Sendai Conference 2018

Zuihoden
(Aoba-ku, Sendai)

2018.7.14 SAT 9:00 - 19:30

Venue : TKP Garden City Sendai
(AER 21F, 1-3-1 Chuo, Aoba-ku, Sendai)

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Alexion Pharma Godo Kaisha,
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Under the auspices of Tohoku University Hospital

Chairpersons

Kazuo Fujihara
Department of Multiple Sclerosis Therapeutics, Fukushima Medical University

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Sendai Conference 2017

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Sendai Conference 2018

Date：14th July, 2018

Venue：TKP Garden City Sendai（AER 21F, 1-3-1 Chuo, Aoba-ku, Sendai）

Time Schedule

9：00	Opening Remarks
9：10	Oral session 1
10：10	Sponsored Session 1 （Sponsored by Takeda Pharmaceutical Co., Ltd.）
11：20	Sponsored Session 2 （Sponsored by Medical Division, Novartis Pharma K.K.）
12：20	Lunch
13：00	Sponsored Session 3 （Sponsored by Biogen Japan Ltd. and Eisai Co., Ltd.）
14：00	Oral Session 2
15：10	Sponsored Session 4 （Sponsored by Alexion Pharma Godo Kaisha）
16：10	Sponsored Session 5 （Sponsored by Chugai Pharmaceutical Co., Ltd.）
17：20	Sponsored Session 6 （Sponsored by AstraZeneca K.K.）
18：20	Closing Remarks
18：30	Photo Session
18：40	Private Seminar （Sponsored by Cosmic Corporation Co., Ltd.）
19：30	Reception Dinner　& Award ceremony

Program

9：00 Opening Remarks
-9：10 Dr. Kazuo Fujihara

9：10 Oral session 1（Chairs：Drs. Kazumasa Yokoyama & Takayuki Kondo）
-10：10 OS1-1 Dr. Daiki Takewaki（National Center of Neurology and Psychiatry）
Gut microbiota dysbiosis in various MS clinical phenotypes and NMOSD
OS1-2 Dr. Cossu Davide（Juntendo University）
Exacerbated experimental autoimmune encephalomyelitis in Parkin deficient mice
OS1-3 Dr. Fumitaka Sato（Kindai University）
Potential prebiotic β-glucan curdlan differently alters viral versus autoimmune models of MS
OS1-4 Dr. Hirohiko Ono（Tohoku University Graduate School of Medicine）
The relationship between clinical response and glatiramer acetate and peripheral lymphocyte subset in multiple sclerosis

10：10 Sponsored Session 1（Chair：Dr. Takashi Yamamura）
-11：10 SS1 Dr. Scott Zamvil,（UCSF）
Copaxone：from mechanism of action to long-term efficacy and safety
Sponsored by Takeda Pharmaceutical Co., Ltd.

11：10 Coffee Break
-11：20

11：20 Sponsored Session 2（Chair：Dr. Izumi Kawachi）
-12：20 SS2 Dr. David Leppert（Novartis Pharma AG）
Neurofilament light chain – a real-time biomarker of neuronal injury in CNS diseases
Sponsored by Medical Division, Novartis Pharma K. K.

12：20 Lunch
-13：00

13：00 Sponsored Session 3（Chair：Dr. Hirofumi Ochi）
-14：00 SS3 Dr. Manuel Comabella（Vall d'Hebron University Hospital）
Update on molecular biomarkers in multiple sclerosis
13：50-14：00 Discussion
Sponsored by Biogen Japan Ltd. and Eisai Co., Ltd.

14：00 Oral Session 2（Chairs：Drs. Takashi Ohashi & Jin Nakahara）

-15：00　OS2-1 Dr Jyh Yung Hor（University of Oxford）
MOG-Antibody Disease and Pregnancy：An International Collaborative Study
OS2-2 Dr. Ryoji Miyano（The University of Tokyo）
Acute encephalomyelitis and demyelinating polyneuropathy associated with serum anti-aquaporin-4 antibody positivity
OS2-3 Dr. Teruyuki Ishikura（Osaka University Granduate School of Medicine）
A case of recurrent cerebellar involvement associated with anti-myelin oligodendrocyte glycoprotein（MOG）antibody
OS2-4 Dr. Yasunobu Hoshino（Juntendo University School of Medicine）
Immunophenotyping of PBMC from patients with multiple sclerosis and neuromyelitis optica spectrum disorder

15：00-15：10　Coffee Break

15：10-16：10　Sponsored Session 4（Chair：Dr. Katsuichi Miyamoto）
SS4 Dr. Brian G. Weinshenker（Mayo Clinic）
Clinical Trial Design Issues in Neuromyelitis Optica Spectrum Disorders
Sponsored by Alexion Pharm Godo Kaisha

16：10-17：10　Sponsored Session 5（Chair：Dr. Tatsusada Okuno）
SS5 Dr. Jerome De Seze（Strasbourg Hospital）
NMO spectrum disorders：new concept new diseases ?
Sponsored by Chugai Pharmaceutical Co., Ltd.

17：10-17：20　Coffee Break

17：20-18：20　Sponsored Session 6（Chair：Dr. Masaaki Niino）
SS6 Dr. Ho Jin Kim（National Cancer Center Korea）
Visualization of neuromyelitis optica spectrum disorder by MRI
Sponsored by AstraZeneca K. K.

18：20　Closing Remarks
Dr. Takashi Yamamura

18：30　Photo Session

18：40　Private Seminar（Chair：Dr. Ichiro Nakashima）
PS Dr. Douglas Kazutoshi Sato（BraIns/ PUCRS）

The Evolving Clinical Spectrum of MOG-IgG associated Optic Neuritis, Encephalitis and Myelitis (MONEM)

Sponsored by Cosmic Corporation Co., Ltd.

19：30 Reception Dinner （& Award ceremony）

Poster Session（Venue：Hall 21D）

P-1 Dr. Ryusei Nishigori（Tokyo Metropolitan Neurological Hospital）
Progressive multifocal leukoencephalopathy under the control of a regulated infectious immune response in a patient with rheumatoid arthritis

P-2 Dr. Morinobu Seki（Keio University School of Medicine）
Anti-myelin oligodendrocyte glycoprotein antibody positive cerebral encephalitis following influenza vaccination

P-3 Ryotaro Ikeguchi（Tokyo Women's Medical University）
Melanoma cell adhesion molecule-expressing CD4+ T cells in CNS-demyelinating diseases

Oral Session 1

Chairs：Kazumasa Yokoyama（Department of Neurology, Juntendo University）
Takayuki Kondo（Department of Neurology, Kansai Medical University Medical Center）

OS1-1　Gut microbiota dysbiosis in various MS clinical phenotypes and NMOSD

Daiki Takewaki[1, 2], Wakiro Sato[1, 2], Wataru Suda[3, 4], Masahira Hattori[3, 5], Takashi Yamamura[1, 2]

[1] Department of Immunology, National Institute of Neuroscience, National Center of Neurology and Psychiatry
[2] Multiple Sclerosis Center, National Center of Neurology and Psychiatry
[3] Laboratory of Metagenomics, Department of Computational Biology and Medical Science, Graduate School of Frontier Sciences, The University of Tokyo
[4] Department of Microbiology and Immunology, School of Medicine, Keio University
[5] Cooperative Major in Advanced Health Science, Graduate School of Advanced Science and Engineering, Faculty of Science, and Engineering, Waseda University

Background

Patients suffering from multiple sclerosis (MS) are explosively increasing in Japan. Given that genetic risk factors have not been changed for many years, some environmental risk factors should be involved. We hypothesized that westernization and alteration of dietary habits in Japan is related to this condition, through dysbiosis in the gut microbiota, and subsequent dysregulation of the immune system.

Methods

We analyzed gut microbiomes by comparing the bacterial 16S ribosomal RNA gene and metagenomic data obtained from the feces of 62 patients with relapsing-remitting conventional MS (CMS), 15 patients with secondary progressive CMS, 21 patients with atypical MS, 20 patients with neuromyelitis optica spectrum disorder (NMOSD), and 55 age-matched healthy controls (HC).

Results

Despite a lack of significant differences in species number or richness among 5 groups, a dysbiosis in the structure of gut microbiota was detected in all MS clinical phenotypes and NMOSD, compared with HC. We are now investigating to identify the specific bacteria relevant to the onset and progression of CMS, which is an especially increasing MS clinical phenotype in Japan (Osoegawa et al., 2009).

Conclusions: A structural dysbiosis of gut microbiota was confirmed in all MS clinical subgroups and NMOSD. The identification of specific bacterial species relating to the pathogenesis of CMS, might explain the reason for the surge of patients with MS in Japan.

Oral Session 1

Chairs：Kazumasa Yokoyama (Department of Neurology, Juntendo University)
Takayuki Kondo (Department of Neurology, Kansai Medical University Medical Center)

OS1-2 Exacerbated experimental autoimmune encephalomyelitis in Parkin deficient mice

Cossu Davide, Yokoyama Kazumasa, Sato Shigeto, Hattori Nobutaka

Juntendo University

Background

Primary contributing factor of demyelination in multiple sclerosis (MS) is an inflammatory process mediated through acquired immunity; however, axonal degeneration may occur independent of acute inflammation, especially in the progressive MS. Innate immunity and mitochondrial dysfunction might be related to pathogenesis of primary and secondary progressive MS, but the underlying molecular mechanisms are not yet clarified. Axonal injury is a critical factor for the entire development of the diseases, and one of the mechanisms behind it seems to be mitochondrial failure.

Objective

To determine the role of mitochondria in axonal degeneration, we used a murine disease model, experimental autoimmune experimental encephalomyelitis (EAE) mice lacking *Parkin* gene, a key factor in mitochondrial quality control. This genetic mouse model of Parkinson's disease shows perturbed mitophagy with neither spontaneous changes in mitochondrial functions before one year nor signs of neurodegeneration within two years.

Methods

Young and middle-aged Parkin-knockout (KO) mice and wild-type controls were submitted to EAE induction by active immunization with MOG_{35-55} peptide. ELISA and FACS analysis were performed at different stages of the disease. Proliferation to MOG_{35-55} peptide was assessed by (3)H-thymidine incorporation. Mitochondrial morphology was characterized by transmission electron microscopy.

Results

KO mice showed more severe and earlier onset of EAE and also suffered unrecovered chronic EAE status, compared to wild-type mice. Alteration in cytokines profile, differences in immune cell subsets and in mitochondrial morphology between KO and wild-type mice were observed during the chronic phase of the disease. T-cells from aged mice exhibit a prolonged proliferative response to MOG_{35-55} stimulation one-year post immunization. Significantly increased numbers of DCs were observed in spleen of middle-aged KO mice with chronic EAE, probably age-related but also reflect mitochondrial dysfunction.

Conclusions

Our results support the idea that mitochondria play a critical role in remyelination and/or axonal degeneration dependent on innate immune mechanisms, and the impact of acquired immunity in EAE seems to be age-related and depends on the stage of the disease.

Oral Session 1

Chairs：Kazumasa Yokoyama (Department of Neurology, Juntendo University)
Takayuki Kondo (Department of Neurology, Kansai Medical University Medical Center)

OS1-3 Potential prebiotic β-glucan curdlan differently alters viral versus autoimmune models of MS

Fumitaka Sato, Ph.D.[1], Nicholas E. Martinez, Ph.D., M.B.A.[2], Seiichi Omura, Ph.D.[1], Ah-Mee Park, Ph.D.[1], Mitsugu Fujita, M.D., Ph.D.[1], Alireza Minagar, M.D.[2], J. Steven Alexander, Ph.D.[2], Ikuo Tsunoda, M.D., Ph.D.[1]

[1] Kindai University, Osaka, Japan, [2] Louisiana State University Health Sciences Center, Shreveport, USA

Multiple sclerosis (MS) is an inflammatory demyelinating disease in the central nervous system (CNS). Although microbial infections have been associated with the MS incidence, it is unclear whether a single component that is in common among various microorganisms could affect the MS pathogenesis. β-glucans are components of a variety of bacteria and fungi and can be used as prebiotics, since they are detected in serum following absorption from the intestinal tract. Among β-glucans, curdlan has immunomodulatory effects, such as activation of the NLRP3 inflammasome and induction of T helper (Th) 17 differentiation via dectin-1. We aimed to investigate whether curdlan exposure could affect clinical and immunological profiles of a viral and autoimmune model of MS, using Theiler's murine encephalomyelitis virus (TMEV) infection and experimental autoimmune encephalomyelitis (EAE), respectively. First, we treated SJL/J mice with curdlan one day before intracerebral TMEV injection. Clinically, the curdlan treatment significantly delayed the onset of TMEV-induced demyelinating disease (TMEV-IDD). Immunologically, however, the curdlan treatment did not alter anti-viral antibody titers or anti-viral T cell responses, compared with the control infected mice without the curdlan treatment. Next, we treated SJL/J mice with curdlan one day before sensitization with the myelin proteolipid protein $(PLP)_{139\text{-}151}$ peptide emulsified in complete Friend's adjuvant (CFA). As we expected, the control EAE mice without the curdlan treatment developed relapsing-remitting disease clinically and had perivascular T cell infiltration with demyelination in the spinal cord pathologically. In contrast, the curdlan-treated EAE mice developed primary progressive fatal disease with massive parenchymal macrophage infiltration and demarcated demyelination not only in the spinal cord but also in the optic nerve. Immunologically, we found enhanced Th17 responses with significant atrophy of the thymus. The distinct clinical and immunological influence on the TMEV and EAE models may reflect diverse and often conflicting etiological reports of human MS.

Oral Session 1

Chairs : Kazumasa Yokoyama (Department of Neurology, Juntendo University)
Takayuki Kondo (Department of Neurology, Kansai Medical University Medical Center)

OS1-4 The relationship between clinical response to glatiramer acetate and peripheral lymphocyte subset in multiple sclerosis

Hirohiko Ono[1], Wakiro Sato[2], Tatsuro Misu[3], Ichiro Nakashima[4], Kazuo Fujihara[5], Takashi Yamamura[2]

[1] Department of Neurology, Tohoku University Graduate School of Medicine
[2] Department of Immunology, National Institute of Neuroscience, National Center of Neurology and Psychiatry
[3] Department of Multiple Sclerosis Therapeutics, Tohoku University Graduate School of Medicine
[4] Department of Neurology, Tohoku Medical and Pharmaceutical University
[5] Department of Multiple Sclerosis therapeutics, Fukushima Medical University

Background : Glatiramer acetate (GA) is a disease-modifying drug for the treatment of multiple sclerosis (MS). Although several immunomodulatory effects of GA in MS have been reported, the immunological profile related to the therapeutic effect of GA is still unknown. In this study, we examined peripheral T and B cell subsets in MS patients with GA treatment and analysed the difference of immunological feature between GA responder and non-responder.

Methods : MS patients who were treated with GA more than 1 year were enrolled and classified as 11 GA responders (age ± SD=40.8 ± 11.6 years old : Male : Female=4 : 7) and 7 non-responders (age ± SD=35.8 ± 7.4 years old : Male : Female=2 : 8). 19 healthy subjects (HS) were enrolled as control. Peripheral blood mononuclear cells were isolated and stained with several antibodies to analyse the proportion of the T cell subsets including Th1, Th2 and Th17 and B cell subsets including naïve B cell, memory B cell and plasmablast using flow cytometry.

Results : The frequency of plasmablast among B cell were significantly increased in both GA responder and non-responder compared to HS. The ratio of Th2/Th1 and Th17/Th1 in GA non-responder was markedly higher than that in HS. In the comparison of B cell subsets before and after GA treatment, the frequency of memory B cell among B cell tended to decrease after GA treatment in GA responder but not in non-responder.

Discussion : The reduction of memory B cell by GA treatment may be associated with good clinical response to GA and the excessive shift toward Th2 and Th17 in GA non-responder may reflect poor clinical response to GA.

Conclusions : The different proportion of peripheral Th2, Th17 and memory B cell between GA responder and non-responder may explain the good or poor clinical response to GA.

MEMO

Sponsored Session 1

Chair : Takashi Yamamura (National Institute of Neuroscience, NCNP)

Sponsored by Takeda Pharmaceutical Co., Ltd.

SS-1 Copaxone: from mechanism of action to long-term efficacy and safety

Scott Zamvil

University of California, San Francisco (UCSF)

CURRICULUM VITAE

EDUCATION:

1979	B.A. Claremont Men's College (Chemistry)
1986	Ph.D. Stanford Medical School (Medical Microbiology)
1988	M.D. Stanford Medical School

POSTGRADUATE TRAINING:

1989	Intern, Internal Medicine, Pacific Presbyterian Medical Center, San Francisco, CA
1990	Resident, Internal Medicine, Stanford University Medical Center, Palo Alto, CA
1990 - 1993	Resident, Neurology, Brigham and Women's Hospital, Boston, MA

LICENSURE:

1989	California Medical License, Registration No. G 66283 (Active)
1990	Massachusetts Medical License, Registration No. 73043
1999	American Board of Psychiatrists and Neurologists, Certification in Adult Neurology, Registration No. 47196 (Active)

ACADEMIC APPOINTMENTS:

1993 - 1994	Instructor in Neurology, Harvard Medical School
1994 - 1998	Assistant Professor in Neurology, Harvard Medical School
1998 - 2004	Assistant Professor of Neurology (Adjunct), UCSF
2004 - 2010	Associate Professor of Neurology (in Residence), UCSF
2010 - present	Professor of Neurology (in Residence) UCSF
2004 - present	Faculty Member, Program in Immunology, UCSF
2004 - present	Faculty Member, Biomedical Sciences Graduate Program, UCSF
2007 - present	Faculty Member, Program in Biological Sciences, UCSF

HOSPITAL APPOINTMENTS:

1993 - 1996	Associate Physician in Medicine (Neurology), Brigham and Women's Hospital
1996 - 1998	Associate Neurologist, Brigham and Women's Hospital
1997 - 1998	Clinical Associate Staff (Neurology), Massachussetts General Hospital
1998 - present	Attending Physician (Neurology), University of California, San Francisco, Moffett-Long Hospitals
1998 - 2000	Attending Physician (Neurology), UCSF/Mt. Zion Hospital (MS Clinic)

HONORS AND AWARDS

1979	Summa cum laude
1979	Department Honor's in Chemistry
1994 - 1999	Harry Weaver Neuroscience Scholar, National Multiple Sclerosis Society
1994 - 2000	Clinician Investigator Development Award (NIH)
2001 - 2005	First Independent Investigator Award (NIH, awarded 2000)
2002	Atorvastatin Research Award
2002	Boehringer Ingelheim Research Award (Federation of Clinical Immunology Societies (FOCIS) for EAE statin research
2003	Fellow, American Neurological Association (FANA)
2009	Fellow, American Academy of Neurology (FAAN) (elected 10/09)
2014	Donnie Smith Chair in Multiple Sclerosis Research

Sponsored Session 2

Chair : Izumi Kawachi (Department of Neurology, Brain Research Institute, Niigata University)

Sponsored by Medical Division, Novartis Pharma K.K.

SS-2 Neurofilament light chain – a real-time biomarker of neuronal injury in CNS diseases

David Leppert

Therapeutic Area Head Neuroinflammation, Neuroscience Development Franchise, Novartis Pharma AG

Neuronal damage is the patho-anatomical substrate for loss of neurological function in acute and chronic neurological disorders. Neurofilament light (NfL) chain is a cytoskeletal protein which is released into the cerebrospinal fluid (CSF) following neuroaxonal injury. In relapsing remitting multiple sclerosis (MS) elevated levels of NfL have been found to correlate with disease severity, long-term outcome and drug response. In a large number of primarily neurodegenerative diseases, and in acute CNS injury, the increase of NfL in CSF is even more pronounced. Compared to brain MRI, NfL is a more comprehensive and a real-time measure of ongoing neuronal damage. However, these findings were of limited clinical use as lumbar puncture is a relatively invasive procedure and cannot be performed repetitively in routine clinical settings. Two developments may allow NfL to become the first fluid biomarker to quantify neuronal damage in drug development, and in the future for individual therapeutic decision making. First, the finding of a strong correlation of levels in CSF versus serum or plasma qualifies blood NfL as an accurate measure of neuronal damage. Second, the introduction of the single molecule array (SIMOA) assay platform increased the sensitivity for reliable measurement of NfL in serum or plasma across the entire range of concentrations in patients and healthy controls. We will discuss the current evidence for blood NfL to become a drug response marker, predictor of long-term disability outcome in MS, and as a monitoring marker for disease activity. The main limitations for an immediate application in routine clinical practice of individual patients are technical validation and standardisation of assays, the definition of a normative data base, and a more in depth understanding how comorbidities affect blood NfL levels.

CURRICULUM VITAE

David Leppert is Therapeutic Area Head in Novartis Neuroscience.

David is a native of Basel, Switzerland, and received his MD from the University of Zurich where he also completed his specialty training in Neurology. He complemented his clinical experience with research fellowships in neuroimmunology and neurophysiology at the University of California, San Francisco. After his return to Switzerland in 1995 he founded the Clinical Neuroimmunology Laboratory at the University Hospital Basel where served as well as head of the epilepsy outpatient clinic. For his research on the role of matrix metalloproteinases, and on genomics in MS he received the 2nd Hoechst-Marion-Roussel prize for MS research (1999), the Ellermann Prize of the Swiss Neurological Society (2001), and the Baasch-Medicus Award (2002).

In 2004 he began his industry career at GSK and GE Healthcare in translational medicine and diagnostic drug development. Between 2007 and 2009, David was Senior Medical Consultant at Novartis and played the role of clinical head for the siponimod MS program. Since 2010 he has been at Roche where he served as Global Development Team Leader for the development of ocrelizumab in MS, and later as the Therapeutic Area Head Neuroinflammation. David holds a faculty position at the University of Basel as Associate Professor at the Department of Neurology at the University Hospital; he has authored over 100 peer reviewed publications. In 2015 David returned to Novartis in the Neuroscience Development Unit.

Sponsored Session 3

Chair：Hirofumi Ochi (Department of Geriatric Medicine and Neurology, Ehime University Graduate School of Medicine)

Sponsored by Biogen Japan Ltd. and Eisai Co., Ltd.

SS-3　Update on molecular biomarkers in multiple sclerosis

Manuel Comabella, MD, PhD

Department of Neurology and Neuroimmunology, Vall d'Hebron University Hospital/Director of Laboratory. MS Centre of Catalonia. Vall d'Hebron University Hospital

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system which is characterized by a high degree of heterogeneity in different disease aspects including clinical manifestations, disease course, neuroradiological findings, histopathological characteristics of lesions, and response to treatment. In this setting, there is a strong need for biomarkers that reliably capture these different aspects of disease heterogeneity and may help, for instance, in MS diagnosis and disease stratification; prediction of disease course; identification of new therapies beneficial for the disease; and in the development of a personalized therapy based on the prediction of treatment response and identification of patients at high risk for side effects. The present review will summarize current knowledge existing on prognostic biomarkers, particularly those determined at the time of the first neurological event or clinically isolated syndrome and treatment response biomarkers, and will propose future directions for personalized therapy in MS patients.

CURRICULUM VITAE

BIOGRAPHICAL SKETCH

Name: [*Last, First, Middle Initial(s), Degree(s)*]	Position/Title:
Comabella, Manuel. MD, PhD	Neurologist. Neurology / Neuroimmunology Department. Vall d'Hebron University Hospital. Director of Laboratory. MS Centre of Catalonia. Vall d'Hebron University Hospital.

Education

[Begin with baccalaureate or other professional education and include postdoctoral training]

Institution and Location	Degree	Year Conferred	Field of Study
Facultat de Medicina, Universitat de Barcelona	MD	1990	Medicine and Surgery
Residence in Neurology	Neurologist	1995	Neurology
Facultat de Medicina, Universitat Autònoma de Barcelona	PhD	2013	Medicine

Research and Professional Experience

[List in chronological order, previous employment, experience and honors]

2015 – Coordinator of the BioMSeu (European Consortium for CSF Biomarker Research; http://www.biomseu.com)

2013 – Coordinator of Neurosciences. Fundació Institut de Recerca Hospital Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

2013 – Member of the Internal Scientific Committee. Fundació Institut de Recerca Hospital Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

2008 – Senior neurologist. Neurology / Neuroimmunology Department, Vall d'Hebron University Hospital. Barcelona, Spain

2004 – Director of Laboratory. MS Centre of Catalonia, Neurology / Neuroimmunology Department, Vall d'Hebron University Hospital. Barcelona, Spain

1999 – 2003 Research Neurologist. Vall d'Hebron University Hospital. Barcelona, Spain

1996 – 1998 Research fellowship in Neuroimmunology, Brigham and Women's Hospital - Center for Neurologic Diseases, Harvard Medical School, Boston (US)

1992 – 1995 Neurology Resident (MIR Program), Vall d'Hebron University Hospital. Barcelona, Spain

Oral Session 2

Chairs：Takashi Ohashi（Tokyo Women's Medical University Yachiyo Medical Center）
Jin Nakahara（Department of Neurology, Keio University School of Medicine）

OS2-1　MOG-Antibody Disease and Pregnancy: An International Collaborative Study

Jyh Yung Hor

MOG-Antibody Disease and Pregnancy Study Group, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

Introduction

Pregnancy has an impact on the course of many autoimmune diseases. In multiple sclerosis（MS）, there is decreased relapse risk during pregnancy, but with an increased risk in early post-partum period. In AQP4-seropositive NMOSD, the relapse rate during pregnancy is not reduced, and there is high risk of relapse post-partum. There is limited data regarding MOG-antibody disease and pregnancy.

Objective

To study the relations between MOG-antibody disease and pregnancy.

Methods

Pregnancy data of MOG-antibody disease patients were collected through an international multicentre collaborative effort from UK, France, Japan, Denmark, and Thailand. Patients who were pregnant after MOG-antibody disease onset, and those with disease onset during pregnancy or within 1-year post-partum period fulfilled the inclusion criteria.

Results

Thirty-three pregnancies from 24 patients were included. Sixteen of the 24 patients（67%）had onset attack during pregnancy（3 patients）or within 1 year post-partum（13 patients）. The annualised relapse rate（ARR）reduced significantly from 0.41 at 1 year pre-pregnancy to 0 during pregnancy（p=0.03）, and it rebounded to 0.53 during 1-year post-partum period（p=0.0006）. Highest ARR was recorded at 0-3 months post-partum: 0.94（p=0.041, when compared to ARR during pregnancy）. During pregnancy, there was no increased risk of pre-eclampsia/eclampsia or miscarriages as seen in AQP4-seropositive NMOSD. No major congenital malformations were reported among children being born. From the UK Oxford MOG-antibody disease patient cohort, of all women with disease onset between 20 and 40 years of age who have ever pregnant, 47%（9/19）had onset related to pregnancy, with 89%（8/9）occurred during 1-year post-partum period.

Conclusions

In MOG-antibody disease, there is significant reduction in ARR during pregnancy, with a post-partum rebound. Its disease course in relation to pregnancy appears to resemble that of MS, rather than that of AQP4-seropositive NMOSD. Larger study is needed to confirm our observation.

Oral Session 2

Chairs：Takashi Ohashi（Tokyo Women's Medical University Yachiyo Medical Center）
Jin Nakahara（Department of Neurology, Keio University School of Medicine）

OS2-2 Acute encephalomyelitis and demyelinating polyneuropathy associated with serum anti-aquaporin-4 antibody positivity

Ryoji Miyano [1], Kenta Orimo [1], Masanori Kurihara [1], Kazuya Sato [1, 2], Kaori Sakuishi [1], Takaahiro Nakayama[2], Ichiro Imafuku [2], Toshihiro Hayashi [1], Tatsushi Toda [1]

[1] Department of Neurology, The University of Tokyo, Tokyo, Japan
[2] Department of Neurology, Yokohama Rosai Hospital, Kanagawa, Japan

A forty-year-old man presented with fever and headache without antecedent infection or vaccination. Brain MRI showed small T2-high lesions with mild enhancement in periventricular deep white matter, corpus callosum, and dorsal medulla oblongata. Cerebrospinal fluid (CSF) showed mononuclear pleocytosis (700 cells/mm3) and elevated protein. Four days after onset, he started to experience dysesthesia in all extremities. Although decreased sensation was observed with peripheral predominance, truncal dysesthesia was also observed, which gradually ascended to the neck. Muscle weakness appeared in lower limbs, then spread to upper limbs. Refractory hiccups and vomiting were also observed. Neurological examination showed pyramidal signs, hypotonia, and mildly decreased deep tendon reflexes. Further MRI showed longitudinally extensive T2-high spinal lesions (LESL) from C2 to Th2 and from Th5 to Th11. Nerve conduction studies showed decreased amplitude and velocity, prolonged distal latency, and temporal dispersion.

Acute encephalomyelitis with concomitant demyelinating polyneuropathy was suspected. Before starting immunotherapy, these symptoms started to improve on day 10, and CSF cell count and protein decreased. CSF myelin basic protein was elevated, but IgG index was normal with negative oligoclonal band. Due to LESL, serum anti-aquaporin-4 (AQP4) antibodies were tested, which turned out positive on cell-based assay. Anti-ganglioside antibodies were negative. Optic neuritis was not observed.

We started intravenous immunoglobulin therapy followed by two courses of steroid pulse therapy and 30 mg of oral prednisolone. Although painful tonic spasm appeared during the course, his symptoms gradually improved and no relapse was observed during 7 months of follow up.

LESL and dorsal medulla oblongata lesion with anti-AQP4 antibody positivity fulfill diagnostic criteria for neuromyelitis optica (NMO). Several reports have shown that peripheral neuropathy can accompany acute disseminated encephalomyelitis; however, development of neuropathy at the onset of NMO has rarely been reported. This case may give valuable insights into the initiating pathomechanisms of this disease.

Oral Session 2

Chairs：Takashi Ohashi（Tokyo Women's Medical University Yachiyo Medical Center）
Jin Nakahara（Department of Neurology, Keio University School of Medicine）

OS2-3 A case of recurrent cerebellar involvement associated with anti-myelin oligodendrocyte glycoprotein (MOG) antibody

Teruyuki Ishikura[1], Tatsusada Okuno[1], Makoto Kinoshita[1], Mikito Shimizu[1], Kimihiko Kaneko[2, 3], Toshiyuki Takahashi[2, 4], Hideki Mochizuki[1]

[1] Department of Neurology, Osaka University Graduate School of Medicine, Osaka, Japan
[2] Department of Neurology, Tohoku University Hospital, Miyagi, Japan
[3] Department of Neurology, Miyagi National Hospital, Miyagi, Japan
[4] Department of Neurology, Yonezawa National Hospital, Yamagata, Japan

A 26-year-old Japanese man with no particular medical history was admitted to other hospital presenting with acute headache and urinary retention in 2013. Any infectious symptoms were not observed prior to the neurological abnormalities. Laboratory investigations including erythrocyte sedimentation rate, C-reactive protein, and antinuclear antibody were negative. Brain MRI revealed hyperintense lesions at bilateral cerebellar peduncles in fluid-attenuated inversion-recovery images, and CSF examination showed pleocytosis with normal protein/glucose levels. The patient was initially diagnosed with viral encephalitis and treated with intravenous acyclovir therapy.

He did not show any relapses over the next 4 years. In March 2017, he developed truncal dysesthesia, and cervical MRI showed T2-hyperintense lesions at C5 and left cerebellar peduncle. CSF IL-6 level was elevated (136pg/ml), and the patient was HLA-A26-positive. Methylprednisolone pulse therapy was initiated, and resolved both the clinical symptoms and radiological abnormalities. Frequent recurrences were observed exclusively at cerebellar peduncles during the following several months. In August 2017, he presented with diplopia and dizziness, and brain MRI showed left cerebellar peduncle lesion. In November 2017, he developed acute headache and dizziness. Relapsed lesion was detected at right cerebellar peduncle in MRI images. Both symptoms showed beneficial response to methylprednisolone pulse therapy.

In December 2017, he developed diplopia with right cerebellar peduncle lesion detected in MRI images, and was referred to our hospital for further investigation. Serum antibodies against SS-A, SS-B, and aquaporin-4 (AQP4) were negative. CSF examination showed mild pleocytosis with normal protein/glucose levels. Oligoclonal band was negative. Serum myelin oligodendrocyte glycoprotein (MOG) IgG turned out to be positive (1:1024), and MOG-IgG related disorder was indicated. He was started on oral prednisone therapy for preventing further relapses.

Our case highlights the clinical and radiological presentation of MOG-IgG positive patient, characterized by rare cerebellar involvement, indicating broader spectrum of MOG-IgG autoimmunity than currently recognized.

Oral Session 2

Chairs：Takashi Ohashi（Tokyo Women's Medical University Yachiyo Medical Center）
Jin Nakahara（Department of Neurology, Keio University School of Medicine）

OS2-4 Immunophenotyping of PBMC from patients with multiple sclerosis and neuromyelitis optica spectrum disorder

Yasunobu Hoshino[1, 2], Kazumasa Yokoyama[2], Daisuke Noto[1], Davide Cossu[2], Nobutaka Hattori[2], Sachiko Miyake[1]

[1] Department of Immunology, Juntendo University School of Medicine,
[2] Department of Neurology, Juntendo University School of Medicine

Introduction

Multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) are central nervous specific inflammatory demyelinating disorders. In Japan, incidence and prevalence of MS/NMOSD patients are increasing. However, we often have some cases who we could not differentiate MS or NMOSD at initial onset. Aquaporin 4(AQP4) antibody seropositive NMOSD is an antibody-mediated disorder. The role of plasmablast(PB) in AQP4 antibody positive NMOSD patient was reported. Therefore, we hypothesized that certain part of the maturation step of B cell lineage is important. Moreover, the existence of peripheral helper T cells ($CD4^+$, $CD45RA^-$, $PD\text{-}1^{hi}$, $CXCR5^-$: Tph) was reported that Tph involved in antibody production in third lymphoid tissues such as synovial tissue in rheumatoid arthritis patients. However, the role of Tph in MS and NMOSD is not studied. Therefore, we examined the fluctuation of these fractions in MS vs NMOSD patients and investigated whether they reflect the pathological autoantibody production and the biological marker for earlier diagnosis.

Methods

We collected MS patients and AQP4 ab positive NMOSD patients in our outpatient clinic. We performed multicolor flow cytometric analysis of peripheral blood mononuclear cells(PBMC).

Results

In NMOSD group, the frequency of switched memory B cells ($CD20^+$, $CD27^+$, IgD^-: SMB) increased statistically significant compared to MS group and healthy subjects(HS). Moreover, frequency of naive B cells ($CD20^+$, $CD27^-$, IgD^+: NB) decreased significantly. The frequency of Tph in memory T cells ($CD4^+$, $CD45RA^-$) was also increased in NMOSD group compared to MS group and HS.

Discussion

Part of the PB originated from SMB was reported to produce AQP4 antibodies. In our experiment, increased frequency of SMB and Tph in the peripheral blood of NMOSD patients and decreased NB suggested that Tph cells have a major role for B cell maturation and producing AQP4 antibodies. We are planning to do the functional analysis of these cells for specific therapy.

Sponsored Session 4

Chair：Katsuichi Miyamoto (Department of Neurology, Kindai University School of Medicine)

Sponsored by Alexion Pharma Godo Kaisha

SS-4 Clinical Trial Design Issues in Neuromyelitis Optica Spectrum Disorders

Brian G. Weinshenker, MD, FRCP(C)

Mayo Clinic, Rochester MN

Current treatment of neuromyelitis optica spectrum disorders (NMOSDs) is based on uncontrolled or retrospective studies. Many challenges have and continue to hinder conduct of clinical trials in NMOSD. Ethical issues related to placebo-controlled studies have been addressed. Improved diagnosis facilitated by a specific biomarker has allowed for sufficient numbers and homogeneity of enrolled subjects to render clinical trials feasible. Three definitive clinical trials have been launched for NMOSD in the past 3 years. A remaining issue is precise definition outcomes. There is broad acceptance of relapse frequency and time to relapse as the most relevant outcomes. However, only a single relapse is allowed for enrolled subjects in placebo-controlled studies; therefore, any misclassification of relapse can have very negative consequences on trial outcome. A typical NMO relapse is severe and easily recognized. However, in the context of a clinical trial where patients are encouraged to report new symptoms immediately and where treatment may mollify the expression of an attack, it may be difficult to be certain on clinical grounds that a true attack has occurred, especially for worsening of preexisting symptoms. Accordingly, the Guthy Jackson Charitable Foundation has commissioned an effort to define relapses in an accurate and precise way. The evolving approach is algorithmic and is based on a specified evaluation of symptoms of an attack and adjudication based on clinical objective findings; when the clinical signs are less than definitive, an opportunity for adjudication of relapse based on MRI findings is allowed. This approach should enhance the sensitivity as well as accuracy and precision of relapse adjudication, and will facilitate comparison of results of different clinical trials. A strategy will need to be developed for simultaneous assessment of multiple promising treatments simultaneously with patient pools of limited size. Similarly, novel treatment strategies such as tolerization of the immune system that may be appropriate for patients who are stabilized with other more rapidly acting treatments need to be developed.

CURRICULUM VITAE

Brian G. Weinshenker, M.D.

Brian G. Weinshenker is Professor of Neurology and Consultant at Mayo Clinic, Rochester MN. Dr. Weinshenker's major research interests are directed at the understanding of inflammatory demyelinating diseases of the central nervous system including multiple sclerosis including: 1) natural history of multiple sclerosis; 2) defining clinical and radiologic differential diagnosis of inflammatory myelopathy; and 3) classification, diagnosis, and treatment of severe inflammatory demyelinating syndromes of the central nervous system including neuromyelitis optica. He was awarded the John J. Dystel award for multiple sclerosis research in 2011 by the American Academy of Neurology and National Multiple Sclerosis Society (USA).

Sponsored Session 5

Chair : Tatsusada Okuno (Department of Neurology, Osaka University)
Sponsored by Chugai Pharmaceutical Co., Ltd.

SS-5 NMO spectrum disorders : new concept new diseases ?

Jerome de Seze

Strasbourg hospital, France

The relationship between neuromyelitis optica (NMO) and multiple sclerosis (MS) has long been controversial. NMO was previously considered a form of MS involving predominantly the spinal cord and optic nerve. However, since the discovery of NMO-IgG/aquaporin-4 (AQP4) antibody, an NMO-specific autoantibody to AQP4, some unique clinical features, and magnetic resonance imaging (MRI) and other laboratory findings in NMO, have been further clarified. AQP4 antibody is now the most important laboratory finding for the diagnosis of NMO. Besides typical NMO, some patients with recurrent optic neuritis or recurrent longitudinally extensive transverse myelitis alone are also often positive for AQP4 antibody. Moreover, studies of AQP4 antibody-positive patients have revealed that brain and brainstem lesions are not uncommon in NMO, and some patterns appear to be unique to NMO. All these findings have expanded the NMO concept into 'NMO spectrum disorder' (NMOSD), and new criteria have recently been published. A new antigenic target, myelin oligodendrocyte glycoprotein (MOG), has also been discovered recently. This new antibody seems to correspond to around 20% of seronegative patients, but its specificity needs to be evaluated more precisely, especially in pediatric populations. These recent findings may also have therapeutic impact, as it has been demonstrated that many MS drugs can exacerbate NMO. The presentation will try to propose an overview of the clinical and neuroimaging features of NMOSD, followed by its treatment, including new therapeutical strategies.

CURRICULUM VITAE

Jerome de Seze

50 years-old

Professor in Neurology

PhD in Immunology

Head of the Neuroimmunological department of the Strasbourg hospital, specialized in Multiple sclerosis and Neuro-ophthalmology

Head of the clinical research center (CIC) of the Strasbourg hospital

Head of the DHU (Department Hospital/University called Neurogenics).

Co-leader of the research team of biopathology of the myelin neuroprotection and therapeutical strategy (BMNST), INSERM laboratory UMR 1119

President of the French Multiple Sclerosis society

Main interest : clinical and research works in inflammatory and autoimmune diseases of CNS and PNS. Neuro-ophtalmology.

Has published more than 300 papers

Sponsored Session 6

Chair：Masaaki Niino (Department of Clinical Research, Hokkaido Medical Center)

Sponsored by AstraZeneca K.K.

SS-6 Visualization of neuromyelitis optica spectrum disorder by MRI

Ho Jin Kim, MD, PhD

Department of Neurology, Research Institute and Hospital of National Cancer Center, Korea

Magnetic resonance imaging (MRI) markers have become important for both distinguishing neuromyelitis optica spectrums disorder (NMOSD) from multiple sclerosis (MS) and elucidating the different pathophysiology between the two diseases. Detection of a longitudinally extensive spinal cord lesion is one of the most characteristic neuroimaging findings of NMOSD and is very uncommon in adult MS. Other spinal cord MRI features characteristic of NMOSD include T2-hyperintense bright spotty lesions and ring-enhancing lesions. Brain lesions in patients with NMOSD are common on conventional MRI and some are relatively unique by virtue of localization and configuration which can be helpful in the diagnosis of NMOSD. Recently revised diagnostic criteria by the International Panel for NMO diagnosis included more detailed neuroimaging characteristics of NMOSD.

In contrast to MS where subclinical MRI activity is common, current clinical and neuroimaging evidence suggests that subclinical activity between attacks is absent in NMOSD. On the other hand, there has been increasing evidence for occult brain injury in normal appearing brain on conventional MRI in NMOSD, although the degree of which is less widespread and severe compared to MS. In addition to conventional MRI findings, advanced quantitative imaging measures are beginning to offer new insights into the pathophysiology of NMOSD and further differentiate the condition from MS.

In this talk, I'll present the current state-of-the-art in conventional and nonconventional MRI of NMOSD.

CURRICULUM VITAE

Dr. Ho Jin Kim is a principal scientist and consultant neurologist at the Research Institute and Hospital of National Cancer Center, Korea. He is also professor of Department of Cancer Biomedical Science, National Cancer Center Graduate School of Cancer Science & Policy.

Dr. Kim received his medical degree from Seoul National University in 1992 where he also completed his residency training in neurology and clinical fellowship in multiple sclerosis (MS) and neuromuscular disease. After successfully completing his residency, Dr. Kim went on to pursue his academic research interest as a Research Fellow in neuroimmunology at the University of Southern California, Keck School of Medicine, Los Angeles, California, USA for a year. Then he spent four years as a senior fellow and staff researcher in MS and neuroimmunology at the Montreal Neurological Institute of McGill University, Montreal, Quebec, Canada.

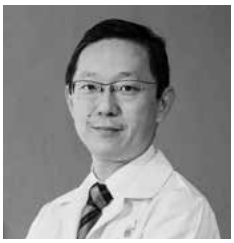
His major research interests lie in studying the development and application of biological assays to monitor the disease process and evaluate the response to novel therapeutics. His other research interests are in studying differences among various autoimmune inflammatory diseases of CNS including multiple sclerosis, neuromyelitis optica spectrum disorder and MOG-IgG encephalomyelitis in both clinical and radiological features as well as underlying pathogenesis.

Dr. Kim is widely published and a member of many prominent professional societies and associations including the American Academy of Neurology, European Neurological Society, The Federation of Clinical Immunology Societies, the Korean Neurological Association, and the Korean Society of Multiple Sclerosis. He is also a member of central organizing committee and scientific committee of PACTRIMS. He also serves as a co-editor for Multiple Sclerosis Journal – Experimental, Translational and Clinical and an associated editor for Journal of Clinical Neurology.

Private Seminar

Chair：Ichiro Nakashima（Department of Neurology, Tohoku Medical and Pharmaceutical University）

Sponsored by Cosmic Corporation Co., Ltd.



PS　The Evolving Clinical Spectrum of MOG-IgG associated Optic Neuritis, Encephalitis and Myelitis（MONEM）

Douglas Kazutoshi Sato

Research and Development at Brain Institute of Rio Grande do Sul（BraIns）and Professor of Medicine at Pontifical Catholic University of Rio Grande do Sul（PUCRS）

Myelin oligodendrocyte glycoprotein（MOG）is a glycoprotein exclusively expressed on the surface of myelin sheath in the central nervous system（CNS）. Although the precise function of MOG is not yet known, it is possibly related to the maintenance of the myelin structure. MOG has been used as an antigen in experimental autoimmune encephalomyelitis（EAE）in rodents as an animal model of demyelinating disorders. Using cell-based assays with MOG transfected cells, we are able to detect conformational sensitive antibodies against MOG（MOG-IgG）. In humans, MOG-IgG has been associated with inflammatory demyelinating CNS disorders distinct from multiple sclerosis. Moreover, it is clear that MOG-IgG is associated with a wider clinical phenotype, not limited to NMOSD, with the majority of cases presenting with optic neuritis, encephalitis with brain demyelinating lesions, and/or myelitis. Therefore, we propose the term MOG-IgG-associated Optic Neuritis, Encephalitis, and Myelitis（MONEM）. Depending on the clinical characteristics, these patients may be diagnosed with acute disseminated encephalomyelitis, cortical encephalitis, pediatric multiple sclerosis, transverse myelitis, or optic neuritis. With the clinical identification of MONEM associated with the development of specific cell-based assays, MOG-IgG is emerging as a potential biomarker of inflammatory disorders of the central nervous system.

CURRICULUM VITAE

Dr. Douglas Kazutoshi Sato is the Superintendent for Teaching, Research and Development at Brain Institute of Rio Grande do Sul (BraIns) and Professor of Medicine at Pontifical Catholic University of Rio Grande do Sul (PUCRS). He holds a collaborating professorship at Tohoku University School of Medicine (Sendai, Japan), where he obtained his PhD. He completed his medical training in internal medicine and clinical neurology, and post-doctoral researcher at the University of Sao Paulo in Brazil. Dr. Sato is board certified in Neurology since 2002, and he is the current coordinator of the Neuroimmunology Department 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, CNPq/Brazil, Ichiro Kanehara foundation, TEVA pharmaceuticals and Euroimmun AG.

Poster Session

P-1 Progressive multifocal leukoencephalopathy under the control of a regulated infectious immune response in a patient with rheumatoid arthritis

Ryusei Nishigori, MD[1,2], Yoko Warabi, MD, PhD[1], Yukiko Shishido-Hara, MD, PhD[3], Kazuo Nakamichi, PhD[4], Takashi Komori, MD, PhD[5], Eiji Isozaki, MD, PhD[1]

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[2] Department of Neurology, Kyoto University Graduate School of Medicine

[3] Department of Anatomic Pathology, Tokyo Medical University

[4] Department of Virology 1, National Institute of Infectious Diseases

[5] Department of Laboratory Medicine and Pathology (Neuropathology), Tokyo Metropolitan Neurological Hospital

Introduction

Although progressive multifocal leukoencephalopathy (PML) has many cases with poor prognosis, PML cases with good prognosis are occasionally observed in recent years. We present a PML patient with mild inflammation that followed good outcome.

Case

A 74-year-old female with rheumatoid arthritis who had received methotrexate and prednisolone over 9 years was admitted to our hospital due to ataxia which was deteriorated for 5 months. Magnetic resonance imaging (MRI) revealed the infratentorial lesion, accompanied by faint dot-shaped or linear enhancement. Neuropathological examination obtained by stereotactic biopsy revealed demyelination and mild inflammation of T cell lineage (CD 4/8 ratio 2.9) and B cell lineage (CD79a, CD138). Sensitive in situ hybridization revealed the presence of a few glial cells harboring JCV genomic DNA in their nuclei. PCR also amplified the JCV DNA from the brain tissue. By PCR, mild level of CSF-JCV-DNA (2124 copies/ml) was detected in the CSF. She was diagnosed with PML, methotrexate and prednisolone was stopped, and mefloquine and mirtazapine was started. While faint enhancement on the MRI remains, her symptoms have not progressed after the admission and the PCR testing of CSF collected at the 7 months after admission revealed negativity of JCV-DNA.

Discussion

In this case, it is considered that the patient's immune response to JCV recovers and follows a good outcome. The mild enhancement of MRI reflected the result of immune response to JCV, not a fatal inflammation. At present, it is difficult to judge the extent of inflammation only with MRI findings. Other than natalizumab associated PML, various extent of inflammation can occur in PML, and accumulation of the study for the state of inflammation in PML is required.

Conclusion

Various extent of inflammation can occur in PML. Mild inflammatory status in PML might have exerted beneficial.

Poster Session

P-2 Anti-myelin oligodendrocyte glycoprotein antibody positive cerebral encephalitis following influenza vaccination

Morinobu Seki [1], Sho Ishigaki [2], Koichi Oki [1], Shigeaki Suzuki [1], , Kimihiko Kaneko [3], Toshiyuki Takahashi [4], Jin Nakahara [1]

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[2] Department of general internal medicine, Kawasaki Municipal Hospital

[3] Department of Neurology, National Hospital Organization Miyagi National Hospital, Department of Neurology, Tohoku University Graduate School of Medicine

[4] Department of Neurology, Tohoku University Graduate School of Medicine

Background

Anti-myelin oligodendrocyte glycoprotein (MOG) antibody can be detected mainly in patients with pediatric acute disseminated encephalomyelitis and aquaporin-4 antibody negative neuromyelitis optica spectrum disorder. Recently, cases with anti-MOG antibody positive encephalitis have been reported, however there is little data on the histological findings of this disease.

Case report

A 15-year-old woman without a past medical history developed headache and nausea one month after influenza rhinovaccination. Brain MRI showed high intensity lesions in the left temporal lobe on T2-weighted and fluid-attenuated inversion recovery images with gadolinium enhancement. She was admitted to our hospital on suspicion of granulomatous meningeal encephalitis. Neurological examination showed amnestic aphasia. Soon after admission, she twice developed a generalized clonic seizure. A cerebrospinal fluid examination showed lymphocytic pleocytosis (66/μl; 73% mononuclear cells) and increased interleukin-6 level with normal protein and glucose concentrations. Both oligoclonal band and myelin basic protein were normal. Blood examination showed no specific findings. Intravenous administration of acyclovir resulted in no improvement, and polymerase chain reaction was negative for HSV-1, HSV-2, CMV, HHV-6, VZV and EBV. Body CT and pelvic MRI showed no neoplasm. Her symptoms gradually worsened. To investigate the diagnosis, a brain biopsy was performed at the left temporal lobe. The pathological examination revealed inflammatory cell infiltration, but no demyelination, neoplastic and granulomatous lesions were observed. Thereafter the MOG antibody was detected in the serum (1:512) and in the CSF (1:64) and she was diagnosed as anti-MOG antibody positive encephalitis. High dose methylprednisolone was started and her symptoms dramatically improved within a few days.

Discussion

The pathogenic contribution of anti-MOG antibodies to the cerebral encephalitis was uncertain since demyelination was not detected in the brain biopsy and myelin basic protein level was normal. Further histological evaluation should be helpful to understand the pathophysiology of anti-MOG antibody related encephalitis.

P-3 Melanoma cell adhesion molecule-expressing CD4+ T cells in CNS-demyelinating diseases

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[1] Department of Neurology, Tokyo Women's Medical University

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

Background

Adhesion molecules expressed on lymphocytes are closely related to the pathogenesis of CNS-demyelinating diseases. In particular, melanoma cell adhesion molecule (MCAM)-expressing helper T (Th) cells are a pathogenic Th cell subset. Here, we elucidated relationships between MCAM expression and the pathogenesis of CNS-demyelinating diseases.

Methods

Forty-five patients with multiple sclerosis (MS), 20 patients with neuromyelitis spectrum disorder (NMOSD), 21 patients with non-inflammatory neurological disorders (NINDs), 20 patients with inflammatory or collagen diseases, and 16 healthy controls (HCs) were enrolled. The frequencies of MCAM-expressing memory Th cells, naïve Th cells, CD8+ T cells, and B cells in peripheral blood were analyzed by flow cytometry. We compared the frequencies of MCAM-expressing lymphocytes between MS and NMOSD patients treated with/without disease-modifying drugs (DMDs) or steroid. The relationships between MCAM expression and clinical parameters were examined.

Results

The frequency of MCAM expression was significantly higher in the memory Th cell subset (5.1 ± 3.6%) than in naïve Th cell (0.4 ± 0.9%), CD8+ T cell (2.1 ± 2.5%), and B cell (1.4 ± 1.5%) subsets. Frequencies of MCAM expression tended to be higher in each lymphocyte subset of patients with NMOSD than other diseases or HCs. The frequency of MCAM-expressing memory Th cells was significantly higher in patients with NMOSD (9.2 ± 4.3%) than MS (3.9 ± 2.4%), NINDs (3.5 ± 1.4%), and inflammatory or collagen diseases (6.4 ± 3.8%), or HCs (3.8 ± 1.5%). The absolute numbers of MCAM-expressing memory Th cells and B cells in patients treated with fingolimod were significantly lower than those in patients treated with IFN-β or without DMDs or steroids. There was no correlation between MCAM expression and disease activity in MS and NMOSD patients.

Conclusions

Our results indicate involvement of MCAM in NMOSD pathogenesis. Fingolimod decreases lymphocytes in peripheral blood, including pathogenic MCAM-expressing Th cells.

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