Sendai Conference 2015 2015.7.11SAT 9:00-18:00

Under the auspices of Department of Multiple Sclerosis Therapeutics, Tohoku University

Venue: TKP Garden City Sendai (AER 21F, 1-3-1 Chuo, Aoba, Sendai)
Co-Sponsored By Biogen Japan Ltd., Chugai Pharmaceutical Co., Ltd., Cosmic Corporation and Mitsubishi Tanabe Pharma Corporation.

Kazuo Fujihara and Ichiro Nakashima
Chairpersons of Sendai Conference 2015
### Sendai Conference 2015

Date: 11th July, 2015  
Venue: TKP Garden City Sendai (AER 21F, 1-3-1 Chuo, Aoba, Sendai)

#### Time Schedule

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Program

8:30  Reception open

9:00  Opening Remarks  Prof. Kazuo Fujihara

9:10  Oral Session 1 (Chairs: Dr. Masaaki Niino and Dr. Shigeru Sato)
9:10  Dr. Yusei Miyazaki (10minutes)
OS1-1  Protein methylation mediates interferon β-induced augmentation of tumor necrosis factor α secretion in human monocytes
9:25  Dr. Jyh Yung Hor (10minutes)
OS1-2  A Natural History Study of the Effect of Pregnancy on Aquaporin 4 Antibody-Positive Neuromyelitis Optica Spectrum Disorder
9:40  Dr. Mariko Tanigawa (10minutes)
OS1-3  Pilot longitudinal follow-up study of Myelin Map in multiple sclerosis
9:55  Dr. Satoru Tanaka (10minutes)
OS1-4  T・B Lymphocyte subset of NMOSD with MOG and AQP4 autoantibody

10:10  NMOSD (Chairs: Dr. Tomoko Okamoto and Dr. Hirofumi Ochi)
10:10  Prof. Sean Pittock (30minutes)
N-1  Current and Future Therapies in NMO
10:45  Coffee Break
10:55  Dr. Maria Isabel Leite (30minutes)
N-2  Pregnancy Outcomes In Aquaporin-4 Positive Neuromyelitis Optica Spectrum Disorder
11:30  Prof. Takashi Yamamura (30minutes)
N-3  Boundary between multiple sclerosis and neuromyelitis optica

12:10  Luncheon Seminar (Chair: Dr. Robert Chan)
12:10  Prof. Volker Limmroth

LS  Treatment Considerations for Highly-Active Relapsing Remitting Multiple Sclerosis Patients
13:10  Coffee Break
Sponsored by Biogen Japan Ltd.

13:20  Multiple Sclerosis (Chairs: Dr. Jin Nakahara and Dr. Tatsusada Okuno)
13:20  Prof. Toshihide Yamashita (30minutes)
M-1  RGMα regulates T cell responses and neurodegeneration in autoimmune encephalomyelitis
13:55  Dr. Silvia Tenembaum (30minutes)
M-2  New consensus diagnostic definitions for Paediatric MS and MRI diagnostic criteria
14:30  Oral Session 2 (Chairs: Dr. Kazumasa Yokoyama and Dr. Yoko Warabi)
14:30  Dr. Hiroki Masuda (10minutes)
OS2-1 Clinical features of neuromyelitis optica patients with antinuclear antibodies
14:45  Dr. Fumihiro Yanagimura (10minutes)
OS2-2 A relapse with seroconversion of several autoantibodies during fingolimod therapy
       in a patient with progressive multiple sclerosis
15:00  Coffee Break
15:10  Dr. Daisuke Kanbe (10minutes)
OS2-3 Parasite Infection may exacerbate disease activity of Neuromyelitis Optica
       (NMO): a Case Report
15:25  Dr. Yuji Tomizawa (10minutes)
OS2-4 Tumefactive demyelinating brain lesions with multiple closed ring enhancement in
       neuromyelitis optica

15:40  Autoantibody
(Chair: Prof. Masakatsu Motomura)
15:40  Prof. Angela Vincent (30minutes)
A-1 Newer antibodies in demyelinating and overlapping diseases
       (Chairs: Dr. Izumi Kawachi and Dr. Katsuichi Miyamoto)
16:15  Prof. Jeffrey Bennett (30minutes)
A-2 Pathomechanisms of Neuromyelitis Optica: From Aquaporin-4 Autoantibodies to
       Oligodendrocyte and Neuronal Injury
16:50  Dr. Douglas Sato (30minutes)
A-3 Seronegative NMOSD and MOG antibodies
17:25  Coffee Break

17:30  Evening Seminar (Chair: Dr. Takahiko Saida)
17:30  Prof. Kenji Chiba
ES  Discovery of Fingolimod, the Sphingosine 1-Phosphate Receptor Modulator and its
     Application for Therapy of Multiple Sclerosis
     Sponsored by Mitsubishi Tanabe Pharma Corporation

18:00  Closing remarks  Prof. Takahiko Saida
19:00  Sponsored Meeting (Chair: Dr. Ichiro Nakashima)
19:00  Introduction  Dr. Ichiro Nakashima
19:10  Prof. Sean Pittock (30minutes)
19:40  Dr. Silvia Tenembaum (30minutes)
20:15  After Party
Sponsored by Cosmic Corporation
OS1-1  Protein methylation mediates interferon β-induced augmentation of tumor necrosis factor α secretion in human monocytes

Yusei Miyazaki\textsuperscript{1,2}, Masaaki Niino\textsuperscript{2}, Eri Takahashi\textsuperscript{2}, Toshiyuki Fukazawa\textsuperscript{3}, Seiji Kikuchi\textsuperscript{2}

Departments of \textsuperscript{1}Clinical Research and \textsuperscript{2}Neurology, Hokkaido Medical Center, \textsuperscript{3}Sapporo Neurology Clinic

\textbf{Background}
Interferon (IFN) β is widely used as a first-line treatment for multiple sclerosis (MS), but its therapeutic mechanism and the reason that some patients are unresponsive to treatment are not clearly understood. In this study, we analyzed the mechanism of cytokine regulation by IFNβ in human monocytes and CD4\textsuperscript{+}T cells.

\textbf{Subjects and methods}
Venous blood samples were obtained from 12 healthy subjects (HS), 13 untreated MS patients (UT-MS), and 9 MS patients treated with IFNβ (IFN-MS). Monocytes and CD4\textsuperscript{+}T cells were isolated by using magnetic beads. Monocytes were stimulated with lipopolysaccharide for 24 h and CD4\textsuperscript{+}T cells were stimulated with phorbol myristate acetate and ionomycin for 48 h. Interleukin (IL)-10 and tumor necrosis factor (TNF) α in the supernatant were quantified by enzyme-linked immunosorbent assay. In some experiments, cells were pre-incubated with recombinant IFNβ and methylthioadenosine as a protein methylation inhibitor before stimulation.

\textbf{Results}
Monocytes from IFN-MS produced less IL-10 and more TNFα compared to monocytes from UT-MS. IFNβ suppressed IL-10 and enhanced TNFα production in HS monocytes \textit{in vitro}; however, IFNβ enhanced IL-10 and suppressed TNFα secretion in HS CD4\textsuperscript{+}T cells. The IFNβ-induced enhancement of TNFα production from monocytes was suppressed by addition of methylthioadenosine, but IL-10 level was not affected.

\textbf{Conclusion}
IFNβ differentially regulated the cytokine profile of human monocytes and CD4\textsuperscript{+}T cells. IFNβ-induced TNFα augmentation in monocytes was suppressed by inhibition of protein methylation. The therapeutic potential of IFNβ for MS might be enhanced by regulating protein methylation.
OS1-2  A Natural History Study of the Effect of Pregnancy on Aquaporin 4 Antibody-Positive Neuromyelitis Optica Spectrum Disorder

Jyh Yung Hor¹, Han Bing Chow¹, Thien Thien Lim¹, Yuen Kang Chia¹, Kenny Tan¹, Chun Fai Cheah¹, Yee Ming Ching², Masita Arip², P E Samuel Easaw³, Gaik Bee Eow¹

¹ Department of Neurology, Penang General Hospital, Penang, Malaysia
² Autoimmune Unit, Allergy and Immunology Research Centre, Institute for Medical Research, Kuala Lumpur, Malaysia
³ Department of Medicine, Penang Medical College, Penang, Malaysia

Background
In multiple sclerosis, there is increased relapse rate in early postpartum period. As in many autoimmune diseases, pregnancy may have an impact on neuromyelitis optica spectrum disorder (NMOSD).

Objective
To study the “natural history” of the effect of pregnancy on aquaporin 4 antibody-positive (AQP4+) NMOSD, in a patient series not exposed to immunomodulatory agents and/or immunosuppressants during pregnancy and in preceding year.

Methods
Female patients diagnosed with AQP4+ NMOSD at Penang General Hospital, Penang, Malaysia were included. Their pregnancy history, number of relapses before pregnancy, during pregnancy and 1-year postpartum period were reviewed.

Results
Nineteen patients were identified. Four patients had never been pregnant. Seven patients had NMOSD onset many years (range: 7-44) after their last pregnancy. Of the remaining 8 patients, there were 12 NMOSD-related pregnancies. NMOSD onset occurred in 5 patients during pregnancy or within 6 months postpartum. The onset occurred in 1st pregnancy in 2 patients, in 2nd pregnancy in 1 patient, and 3rd pregnancy in 2 patients. For the other 7 pregnancies (in 5 patients) that occurred after NMOSD onset, there were 8 relapses - 2 during 2nd trimester of pregnancy, and 6 at 0-3 months postpartum. Of note, after disease onset, all subsequent pregnancies were associated with relapses. 90% postpartum relapses/onset occurred during 0-3 months postpartum. Mean annualized relapse rate (ARR) was 0.57 before pregnancy, and it rose to 3.43 at 0-3 months postpartum (p<0.05). Importantly, all children being born were healthy, and none developed NMOSD.

Conclusions
NMOSD onset and relapses during pregnancy and early postpartum period observed in this series suggest that pregnancy adversely affects the disease course of AQP4+ NMOSD. 0-3 months postpartum is the high-risk period. Treatment guidelines for NMOSD during pregnancy and peripartum period is very much needed. An international NMOSD pregnancy registry may be useful to address this issue.
OS1-3  Pilot longitudinal follow-up study of Myelin Map in multiple sclerosis

Mariko Tanikawa¹, Jin Nakahara¹, Kanehiro Fujiiyoshi²,³, Keigo Hikishima¹, Junichi Hata⁴, Suketaka Momoshima⁵, Shinichi Takahashi¹, Masahiro Jinzaki⁵, Hideyuki Okano⁴, Masaya Nakamura², Norihiro Suzuki¹

¹Department of Neurology, Keio University School of Medicine
²Department of Orthopaedic Surgery, Keio University School of Medicine
³Department of Orthopaedic Surgery, National Hospital Organization Murayama Medical Center
⁴Department of Physiology, Keio University School of Medicine
⁵Department of Diagnostic Radiology, Keio University School of Medicine

Objectives
Diagnosis and treatment decision-making in multiple sclerosis (MS) greatly depend on magnetic resonance imaging (MRI). MS plaques in conventional MRI are defined as T2-hyperintense lesions. The major limitation of T2-hyperintensity is that it cannot discern remyelinated lesions from chronic demyelinated lesions. A sensitive measure to visualize myelin satatus is mandatory for a better clinical practice. We developed a novel q-space imaging-based MRI method named "Myelin Map", and we have previously shown the ability of Myelin Map to differentiate remyelinated T2-lesions among MS plaques. In the current study, we aimed to testify the feasibility of Myelin Map to monitor demyelination and remyelination in a longitudinal axis in selected MS cases.

Methods
Ten MS cases without clinical deterioration during the observation period (three benign, two relapsing-remitting (RR), four secondary progressive (SP) and one primary progressive (PP) MS) with or without treatment were included in the study. Myelin Map was performed with a 3-tesla MR scanner at an interval of 3-16 months for each patient.

Results
All 3 benign MS patients had limited disease activity. All 4 SPMS patients had progressive brain atrophy. PPMS patient showed the most severe disease activity. Remyelinated activity was evident in 1 benign, 1 RRMS and 1 SPMS patients.

Conclusions
Our results suggest that there are inter-individual difference in remyelination capacity among MS patients. Myelin Map may be a useful tool to monitor myelin status in MS and further studies are warranted.
OS1-4  T · B Lymphocyte subset of NMOSD with MOG and AQP4 autoantibody

Satoru Tanaka¹, Akihiro Kubota¹, Miki Kojima¹, Shoko Izaki¹, Hikoaki Fukaura¹, Kimihiko Kaneko², Douglas Sato², Kazuo Fujihara², Kyoichi Nomura³

¹ Saitama Medical University, Saitama Medical Center
² Tohoku University

Objectives
We determined the subsets of T and B cells that are present in the peripheral blood of patients with neuromyelitis optica spectrum disorder (NMOSD) who tested positive for myelin oligodendrocyte glycoprotein (MOG) or aquaporin 4 (AQP4) antibody (Ab) to reveal the immunological features of the disease.

Design and Methods
Subjects were 10 patients with MOG-Ab-positive NMOSD, 24 patients with AQP4-Ab-positive NMOSD, and 55 healthy individuals as controls. Reactivity to anti-MOG and anti-AQP4 antibodies was tested at Tohoku University. Approximately 2 ml of peripheral venous blood was collected from each subject. Without removing red blood cells, the whole blood was stained for various T and B cell surface markers to identify T cell subsets comprising cytotoxic T (CD8+, CD11b⁻), suppressor T (CD8⁹⁺, CD11b⁸⁻), activated CD4 (CD4⁺ HLA⁺), activated CD8 (CD8⁺ HLA⁺), regulatory T (CD4⁺, CD25⁹⁺), and natural killer cells (CD3⁻, CD16/56⁻), as well as B cell subsets of plasmablasts (CD19⁺, CD27⁺, CD38⁹⁺, CD180⁻), memory B (CD19⁺, CD27⁺), naive B (CD19⁺, CD27⁻), and transitional B cells (CD19⁺, CD24⁹⁺, CD38⁹⁺). Flow cytometry was performed using FACS Canto II (Becton, Dickinson and Company). Statistical analysis was performed to compare the MOG-NMOSD, AQP4-NMOSD, and control groups.

Results
No significant differences in T cell subsets were observed between the three groups. With regard to B cell subsets, the level of transitional B cells in the MOG-NMOSD group was significantly higher than that in the AQP4-NMOSD or control group (p<0.01 and p<0.01, respectively). Similarly, the level of naive B cells in the MOG-NMOSD group was significantly higher than that in the AQP4-NMOSD or control group (p<0.05 and p<0.01, respectively). The level of memory B cells was significantly higher in the MOG-NMOSD group than in the control group (p<0.05), while the level of plasmablasts was significantly higher in the AQP4-NMOSD group than in the control group (p<0.01).
Neuromyelitis optica (NMO) spectrum disorders (SD) represent an evolving group of CNS-inflammatory autoimmune demyelinating diseases unified by a pathogenic autoantibody specific for the aquaporin-4 (AQP4) water channel. These diseases were historically misdiagnosed as multiple sclerosis (MS) which lacks a distinguishing biomarker. Disability is attack related and accrues incrementally, in contrast to MS where disability generally occurs progressively in the later phase of the disease. There are 3 main aspects to treating NMO: minimizing the extent of injury from an acute attack, ameliorating the symptoms of an attack (e.g. pain) and preventing relapses. Improved understanding of the pathogenic impact of binding of NMO-IgG to AQP4 on the astrocytic end foot has led to the discovery of novel therapeutic targets. AQP4-IgG antibody binding to astrocytic AQP4 causes complement-dependent cytotoxicity and secondary inflammation with granulocyte and macrophage infiltration, blood-brain barrier disruption and oligodendrocyte injury. General immunosuppression, B-cell depletion, and plasma exchange are currently the mainstay of NMO treatment, but no randomized controlled trials have tested any specific medication. Therapeutic strategies targeting complement proteins, the IL-6 receptor, CD19, neutrophils and eosinophils are in use for other diseases and are under clinical evaluation for treatment of NMO and provide an impressive therapeutic pipeline. Emerging candidates specific to AQP4 include AQP4-blocking antibodies. Potential future treatment options under consideration include stem cell transplantation, enhancement of complement inhibitor expression, restoration of the blood-brain barrier, glutamate antagonists, and induction of immune tolerance. Better understanding of the underlying mechanisms of pain in NMO should enable customized analgesic therapy. Challenges for future clinical trials include paucity of patients for enrollment, heterogeneity of symptoms, coexisting autoimmune disorders and reluctance to incorporate placebo-only arms. A pressing goal is to develop effective and more selective drug therapy lacking pan-immunosuppression or off-target toxicity.
CURRICULUM VITAE

PRESENT ACADEMIC RANK AND POSITION:

2005-01/2015  Co-Director – Neuroimmunology Laboratory
               Department of Laboratory Medicine and Pathology
               Mayo Clinic, Rochester, MN

2005-2008  Consultant – Division of MS and Autoimmune Neurology
               Department of Neurology
               Mayo Clinic, Rochester, MN

2006-present  Associate Director – Autoimmune Neurology Fellowship Program
               Department of Laboratory Medicine and Pathology
               Mayo Clinic, Rochester, MN

2008-2011  Associate Professor of Neurology
               College of Medicine
               Mayo Clinic, Rochester, MN

2008-present  Consultant – Division of Multiple Sclerosis and Autoimmune Neurology
               Department of Neurology
               Mayo Clinic, Rochester, MN

2008-present  Consultant – Division of Clinical Biochemistry & Immunology
               Department of Laboratory Medicine and Pathology
               Mayo Clinic, Rochester, MN

2011-present  Professor of Neurology
               College of Medicine
               Mayo Clinic, Rochester, MN.

1/2015-present  Director – Neuroimmunology Laboratory
               Department of Laboratory Medicine and Pathology
               Mayo Clinic, Rochester, MN.

2015  Director of the Center for Multiple Sclerosis and Autoimmune Neurology
               Department of Neurology
               Mayo Clinic, Rochester, MN

EDUCATION:

1987-1993  MB BCh/BAO, Honors Medical Degree, University College Dublin, Ireland

1993-1994  Internship, St. Vincent’s Hospital, Dublin, Ireland

1994-1995  MMedSc, University College Dublin, Ireland

1995-1997  Residency, Internal Medicine, Federated Dublin Hospital Scheme,
             Trinity College, Ireland

1997-1998  Fellowship, Fellow in Neurological Sciences, Royal College of Surgeons in Ireland

1998-1999  Specialist Registrar, Neurology, Department of Neurology
             Beaumont Hospital, Dublin, Ireland

1998-2002  M.D., Postdoctoral Degree, Royal College of Surgeons in Ireland

1999-2002  Residency, Neurology, Mayo Clinic

2002-2003  Residency, Internal Medicine-fulfilling criteria for ABPN Board eligibility, Mayo Clinic

2003-2005  Fellowship, Neuroimmunology, Department of Neurology and Department of
            Laboratory Medicine and Pathology, Mayo Clinic,
N-2 Pregnancy Outcomes In Aquaporin-4 Positive Neuromyelitis Optica Spectrum Disorder

M. Isabel Leite, MD DPhil-University of Oxford,UK

In collaboration with the prestigious colleagues from Tohoku University Graduate School of Medicine, Sendai, Japan (See authors list in footnote):

Objective
Neuromyelitis optica spectrum disorder (NMOSD) predominantly affects women and is often active during childbearing years. We investigated the association between NMOSD and pregnancy outcome.

Methods
An international cohort of 60 women with aquaporin-4 antibody-positive NMOSD and ≥ 1 pregnancy was studied. Multivariate logistic regression was used to investigate whether pregnancy after NMOSD onset was independently associated with an increased odds ratio of miscarriage or preeclampsia.

Results
Pregnancies after NMOSD onset were associated with an increased rate of miscarriage (42.9%) compared to pregnancies before NMOSD onset (7.04%). Moreover, pregnancies conceived after, or within 3 years of, NMOSD disease onset had an increased odds ratio (OR) of miscarriage (OR 7.28–11.6), independent of the risk associated with maternal age or past medical history of miscarriage. Pregnancies after NMOSD onset ending in miscarriage had increased disease activity in the peri-pregnancy period compared to viable pregnancies (mean annualized relapse rate 0.894 vs. 0.311, respectively). The preeclampsia rate (11.5%) was significantly higher than reported in population studies (3.2%) and odds of preeclampsia were greater in women who had multiple other autoimmune disorders or a miscarriage in the most recent previous pregnancy, but not in pregnancies after NMOSD onset.

Conclusions
Pregnancy after NMOSD onset is an independent risk factor for miscarriage, and pregnancies conceived at times of high disease activity may be at increased risk of miscarriage. Women who develop NMOSD and have multiple other autoimmune disorders are at an increased risk of preeclampsia, independent of timing of NMOSD onset. These conclusions have great clinical relevance.

Co-authors
Matthew M Nour, BM BCh; Ichiro Nakashima, MD, PhD; Ester Coutinho, MD; Mark Woodhall, PhD; Filipa Sousa, MD; Jon Revis, BSc; Yoshiki Takai, MD; Jithin George, MD; Joanna Kitley, MD, DPhil; Maria Ernestina Santos, MD; Joseph M Nour, BA; Fan Cheng, BM BCh; Hiroshi Kuroda, MD, PhD; Tatsuro Misu, MD, PhD; Ana Martins-da-Silva, MD, PhD; Gabriele C DeLuca, MD, DPhil; Angela Vincent, FRS, FMedSci; Jacqueline Palace, MD, FRCP; Patrick Waters, PhD; Kazuo Fujihara, MD, PhD,
Maria Isabel Leite, MD, DPhil\textsuperscript{1}.

\textbf{Affiliations}

\textsuperscript{1}Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, UK

\textsuperscript{2}Department of Neurology, Tohoku University Graduate School of Medicine, Sendai, Japan

\textsuperscript{3}Department of Clinical Neurology, Hospital de São Marcos, Braga, Portugal

\textsuperscript{4}Department of Clinical Neurology, Hospital Geral Santo Antonio, Porto, Portugal

\textsuperscript{5}Department of Multiple Sclerosis Therapeutics, Tohoku University Graduate School of Medicine, Sendai, Japan

\textbf{CURRICULUM VITAE}

\textbf{ACADEMIC QUALIFICATIONS:}

2008 \hspace{1em} D. Phil degree by the University of Oxford. Title of the thesis : “Investigations into seronegative myasthenia gravis”.

1983 \hspace{1em} Degree in Medicine (MD), Institute of Biomedical Sciences, University of Porto, Portugal (16 marks out of 20).

\hspace{1em} Awarded the “D. Lopo do Nascimento” and “Fundação Eng. António Almeida” prizes for the best medical student of the Institute of Biomedical Sciences.

\textbf{PROFESSIONAL QUALIFICATIONS:}

At the Hospital Geral Santo António, Porto:

1993 \hspace{1em} Consultant Neurologist (19 marks out of 20)

1992 \hspace{1em} Neurologist (19.7 marks out of 20)

1985 \hspace{1em} General Physician (internship successfully completed)

\textbf{CURRENT CLINICAL AND RESEARCH POSITIONS:}

2012-\hspace{1em} Honorary Consultant Neurologist-Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford

2012-\hspace{1em} Senior Clinical Research Fellow-Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford
N-3  Boundary between multiple sclerosis and neuromyelitis optica

Takashi Yamamura MD, PhD
Department of Immunology, National Institute of Neuroscience, NCNP
Multiple Sclerosis Center, NCNP

Recent development of disease modifying drugs has provided significant benefits to patients with multiple sclerosis (MS). However, it is also true that efficacy of each drug is rather limited to a proportion of the patients who are in earlier stages of disease. Many patients are nonresponsive to a given drug, indicating the necessity of basic studies to understand the heterogeneity of MS. Personalized medicine or precision medicine is our goal in autoimmune diseases like MS. The importance of sub-classification of MS by biomarkers has been well appreciated since neuromyelitis optica (NMO) was separated from MS. NMO is characterized by elevation of autoantibodies against anti-aquaporin 4 water channel (anti-AQP4 Ab), which can cause astrocyte damage. We reported previously that NMO is characterized by an increase of IL-6 dependent plasmablast (PB) producing anti-AQP4 Ab (Chihara et al. 2011). Patients with NMO do not respond to MS drugs such as interferon-β, but are responsive to anti-IL-6 receptor antibody tocilizumab (Araki et al. 2012; 2014). Here I question if patients who come to our MS clinic are simply separated into two diseases; MS and NMO. We have recently reanalyzed the PB frequencies among CD20⁺ B cells in the peripheral blood of MS. Consistent with our previous report, the PB frequencies were not increased in IFN-β responders of MS. However, the PB numbers are significantly increased in patients with MS, who stopped IFN-β due to its inefficacy or serious side effects. This result hinted us that such patients as having high PB frequencies might respond to tocilizumab. Our experiences in treating the MS patients with higher PB frequencies with tocilizumab will be presented in this meeting.
Dr. Takashi Yamamura was appointed Director of the Department of Immunology, National Institute of Neuroscience, NCNP, Tokyo, in 1999, after being Chief of the Section of Demyelinating Disease. He was also appointed Director of Multiple Sclerosis Center, NCNP, in 2010. He graduated Kyoto University, Faculty of Medicine in 1980, and received MD, PhD from Kyoto. He was trained at Max-Planck Society, Clinical Research Unit for multiple sclerosis (MS), Germany, as a recipient of Alexander von Humboldt fellowship, and also worked at Harvard Medical School as a research fellow. He also worked as a visiting scientist at the Weizmann Institute of Science in 1995 and was invited to Munich in 2011 by the special Alumni program of Humboldt fellowship.

Dr. Yamamura’s main interests are the immunological pathogenesis of multiple sclerosis and related disease (neuromyelitis optica) and development of new treatment options for neuroimmunological disorders. NKT cell biology, nuclear receptors, and gut flora with regard to MS pathogenesis are the major targets of his research. He is past international advisory board member of International Society of Neuroimmunology (ISNI). He is past co-chair or Federation of Clinical Immunology Societies (FOCiS) (2007). He also served as Vice President of 5th International Symposium on CD1/NKT cells (2009), Chair or Neuroimmunology Satellite symposium for ICI 2010, Congress President for Japanese Society for Neuroimmunology in 2010, Congress President for Japanese Society for Clinical Immunology in 2013. As PI, he has received a number of prestigious research grants in Japan, including those from the government, The Mitsubishi Foundation and Uehara Memorial Foundation.
LS Treatment Considerations for Highly-Active Relapsing Remitting Multiple Sclerosis Patients

Volker Limmroth

Department of Neurology, Cologne City Hospital, Köln, Germany

Multiple sclerosis is a chronic, progressively debilitating auto-immune disease that has eluded a cure for centuries. However, in the past three decades, the scientific community has been able to move the needle by introducing different disease-modifying therapies that meant a better and longer quality of life for patients with multiple sclerosis. We have also learned that treatment of patients earlier on in their disease course helps delay the progression of their disabilities.

But questions still remain. How do we determine high disease activity in our patients? What happens if we do not treat these patients? When should we start treating them? With the advent of newer and highly efficacious treatments, how do we choose the right drug for these patients? How do we balance the benefits of treatments like natalizumab with the risks that come along with it?

CURRICULUM VITAE

Name: Prof. Dr. Volker Limmroth

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Current positions:
Chairman, Department of Neurology, Hospitals of the City of Cologne (Merheim)
Professor of Neurology, University of Cologne

Professional appointments:
2010-2013 Chief Medical Officer, Cologne General Hospital
2008-2010 Chief Medical Officer (Deputy), Cologne General Hospital
Professor of Neurology, University of Cologne
2006-now Chairman, Department of Neurology, Cologne General Hospital, University of Cologne
2004 Deputy member, Ethic – committee, University of Essen
2002 Vice Chairman, Department of Neurology
Associate Professor of Neurology, University of Essen
Executive Board Member, European Headache Federation

2001 Director, Multiple Sclerosis Center, University Hospital Essen
Coordinator, German Headache Consortium

1999 Consultant Neurologist, Assistant Professor of Neurology

1998 Head, Multiple Sclerosis Center, University Hospital Essen

1997 Head, Laboratory of neurochemistry and cerebral spinal fluid (CSF)

1997-1999 Associate Consultant in Neurology

1996-1997 Resident in psychiatry, University Hospital, University of Essen (Prof. M. Gastpar)

1993-1996 Postdoctoral fellow in Neuroscience, Lab for neurovascular disease and stroke
Neuroscience Center, Massachusetts General Hospital,
Harvard Medical School, Boston, USA (Prof. M.A. Moskowitz)

1990-1993 Resident in Neurology, Department of Neurology, University Hospital,
Essen Medical School, Germany (Prof. H.C. Diener)

Education / Board examination:

2005 Board Certification for Intensive Care Medicine

1998-2002 PhD-Program of Clinical Pharmacology
Department of Pharmacology, University of Essen (Prof. K. Jacobs, Prof. M.C. Michel)

1998 Board Certification in Neurology, Germany / EU
Board Certification for CSF-Analysis


1990 Final national board examination, License to practice medicine (Approbation)

1989-1990 Internship, Hospital das Clinicas Recife / Brasil
University Hospital, Georg-August-Universität Göttingen, Germany

1984-1990 Medical School, Georg-August-Universität Göttingen, Germany,
Universidade de Recife, Universidade de Rio de Janeiro, Brasil (1987-1988)

Université de Lausanne and Université de Geneve, Switzerland
M-1 RGMα regulates T cell responses and neurodegeneration in autoimmune encephalomyelitis

Toshihide Yamashita

Department of Molecular Neuroscience, Graduate School of Medicine, Osaka University

In multiple sclerosis (MS), immune cells, such as T cells and monocytes, infiltrate into the central nervous system (CNS) and induce inflammation, demyelination, and neurodegeneration. Previous studies have demonstrated that CD4+ T cells play critical roles in inducing CNS inflammation. A more recent study identified T helper type 17 cells (Th17 cell) as critical drivers for MS, and the mechanism of inflammation has been extensively investigated. On the other hand, neurodegeneration, which is often accompanied by demyelination, is the major cause of permanent neurological disability in MS, but this phenomenon has been rather poorly understood. Elucidation of the molecular mechanism of neurodegeneration under MS may provide efficient neuroprotective therapy to treat progressive MS. In recent years, we pursued a strategy with a focus on common pathological feature of MS and other CNS diseases, that elicit neurodegeneration, and found that repulsive guidance molecule-a (RGMα) is a promising target for the treatment of MS. RGMα is expressed in dendritic cells and CD4+ T cells express receptor for RGMα. Treatment with neutralizing antibodies to RGMα prevented mouse experimental autoimmune encephalomyelitis (EAE) and reduced invasion by inflammatory cells. In humans, RGMα-specific antibody could modulate T cell proliferative responses and cytokine expression in peripheral blood mononuclear cells isolated from patients with relapsing-remitting MS. These results show that RGMα-specific antibody suppresses T cell response to antigens. Furthermore, we recently demonstrated that RGMα is associated with neurodegeneration in EAE. RGMα was highly expressed in Th17 cells. We induced EAE by adoptive transfer of myelin oligodendrocyte glycoprotein-specific Th17 cells. Inhibition of RGMα improved EAE scores and reduced neuronal degeneration without altering immune or glial responses. Targeting the molecules that induce neurodegeneration would be a promising strategy to treat MS.
CURRICULUM VITAE
Toshihide Yamashita

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Degrees:
1997, Ph.D. (Medical Science, Osaka University)
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Professional Experience:
2007.12-present Professor and Chairman, Department of Molecular Neuroscience, Graduate School of Medicine, Osaka University
2003.11-2007.11 Professor and Chairman, Department of Neurobiology, Graduate School of Medicine, Chiba University
2001-2003.10 Associate Professor, Department of Anatomy and Neuroscience, Graduate School of Medicine, Osaka University
1998-2000 Research Fellow, Department of Neurobiochemistry, Max-Planck Institute of Neurobiology
1996-1998 Assistant Professor, Department of Anatomy and Neuroscience, Graduate School of Medicine, Osaka University
1994-1996 Graduate Student, Department of Neurosurgery, Graduate School of Medicine, Osaka University
1990-1994 Internship in Department of Neurosurgery, Osaka University Hospital

Awards:
2005 Ameritec Prize (USA)
2010 Japan Society for the Promotion of Science Prize (Japan)
2011 Osaka Science Prize (Japan)
2014 Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology
M-2 New consensus diagnostic definitions for Paediatric MS and MRI diagnostic criteria

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The advent of MRI has contributed to increase the interest and awareness in paediatric acquired white matter disorders. Paediatric inflammatory demyelinating diseases of the central nervous system (CNS) are clinically heterogeneous with respect to their mode of presentation, clinical severity, rate of progression, and prognosis.

In addition, there is increasing appreciation that multiple sclerosis (MS) can begin in childhood or adolescence. Nevertheless, paediatric MS continues to be a rare entity with an estimated 2 to 5% of MS patients experiencing their first clinical event before age 18. The onset of MS in a child poses diagnostic and therapeutic challenges, particularly if the clinical syndrome at presentation resembles acute disseminated encephalomyelitis (ADEM).

In 2007, the initial International Paediatric Multiple Sclerosis Study Group (IPMSSG) proposed provisional definitions for paediatric acquired demyelinating disorders of the CNS. These definitions addressed paediatric MS, ADEM, neuromyelitis optica (NMO), and clinically isolated syndrome (CIS). The definitions were designed to improve consistency in terminology, distinguish transient syndromes from relapsing lifelong diseases, foster clinical research, and facilitate epidemiological studies in paediatric demyelination. Subsequent research has illustrated the strengths and limitations of the 2007 IPMSSG definitions. In particular, updates reflecting the most recent advances in delineating the clinical and neuroradiologic features of paediatric MS were necessary to facilitate clinical decision-making concerning the initiation of disease modifying therapy (DMT) in children.

Accordingly, 2007 consensus definitions were reviewed and published in 2013. The utility of the modifications incorporated into the final definitions will depend on the outcomes of their application in prospective research.
CURRICULUM VITAE

Dr Silvia Tenembaum received her MD with honors from the University of Buenos Aires (UBA) during the period 1974-1979. She acquired much of her early medical training as well as her Paediatric Neurology specialization in Argentina. Currently, Dr. Tenembaum is staff neurologist at the National Paediatric Hospital Dr. J. P. Garrahan in Buenos Aires.

She has successfully completed her administrative responsibilities as active member and chair of the steering committee, International Paediatric MS Study Group (IPMSSG); chair of the paediatric subcommittee, Latin American Committee for the Treatment and Research in Multiple Sclerosis (LACTRIMS); she is currently active member and chair of the paediatric subcommittee, International Panel for NMO diagnostic criteria task force, and member of the executive board, International Child Neurology Association (ICNA).

Dr. Tenembaum’s main interest is the investigation of neurological inflammatory and demyelinating disorders in the paediatric population, developing a Paediatric MS Clinic for the comprehensive study and care of children and adolescents with this spectrum of acquired CNS disorders at her hospital.


Dr. Tenembaum has published in the field of paediatric ADEM, MS, and NMO in a number of first class journals, as well as chapters in national and international books. She is an active member of leading neurology societies, including the IPMSSG, NMO Roundtable Study Group, ICNA, LACTRIMS, ECTRIMS, Argentine Society of Child Neurology, Argentine Society of Neurology.
OS2-1 Clinical features of neuromyelitis optica patients with antinuclear antibodies.

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Background and objectives
Antinuclear antibody (ANA)-positive multiple sclerosis (MS) patients were reported to have shorter disease duration and lower EDSS score. The aim of this study was to compare clinical and laboratory features between MS and neuromyelitis optica (NMO) patients with and without autoantibodies and to research the prognosis of NMO in patients with and without autoantibodies.

Methods
We tested antinuclear, SSA/Ro, SSB/La, and thyroid peroxidase antibodies in sera of 75 NMO patients (48 with NMO and 27 with partial NMO) and 131 MS patients. We studied the frequency of those antibodies between NMO and MS, and compared clinical and laboratory profiles including annual relapse rate (ARR) between NMO patients with and without autoantibodies. Additionally, we also compared the time from onset of NMO to Krutzke’s Expanded Disability Status Scale (EDSS) score of 4.0 (limited walking but without aid) and 6.0 (walking with unilateral aid) using Kaplan-Meier curve analysis.

Results
Compared with MS patients, NMO patients more frequently had antinuclear (31% versus 10%; P<0.001) and anti-SSA/Ro (21% versus 3%; P<0.001) antibodies. Among NMO, ANA-positive patients showed a lower ARR from the NMO onset to serum sampling than ANA-negative patients (0.30 versus 0.58; P<0.001), independent on immune treatments. ANA-negative NMO patients reached EDSS 6.0 earlier than ANA-positive NMO patients (median time, 29.7 years versus 10.5 years; P=0.026). Cerebrospinal fluid cell counts were higher in anti-SSA/Ro-positive than in anti-SSA/Ro-negative patients. Anti-thyroid peroxidase antibody-positive NMO patients tended to have oligoclonal IgG bands more frequently than Anti-thyroid peroxidase antibody-negative NMO patients (60% versus 11%; P=0.048).

Conclusions
Autoantibodies possibly modulate the pathophysiology of NMO. ANA may be associated with less severe disease activity or less disability in NMO.
OS2-2  A relapse with seroconversion of several autoantibodies in a patient with progressive multiple sclerosis

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Although the benefit of treatment with interferon β and fingolimod for multiple sclerosis is firmly established, these may be ineffective or worsen clinical status in some cases. A 53-year-old woman was diagnosed as having multiple sclerosis with six-year history of slowly progressive course, and she presented with cognitive impairment, bilateral internuclear ophthalmoplegia, spastic gait, systemic hyperreflexia, and limb ataxia. MRI findings revealed the presence of periventricular, corpus callosum, brainstem and spinal cord lesions (<1.5 vertebral segments) that did not extend longitudinally. CSF analysis revealed an elevated IgG index and positive oligoclonal bands. Serum testing via a cell-based indirect immunofluorescence assay repeatedly yielded negative results for aquaporin-4 antibody. Interferon β-1a treatment with four-year history was replaced by fingolimod treatment at age 57. During the first 12 months of fingolimod therapy, she suffered a relatively severe longitudinally extensive myelitis with seroconversion of several autoantibodies including proteinase 3 anti-neutrophil cytoplasmic antibody. She was immediately treated with a course of intravenous methylprednisolone with cessation of fingolimod, and her symptoms showed marked improvement. These data suggest that interferon β-1a and/or fingolimod may cause aberrant humoral immune responses with unique CNS involvement.
OS2-3 Parasite Infection may exacerbate disease activity of Neuromyelitis Optica (NMO): a Case Report

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Patient is a 53 years old female. She had the past medical history of right optic neuritis at the age of 46 years old. She had a pain below her chest 11 days before admission and it had worsened gradually. On admission, she had muscle weakness of both legs, and sensory loss and pain below her chest. Deep tendon reflexes were increased in all extremities. She had constipation. She had no abnormalities in blood examination other than antinuclear antibody titer (1280 times). In her cerebrospinal fluid (CSF) examination, mononuclear cells, segmented nuclear cells and total protein were increased to 21/μl, 6/μl, and 71mg/dl, respectively. Contrast-enhanced MRI demonstrated a long cord lesion from C7 to Th6. She was diagnosed as Neuromyelitis Optica (NMO), because she had anti aquaporin-4 antibody. Methylprednisolone pulse treatment and plasma exchange initially alleviated her symptoms, but they got exacerbated soon after end of these treatments. She was diagnosed as spinal toxicarisis because serum anti-parasite antibody was positive, and oral albendazole administration improved her symptoms gradually. As per our knowledge, this is the first case report of NMO accompanying parasite infection.
We report a case of tumefactive demyelinating lesion in a 54-year-old man who fulfilled the diagnosis criteria of neuromyelitis optica (NMO). At the initial onset he was 42 years of age and suffered multiple attacks and showed optic neuritis and myelitis with a long extensive spinal cord lesion. Serum anti-aquaporin-4 antibody was positive and he fulfilled the diagnosis criteria of NMO. After each of his previous three relapses he responded to steroid pulse therapy very well. He was on alternative 5 mg of prednisolone and stable for a couple of years. He was referred to our hospital because he had difficulty concentrating at his job and gradually worsening left hemiparesis. Brain MRI revealed multiple edematous tumefactive lesions with closed-ring enhancement. Serum anti-AQP4 antibody was negative at this time. CSF study showed a normal cell count, oligoclonal-IgG band with isoelectric focusing, elevated MBP and 0.4 IgG index. DWI showed mixed areas of diffusion restriction and facilitated diffusion. MRS displayed high Cho/Cr, low NAA, and high lactate peak suggesting malignancy levels. FDG-PET showed no abnormal accumulation in the body. The primary brain tumor including primary central nervous system lymphoma, glioma, and brain abscess were highly suspected of differential diagnosis. Brain biopsy was performed and the result of the histopathological study showed perivascular cuffing, reactive astrocyte, increased AQP4 staining at active inflammation area, macrophage containing GFAP positive debris, and Creutzfeldt cells, but no vascular hyalinization or granulocyte infiltration. The pathological diagnosis was primary demyelinating lesion of multiple sclerosis. We therefore administered intravenous methylprednisolone and steroid taper. After the treatment, the lesions shrunk markedly and the patient recovered with minimum disability.
A-1  Newer antibodies in demyelinating and overlapping diseases

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Since 2001 it has been apparent that antibodies can cause CNS disease. Firstly in patients with Morvan’s disease (neuromyotonia, autonomic and sleep disturbance) and then in limbic encephalitis. Antibodies to components of the voltage-gated potassium channel bind to hippocampal neurons and other brain regions, and directed against LGI1 and CASPR2. LGI1 antibodies are associated with limbic encephalitis which is often preceded by a novel form of epilepsy, faciobrachial dystonic seizures. CASPR2 antibodies are associated with Morvan syndrome and the peripheral neuromyotonia. Other peripheral nerve antigens have been identified in some patients.

The most frequent condition is associated with antibodies to NMDA receptors (NR1 principally) and found initially in younger patients, often women and small children, with a severe encephalopathy with movement disorders. Experimental data published and in preparation (Wright et al unpublished) show that these antibodies can cause cognitive impairment and reduce seizure thresholds in mice. Antibodies to glycine receptors are associated with extreme rigidity and brainstem disturbance which can be life threatening. Passive transfer experiments indicate that these antibodies cause motor disturbance and perhaps anxiety (Carvajal-Gonzalez et al unpublished).

Concurrently, as well as aquaporin-4 antibodies, antibodies to MOG are proving to be helpful in the diagnosis of children and adults with a non-multiple sclerosis form of demyelinating disease that responds well to treatments, often without relapse, and with relatively little long-term disability.

One surprise is that the antibodies are not always syndrome specific. In particular, NMDAR antibodies have now been found in children with white matter disease predominantly, sometimes with AQP4 or MOG antibodies as well. And in herpes simplex viral encephalitis relapses, which appear to be NMDAR-antibody driven. GABA A receptor antibodies, newly discovered, are not always associated with an identifiable syndrome, despite having all of the hallmarks of pathogenic antibodies.

Ultimately, the fact that each of these antibodies bind to extracellular epitopes on the target proteins is evidence of their potential pathogenicity which is beginning to be explored in animal models. Although rare, these syndromes can now be diagnosed regularly by serological tests and the patients treated with immunotherapies which lead to substantial improvement.

References


CURRICULUM VITAE

Angela Vincent qualified as a doctor in London but went on to do an MSc in Biochemistry at University College and did not pursue further clinical training. She is an Honorary Consultant in Immunology and runs the Oxford Neuroimmunology Service for detection of autoantibodies in neurological diseases. Her clinical interests are in the role of auto-antibodies to ion channels and receptors in peripheral and central disorders, and in helping to diagnose immunotherapy-responsive conditions. Her research interests include models of neuromuscular junction and CNS diseases, and the influence of maternal antibodies on development.
A-2 Pathomechanisms of Neuromyelitis Optica: From Aquaporin-4 Autoantibodies to Oligodendrocyte and Neuronal Injury

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The majority of patients with neuromyelitis optica (NMO) have serum autoantibodies (AQP4-IgG) against the astrocyte water channel aquaporin-4 (AQP4). From in vitro, animal model, and histopathologic data, the working hypothesis for NMO lesion pathogenesis involves the binding of autoantibodies to AQP4 on perivascular astrocyte endfeet resulting in activation of the complement cascade, granulocyte and macrophage infiltration, and secondary oligodendrocyte and neuronal death. We have generated monoclonal recombinant antibodies from AQP4-specific cerebrospinal fluid (CSF) plasmablasts of NMO patients and used them to investigate the epitope-specificity of AQP4-IgG and develop experimental systems for deciphering the mechanisms that initiate and propagate central nervous system (CNS) tissue injury in NMO. The initial step in CNS tissue injury is the binding of AQP4-IgG to one of two major conformational epitopes formed by the extracellular loops of membrane-expressed AQP4. Activation of the complement cascade requires AQP4 to be assembled in large orthogonal arrays and is dependent on AQP4-IgG Fc interactions. The formation of complete CNS lesions in vivo requires both complement dependent (CDC) and antibody dependent cell-mediated cytotoxicity (ADCC); animal models lacking ADCC or CDC show limited or no astrocyte damage without secondary demyelination and neuronal loss. In vivo intracerebral injection models and ex vivo CNS slice cultures demonstrate that tissue injury in NMO CNS lesions begin with astrocyte destruction and proceed through subsequent stages of oligodendrocyte apoptosis and neuronal destruction, processes which are facilitated by an orchestrated influx of immune cells into the CNS. Pathologic mechanisms driving this damage are protean and include CDC, ADCC, excitotoxicity, oxidative injury, and disruption of intrinsic CNS glial networks. Further understanding of the mechanisms governing the initiation and progression of CNS damage in NMO will promote the development and optimization of therapies to prevent lesion formation, retard the progression of CNS tissue injury, and reduce disability in affected individuals.
CURRICULUM VITAE

Dr. Jeffrey L. Bennett is currently Professor of Neurology and Ophthalmology at the University of Colorado Denver and is a faculty member of the Rocky Mountain MS Center at Anchutz Medical Campus.

Dr. Bennett received his medical and doctoral degrees at Stanford University and completed his internship and residency in Neurology at the University of Colorado. He subsequently completed a clinical fellowship in neuro-ophthalmology at the University of Pennsylvania and post-doctoral research at the University of Colorado, Boulder.

Dr. Bennett directs basic, translational, and clinical research programs on optic neuritis, multiple sclerosis, and neuromyelitis optica and maintains active specialty practices in neuro-ophthalmology and neuro-immunology. He has received the Stephen Reingold Award from the National Multiple Sclerosis Society and the CU Inventor of the Year Award from the University of Colorado.

Dr. Bennett has generated a panel of aquaporin-4 (AQP4) specific recombinant monoclonal antibodies (mAbs) from single B-lymphocytes and plasma cells isolated from NMO cerebrospinal fluid and used these unique reagents to establish the pathogenicity of AQP4 autoantibodies, identify B cell epitopes on the AQP4 protein, dissect the molecular pathogenesis of astrocyte-mediated demyelination, and developed novel antigen specific blocking therapies for the treatment of NMO patients.

Dr. Bennett is widely published, is a regular member of scientific review committees for the National Multiple Sclerosis Society and the National Institutes of Health. He performs editorial services for numerous scholarly publications in neurology and ophthalmology.
A-3  Seronegative NMOSD and MOG antibodies

Douglas Sato

Tohoku University School of Medicine

Neuromyelitis optica spectrum disorders (NMOSD) are characterized by severe optic neuritis and/or longitudinally extensive transverse myelitis, and some brain lesions are also unique to NMOSD. Serum autoantibodies against aquaporin-4 (AQP4) are detected in most cases of NMOSD. However, some patients with NMOSD remain seronegative despite repetitive testing during attacks with highly sensitive cell-based assays. The differential diagnosis of NMOSD is not restricted to multiple sclerosis and it includes many diseases that can produce longitudinally extensive myelitis and/or optic neuritis. Some clinical features, imaging, and laboratory findings can be helpful to distinct NMOSD patients with AQP4 antibodies from those who are negative. More recently, we found also that a fraction of seronegative NMOSD patients had antibodies against myelin oligodendrocyte glycoprotein (MOG), and these patients seems to have a more limited phenotype with single or low number of attacks. Patients with MOG antibodies usually respond well to high-dose intravenous corticosteroids compared to patients with AQP4 antibodies.
CURRICULUM VITAE

Dr. Douglas Kazutoshi Sato is an Assistant Professor at Tohoku University School of Medicine (Sendai, Japan), where he obtained his PhD. He completed his medical degree at the State University of Londrina and residency training in internal medicine and clinical neurology at the University of Sao Paulo in Brazil. Dr. Sato is board certified in Neurology since 2002, and he is an associate editor of the ‘Arquivos de Neuropsiquiatria’, the official journal of the Brazilian Academy of Neurology. Dr Sato has received the ACTRIMS/ECTRIMS/MSJ Award, PACTRIMS Investigator Award, BCTRIMS Gilberto Belisario Award, among others. He was a recipient of the Japanese government (Mombukagakusho) scholarship, and has received research grants from JSPS/MEXT (KAKENHI), CAPES Brazil and Ichiro Kanehara foundation.
ES Discovery of Fingolimod, the Sphingosine 1-Phosphate Receptor Modulator and its Application for Therapy of Multiple Sclerosis

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Sphingosine 1-phosphate (S1P), a multi-functional phospholipid mediator, is generated from sphingosine by sphingosine kinases and binds to five known G protein-coupled S1P receptors (S1P₁, S1P₂, S1P₃, S1P₄, and S1P₅). It has been widely accepted that S1P receptor 1 (S1P₁) plays an essential role in lymphocyte egress from the secondary lymphoid organs (SLO) because lymphocyte egress from these organs to periphery is extremely low level in mice lacking lymphocytic S1P₁. Fingolimod (FTY720) is a first-in-class, orally active S1P₁ functional antagonist which was discovered by chemical modification of a natural product, myriocin. Since fingolimod has a structure closely related to sphingosine, phosphorylated fingolimod (fingolimod-P) is generated by sphingosine kinases and binds 4 types of S1P receptors (S1P₁, S1P₃, S1P₄, and S1P₅). Fingolimod-P strongly induces down-regulation of S1P₁ by internalization and degradation of this receptor and acts as an S1P₁ functional antagonist. Consequently, fingolimod reduces circulation of lymphocytes including autoreactive Th17 cells by inhibiting S1P₁-dependent lymphocyte egress from the SLO and is highly effective in experimental autoimmune encephalomyelitis (EAE), an animal model for multiple sclerosis (MS). Recently, it has been strongly suggested that fingolimod-P directly acts as a functional antagonist at S1P₁ on neural cells, particularly astrocytes because fingolimod can distribute to the central nervous system (CNS) beyond blood brain barrier. Furthermore, S1P can induce production of interleukin (IL)-6, IL-8 and CC-chemokine ligand 2 in human astrocytes and fingolimod-P inhibits S1P-induced production of these cytokines by down-regulation of S1P₁. In relapsing remitting MS patients, oral FTY720 showed superior efficacy compared with intramuscular interferon-β -1a with regard to reducing the rate of relapse and the number of inflammatory lesions in the CNS. Based on these results, fingolimod has been approved as a new therapeutic drug for MS in more than 80 countries, including the USA, EU, and Japan.
CURRICULUM VITAE

1980: Pharmaceutical Institute, Tohoku University, pharmacist
1985: Department of Hygiene chemistry, Pharmaceutical Institute, Tohoku University Graduate School, Ph.D. (Immunoregulatory cytokines)
1985: Researcher, Research Laboratories Tokyo, Yoshitomi Pharmaceutical Industries, Ltd.
1994: Senior Researcher, Group Manager (Immunology), Project Manager (FTY720)
1998: Senior Principal Researcher
2002: Head of Research Laboratories III (Immunology), General Manager, in Mitsubishi Pharma Corporation (merger)
2007: Head of Pharmacology Research Laboratories, Mitsubishi Tanabe Pharma Corporation (merger)
2011: General Manager, Project Management Department
2012: Head of Advanced Medical Research Laboratories
2014: Research Fellow

Awards
2012: Innovative Drug Development Science Prize, Pharmaceutical Society of Japan
2012: Invention Prize, Japan Institute of Invention and Innovation
PS-1  Chemokine receptor CCR4 antagonists ameliorate experimental autoimmune encephalomyelitis.

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Objective
Chemokine and chemokine receptors (CCRs) play important roles in the immune response by regulating leukocyte migration. We previously reported the pathogenetic role of CCR4 in experimental autoimmune encephalomyelitis (EAE) using CCR4 and CCR6 knockout mouse model. We examined whether CCR4 antagonism ameliorate EAE disease course.

Method
C57BL6 female mice were injected subcutaneously with 0.2 ml of inoculums containing 400 microgram of MOG\(_{35-55}\) in complete Freund’s adjuvant. Mice were given 10mg/kg of Compound 22, small-molecule antagonist of CCR4 (n = 9), or dimethyl sulfoxide (DMSO) as a control (n = 10) intraperitoneally on day 0, day 7, day 14, day 21, day 28 postimmunization. Immunized mice were examined and scored daily.

Results
Compound 22 significantly ameliorates EAE disease severity. In max score, Compound 22 v.s DMSO were 0.80 ± 1.1 v.s 2.6 ± 1.5, mean ± standard division, P <0.05. In cumulative score, Compound 22 v.s DMSO were 10.3 ± 10.6 v.s 23.0 ± 12.3, mean ± standard division, P <0.05.

Conclusions
CCR4 antagonists might be therapeutic targets of human multiple sclerosis.
PS-2  Depressive State and Chronic Fatigue in Neuromyelitis Optica.

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Background
In patients with multiple sclerosis (MS), depression and chronic fatigue are frequently seen and often affect their daily life, which is believed to be caused by disseminated demyelination that disturbs nerve conduction. In contrast, these symptoms have not been assessed in neuromyelitis optica (NMO). Effectiveness of levocarnitine (L-carnitine) for chronic fatigue in NMO as well as MS is still unknown.

Material and methods
Consecutive 39 NMO patients and 75 MS patients seen at Tohoku University Hospital between June and September in 2014 were compared by self-rating questionnaires for depressive state (Quick Inventory of Depressive Symptomatology: QIDS-SR), daily activity (Performance Status: PS), and fatigue (Chalder Fatigue Scale: ChFS), together with the simultaneously measured serum carnitine levels. L-carnitine was administered to those with low serum carnitine levels, and their scores of those questionnaires were reassessed after one month treatment.

Results
Abnormal scores of QIDS-SR and ChFS were observed in more than 70% of both NMO and MS patients. Prevalence and the degree of depressive state and fatigue were the same between MS and NMO. In both diseases, strong correlations were observed between QIDS-SR and ChFS (p<0.0001), EDSS and PS (p<0.0001). Though the serum carnitine level was decreased in about 20% of patients with both diseases, it didn’t correlate with the level of depressive state or fatigue. Moreover, administration of L-carnitine didn’t improve those symptoms assessed by the questionnaires.

Conclusion
NMO patients showed the same level of depressive state and fatigue as in MS patients. Fatigue in NMO seemed to be strongly associated with depressive state as in MS. Decreased serum carnitine level was not associated with these symptoms, and medications other than L-carnitine should be sought for the fatigue in these diseases.
PS-3  Binding Properties of Anti-AQP4 Antibodies Influencing Endocytosis of AQP4 and Complement-Dependent Cytotoxicity

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BACKGROUND

Neuromyelitis optica (NMO) is an autoimmune disease characterized by disease specific autoantibody NMO-IgG [aquaporin-4 (AQP4) antibody] which recognizes the extracellular domains (ECDs) of AQP4. AQP4 has two different isoforms, M1 and M23. Most of the NMO-IgGs preferentially bind to M23-AQP4, which can form a supramolecular structure called orthogonal arrays of particles (OAPs). Recently, several groups revealed NMO-IgG-induced endocytosis of AQP4 which depend on isoform. However, they reached opposite conclusions. Although this discrepancy could be derived from the difference in binding properties of antibodies they used, it is still unclear whether there is a correlation between binding properties of anti-AQP4 antibodies and endocytosis of AQP4.

OBJECTIVE

To clarify whether the difference in binding properties of AQP4 antibodies influences consequent endocytosis of AQP4 and complement-dependent cytotoxicity (CDC).

METHODS

Two types of monoclonal antibodies against the ECDs of mouse AQP4 were established: mAb-A efficiently recognized both M1 and M23, while mAb-B preferentially recognized M23. The effect of these antibodies on endocytosis and CDCs in stable CHO-cell lines expressing AQP4 and primary cultured astrocytes were analyzed by means of live cell imaging, Western blotting, and cell viability assay.

RESULTS

Live imaging and Western blotting revealed that mAb-A enhanced endocytosis, followed by degradation of both M1 and M23, while mAb-B showed much less endocytosis. Consistent with these observations, a prolonged incubation with mAb-A before complement treatment rescued cells from cytotoxicity.

CONCLUSIONS

Binding properties of AQP4 antibodies influence CDC probably due to the reduction of AQP4 on the cell surface by antibody-induced endocytosis.
Objective
To evaluate astrocyte and myelin injury in inflammatory central nervous system disorders with positivity to antibodies against aquaporin-4 (AQP4) or myelin-oligodendrocyte glycoprotein (MOG) in the cerebrospinal fluid (CSF).

Methods
We enrolled 59 anti-AQP4+ and 30 anti-MOG+ seropositive patients with stored CSF samples from Japan, Brazil, France, South Korea, Austria, Spain and Thailand. CSF was blindly tested for anti-AQP4 and anti-MOG using cell-based assays. Astrocyte and myelin damage was evaluated measuring glial fibrillary acidic protein (GFAP) and myelin basic protein (MBP) respectively using commercial ELISA.

Results
Among 89 patients with serum positivity to anti-AQP4 or anti-MOG, 67 were positive in the CSF, representing 76% of anti-AQP4+ (45/59) and 73% of anti-MOG+ (22/30) cases. All antibody results in their CSF identified the same antibody present in sera. No CSF samples were positive for both antibodies. The median GFAP level in the CSF was remarkably elevated in the anti-AQP4+ CSF compared to anti-MOG+ CSF (p < 0.0001). On the other hand, elevation of MBP was similar between AQP4+ and MOG+ patients (p=0.6531). The concentration of GFAP correlated with anti-AQP4 titers in the CSF (Spearman rho = 0.5, p = 0.0005), especially in samples collected within a few days from attack and before any treatment.

Conclusion
Our study confirmed a significant astrocyte damage in anti-AQP4+ CSF, and suggested a pathogenetic role of anti-AQP4 in causing astrocytopathy. In contrast, anti-MOG+ disease seems to be predominantly demyelinating without evidence of astrocytopathy.
PS-5 Large multi-vessel astrocytopathy in passive IgG transfer NMO model rat


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3 Department of Pharmacology, Keio University Graduate School of Medicine.

Background
Though several in-vivo Neuromyelitis optica (NMO) model have been reported, astrocytopathic size is small, compared with that of NMO patient’s postmortem pathology especially in the “severe” case.

Purpose
To elucidate the acute pathological feature of passive IgG transfer NMO rat model with high affinity mouse anti-AQP4 antibody (mAQP4 model) to rat AQP4.

Method
Here, anti-AQP4 antibodies were intraperitoneally injected at the time of the clinical onset of experimental autoimmune encephalomyelitis induced by emulsion of myelin basic protein and complete Freund’s adjuvant without making use of encephalotogenic T cell lines. 48 hours later from the NMO-IgG injections, we dissected them, and pathologically examined spinal cords of 6 rats in mAQP4 model, compared with those of 5 rats in almost the same model with 40mg of IgG purified from a seropositive NMO patient’s serum (hAQP4 model) - 98 axial slices in mAQP4 model, 84 slices in hAQP4 model.

Results
In hAQP4 model, 23/84 slices showed AQP4 loss – 0/84 in white matter (WM), 14/86 in gray matter (GM), 12/84 in cortico-medurally junction (CMJ), but each vasculo-centric astrocytopathy was small and generally limited in a single vessel as previously reported. On the other hand, AQP4 loss was found in 94/98 slices of mAQP4 model - 39/98 in WM, 55/98 in GM, 93/98 in CMJ. We found large multi-vessel AQP4/GFAP/EAAT2 loss and intensive neutrophil infiltration with tissue vacuolation in Iba1+ perivascular. Each vasculo-centric astrocytopathy showed tendency to fusion, and LETM-like lesion was found. There were also several lesions with subpial AQP4 loss facing CSF space, possibly suggesting the direct IgG penetration from the CSF.

Interpretation
NMO-like lesion in mAQP4 model shows large multi-vessel astrocytopathy, which may compatible with “severe” NMO pathology.
PS-6  Neuromyelitis optica presenting with spinal cord ring enhancement

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**Introduction**

Neuromyelitis optica (NMO) is an inflammatory disease that predominantly affects the optic nerves and the spinal cord with longitudinally extensive spinal cord lesion. Enhancement on T1-weighted magnetic resonance imaging (MRI) after administration of gadolinium (Gd) in NMO indicates increased blood-brain barrier permeability with active inflammation. In multiple sclerosis (MS), ring enhancement (RE) on MRI is a frequently observed in the brain, but rare in the spinal cord. The purpose of this study is to examine the prevalence of spinal cord RE in NMO and to determine the association between clinical characteristics and spinal cord RE.

**Patients & Methods**

We investigated retrospectively Gd-enhanced spinal cord MRI scans during the acute phase in patients with Anti-AQP4-positive NMO, including NMO spectrum disorder (NMOSD), with spinal cord lesion. We then analyzed their clinical features and MRI imaging characteristics of spinal cord lesion.

**Results**

Of the 31 patients with NMO, 13 patients with 18 Gd-enhanced spinal cord MRI scans were enrolled in this study. Ring enhancement was seen in 6 scans (33.3%). Male ratio in patients with RE was significantly higher than those in patients without RE ($p=0.025$). Disease duration of patients with RE tended to be shorter than those of patients without RE, although the significance was marginal ($p=0.057$).

**Conclusion**

Spinal cord RE is common in patients with NMO. Greater male ratio and shorter disease duration might suggest distinct pathogenesis from NMO patients without spinal cord ring enhancement.
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Duration:
Approx. 2 minutes from JR Sendai Station on foot.