhof F, Rocca M, Francis G, Van Waesberghe JH, Uitdehaag BM, Hommes OR, Hartung HP, Durelli L, Edan G, Fernandez O, Seeldrayers P, **Sorensen P**, Margrie S, Rovaris M, Comi G, Filippi M; Early Treatment of Multiple Sclerosis Study Group. Validation of diagnostic magnetic resonance imaging criteria for multiple sclerosis and response to interferon beta1a. Ann Neurol 2003;53:718-24

Sorensen PS, Ross C, Clemmesen KM, Bendtzen K, Frederiksen JL, Jensen K, Kristensen O, Petersen T, Rasmussen S, **Ravnborg M**, Stenager E, Koch-Henriksen N, and the Danish Multiple Sclerosis Study Group. Clinical importance of neutralizing antibodies against interferon beta in patients with relapsing-remitting multiple sclerosis. Lancet 2003;362:1184-91

Sorensen PS. Antibodies to IFN-beta. The Danish National IFN-beta Project. Neurology 2003;61 (suppl. 5):S27-8

Harbo HF, **Datta P, Oturai A**, Ryder LP, Sawcer S, Setakis E, Åkesson E, Celius EG, Modin H, Sandberg-Wollheim M, Myhr KM, Andersen O, Hillert J, **Sorensen PS**, Svejgaard A, Compston A, Vartdal F, Spurkland A. Two genome-wide linkage disequilibrium screens in Scandinavian multiple sclerosis patients. J Neuroimmunol 2003;143:101-6

Hummelshoj T, Bodtger U, **Datta P**, Malling HJ, Oturai A, Poulsen LK, Ryder LP, **Sorensen PS**, Svejgaard E, Svejgaard A. Association between an interleukin-13 promoter polymorphism and atopy. Eur J Immunogenet 2003;30:355-59

Jønsson A, **Tscherning T, Storr L**, Andreasen J, **Sørensen PS, Ravnborg M**. A longitudinal study of cognitive functioning in newly diagnosed multiple sclerosis patients. Multiple Sclerosis 2003;9,suppl. 1:132.

Oturai AB, Ryder L, Fredrikson S, Myhr K-M, Celius E, Harbo HF, Andersen O, Åkesson E, Hillert J, Madsen HO, Nyland H, Spurkland A, **Datta P**, Svejgaard A, **Sorensen PS**. Corcordance for disease course and age of onset in Scandinavian MS co-affected sib pairs. Multiple Sclerosis 2004;10:5-8

Harbo HF, Lie BA, Sawcer S, Celius EG, Dai K-Z, **Oturai A**, Hillert J, Lorentzen ÅR, Laaksonen M, Myhr K-M, Ryder LP, Fredrikson S, Nyland H, **Sorensen PS**, Sandberg-Wollheim M, Andersen O, Svejgaard A, Edland A, Mellgren SI, Compston A, Vartdal F, Spurkland A. Genes in the HLA class I region may contribute to the HLA class II-associated genetic susceptibility to multiple sclerosis. Tissue Antigens 2004;63:237-47

Hommes OR, **Sorensen PS**, Fazekas F, Enriquez MM, Koelmel HW, Fernandez o, MD, Carlo Pozzilli C, O'Connor P, Blumhardt L, for the ESIMS trialists. A randomized, placebo-controlled trial of intravenous immunoglobulin in secondary progressive multiple sclerosis: the European Study on Immunoglobulin in MS (ESIMS). Lancet 2004 (in press)

Andersen O, Elovaara I, Färkkilä, Hansen HJ, Mellgren SI, Myhr KM, Sandberg-Wollheim M, **Sorensen PS**, and the Nordic SPMS Study Group. Multicenter, randomised, double-blind, placebo-controlled, phase III study of weekly low dose, subcutaneous IFN-beta-1a in secondary progressive MS. J Neurol Neurosurg Psychiatry, 2004 (in press)

Sorensen PS. Early-Stage Multiple Sclerosis: What are the Treatment Options? Drugs 2004, (in press)

3.2. Reviews and editorials

Freedman MS, Blumhardt LD, Brochet B, Comi G, Noseworthy JH, Sandberg-Wollheim M, **Sorensen PS**. International consensus statement on the use of disease-modifying agents in multiple sclerosis. Multiple Sclerosis 2002;8:19-23
Rosenberg RN, Aminoff M, Boller F, **Soerensen PS**, Griggs RC, Hachinski V, Hallett M, Johnson RT, Kennard C, Lang AE, Lees AJ, Lisak R, Newsom-Davis J, Pedley TA, Selzer ME, Zochodne D. Reporting Clinical Trials: Full Access to All of the Data. Arch Neurol 2002;59:27-8

Sorensen PS. The Role of Intravenous Immunoglobulin in the Treatment of Multiple Sclerosis. J Neurol Sci 2003;206:123-30

Sorensen PS. Treatment of multiple sclerosis with intravenous immunoglobulin: review of clinical trials. Neurol Sci 2003;24:S227-30

Jønsson A. Dissemineret sklerose og seksualitet. Ugeskr Læg 2003;165:2642-46

Vartanian T, **Sorensen PS**, Rice G. The Impact of Neutralizing Antibodies on the Clinical Efficacy of Interferon Beta in Multiple Sclerosis. J Neurol 2004 (In press)

Bertolotto A, Deisenhammer F, Gallo P, **Sorensen PS**. The Immunogenicity of Interferon Beta: Differences Among Preparations. J Neurol 2004 (In press)

3.3. Books and book chapters

Sorensen PS, Ravnborg M, Jønsson A. Dissemineret sklerose. En bog for patienter, pårørende og behandlere. 2. udgave. Munksgaard, Copenhagen, Denmark, 2004

Paulson OB, Boysen GM, Krarup C, Knudsen GM, **Sorensen PS**. Neurologi In: Hansen NE, Haunsø S, Schaffalitzky de Muckadelle OB. Medicinsk Kompendium. Nyt Nordisk Forlag, Arnold Busch, Copenhagen, Denmark, 2004, pp 63,1 - 63.199

Blumhart L, Lin X, Constantinescu CS, Ebers GC, Giovanoni G, Kesselring J, Kurtzke JF, Lassmann H, Lie DKB, Liu C, **Sorensen PS**, Whitaker JN. Dictionary of Multiple Sclerosis. Martin Dunitz, London, United Kingdom, 2004.

4. SCIENTIFIC PRESENTATIONS AND ABSTRACTS 2003

Sorensen PS. Long-term effect of interferon-beta treatment. Guestlecture. Westmead Millennium Institute, Sydney, Australia, February 2003

Datta, P. Two Scandinavian genome-wide linkage disequilibrium screen in MS
Annual Meeting of the American Academy of Neurology, Hawaii, March 2003 (oral presentation)

Datta, P. Two Scandinavian genome-wide linkage disequilibrium screen in MS
Mogens Fog competition, 1. price, Danish Neurology Society Annual Meeting, March 2003 (oral presentation)

Sorensen PS. Clinical impact of neutralising anti-interferon antibodies on the course of multiple sclerosis. Austrian Neuroscience winter meeting (invited speaker). Kitzbühel, Austria, March 2003

Sorensen PS. Effect of neutralising antibodies against interferon-beta on long-term treatment response. Canadian National Conference on Neutralising antibodies (invited speaker). Alberta, Canada, May 2003
Sorensen PS. Neutralising antibodies against interferon-beta: Effect on biologic, clinical and MRI response. Montreal MS Group (invited speaker), Montreal, Canada,. May 2003

Sorensen PS. The Danish experience on neutralising interferon-beta antibodies in multiple sclerosis. Consortium of Multiple Sclerosis Centers: Anti-interferon antibodies in interferon treated MS patients - current knowledge and future directions (invited speaker). London, United Kingdom, May 2003

Datta, P. Genetik og Sklerose
Department of Neurology, Copenhagen University Hospital, Rigshospitalet, June 2003 (oral presentation)

Jønsson A, **Tscherning T, Storr L**, Andreasen J, **Sørensen PS, Ravnborg M**. A longitudinal study of cognitive functioning in newly diagnosed multiple sclerosis patients. Multiple Sclerosis 2003;9(suppl. 1);1:132 (abstract)

Ravnborg M, Blinkenberg M, Sellebjerg F, Ballegaard M, Sorensen PS. Does a shift from a high to a low individual variability in the speed of disease progression at extended disability status score 4 reflect a transition from the inflammatory to the degenerative stage of multiple sclerosis? ECTRIMS, Milan, Italy, September 2003

Sorensen PS, Haas J, Sellebjerg F, Olsson T, Ravnborg M and the TARIMS Study Group. Intravenous Immunoglobulins as add-on treatment to methylprednisolone for acute relapses in multiple sclerosis. ECTRIMS, Milan, Italy, September 2003

Jensen PEH, Jørgensen SH, Datta P, Sørensen PS. Alpha2-macroglobulin involvement in multiple sclerosis.
The 19th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, Milan, Italy, September, 2003 (poster). Multiple Sclerosis 2003;9(suppl. 1):293,S70 (abstract)

Oturai A: "Spiller generne en rolle ved MS?". MS seminar (Biogen). Nyborg, november, 2003 (oral presentation)

Jørgensen SH, Jensen PEH, Laursen H, **Sørensen PS**. IVIG treatment of experimental autoimmune encephalomyelitis in the rat. The European Charcot Foundation Symposium 2003. Lisbon, Portugal, December 2003 (oral presentation).

5. COLLABORATORS

5.1. National

Laboratory of Neuropathology, Copenhagen University Hospital, Rigshospitalet (Henning Laursen, MD, DMSc)
Neurobiology Research Unit, Copenhagen University Hospital, Rigshospitalet (Olaf Paulson, MD, DMSc)

Multiple Sclerosis Treatment Registry, Copenhagen (Nils Koch-Henriksen, MD, DMSc)
Multiple Sclerosis Registry, Copenhagen (Nils Koch-Henriksen, MD, DMSc)
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Department of Clinical Biochemistry, AKH Århus University Hospital, (Holger Jon Møller, MD)
Danish Multiple Sclerosis Study Group (Sørensen PS, MD, DMSc, Ross C, MD, Clemmesen KM, MD, Bendtzen K, MD, Frederiksen JL, MD, DMSc, Jensen K, MD, Kristensen O, MD, Petersen T, MD, DMSc, Rasmussen S, MD, Ravnborg M, MD, DMSc, Stenager E, MD, Koch-Henriksen N, MD, DMSc)

5.2. International

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Department of Neurology, Helsinki University Hospital, Helsinki, Finland (Dr. Markus Färkkilä, MD, DMSc)
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DeCODE: Genetic center, Reykjavik, Iceland (Jeffrey Gulcher, MD, DMSc, Kari Stefansson, MD, DMSc, Ragnheidur Fossdal, M.Sc., Aslaug Jonasdottir, M.Sc., Theodora Thorlacius, M.Sc., Jeffrey Gulcher, MD, Ragnheidur Fossdal, cand.scient.)
Genetic group in Cambridge, United Kingdom (Stephen Sawcer, MD, Ph.D, professor Alastair Compston)
The London, Ontario Multiple Sclerosis Database and the Department of Clinical Neurology, University of Oxford, England (professor George C. Ebers)
Department of Neurology, Duesseldorf University Hospital, Duesseldorf, Germany (Professor Hans-Peter Hartung, MD, DMSc, Bernd Kieseier, MD)
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Department of Neurology, Charlerois Hospital, Belgium (Professor Pierette Seeldrayers, MD, Phd)
Department of Neurology, Karl-Franzens-University, Graz, Austria (Franz Fazekas, MD, DMSc)

5.3. Collaboration with pharmaceutical companies on clinical trials

IPC Nordic, Denmark
Novartis, Denmark
Serono Nordic, Denmark, Norway and Sweden
Biogen Idec, Denmark and USA
Teva/Aventis, Israel and Denmark
Bayer Vital, Germany
Baxter, Belgium, Austria and USA
Octapharma, Vienna

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Ejner Jonassons og Hustrus Mindelegat
Christenson - Cesons Familiefond
Emmy Langes, født Kramps Legat
Copenhagen University
Fonden For Neurologisk Forskning

7. OTHER ACTIVITIES

7.1. Awards

Pameli Datta. Two Scandinavian genome-wide linkage disequilibrium screen in MS. Mogens Fogs competition, 1. price, Danish Neurology Society Annual Meeting March 2003

Agnete Jønsson. Torben Fogs Jubilee Foundation, prize of 40.000 DKR. Received in January 2003 and given for the contribution in the exploration of multiple sclerosis

Per Soelberg Sørensen. The Rose-Liv price for research in multiple sclerosis, 2004

7.2. National and international committees

International committees:

European Charcot Foundation for Research in Multiple Sclerosis. Professor, dr.med. Per Soelberg Sørensen, member of the committee
Committee: Prof. O.R. Hommes, prof. L. Kappos, prof. G. Comi, prof. H. Lassman, prof. P. Soelberg Sørensen

Sylvia Lawry Center for MS Research. Per Soelberg Sørensen, member of clinical working group

International Medical Advisory Board of the Multiple Sclerosis International Societies. Professor Per Soelberg Sørensen, member

Advisory Committee on Clinical Trials of New Drugs in MS of the American National Multiple Sclerosis Society. Professor Per Soelberg Sørensen, member

Rehabilitation In Multiple Sclerosis (R.I.M.S.). Chief neuropsychologist Agnete Jønsson and Mads Ravnborg, MD, members of the Executive Board

Special Interest Group (S.I.G.) on Neuropsychology and Psychology. European interest and working group within R.I.M.S. Chairman: Päivi Hämälainen, co-chairman: Agnete Jønsson

Scientific panel on Demyelinating Diseases of the European Federation of Neurological Societies. Professor Per Soelberg Sørensen, chairman

EFNS task force on Anti-interferon-beta Antibodies in Multiple Sclerosis. Professor Per Soelberg Sørensen, chairman

Publication committee of the European Federation of Neurological Societies. Professor Per Soelberg Sørensen, chairman

National committees:

Research Committee of the Danish Multiple Sclerosis Society: Professor Per Soelberg Sørensen, member

Danish Multiple Sclerosis Group: Professor Per Soelberg Sørensen, chairman

Research Committee of Copenhagen University Hospital, Rigshospitalet: Professor Per Soelberg Sørensen, vice-president

Danish Society for Research in Multiple Sclerosis, (DAREMUS): Mads Ravnborg, chairman, Annette Oturai, treasurer

The Treatment Board of the Danish MS Society: Professor Per Soelberg Sørensen, chairman, Agnete Jønsson, member

The Expert Panel of The Danish Multiple Sclerosis Society: Agnete Jønsson, member

7.3. Congress and meeting organisation

The European Charcot Foundation Symposium 2003. Preserve the Neuron. Lisbon, Portugal, December 2003. Professor Per Soelberg Sørensen, member of the organising committee

7.4. Pre- and postgraduate teaching (incl. Osval supervision)

Supervisor: Signe Humle Jørgensen, Ph.D., Medical biologist.
Student: Medical student Nicolas Storm participated in the research project "Blood-brain barrier passage of ^{99}Tc-labelled IVIG during the acute attack in EAE".

8. PROSPECTS 2004 AND ONWARDS

The activities of Copenhagen Multiple Sclerosis Centre will increase in 2004. In the MS Clinic an increasing number of patients from all over the country will receive specialised immunosuppressive therapy with Mitoxantron. Patients will be enrolled in several randomised trials of new immunomodulatory products, and, in particular, in trials employing combination therapy for multiple sclerosis.
The main research activities will include the following domains: Management of the MECOMBIN, IVIMS and NORMIMS clinical trials. These studies are investigator driven international multi-centre studies initiated and directed by senior physicians from the Copenhagen MS Centre.
The Neuroimmunology Laboratory has procured a real-time PCR system, and much interest will be centred on new projects employing molecular biology. A number of studies will focus on immunological changes induced by disease modifying therapies utilising real-time PCR, gene-chip and proteomics technologies.
The collaboration with the MRI Centre at Hvidovre Hospital will be intensified in projects that will use new MRI technologies to assess treatment response in patients receiving immunomodulatory therapy and to correlate MRI changes with cognitive deficits in newly diagnosed MS patients.
The MS Research Unit will continue the collaboration with partners in the Nordic MS Genetics Consortium and extend the collaboration to the European MS Genetics Collaboration (GAMES).
Experimental studies will be made seeking new compounds with effect on experimental autoimmune encephalomyelitis as a model of MS. We anticipate to increase the number of staff members at the Copenhagen MS Centre and welcome these new colleagues. Finally we are looking forward to continue and extend our collaboration with current and new national and international collaborators.