Sendai Conference 2023

多発性硬化症および視神経脊髄炎に関する国際会議

●会　期

2023年7月1日(土)

9:00~17:15

TKPガーデンシティ仙台　〒980-6130　仙台市青葉区中央1-3-1

●主　催

NPO法人日本多発性硬化症ネットワーク

●世話人

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【共催企業】

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NPO法人 日本多発性硬化症ネットワーク
JAPAN MULTIPLE SCLEROSIS NETWORK

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Sendai Conference 2023

Date: 1st July, 2023
Venue: Hall 21C, TKP Garden City Sendai
(AER 21F, 1-3-1 Chuo, Aobaku, Sendai) and Online

Time Schedule

9:00～ 9:05	Opening Remarks
9:05～10:05	Oral session 1
10:10～11:00	Sponsored Session 1 (Sponsored by Alexion Pharma GK)
11:00～11:15	Coffee Break
11:15～12:05	Sponsored Session 2 (Sponsored by Biogen Japan Ltd.)
12:05～12:50	Lunch & Poster viewing / General Membership Meeting of NPO
12:50～13:40	Sponsored Session 3 (Sponsored by Mitsubishi Tanabe Pharma)
13:45～15:00	Oral session 2
15:00～15:10	Coffee Break
15:10～16:00	Sponsored Session 4 (Sponsored by Novartis Pharma K.K.)
16:05～16:55	Sponsored Session 5 (Sponsored by Chugai Pharmaceutical Co., Ltd.)
16:55	Closing Remarks (& Award ceremony)
17:05	Photo Session
17:15	Reception Dinner

Sendai Conference 2023 Program

9:00～ 9:05 Opening Remarks

OR Dr. Kazuo Fujihara

9:05～10:05 Oral session 1 (Chair: Dr. Kazumasa Yokoyama, Dr. Yoshiki Takai)

OS1-1 Dr. Yuki Matsumoto (Tohoku University)
Diagnostic implications of MOG-IgG detection in sera and cerebrospinal fluids

OS1-2 Dr. Taichi Nomura (Hokkaido Medical Center)
A case of neuromyelitis optica spectrum disorder with macrophage activation syndrome

OS1-3 Dr. Eizo Tanaka (Kyushu University)
Ofatumumab-refractory multiple sclerosis; presentation of two cases

OS1-4 Dr. Kensuke Kimura (Hachinohe-City Hospital)
Coexistence of rebound after fingolimod discontinuation and IRIS during PML treatment

10:10～11:00 Sponsored Session 1 (Chair: Dr. Makoto Kinoshita)

SS-1 Dr. Michael Barnett (University of Sydney / Royal Prince Alfred Hospital)
Precision medicine: targeting complement in the prevention of NMOSD relapses

(Sponsored by Alexion Pharma GK)

11:00～11:15 Coffee Break

11:15～12:05 Sponsored Session 2 (Chair: Dr. Izumi Kawachi)

SS-2 Dr. Stephen Reddel (Concord Repatriation and General Hospital/Sydney Neurology)
Immunity in the treatment of MS

(Sponsored by Biogen Japan Ltd.)

12:05～12:50 Lunch & Poster viewing / General Membership Meeting of NPO

12:50～13:40 Sponsored Session 3 (Chair: Dr. Noriko Isobe)

SS-3 Dr. Jeffrey Bennett (University of Colorado)
B cell Depletion in AQP4-IgG Seropositive NMOSD: Rationale and Clinical Management

(Sponsored by Mitsubishi Tanabe Pharma)

13:45～15:00 Oral session 2 (Chair: Dr. Tatsuro Misu, Dr. Juichi Fujimori)

OS2-1 Dr. Ayako Koguchi (Teikyo University)
Gene expression analysis of follicular helper T cell in relation to the disease activity of multiple sclerosis

OS2-2 Dr. Fumitaka Sato (Kindai University)
IgA deficiency ameliorates an autoimmune model of multiple sclerosis

OS2-3 Dr. Ijaz Ahmad (Kindai University)
Platelet depletion suppresses viral persistence in the Theiler's virus model of multiple sclerosis

OS2-4 Dr. Davide Cossu (Juntendo University)
Impact of mitophagy and aging on experimental autoimmune encephalomyelitis

OS2-5 Dr. Hiroki Masuda (Chiba University)
Progressive brain white matter atrophy in NMOSD: an MRI volumetric study

15:00～15:10 Coffee Break

15:10～16:00 Sponsored Session 4 (Chair: Dr. Norio Chihara)

SS-4 Dr. Ludwig Kappos (University Hospital Basel / University of Basel)
The Mechanisms of Disease Progression in Multiple Sclerosis
(Sponsored by Novartis Pharma K.K.)

16:05～16:55 Sponsored Session 5 (Chair: Dr. Takashi Yamamura)

SS-5 Dr. Ingo Kleiter (Marianne-Strauß-Klinik / Ruhr-University Bochum)
NMOSD Treatment Strategies with a Focus on IL-6 Inhibition
(Sponsored by Chugai Pharmaceutical Co., Ltd.)

16:55 Closing Remarks (& Award ceremony)

CR Dr. Ichiro Nakashima

17:05 Photo Session

17:15 Reception Dinner

Poster Session (Venue: Hall 21D)

P-1 Dr. Yuta Inagawa (National Center of Neurology and Psychiatry / Tokyo Medical University)
A Study of Childhood Adversity Experiences and Mental Health in Patients with MS and NMOSD

P-2 Dr. Masahiro Mimori (National Center of Neurology and Psychiatry / The Jikei University School of Medicine)
Clinical outcome of ofatumumab for multiple sclerosis patients in our facility

P-3 Dr. Yoshiki Takai (Tohoku University)
Histopathological classification in tumefactive inflammatory demyelinating lesions

Oral Session 1

Chair: Kazumasa Yokoyama
(Tohsei Center for Neurological Diseases)
Yoshiki Takai
(Department of Neurology, Tohoku University Graduate School of Medicine)

OS1-1 Diagnostic implications of MOG-IgG detection in sera and cerebrospinal fluids

Yuki Matsumoto[1], Kimihiko Kaneko[1], Toshiyuki Takahashi[2], Yoshiki Takai[1], Chihiro Namatame[1], Hiroshi Kuroda[3], Tatsuro Misu[1], Kazuo Fujihara[3], and Masashi Aoki[4]

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The spectrum of myelin oligodendrocyte glycoprotein (MOG)-IgG-associated disease (MOGAD) includes optic neuritis (ON), myelitis (MY), acute disseminated encephalomyelitis (ADEM), brainstem encephalitis, cerebral cortical encephalitis (CE), and aquaporin-4-IgG (AQP4-IgG)-negative neuromyelitis optica spectrum disorder (NMOSD). In MOGAD, MOG-IgG are usually detected in sera (MOG-IgG-SERUM), but there have been some seronegative MOGAD cases with MOG-IgG in CSF (MOG-IgG-CSF) and its diagnostic implications remains unclear.

In this cross-sectional study, we identified patients with paired serum and CSF sent from all over Japan for testing MOG-IgG. The MOG-IgG titers were assessed with serial two-fold dilutions to determine endpoint titres [≥1:128 in serum and ≥1:1 (no dilution) in CSF were considered positive]. We analysed the relations between MOG-IgG-SERUM, MOG-IgG-CSF, and the phenotypes with multivariable regression.

405 with suspected MOGAD, 99 with multiple sclerosis, 48 with AQP4-IgG-positive NMOSD, and 119 with other neurological diseases [OND]) were tested before treatment. In suspected MOGAD, 133 patients (33%) tested MOG-IgG-positive in serum and/or CSF; 94 (23%) double-positive (ADEM 36, CE 15, MY 8, NMOSD 9, ON 15, and Others 11), 17 (4.2%) serum-restricted-positive (ADEM 2, CE 0, MY 3,NMOSD 3, ON 5, and Others 4), and 22 (5.4%) CSF-restricted-positive (ADEM 3, CE 4, MY 6, NMOSD 2, ON 0, and Others 7) cases. None of patients except for suspected MOGAD tested positive for MOG-IgG-SERUM but two with multiple sclerosis were MOG-IgG-CSF-positive; the specificity of MOG-IgG-SERUM and MOG-IgG-CSF in suspected MOGAD were 100% (95%CI 99%–100%) and 99% (97%–100%), respectively. Multivariable regression analyses revealed MOG-IgGS-ERUM were associated with ON, whereas MOG-IgG-CSF were associated with CE.

The 70% of MOGAD cases were MOG-IgG double-positive in both serum and CSF, while the remaining cases showed either serum-restricted or CSF-restricted MOG-IgG. MOG-IgG in serum and CSF was independently associated with clinical phenotypes, emphasizing the priority of testing serum and/or CSF.

Oral Session 1

Chair: Kazumasa Yokoyama
(Tohsei Center for Neurological Diseases)
Yoshiki Takai
(Department of Neurology, Tohoku University Graduate School of Medicine)

OS1-2 A case of neuromyelitis optica spectrum disorder with macrophage activation syndrome.

Taichi Nomura[1,5], Masaaki Niino[2], Toshio Odani[3], Ryoji Naganuma[1], Itaru Amino[1], Yusei Miyazaki[1], Sachiko Akimoto[1], Zen-ichi Tanei[4], Naoya Minami[1], Seiji Kikuchi[1], Ichiro Yabe[5]

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[5] Department of Neurology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University

Macrophage activation syndrome (MAS) involves excessive acute inflammatory responses with cytokines, especially interleukin-6 (IL-6). IL-6 also plays a key role in neuromyelitis optica spectrum disorders (NMOSD). We present a case with NMOSD complicating MAS. A 50-year-old woman complained numbness below the abdomen and weakness in her right leg. A surgical biopsy of her spinal cord showed a remarkable accumulation of CD68-positive macrophages and blood test results were positive for aquaporin 4 antibody. We performed steroid pulsed therapy followed by immunoadsorption plasmapheresis (IAPP). Although she recovered, she showed frequent relapses and needed immunosuppressive therapies. Four years later, she revealed femoral neck fracture and presented erythema and a fever without signs of infection or malignancy. Laboratory tests showed elevated liver enzymes, serum ferritin (8,281 ng/mL), serum IL-6 (75 pg/mL) levels, decreased platelets and negative for rheumatoid factor and anti-nuclear antibody. Because her clinical course was well consistent with MAS, steroid pulsed therapy was performed and she was recovered. However, in spite of further immunosuppressive treatment, she still displayed frequent relapses. We started satralizumab and she did not show any relapses of NMOSD or MAS thereafter. After that, oral steroid and immunosuppressant could be discontinued. This is the first report of NMOSD complicating MAS. In this case, excessive production of IL-6 is considered to play a role in the pathophysiology. MAS can be complicated with NMOSD and in such cases, inhibition of IL-6 function may be effective.

Oral Session 1

Chair: Kazumasa Yokoyama
(Tohsei Center for Neurological Diseases)
Yoshiki Takai
(Department of Neurology, Tohoku University Graduate School of Medicine)

OS1-3 Ofatumumab-refractory multiple sclerosis; presentation of two cases

Eizo Tanaka[1], Mitsuru Watanabe[1], Yuta Honkawa[1], Katsuhisa Masaki[1], Takuya Matsushita[1 2], Noriko Isobe[1]

[1] Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University
[2] Department of Neurology, Kochi Medical School, Kochi University

Ofatumumab, a fully human anti-CD20 monoclonal antibody, is one of disease modifying drugs (DMDs) for multiple sclerosis (MS). Because of its high-efficacy and safety, it has been widely used in Japan. Here we present two patients with relapsing-remitting MS (RRMS) for whom ofatumumab was not effective enough to inhibit their disease activity.

Case 1: 41-year-old female RRMS patient, who switched DMD from dimethyl fumarate to ofatumumab as the clinical trial at the disease duration of seven years. After two months of ofatumumab treatment, she experienced right facial sensory loss and right lower limb weakness. Brain MRI showed newly-developed multiple Gd-enhanced lesions. Intravenous methylprednisolone (IVMP) relieved her symptoms. Then after seven months of ofatumumab treatment, she again experienced right facial sensory loss, left hemiparesis, hiccup, and nausea. Brain MRI showed a novel lesion in her middle dorsal medulla. IVMP relieved her symptoms and after that, ofatumumab was switched to glatiramer acetate, with no disease activity observed for three years.

Case 2: 46-year-old female RRMS patient, who switched DMD from dimethyl fumarate to ofatumumab at the duration of 23 years. After eleven months of ofatumumab treatment, she experienced left lower limb monoparesis, left girdle sensation, and pollakiuria. Peripheral blood flowcytometry exhibited 0.02% of lymphocytes were CD20-positive and no cells were CD19-positive, indicating B-cell depletion was successfully achieved. Clinical relapse at left thoracic spine was suspected and two courses of IVMP relieved her symptoms. Ofatumumab was thought to be inefficient in this patient and was switched to natalizumab. Although it might be rare, there are some patients with RRMS for whom ofatumumab is insufficient to inhibit their disease activity.

Oral Session 1

Chair: Kazumasa Yokoyama
(Tohsei Center for Neurological Diseases)
Yoshiki Takai
(Department of Neurology, Tohoku University Graduate School of Medicine)

OS1-4 Coexistence of rebound after fingolimod discontinuation and IRIS during PML treatment.

Kimura Kensuke, Tanosaki Masato, Okushima Toshimi

Hachinohe-City Hospital, Department of Neurology

A 40-year-old woman was diagnosed with multiple sclerosis (MS) at age 23. She was started on betaferon and switched to fingolimod at age 32 due to redness and induration at injection site; at age 40, she developed gait disturbance, ataxia and mild muscle weakness in both lower extremities, and was diagnosed with progressive multifocal leukoencephalopathy (PML) based on head MRI findings and JC virus-PCR of cerebrospinal fluid. Fingolimod was discontinued and mefloquine and mirtazapine was started, but one month later, neurological symptoms worsened, EDSS increased to 8.5, and head MRI showed large contrast enhanced punctate lesions in the brainstem and ring-shaped enhancing contrast lesions in the deep white matter of the cerebrum. We judged that both immune reconstitution syndrome (IRIS) and rebound after fingolimod discontinuation were occurring at the same time. She was first treated with methylprednisolone (IVMP, 1 g/day, 3days), the lesions in the brainstem area disappeared after IVMP, but ring enhancement lesions in the deep white matter remained. Four months after fingolimod discontinuation, she developed nystagmus at rest and slightly worsened level of consciousness, head MRI showed increased ring enhancement lesions. We initiated IVMP for MS relapses, then followed by ofatumumab to prevent relapse five months after fingolimod discontinuation. Thereafter no further increase in lesions was observed.

There are cases in which it is difficult to determine whether rebound after discontinuation of fingolimod or IRIS during PML treatment. But MRI findings is different between both cases. We must carefully examine the MRI findings to differentiate between the two in order to select the appropriate treatment.

Sponsored Session 1

Chair: Makoto Kinoshita
(Department of Neurology, Osaka University Graduate School of Medicine)

SS-1 Precision medicine: targeting complement in the prevention of NMOSD relapses

Michael Barnett, MD, PhD

1.Brain and Mind Centre, University of Sydney, Sydney, New South Wales, Australia
2.Department of Neurology, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune neuroinflammatory disease of the central nervous system. Most people with NMOSD produce autoantibodies to aquaporin-4 that can inappropriately activate the complement system, a part of the immune system, causing inflammation and astrocyte destruction.

The pivotal phase 3 placebo-controlled PREVENT trial was instrumental in securing approval for the terminal complement inhibitor eculizumab. This made eculizumab the first terminal complement inhibitor to receive approval for the prevention of relapses in patients with anti-aquaporin-4 antibody-positive NMOSD. More recently, the phase 3 CHAMPION-NMOSD trial of the long-acting terminal complement inhibitor ravulizumab also met its primary endpoint of relapse risk reduction compared with the placebo group from PREVENT. The landscape of NMOSD treatment continues to evolve, providing patients with a greater choice of effective relapse-preventative treatments than ever before.

In this presentation, I will describe the role of the complement system in NMOSD and review available data from the PREVENT trial, its open-label extension, and data from the Japanese post-marketing surveillance of eculizumab. Additionally, I will summarize key findings from the CHAMPION-NMOSD trial, which will inform attendees about the latest advances for relapse prevention in NMOSD.

CURRICULUM VITAE

Michael Barnett is Professor of Neurology at the Brain and Mind Centre (BMC), University of Sydney, consultant neurologist and neuroimmunologist at Royal Prince Alfred Hospital Sydney, and Director of the MS Clinic and MS Clinical Trials Unit at the BMC. He trained in neurology at Royal Prince Alfred Hospital and received further subspecialty training at the National Hospital for Neurology and Neurosurgery in London. He subsequently completed a PhD in MS pathophysiology at the University of Sydney. He has particular research interests in MS neuropathology and neuroimaging. He co-founded the Sydney Neuroimaging Analysis Centre (SNAC) in 2012 to develop novel MRI biomarkers of MS disease progression and provide the first regulatory-compliant neuroimaging analysis / central MRI reading for MS clinical trials in the Southern hemisphere. He is a leader in the Brain and Mind Centre's Computational Neuroimaging Team, which is spearheading the development and application of AI-derived algorithms and imaging biomarkers to further understanding of the mechanisms of neurological disease, improve diagnostic specificity and enhance treatment paradigms. He is also Co-Director of the MS Research Australia Brain Bank, and previously Chairman of the PACTRIMS Scientific Program Committee.

Chair: Iumi Kawachi
(Niigata University)

SS-2 Immunity in the treatment of MS

Stephen Reddel

Concord Repatriation and General Hospital/Sydney Neurology

Abstract: A healthy immune system can control infections and sometimes malignancy. Immune dysfunction with autoimmunity is a cause of human neurological diseases such as multiple sclerosis or myasthenia gravis, and is treatable with immunotherapies. Autoimmunity can also be beneficial, for instance immune control of malignancy is a type of autoimmunity. The alloimmune response to pathogens is not necessarily the same as the autoimmune response, but overlaps.

Most immunotherapies are immunosuppressive in some way. As a general principle we should assume that immunosuppressive drugs are likely to affect an alloimmune pathway that exists to fight an infection, or a malignancy. The absence of a signal for infection or malignancy in a selected population randomised controlled trial does not prove that such a drug is without risk in the real world.

The COVID-19 pandemic has illustrated how immunotherapy mechanisms of action can predict adverse consequences in the real world, for instance with pulsed anti-CD20 monoclonals affecting COVID-19 severity and vaccination responses.

The discussion of the infectious and malignant consequences of immunosuppression is not to undermine the excellent benefits of therapy in disorders such as MS or MG, but it may influence choice, assist in screening and to promptly diagnose events when they occur.

CURRICULUM VITAE

MB BS PhD FRACP

Stephen Reddel is a staff specialist neurologist at Concord Repatriation & General Hospital Sydney, and consultant neurologist at the Brain & Mind Research Institute, University of Sydney. He trained in neurology at Royal Prince Alfred Hospital, Sydney, and at the Radcliffe Infirmary, Oxford, and has a PhD in the immunology of the Anti-Phospholipid Syndrome.

Stephen Reddel and Sean Riminton founded the first Australian neuroimmunology clinic at Concord Hospital, which specialises in the safe treatment of neurological conditions requiring immunotherapy, including multiple sclerosis, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy and a host of rarer diseases.

He has a longstanding interest in clinical safety. This focus on safety has also included www.immunosuppressionscreen.net, and in 2014 the Alemtuzumab in MS Safety Study (AMS3), and multiple invited international presentations.

Dr Reddel's academic appointment is Associate Professor, Sydney University where he has been involved in the neurology course development, ensuring standards of institutional sartorial elegance, online lectures and teaching of medical students, post graduate clinical training and post graduate research student supervision. He serves as the chair of the neurology working group for immunoglobulins and as the representative on the National Immunoglobulin Government Advisory Committee (NIGAC).

He has research interests in myasthenia gravis, examining the function of anti-MuSK antibodies and the homeostasis of the neuromuscular junction; in neuroimmunology and MS, and in neurogenetics including the muscular dystrophies and inherited neuropathies. Funding support in the last 5 years has included NH&MRC and the muscular dystrophy associations of the USA and NSW. He has published in journals including Brain, Annals of Neurology and Current Opinion in Neurology in this period.

Chair: Noriko Isobe
(Department of Neurology,Graduate School of Medical Sciences, Kyushu University)

SS-3 B cell Depletion in AQP4-IgG Seropositive NMOSD: Rationale and Clinical Management

Jeffrey L. Bennett, MD, PhD

Gertrude Gilden Professor of Neurology
Departments of Neurology and Ophthalmology, Programs in Neuroscience and Immunology
University of Colorado School of Medicine, Anschutz Medical Campus
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AQP4-IgG seropositive NMOSD is a relapsing neuroinflammatory disorder of the CNS defined by the production of pathogenic autoantibodies against the aquaporin-4 (AQP4) water channel. Retrospective and prospective clinical studies have demonstrated that B cell-depleting therapies lower relapse activity, diminish attack severity, and lessen disability progression. Therapeutic efficacy following B cell depletion occurs despite the continued presence of circulating serum AQP4-IgG, indicating that the therapeutic benefit extends beyond the simple reduction of autoantibody titers. Indeed, multiple lines of investigation indicate that memory B cell and extra-follicular plasmablast differentiation, altered regulatory B cell function, and proinflammatory B cell - T cell interactions combine to drive disease activity. Hence, disparities in the depth, breadth, and mechanism of B cell depletion using anti-CD19 and anti-CD20 targeted therapeutics may result in diverse responses to treatment amongst affected patients. Understanding the multiple roles of B cells in AQP4-IgG seropositive NMOSD will help to advance our knowledge of disease pathogenesis and improve patient care.

CURRICULUM VITAE

Jeffrey L. Bennett April 2023

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1982-1986 BA Case Western Reserve University (Biochemistry, Philosophy)
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1986-1993 MD Stanford University Medical School

1986-1993 PhD Stanford University Medical School

Postgraduate Training:

1993-1994 Internship, University of Colorado School of Medicine, Denver

1994-1996 Residency (Neurology), University of Colorado School of Medicine, Denver
Chief Resident, Department of Neurology (1996-1997)

1996-1997 Postdoctoral Fellowship, Department of Molecular, Cellular & Developmental Biology, University of Colorado, Boulder

1997-1998 Neuro-ophthalmology Fellow, Department of Neurology, University of Pennsylvania, Philadelphia

Academic Appointments:

1998-2005 Assistant Professor, Departments of Neurology and Ophthalmology, University of Colorado School of Medicine

2005-2009 Associate Professor, Departments of Neurology and Ophthalmology, University of Colorado School of Medicine

2009-Present Professor with Tenure, Departments of Neurology and Ophthalmology University of Colorado School of Medicine

2011-2019 Associate Director, Translational Research, Center for NeuroScience (CNS), University of Colorado School of Medicine

2011-Present Graduate Faculty, Neurosciences Programs, University of Colorado School of Medicine

2017-Present Immunology Graduate Program, University of Colorado School of Medicine

2017-Present Gertrude Gilden Professor for Neurodegenerative Disease Research, University of Colorado School of Medicine

2019-2020 August-Wilhelm Scheer Visiting Professor, Technical University of Munich

Oral Session 2

Chair: Tatsuro Misu
(Tohoku University)
Juichi Fujimori
(Tohoku Medical and Pharmaceutical University)

OS2-1 Gene expression analysis of follicular helper T cell in relation to the disease activity of multiple sclerosis

Ayako Koguchi[1], Reiko Kawasaki[2], Daisuke Motooka[3], Takashi Matsukawa[2], Hiroyuki Ishiura[4], Kaori Sakuishi[1], Tatsushi Toda[2]

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[Background and Purpose] Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system characterized by recurrent episodes of relapses/remissions. The immunopathogenesis of MS has long been attributed to the break in tolerance and activation of autoreactive Th17 and Th1 cells. More recently, however, B cell-depleting therapy has been shown to successfully suppress MS relapses, pointing to a critical role of B cells in modulating disease activity. We hypothesized that follicular helper T cells (Tfh), a cell subset specialized in helping B cells function, plays an important role in regulating MS relapses. To investigate our hypothesis, we conducted a comprehensive expression analysis of Tfh in MS relapses and remissions (MS-rel and MS-rem).

[Methods] CXCR5+ CD4+ T cells were FACS cell sorted from PBMC of MS-rel, MS-rem or healthy subjects. Their gene expression profiles were analyzed by RNA-seq on Illumina. Some of the functional gene products of key differentially expressed genes (DEGs) were further investigate by FACS analysis.

[Results] There were no significant differences in the PBMC cell frequency of Tfh among all three groups. Gene ontology biological pathway analysis of Tfh RNA-seq data indicated that transcription of genes related to B cell activation and B cell receptor signaling were significantly upregulated in MS-rel compared to HS or MS-rem. DEGs analysis revealed Bruton tyrosine kinase gene (BTK) as one of the most highly expressed relapse-related genes in Tfh. FACS analysis confirmed that the expression of phosphorylated BTK in Tfh was significantly upregulated in relapsed patients.

[Discussion] Our transcriptome analysis suggests that B cell-activating function in Tfh is upregulated in relapsing phase of MS. BTK was differentially expressed in Tfh of MS patients in relapse. Dysregulated aberrant BTK expression in Tfh may be one of the mechanisms promoting relapses in MS.

Oral Session 2

Chair: Tatsuro Misu
(Tohoku University)
Juichi Fujimori
(Tohoku Medical and Pharmaceutical University)

OS2-2 IgA deficiency ameliorates an autoimmune model of multiple sclerosis

Fumitaka Sato, Ph.D.[1], Reona Shiro, M.D.[1], Kota Moriguchi, M.D., Ph.D.[1,2], Cong Thanh Nguyen, M.D., Ph.D.[1], Ijaz Ahmad, M.S.[1], Seiichi Omura, Ph.D.[1], Ah-Mee Park, Ph.D.[1], Namie Sakiyama[1], Takahiro Adachi, Ph.D.[3], Ikuo Tsunoda, M.D., Ph.D.[1]

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Multiple sclerosis (MS) is an inflammatory demyelinating disease in the central nervous system (CNS), although the precise pathomechanisms are unclear. Previously, we demonstrated IgA deposition in CNS demyelinating lesions using a viral model of MS, Theiler's virus infection. IgA-producing B cells have been detected in the CNS of MS patients; IgA-producing B cells have also been reported to play protective roles in experimental autoimmune encephalomyelitis (EAE), an animal model of MS, by producing interleukin (IL)-10. Although IgA plays central roles in the mucosal tissues, the roles of IgA in the CNS are unknown. Thus, we generated IgA-deficient ($IgA^{-/-}$) C57BL/6 mice and compared antibody isotype productions with littermate wild-type (WT) and $IgA^{+/-}$ mice: 1) $IgA^{-/-}$ mice had no IgA production; $IgA^{+/-}$ mice tended to have higher IgA concentrations compared with WT mice, and 2) the levels of IgG1 and IgG2c were significantly higher in $IgA^{-/-}$ mice than in WT and $IgA^{+/-}$ mice. In this study, to determine the roles of IgA in EAE, we sensitized the three mouse substrains with the myelin oligodendrocyte glycoprotein $(MOG)_{35-55}$ peptide and examined the clinical signs and neuropathology. Compared with WT mice, $IgA^{-/-}$ mice had less severe EAE; $IgA^{+/-}$ mice exhibited more severe EAE. Consistent with the clinical scores, $IgA^{-/-}$ mice had less severe inflammatory demyelination in the CNS with the lower IL-17 production than WT and $IgA^{+/-}$ mice. These results suggest that IgA deficiency could be protective in EAE by modulating antibody isotype responses.

Oral Session 2

Chair: Tatsuro Misu
(Tohoku University)
Juichi Fujimori
(Tohoku Medical and Pharmaceutical University)

OS2-3 Platelet depletion suppresses viral persistence in the Theiler's virus model of multiple sclerosis

Ijaz Ahmad [1], Seiichi Omura [1], Fumitaka Sato [1], Sundar Khadka [1,2], Ah-Mee Park [1,3], Reona Shiro [4], Cong Thanh Nguyen [1], Felicity N. E. Gavins [5], and Ikuo Tsunoda [1]

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Theiler's murine encephalomyelitis virus (TMEV) has been used as a viral model of multiple sclerosis (MS), since TMEV induces inflammatory demyelination with viral persistence in the central nervous system (CNS), 1-month post infection (p.i.). Both viral persistence and immunopathology have been shown to be essential to cause MS-like lesions in the CNS. Although platelets have been reported to play immunomodulatory roles in viral infections and immune-mediated diseases, their roles in MS and its animal models are largely unknown. To determine the role of platelets in TMEV infection, we harvested the platelets and CNS tissues from TMEV-infected mice on days 4 and 7, and 1-month p.i. In the transcriptome analysis using mRNAs isolated from platelets, we found that distinct sets of genes were up- and down-regulated depending on the time points of TMEV infection: day 4 p.i., innate immunity (*H2-D1*, *Ifit1*, and *F2rl1*); day 7 p.i., cell adhesion (*Tjp2* and *Itgb1*) and platelet aggregation (*Itgb3* and *Itga2b*); and 1-month p.i., chemotaxis (*Cxcr2* and *Il16*). In the CNS, we found platelet accumulation adjacent to inflammatory lesions. Next, we depleted platelets from TMEV-infected mice by injecting antibodies against platelet-specific glycoprotein Ib α chain (GPIbα). Histologically, in the CNS, platelet-depleted mice had significantly fewer numbers of viral antigen- positive cells with a tendency for the reduction of inflammatory demyelinating lesions, compared with control TMEV-infected mice. Immunologically, platelet-depleted mice had changes in serum anti-TMEV antibody isotype responses, although there were no differences in TMEV-specific lymphoproliferative responses or productions of interleukin (IL)-4, IL-10, IL-17, and interferon-γ between mice with and without platelet depletion. Thus, platelets could play a detrimental role in TMEV infection by the modulation of anti- viral antibody responses, enhancing viral persistence in the CNS.

Oral Session 2

Chair: Tatsuro Misu
(Tohoku University)
Juichi Fujimori
(Tohoku Medical and Pharmaceutical University)

OS2-4 Impact of mitophagy and aging on experimental autoimmune encephalomyelitis

Cossu Davide, Tomizawa Yuji, Kazumasa Yokoyama, Shigeto Sato, Noda Sachiko, Hoshino Yasunobu, Suwa Kenji, Hattori Nobutaka

Juntendo University, Department of Neurology

Inflammation driven by altered mitophagy can occur in the context of aging, as the accumulation in the cytosol of molecular patterns associated with mitochondrial damage leads to the production of inflammatory cytokines and activation of the immune response. We studied the impact of aging and mitochondrial dysfunction on neuroinflammation by generating an active experimental autoimmune encephalomyelitis (EAE) in middle-aged (10 months old) and aged (18 months old) mice lacking the Parkin and PINK1 genes linked to mitophagy. Systemic deletion of these genes causes an exacerbation of EAE in terms of disease severity, through a modulation of the peripheral and central nervous system immune response. Parkin and Pink1 proteins had an age-related modulatory effect in different subpopulations of innate cells at different times of disease progression. During the induction phase of EAE, Parkin and Pink1 knockout mice are characterized by a large expansion of neutrophils in secondary lymphoid organs, which probably contributes to the early onset of the disease. While an increase in the number of monocytes and dendritic cells was detected during the acute and recovery phases, respectively. Furthermore, the Parkin and Pink1 proteins also have a direct effect on adaptive immune system, as knockout mice during the acute phase displayed an increased number of CD8+ T cells in the spleen and brain compared to wild type controls, while B-cells showed a higher percentage during the recovery phase. Pathological examination of the brains and spinal cords revealed an increased number of astrocytes in knockout mice with chronic EAE. In conclusion, mitophagy appears to play a critical role in age-associated neuroinflammation, particularly in the modulation of innate cells.

Oral Session 2

Chair: Tatsuro Misu
(Tohoku University)
Juichi Fujimori
(Tohoku Medical and Pharmaceutical University)

OS2-5 Progressive brain white matter atrophy in NMOSD: an MRI volumetric study

Hiroki Masuda [1], Masahiro Mori [1], Shigeki Hirano, [1] Akiyuki Uzawa [1],Tomohiko Uchida [1,2], Mayumi Muto [1,3], Ryohei Ohtani [1,4], Reiji Aoki [1], Yoshiyuki Hirano [5], and Satoshi Kuwabara [1]

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[Objective] To compare longitudinal brain atrophy rates in patients with neuromyelitis optica spectrum disorder (NMOSD) with healthy controls (HCs).

[Methods] The longitudinal brain atrophy rate in patients with anti-aquaporin-4 antibody-positive NMOSD (AQP4+NMOSD) was compared with age-sex-matched HCs recruited from the Japanese Alzheimer's Disease Neuroimaging Initiative study and another study performed at Chiba University.

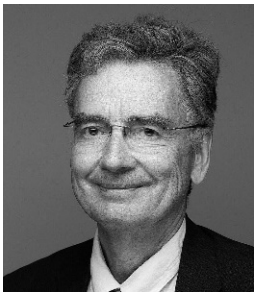
[Results] Twenty-nine patients with AQP4+NMOSD and 29 HCs were included. Both groups included 75.9% females. The median patient age, disease duration and Kurtzke's expanded disability status scale score were 59.0 years, 7.0 years, and 3.5, respectively. The numbers of patients with a history of optic neuritis, myelitis, and myelitis with a long cord lesion were 20, 25 and 18, respectively. The time between MRI scans was longer in the AQP4+NMOSD group compared with the HCs (median; 3.2 vs 2.9 years, P = 0.009). The annualized normalized white matter volume (NWV) atrophy rate was higher in the AQP4+NMOSD group compared with the HCs (median; 0.37 vs −0.14, P = 0.018). In patients with AQP4+NMOSD, the maximum spinal cord lesion length negatively correlated with NWV at baseline MRI and the annualized NWV atrophy rate negatively correlated with years of continuous prednisolone usage at baseline MRI (Spearman's rho = −0.41 and −0.43, P = 0.027 and 0.019, respectively).

[Conclusions] Not only dying back degeneration but also subclinical active lesions may be involved in the pathogenesis of higher brain white matter atrophy rate in patients with AQP4+NMOSD.

Sponsored Session 4

Chair: Norio Chihara
(Division of Neurology, Kobe University Graduate School of Medicine)

SS-4 The Mechanisms of Disease Progression in Multiple Sclerosis



Ludwig Kappos

Director, Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB) , University Hospital Basel / University of Basel

The goal of this lecture is to discuss recent developments in our definition and understanding of the mechanisms driving MS progression. Traditionally, Multiple Sclerosis (MS) is classified in two main and distinct diagnostic categories: relapsing-remitting (RR) or progressive MS, based on episodes of relapse associated clinical worsening as distinguished from continuous disability progression. Recent studies in systematically observed patient cohorts and the introduction of highly effective treatments suppressing or even abrogating relapses have facilitated recognition of the fact that steady progression independent of relapses (PIRA) is also a common feature and the most frequent manifestation of disability accumulation in typical RRMS. A study including patients after the first demyelinating event (CIS) found that even in this very early population PIRA occurred in 25% of patients, contributing to 66% of disability worsening events. Importantly early PIRA predicted accelerated disability accumulation, emphasizing the importance of early detection of progression. Early monitoring for MS progression needs to integrate digital, neuroimaging and blood biomarkers, such as serum neurofilament light chain (sNfL) and Glial fibrillary acidic protein (GFAP). Such comprehensive monitoring will ultimately contribute to innovative treatment options and improved management strategies for this complex disease.

CURRICULUM VITAE

EDUCATION

1958-1970	Primary, Secondary and High School in Athens (Greece)
1970-1977	Medical studies, University of Würzburg (Germany)
1973-1980	Diploma in Psychology, University of Würzburg
1976-1980	Training in Behavioral Therapy and Group Psychotherapy

ACADEMIC CAREER

1980	Medical Doctor, University of Würzburg
1988	Venia legendi, Neurology, University of Würzburg
1988	Assistant Professor, State of Bavaria
1994	Professor of Neurology, Clinical Neuroimmunology, Medical Faculty, University of Basel
2008	Chair, Neurology, University Hospital Basel

PROFESSIONAL CAREER

1977-1985	Internships in Internal Medicine, Surgery and Psychiatry, Residency in Neurology
May 1982-Sep 1985	Research Associate, Max-Planck-Society, Clinical Research Unit for MS, University of Würzburg
Sep 1983-Feb 1990	Staff Attending Neurologist, Dept Neurology, University of Würzburg
Oct 1985-Feb 1990	Deputy Chief, Division Clinical Neurology, Max-Planck-Society, Clinical Research Unit for MS, University of Würzburg
Mar 1990-June 2007	Head Outpatient Clinic Neurology-Neurosurgery, Vice Chair, Neurology, University Hospital, Basel
July 2007-Nov 2008	Acting Chair, Neurology, University Hospital, Basel
Dec 2008-Oct 2020	Chair, Neurologic Clinic and Policlinic, University Hospital, Basel
Jun 2008-Oct 2020	Academic Head Departments of Medicine and Neurology, Medical Faculty
Since Nov 2020	Director (CEO), Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB)
Since Jan 2023	Senior Consultant for MS and Neuroimmunology, Department of Neurology, University Hospital Zurich

PUBLICATIONS

>760 original papers, chapters and reviews in peer reviewed scientific journals and books, >1000 published abstracts, >600 invited lectures and seminars

Pubmed: https://pubmed.ncbi.nlm.nih.gov/?term=Kappos+L&sort=pubdate

Chair: Takashi Yamamura
(Director, Department of Immunology, National Institute of Neuroscience, NCNP / Director, Multiple Sclerosis Center, NCNP)

SS-5 NMOSD Treatment Strategies with a Focus on IL-6 Inhibition

Dr. Ingo Kleiter

1.Marianne-Strauß-Klinik, Behandlungszentrum Kempfenhausen für Multiple Sklerose Kranke, Berg, Germany
2.Department of Neurology, Ruhr-University-Bochum, Bochum, Germany

Neuromyelitis optica spectrum disorder (NMOSD) with or without autoantibodies targeting aquaporin-4 (AQP4-IgG) is characterized by disabling attacks to the optic nerve and spinal cord. Disability accumulates from incomplete recovery of attacks. Therefore, both rigorous treatment of acute attacks and prevention of further disease activity by immunotherapy are important. The interleukin-6 receptor (IL6R) is a therapeutical target in NMOSD, since IL6R-mediated signaling is involved in many pathological processes in NMOSD, e.g. production of AQP4-IgG, migration of immune cells to the CNS and maintenance of proinflammatory damage in CNS lesions.
Treatment strategies for NMOSD include high-dose steroids and apheresis for acute attacks and classical immunosuppressants as well as newly approved biologicals for prevention of further attacks. I will briefly review the history of IL6R-blockade, which proved to be safe and effective in attack prevention in NMOSD cohorts and focus on current treatment strategies, particularly the short- and long-term efficacy of the IL6R-inhibitor satralizumab for AQP4-IgG-seropositve NMOSD. Recent evidence suggested that also myelin-oligodendrocyte-glycoprotein antibody-associated disease (MOGAD) can be successfully treated with IL6R-inhibition and currently a randomized-controlled trial is done in this indication.

CURRICULUM VITAE

PROFESSOR DR. MED. INGO KLEITER

born 29-Oct-72 in Erlangen, Germany

CURRENT POSITION

Since 2017 Medical Director of Marianne-Strauß-Klinik (Multiple Sclerosis and Demyelinating Disorders Clinic), Behandlungszentrum Kempfenhausen für Multiple Sklerose Kranke gGmbH, Berg, Germany

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EDUCATION & PROFESSIONAL EXPERIENCE

• Previous appointments

2011-2017 Department of Neurology, St. Josef Hospital, Ruhr-University Bochum, Germany (Prof. R. Gold)

Consultant & Assistant Professor for Clinical and Experimental Neuroimmunology

2000-2011 Department of Neurology, University of Regensburg, Germany (Prof. U. Bogdahn)

Resident in Neurology & Board-certified neurologist

2003-2004 Research postdoc at the at the Institute of Genetics, University of Cologne, Germany (Prof. A. Waisman) and the University of Regensburg, Neuroimmunology Group

• Medical Education

1992-1999 Medical Faculty, University of Erlangen-Nürnberg, Germany & Univ. of Aberdeen, UK

MEMBERSHIPS

Since 2017 German MS Society (Deutsche Multiple Sklerose Gesellschaft, DMSG)

Member national medical advisory committee (Ärztlicher Beirat Bundesverband)

Chair Bavarian medical advisory committee (Ärztlicher Beirat DMSG Bayern)

Since 2016 Clinical Competence Network Multiple Sclerosis (KKNMS)

Core member (Fachausschuss Versorgungstrukturen/Therapeutika)

2011-2019 European Medicines Agency (EMA)

Core member, Special Advisory Group (SAG) Neurology

Since 2009 Neuromyelitis optica study group (NEMOS)

Member of steering committee NEMOS e.V. (since 2019)

Since 2008 German Society of Clinical Neurophysiology (Deutsche Gesellschaft für Klinische Neurophysiologie, DGKN)

Since 2003 German Society of Neurology (Deutsche Gesellschaft für Neurologie, DGN)

P-1 A Study of Childhood Adversity Experiences and Mental Health in Patients with MS and NMOSD

Yuta Inagawa [1,2], Tomoko Okamoto [1], Shintaro Ogawa [3], Sumiko Yoshida [4], Youwei Lin [1], Takashi Yamamura [5], Yuji Takahashi [1].

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[5] Department of Immunology, National Institute of Neuroscience, National Center of Neurology and Psychiatry

[Objective] Childhood adverse experiences (ACEs) have reportedly been linked to the development of diseases such as multiple sclerosis (MS) through epigenetic modifications that persist into adulthood. This study aims to exploratively investigate the relation of ACEs in patients with MS and neuromyelitis optica spectrum disorder (NMOSD) and their associated neuro-psychological evaluation scores.

[Methods] Herein, 29 patients with MS and 11 patients with NMOSD were evaluated for ACEs and neurological symptoms based on Childhood Trauma Questionnaire-Short Form (CTQ-6) and Expanded Disability Status Scale (EDSS), respectively.

The Symbol Digit Modalities Test (SDMT) and Japanese Adult Reading Test (JART) were employed as the cognitive function evaluation scales, whereas the SF-8, State-Trait Anxiety Inventory (STAI), and Beck Depression Inventory-II (BDI-II) assisted in other psychological evaluation.

[Results] In MS group, 7 patients had experienced physical and 11 patients had experienced emotional abuses. In NMOSD group, none had experienced physical abuse whereas 3 patients had experienced emotional abuse.

In MS patients, a negative correlation was observed between the total scores of physical and emotional abuse items on the CTQ-6 and the age of onset (ρ = -0.58, $p < 0.01$), but no such significant correlation was found among NMOSD patients (ρ = -0.55, $p = 0.08$).

In MS patients, a positive correlation was observed between the total CTQ-6 and BDI-II scores (ρ = 0.60, $p < 0.01$). Among NMOSD patients, a positive correlation was observed between the total CTQ-6 and STAI scores (ρ = 0.77, $p < 0.01$).

[Conclusion] This study suggests that ACEs may particularly affect the onset age of MS as well as the depression and anxiety status of patients.

P-2 Clinical outcome of ofatumumab for multiple sclerosis patients in our facility

Masahiro Mimori [1,2,3], Atsuko Katsumoto [1,2], Wakiro Sato [2,3], Lin Youwei [1,2,3], Reiko Saika [1,2], Tomoko Okamoto [1,2], Takashi Yamamura [2,3], Yuji Takahashi [1]

[1] Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry
[2] Multiple Sclerosis Center, National Center Hospital, National Center of Neurology and Psychiatry
[3] Immunology Department, Institute of Neuroscience, National Center Hospital, National Center of Neurology and Psychiatry

[Objective] Although the ASCLEPIOS trial demonstrated favorable suppressive effects of ofatumumab on relapse rates and disability progression in multiple sclerosis (MS), clinical outcomes for cases with severe expanded disability status scale (EDSS) scores remain unclear. We evaluated the clinical outcomes of patients with MS with severe EDSS scores who received ofatumumab at our facility.

[Method] We included all patients with MS in whom we could monitor the clinical course for 12 months before and after initiating ofatumumab treatment. We defined the criteria for ofatumumab ineffectiveness if any of the following conditions were met: (1) EDSS score increment 12 months post-introduction; (2) discontinuation of ofatumumab or addition of other drugs due to worsening MS symptoms; and (3) the number of additional treatments with glucocorticoid pulse, apheresis, or intravenous immunoglobulin after the introducing ofatumumab is ≧50% of before that.

[Results] Between September 2020 and May 2023, 63 patients (46 [73%] females) were included: 34 with relapsing-remitting (RR), 29 with secondary progressive (SP) MS. The mean age at introduction, mean onset age, and mean disease duration were 49.2 (±9.9), 34.3 (±10.5), and 14.1 (±9.3) years, respectively. The median EDSS score was 5.0 (3.0–6.5). Thirty-six patients showed ineffectiveness; the ineffectiveness rate by disease type was 35% (12/34), 65% (24/29) for RR, SPMS, respectively. In multivariate analysis, EDSS at the time of ofatumumab initiation was independently associated with ineffectiveness at 12 months (OR = 0.686, 95% CI = 0.479–0.982, p = 0.0397).

[Conclusion] Ofatumumab may have greater benefits when initiated in MS with low EDSS.

P-3 Histopathological classification in tumefactive inflammatory demyelinating lesions.

Yoshiki Takai [1], Tatsuro Misu [1], Chihiro Namatame [1], Yuki Matsumoto [1], Hirohiko Ono [1], Kimihiko Kaneko [1], Kazuo Fujihara [1,2], Masashi Aoki [1].

[1] Department of Neurology, Tohoku University Graduate School of Medicine.
[2] Department of Multiple Sclerosis Therapeutics, Fukushima Medical University.

[Background] Tumefactive inflammatory demyelinating lesion (TDL) is defined as one with >2 cm in diameter on MRI imaging and has pathologic characteristics of inflammatory demyelination. Its neuropathological findings are diverse and comprise a variety of pathologies, but there have been no attempts on its histopathological classification.

[Objective] To classify the histopathological features of TDLs and identify unique subgroups.
Methods: We used samples of brain biopsies from 38 cases of TDLs collected during the period between 1998 and 2021. Using immunohistochemistry, all demyelinating lesions were classified on the basis of established features of inflammatory demyelinating disease.

[Results] Confluent demyelinating lesions with well-defined borders and myelin-phagocytic macrophages localized at the lesion edges, typically seen in multiple sclerosis, accounted for 18% (7/38) of all cases. This was followed by perivenous demyelinating lesions, a feature of acute disseminated encephalomyelitis, in 16% (6/38) of them, and those with combinations of these pathologies were present in three cases. Balo's disease-like concentric demyelinating lesions were also seen in three other cases. In addition, an unclassified demyelinating pattern characterized by widespread infiltration of myelin-phagocytosing macrophages in the tissue with myelin paler on KB staining was observed in five cases.
On the other hand, there were 14 other cases with necrotic tissue damage with loss of aquaporin 4 and astrocytes. Among them, five had relatively minor perivascular tissue damage and necrotic demyelinating lesions around them, and four others showed inflammatory demyelinating lesions around extensive coagulation necrosis.

[Conclusion] TDL are a group of diseases with a very diverse demyelinating pattern, but there are some cases with a common background pathology.

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