ABSTRACTS

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Passive transfer of rabbit antibodies against human NMDA-type GluR into mice: effect of antibodies to GluN1
Yukitoshi Takahashi, Shigeko Nishimura, Emiko Takao, Risa Kasai, Kaoru Enokida and Yushif Inoue
National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorder, Shizuoka, Japan

Rationale: Antibodies to NMDA-type GluR are pivotal factors in patients with non-herpetic acute limbic encephalitis and NMDAR encephalitis with ovarian teratoma. Cell-based assay revealed the antibodies in patients with schizophrenia, epilepsy, brain tumor, etc., and the antibodies may contribute pathophysiology in many kinds of neurological diseases. In the last year, we reported that antibodies to GluN2B-NT2 may induce excitable behavior and memory dysfunction in space (27th Neuro-immunology congress). We conducted behavioral analyses of mice with passive transfer of rabbit antibodies against human GluN1.

Methods: Rabbits were immunized by human GluN1-NT peptide, and their sera were purified with protein-A column into polyclonal antibodies to GluN1-NT. The antibodies to GluN1-N (3 microl) were introduced into hippocampi of mice, twice with 1 week interval by the cannulas. Behavioral analyses were done by blind researchers to three groups (antibodies to GluN1-NT, control rabbit antibodies and saline).

Results: Observation by Irwin method revealed no significant difference among three groups. The mice with GluN1-NT antibodies showed significant evolitional decrease of entry to open arms in elevated plus maze test, suggesting increased fear or anxiety. The mice showed significant decrease of latency in passive avoidance test, suggesting impairment of long-term memory. Social interaction tests showed significant decrease of sniffing, suggesting decrease volition of social interaction. Novel object recognition tests showed no significant difference among three groups. Histological examination of brain showed no significant difference among three groups.

Conclusion: Antibodies to GluN1-NT may induce fear/ anxiety, impairment of long-term memory, and decreased social interaction.

Validity and pitfall in diagnostic criteria of probable anti-NMDA receptor encephalitis
Atsushi Kaneko,1 Takahiro Iizuka,1 Juntaro Kaneko,1 Naomi Kanazawa,1 Josep Dalmau2 and Kazutoshi Nishiyama1
1Department of Neurology, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan, 2Service of Neurology, Hospital Clinic, University of Barcelona, Barcelona, Spain

Background: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an immune-mediated disorder caused by IgG antibodies against the GluN1 subunit of NMDAR, and diagnostic criteria for probable and definite anti-NMDAR encephalitis have recently been proposed.

Objective: To assess diagnostic criteria for probable anti-NMDAR encephalitis.

Methods: Retrospective reviews of clinical information of 160 consecutive patients suspected to have autoimmune neurological disorders at early evaluation, whose sera and/or CSF were sent from Kitasato University to Dalmau Lab and examined for antibodies against neuronal surface antigens and synaptic proteins between January 1, 2007 and May 6, 2016, using cell-based assay, frozen sections of rat brain, and live hippocampal neurons. We assessed sensitivity and specificity of criteria of probable anti-NMDAR encephalitis.

Results: Anti-NMDAR antibodies were identified in 29 patients (22 [75.9%] female; median age 26 years [14–47 years]). The antibodies were identified in 26 (89.7%) of 29 patients who fulfilled the probable criteria but not in three patients including 1 with ovarian teratoma. In contrast, the antibodies were detected in three patients who did not fulfill probable criteria; these patients presented with isolated epilepsy in 2 and progressive hemiparesis due to demyelinating lesions in 1. The sensitivity and specificity of criteria of probable anti-NMDAR encephalitis was 89.7% and 97.7%, respectively.

Conclusion: The probable criteria are valid, but diversity of phenotypic spectrum of the disease should be taken into account in diagnosing anti-NMDAR encephalitis.

RNA-Seq data analysis identifies the comprehensive profile of in vivo IFNB-stimulated genes in MS
Jun-ichi Satoh, Kenji Sakai, Youhei Tosaki, Motoaki Yamaizu and Yoshihiro Kino
Department of Bioinformatics and Molecular Neuropathology, Meiji Pharmaceutical University, Tokyo, Japan

Objectives: Interferon-beta (IFNB) is the most widely used drug for reducing disease activity of MS, although a considerable population of MS patients are refractory to IFNB. To establish the personalized therapy for MS, the molecular mechanism underlying therapeutic effects of IFNB in MS should be thoroughly characterized by aid of the next-generation sequencing (NGS) technology.

Methods: To elucidate a comprehensive profile of in vivo IFNB-stimulated genes (ISGs) in MS patients, we analyzed a RNA sequencing (RNA-Seq) dataset numbered SRP045500, composed of the genome-wide transcriptome of whole blood and purified populations of CD4 + T cells.
B cells, and monocytes isolated from MS patients at the time point before and 24 h after the first treatment with IFNB1a.

Results: We identified the set of 914 in vivo ISGs, containing a number of non-coding RNAs and pseudogenes, along with differential spliced genes in whole blood of MS. The set of 914 ISGs were relevant to the molecular pathways defined as Interferon Signaling and Proteasome, and were closely associated with Gene Ontology terms of antiviral and immune responses. We also identified 640, 653, and 1018 ISGs from CD4+ T cells, B cells, and monocytes of MS patients on IFNB treatment, respectively. They included 78 genes that might serve as the most consistent blood biomarkers for assessment of the immediate early in vivo response to IFNB treatment in MS.

Conclusions: RNA-Seq data analysis promotes us to characterize the comprehensive profile of in vivo ISGs in MS patients on IFNB treatment.

Intrathecal overproduction of inflammatory cytokines and chemokines in febrile infection-related epilepsy syndrome
Hiroshi Sakuma
Department of Brain Development and Neural Regeneration, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan

Objective: Cytokines and chemokines are increasingly receiving attention because they act not only as inflammatory mediators, but also as neuromodulators in seizures and epilepsy. To clarify how neuroinflammation is involved in inflammatory refractory status epilepticus, we extensively studied inflammatory mediators in acute encephalitis with refractory, repetitive partial seizures (AERRPS) or febrile infection-related epilepsy syndrome (FIRES), a recently proposed condition characterized by refractory status epilepticus of unknown cause.

Methods: Using multiplex bead-based assays, we measured a total of 67 cytokines and chemokines in serum and cerebrospinal fluid (CSF) specimens of 3 patient groups including 27 patients with AERRPS, 16 with other inflammatory neurological diseases (OIND), and 27 with non-inflammatory neurological diseases (NIND).

Results: Comparison among the three groups revealed significant differences of 17 analytes in the sera (8 increased and 9 decreased in the AERRPS group) and 27 analytes in the CSF (25 increased and two decreased). CSF levels of interleukin (IL)-6, IL-8, and CXCL10 increased most strikingly in the AERRPS group and were significantly higher than the levels in both NIND and OIND groups. High level of CSF CXCL10 was predictive of poor outcome.

Conclusions: Augmented intrathecal production of pro-inflammatory cytokines and chemokines demonstrate strong activation of innate immunity in the central nervous system of patients with AERRPS.

Clinical and immunological features in patients with myasthenia gravis and thyroid ophthalmopathy
Mayuko Osaka
Department of Neurology, Keio University School of Medicine, Tokyo, Japan

Myasthenia gravis (MG) and thyroid associated ophthalmopathy (TAO) potentially cause diplopia, however the clinical picture of TAO in patients with MG has not been fully elucidated. To determine the clinical and immunological characteristics of TAO with MG, we studied 458 MG patients in clinics. We investigated the medical record retrospectively, and determined MG and thyroid related autoantibodies and HLA-A, -B, -DRB1 genotyping. Forty-six patients had autoimmune thyroid diseases (24 Basedow’s disease and 22 Hashimoto’s disease). Among them, 7 (1.5%, M:F = 4:3) developed ophthalmoplegia due to TAO. The onsets of MG and TAO were at same time in three patients. There were 4 early-onset and 3 late-onset MG. All patients showed ptosis and diplopia. Ptosis, but not diplopia disappeared after edrophonium injection. MGFA classification showed class I in six patients. Although electrophysiological tests indicated waning phenomenon in only one patient, we could detect the impairment of neuromuscular injection using a single fiber electromyogram in five patients. Orbital MRI demonstrated the thickness of inferior rectus muscle in all patients. HLA genotyping failed to detect the common HLA alleles. Treatment regimens included oral prednisolone in 5, intravenous methylprednisolone pulse in 2, and local injection of steroid to rectus muscle in all patients. HLA genotyping failed to detect the common HLA alleles. Treatment regimens included oral prednisolone in 5, intravenous methylprednisolone pulse in 2, and local injection of steroid to extraocular muscle in four patients. The responses of immunotherapy were generally favorable. MG patients with TAO tended to have mild manifestations of MG. However, the clinical and immunological features of MG and TAO are variable. The concomitant of TAO should be considered, when MG patients show the intractable diplopia.

Anti-neuronal surface antigen-antibodies in possible autoimmune epilepsy
Juntaro Kaneko,1 Takahiro Iizuka,1 Atsushi Kaneko,1 Naomi Tominaga,1 Eiji Kitamura,1 Naomi Kanazawa,1 Josep Dalmau2 and Kazutoshi Nishiyama1
1Department of Neurology, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan, 2Service of Neurology, Hospital Clinic, University of Barcelona, Barcelona, Spain

Background: Autoantibodies against neuronal surface antigens (anti-NSA-abs) have increasingly been recognized to play an important role in epileptic disorders.

Objectives: To study anti-NSA-abs in various neurological disorders presenting with seizure.

Methods: Retrospective reviews of clinical information of 161 consecutive patients suspected to have autoimmune neurological disorders at early evaluation, whose sera and/or CSF were sent from Kitasato University to Dalmau Lab and examined for anti-NSA-abs between January 1, 2007...
and May 6, 2016, using cell-based assay, tissue-based assay, and live hippocampal neurons. We also assessed other abs in serum and oligoclonal bands (OCBs).

**Results:** Anti-NSA-abs were identified in 28 (40%) of 70 patients with seizure; anti-NMDA receptor (NMDAR)-abs (n = 25), anti-LGI1-abs (n = 2), and abs not characterized yet (n = 1). No anti-NSA-abs were identified in the remaining 42 patients, including 10 with cryptogenic new-onset of refractory status epilepticus (NORSE). The serum abs-detection frequency for GAD, Tg and TPO, were 12% (3/25), 15% (6/39), and 9% (4/45), respectively, but the antibody titer was low. OCBs were frequently detected in patients with anti-NSA-abs than those without (10/21 vs 3/32, P = 0.003), but there was no significant difference in elevated IgG index (5/15 vs 4/28, P = 0.24).

**Conclusion:** Anti-NSA-abs were detected in 40% of patients with initially suspected to have autoimmune epilepsy, suggesting an importance of early recognition of possible autoimmune epilepsy in patients with seizures. However, cryptogenic NORSE should not be confused with anti-NMDAR encephalitis.

**Early- and late-activated microglia show distinct localizations in amyotrophic lateral sclerosis spinal cord**

Shintaro Hayashi and Jun-ichi Kira

Department of Neurology, Neurological Institute, Graduate School of Medical Science, Kyushu University, Fukuoka, Kyushu, Japan

**Objectives:** In ALS spinal cord, marked microglial infiltrations are observed in the anterolateral funiculus outside the corticospinal tract (ALFoc). Microglia express temporally distinct genes after activation and, among them, osteopontin (Ost) is expressed in an early phase (4-24 h), and galectin-3 (Gal3) in a later phase (3-7 days). This study aimed to detect to what extent early- and late-activated microglia contribute to this pathology.

**Methods:** Paraffin-embedded 5-micrometer-thick transverse spinal cord sections of ALS cases (n = 7) and non-ALS cases (n = 5) were examined immunohistochemically. The antibodies used were against Iba-1, CD68, Ost, Gal3, and TDP-43. The numbers of immunoreactive (ir) cells in the ALFoc, corticospinal tract (CST), and anterior horn (AH) were quantified.

**Results:** Ost-ir cells were localized only in the AH with a rod or dot appearance, while Gal-3-ir cells populated the ALFoc and CST with foamy profiles. Iba-1-ir and CD68-ir cells were widely distributed in the ALFoc, CST, and AH. The rates of Ost-ir/Gal3-ir to Iba-1-ir cells were 58.5/36.4%, and the number of Gal3-ir cells showed a significant correlation with that of degenerated motor neurons (r = 0.559, P = 0.018).

**Conclusions:** This study clearly showed that in the ALS spinal cord, microglia activated in the later phase were present in the ALFoc, and those activated in the early phase were in the AH, suggesting that microglia infiltration may occur in the ALFoc first and then spread to the AH. Gal-3 was suggested to be a novel therapeutic target to protect motor neurons from ALS.

**Effect of horizontal infection to the prevalence of HTLV-1 in female in Kagoshima, Japan**

Eiji Matsuura, Yuichi Tashiro, Kunihiro Ando, Satoshi Nozuma and Hiroshi Takashima

Department of Neurology and Geriatrics, Kagoshima University, Kagoshima, Japan

**Background:** The major infection route of HTLV-1 is thought to be a mother-to-child infection with breast feeding. A recent report suggests that about 3000 people a year are newly infected to HTLV-1 by male-to-female sexual transmission in Japan. In addition, some studies reported that the rate of HTLV-1 carrier in female is obviously higher than that in male in more than 50s although those ratios are same between the sexes until the 50s.

**Aims:** We study on the effect of horizontal infection to the infection ratio of male and female after the 60s in Kagoshima, Japan.

**Patients and methods:** The patients who had surgery at the operating room of Kagoshima University Hospital from January 2001 to December 2014 were investigated. Of those patients, 20427 patients had a screening test for HTLV-1 antibody. HTLV-1 prevalence rate is obtained for each category defined by age, sex and birthday. We estimated the number of the carrier in Kagoshima prefecture by projecting the detected prevalence rate to the population of that category in 2014.

**Results:** 11.0% of the samples were positive for anti-HTLV-1 antibody. The estimated number of HTLV-1 seropositive people is 113129 (7.0% of population) at Kagoshima prefecture in 2014. The prevalence ratio was over 20% in the 80s. The ratio in female is significantly higher than that in male in more than their 60s. However, the prevalence ratios in female in every decade did not increase after 10 years.

**Conclusion:** The higher prevalences in female in more than the 50s are not attributed with horizontal transmission.

**Anti-GM1 antibody with a preferential response to dimeric GM1 is associated with an axonal variant of Guillain-Barre syndrome following gastrointestinal infection**

K Kaida,1 K Nakagawa,1 M Kuwahara,2 H Takazaki,1 M Kadoya,1 MG Ciampa,3 L Mauri,3 S Sonnino,3 S Kusunoki3 and K Ikewaki1

1National Defense Medical College, Tokorozawa, Japan, 2Kinki University School of Medicine, Osaka, Japan, 3University of Milan, Milan, Italy

Antiganglioside antibodies play a pathogenic role in development of Guillain-Barre syndrome (GBS), and the antibody-antigen interaction is influenced by glycolipid environment around antigens. The aim of this study is to
investigate whether clustered glycoepitopes influence the avidity of antiganglioside antibodies, with use of synthetic dimeric GM1, and to clarify association between the reactivity of anti-GM1 antibodies to the dimeric GM1 and clinical features. We analyzed sera from 40 GBS patients with IgG anti-GM1 antibody in a conventional ELISA screening. Patients which serum anti-GM1 dimer activities (corrected optical density, cOD) were higher by 0.1 than anti-natural GM1 activities were defined as a dimer GM1 (Dimer) group and the rest as a natural GM1 (nGM1) group. The Dimer group consisted of 19 patients and the nGM1 group of 21 patients. The mean cOD to GM1 dimer was 0.77 in the Dimer and 0.41 in the nGM1 groups (P = 0.02). Females (68.2%, P = 0.01) and antecedent gastrointestinal infection (78.9%, P = 0.02) were more frequent in the Dimer group. Electrophysiological findings indicative of an axonal variant were more in the Dimer group. Immunoabsorption studies showed that anti-GM1 antibodies were more specific to GM1 in the Dimer group. Anti-GM1 antibodies with a preferential response to dimeric GM1 are likely to predispose GBS patients to a motor-axonal variant following gastrointestinal infection.

Molecular analyses of HTLV-1 subgroups associated with the risk of developing HAM/TSP
Mineki Saito and Tadasuke Naito
Department of Microbiology, Kawasaki Medical School, Okayama, Japan

Background: Among human T-lymphotropic virus type 1 (HTLV-1)-infected individuals, the lifetime risk of developing HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) differs between ethnic groups. Also, there is an association between HTLV-1 tax gene subgroups (i.e. tax-A or -B) and the risk of HAM/TSP.

Methods: In an attempt to understand the molecular mechanism responsible for this association, we studied the functional difference in the viral transcriptional regulator Tax between each subgroup by microarray analysis of tetracycline inducible Tax expression system, reporter gene assays with constructs containing the CXCL10 promoter, and analysis of Tax-host protein interactions by co-immunoprecipitation.

Results: The results indicated that (1) Tax-A can induce CXCL10, prognostic biomarkers for HAM, seven times more efficiently than Tax-B; (2) no functional differences were observed in Tax between each subgroup based on the reporter gene assays using CXCL10 promoter constructs; and (3) Tax-A bound more efficiently to RelB, which is a transcription factor of NFκB transcription complex responsible for the expression of CXCL10, than Tax-B did.

Conclusions: Our results indicate that although reporter gene assays with the CXCL10 promoter constructs did not show a significant difference in activity between the Tax-A and Tax-B, it remains possible that Tax-A more efficiently induce CXCL10 through the non-canonical NFκB pathway via high affinity interactions with RelB.

A follow-up study of therapeutic efficacy and antibody titers in anti-HMGCR antibody-positive myopathies
Masato Kadoya,1 Kenichiro Taiba,2 Chiseko Ikenaga,2 Naohiro Uchio,2 Ayumi Hida,2 Meiko Maeda,2 Kenichi Kaida,3 Shoji Tsuji2 and Jun Shimizu2
1Department of Neurology and Anti-aging Medicine, National Defense Medical College, Tokorozawa, Japan, 2Department of Neurology, The University of Tokyo, Tokyo, Japan

In anti-HMGCR autoantibody-positive myopathy, antibody titers are considered to reflect the disease activities, and several reports recommended immunosuppressive therapy should be intensified to keep the low CK level. Some patients, however, are able to preserve muscle strength without significant decrease in CK levels. Our aim is to clarify long-term therapeutic efficacy and changes in antibody titers of anti-HMGCR Ab-positive myopathies. Thirty-three patients with anti-HMGCR Ab-positive myopathies were identified among 621 HMs patients (5.3%) by ELISA and western blot analysis. The antibody titers were evaluated by ELISA with multiplicative serum concentrations, ranging from 1/400 to 1/6400. There were no significant correlation between antibody titers and pretreatment disease activities (CK level, muscle strength, and modified Rankin scale). The analysis of posttreatment sera obtained from five patients more than one year after initiation of immunotherapy showed decline in antibody titers in three patients. One patient showed significant correlation between CK level and antibody titers during the longitudinal follow-up (6.5 years). Among 12 patients followed up for more than three years, seven patients achieved normalization of CK level with good recovery of muscle strength. The remaining five patients had sustained increase in CK level, despite adequate recovery of muscle strength in three patients. The optimal treatment strategy for patients with preserved muscle strength but showing high CK level remains unknown. The antibody titers may be a surrogate marker for disease activities in each individual patient.

T and B lymphocyte subsets of anti-myelin oligodendrocyte glycoprotein-related disorder and anti-aquaporin 4 antibody-positive neuromyelitis optica spectrum disorder in remission
Satoru Tanaka,1 Akihiro Kubota,1 Miki Kojima,1 Satoru Oji,1 Kimihiko Kaneko2, Sato Douglas,3 Ichiro Nakashima,2 Denpo Norihisa,1 Hikoaki Fukaura1 and Kyoichi Nomura1
1Department of Neurology, Saitama Medical Center, Saitama Medical University, Saitama, Japan, 2Department of Neurology, Tohoku University, Sendai, Japan, 3University of São Paulo, São Paulo, Brazil

Objective: We study the subsets of T and B lymphocytes present in the active and remission phases of anti-myelin oligodendrocyte glycoprotein (MOG)-related disorder

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Axonal degeneration by the Nogo receptor-1

Objectives: Medical Life Science, Yokohama, Japan Life Science, Yokohama City University Graduate School of Medicine, Yokohama, Japan, much lower than those of wild-type mice. In contrast, the

Results: We generated MOG-induced EAE in LOTUS knock-out (LOTUS-KO) mice and LOTUS transgenic (LOTUS-Tg) mice. As the ex vivo study, EAE splenocytes were cultured in the presence of LOTUS. Cytokine production were examined using specific ELISAs.

Methods: We cultured in the presence of LOTUS. Cytokine production were examined using specific ELISAs.

Results: No significant difference in T cell subsets was observed between the two disorders. As for B cell subsets, the level of plasmablasts was significantly higher in patients with AQP4-NMOSD (1.9 1.72) than in those with MOG-RD (0.74 0.62), whereas no significant difference was observed in transitional, naive, and memory B cells.

Conclusion: Plasmablasts might be involved in the pathogenesis of AQP4-NMOSD, but not MOG-RD, even in the remission phase.

LOTUS is associated with the immuno-pathogenesis of experimental autoimmune encephalomyelitis

Keita Takahashi,1,2 Yuji Kurihara,2 Hideyuki Takeuchi,1 Kohtarou Takeki2 and Fumiaki Tanaka1
1Department of Neurology and Stroke Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan, 2Molecular Medical Bioscience Laboratory, Department of Medical Life Science, Yokohama City University Graduate School of Medical Life Science, Yokohama, Japan

Objectives: Axonal degeneration by the Nogo receptor-1 (NgR1) signaling pathway was recently recognized as an important factor contributing to the pathogenesis of multiple sclerosis (MS). We previously identified lateral olfactory tract uster substance (LOTUS) as an endogenous NgR1 antagonist and showed that the reduction of LOTUS in the cerebrospinal fluid correlated with the disease activity of MS. This finding suggests that reduction of LOTUS enhances the NgR1 signaling pathway leading to axonal degeneration in MS. To clarify this hypothesis, we investigated the pathogenic role of LOTUS in experimental autoimmune encephalomyelitis (EAE) mice.

Methods: We generated MOG-induced EAE in LOTUS knock-out (LOTUS-KO) mice and LOTUS transgenic (LOTUS-Tg) mice. As the ex vivo study, EAE splenocytes were cultured in the presence of LOTUS. Cytokine production were examined using specific ELISAs.

Results: The clinical EAE scores of LOTUS-KO mice were much lower than those of wild-type mice. We also found that LOTUS directly induces splenocytes to release IL-17, but it was not NgR1-mediated effect.

Conclusion: Our data suggest that LOTUS enhances inflammatory response via unidentified receptor(s) rather than NgR1 in EAE. The molecule(s) bound by LOTUS may be a new therapeutic target in MS although further investigation is needed to identify the precise signaling pathways of LOTUS especially in lymphocytes.

Potential benefits of anti-IL-6 receptor monoclonal antibody in patients with multiple sclerosis and seronegative neuromyelitis optica spectrum disorders

Manabu Araki, Masakazu Nakamura, Wakiro Sato and Takashi Yamamura
Multiple Sclerosis Center, National Center of Neurology and Psychiatry, and Department of Immunology, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan

We previously reported the clinical efficacy of tocilizumab (TCZ), a humanized anti-IL-6R monoclonal antibody, in patients with anti-AQP4 antibody positive NMOSD (Araki, Neurology 2014). However, the interferon-beta non-responders, but not the responders with MS, tended to have a higher PB frequency. We performed an exploratory open-label study to evaluate the efficacy of TCZ in MS patients showing a higher PB frequency. The number of relapses, and EDSS, were evaluated over the TCZ treatment period. Six patients (four women and two men) were enrolled in the study. All patients were negative for anti-AQP4 antibody, and had been diagnosed with MS (three relapsing-remitting, RR; three secondary progressive, SP). One patient was later satisfied the NMOSD diagnostic criteria (Wingerchuk, Neurology 2015). Each participant was given 8 mg/kg of TCZ monthly. Three RR-MS patients showed reduced ARR (TCZ responders), while the other three patients experienced several relapses or progression of EDSS (TCZ non-responders), resulting in the discontinuation of TCZ treatment within a year. Notably, two patients with longitudinally extensive spinal cord lesions were among the responders. In contrast, TCZ non-responders included SP-MS patients and also tended to show long disease durations and high EDSS scores. There were no serious adverse events during the course of TCZ treatment. TCZ shows potential efficacy in the treatment of patients with RR-MS and seronegative NMOSD. However, a diagnosis of SP-MS may be predictive of low TCZ efficacy.

Early aggressive treatment strategy against generalized myasthenia gravis

Kimiai Utugisawa,1 Yuriko Nagane,1 Yasushi Suzuki,2 Tomihiro Imai,1 Naoya Minami,4 Naoki Kawauchi,3 Masayuki Masuda,6 Shingo Konno,7 Hidekazu Suzuki8 and Hiroyuki Mura1

Potential benefits of anti-IL-6 receptor monoclonal antibody in patients with multiple sclerosis and seronegative neuromyelitis optica spectrum disorders

Manabu Araki, Masakazu Nakamura, Wakiro Sato and Takashi Yamamura
Multiple Sclerosis Center, National Center of Neurology and Psychiatry, and Department of Immunology, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan

We previously reported the clinical efficacy of tocilizumab (TCZ), a humanized anti-IL-6R monoclonal antibody, in patients with anti-AQP4 antibody positive NMOSD (Araki, Neurology 2014). However, the interferon-beta non-responders, but not the responders with MS, tended to have a higher PB frequency. We performed an exploratory open-label study to evaluate the efficacy of TCZ in MS patients showing a higher PB frequency. The number of relapses, and EDSS, were evaluated over the TCZ treatment period. Six patients (four women and two men) were enrolled in the study. All patients were negative for anti-AQP4 antibody, and had been diagnosed with MS (three relapsing-remitting, RR; three secondary progressive, SP). One patient was later satisfied the NMOSD diagnostic criteria (Wingerchuk, Neurology 2015). Each participant was given 8 mg/kg of TCZ monthly. Three RR-MS patients showed reduced ARR (TCZ responders), while the other three patients experienced several relapses or progression of EDSS (TCZ non-responders), resulting in the discontinuation of TCZ treatment within a year. Notably, two patients with longitudinally extensive spinal cord lesions were among the responders. In contrast, TCZ non-responders included SP-MS patients and also tended to show long disease durations and high EDSS scores. There were no serious adverse events during the course of TCZ treatment. TCZ shows potential efficacy in the treatment of patients with RR-MS and seronegative NMOSD. However, a diagnosis of SP-MS may be predictive of low TCZ efficacy.

Early aggressive treatment strategy against generalized myasthenia gravis

Kimiai Utugisawa,1 Yuriko Nagane,1 Yasushi Suzuki,2 Tomihiro Imai,1 Naoya Minami,4 Naoki Kawauchi,3 Masayuki Masuda,6 Shingo Konno,7 Hidekazu Suzuki8 and Hiroyuki Mura1
Purpose: To clarify the effects of early aggressive treatment (EAT) strategies on the time course for achieving the treatment target in generalized myasthenia gravis (MG).

Methods: This study of 923 consecutive MG patients retrospectively analyzed 688 generalized MG patients who had received immunotherapy during the disease course. The time course to first achieve minimal manifestations (MM) for longer than or equal to 6 months was compared between the EAT and non-EAT patients. Patient 1: 84-year-old female who had a relapse during tapering oral predonisolone. Patient 2: The 15-year-old female had headache, transient right foot weakness, and convulsion. Her brain MRI showed the characteristic enhanced leptomeniges. She was treated by four times mPSL pulse, oral predonisolone, and anti-epileptic drugs (AED). Patient 3: The 15-year-old female had headache, transient right foot weakness, and convulsion. Her brain MRI showed the characteristic enhanced leptomeninges. She was treated by four times mPSL pulse and AED.

Results: Flow cytometry and immunohistochemistry revealed widespread activation of microglia in naive Cx30-KO mice without any behavioral phenotype. Clinical signs of EAE were significantly ameliorated in Cx30-KO mice compared with wild type mice at chronic progressive phase, but not in acute phase. Immunohistochemistry of the fourth lumbar segment, brain and optic nerves revealed enhanced activation of astroglia in acute phase while less demyelination and exaggerated microglial activation in chronic progressive phase in Cx30-KO mice.

Conclusion: Lack of astroglial Cx30 induces widespread activation of microglia in the central nervous system, which ameliorates chronic progressive EAE possibly through neuroprotective actions.

Clinical and neuroradiological features of pediatric MOG antibody associated-ADEM

Takao Kiriyama,1 Hioki Nanamura,1 Hiroshi Kataoka,1 Kazuma Sugie,1 Toshiyuki Takahashi,2 Kimihiko Kaneko,2 Ichiro Nakashima2 and Satoshi Ueno1

1Department of Neurology, Nara Medical University, Kashihara, Japan, 2Department of Neurology, Tohoku University Hospital, Sendai, Japan

Anti-myelin oligodendrocyte glycoprotein (MOG) antibody is occasionally detected in pediatric patients of acute disseminated encephalomyelitis (pADEM), but the clinical features are variously reported. We reported three patients of pADEM with MOG antibody, and described clinical and neuroradiological characterization of pediatric MOG antibody associated-ADEM.

Patient 1: The 13-year-old female had transient involuntary movement, headache, fever, and convulsion. At first pleocytosis on CSF and enhanced leptomeninges on FLAIR were present. Afterwards, multiple white matter lesion and optic neuritis appeared. She was treated by three times methylpredonisolone pulse therapy (mPSL pulse), oral predonisolone, and anti-epileptic drugs (AED). Patient 2: The 11-year-old female with fever and headache developed transient weakness of left limbs, convulsion and optic neuritis. The high intensity lesion parallel to left parietal cortex spread to white matter on FLAIR. The peak of Lactate and Choline elevated on MR spectroscopy. She was treated by four times mPSL pulse, oral predonisolone, and AED. She had a relapse during tapering oral predonisolone. Patient 3: The 15-year-old female had headache, transient right foot weakness, and convulsion. Her brain MRI showed the characteristic enhanced leptomeninges. She was treated by four times mPSL pulse and AED.

All three patients of pADEM with MOG antibody had headache, fever, transient symptom and convulsions seen for epilepsy, and pleocytosis. In addition, on brain MRI sulcal hyperintensity sign appeared and the cortical and subcortical lesions had spotted or curved linear enhancement. Invasion of cortex was common in pADEM with MOG. Clinical and MRI outcome was almost complete resolution, but we needed to repeat steroid pulse therapy for several months.
A 71-year-old male case of progressive encephalomyelitis with rigidity and myoclonus which revealed chronic rigidity, subacute brainstem symptoms and favorable response to corticosteroids

K Yamazaki, M Kadoya, K Nakagawa, T Wada, A Kadoya, H Takazaki, K Ikewaki and K Kaida
Department of Neurology, National Defense Medical College, Tokorozawa, Japan

Anti-glycine receptor antibodies (GlyR-Ab) have recently been identified in cases of progressive encephalomyelitis with rigidity and myoclonus (PERM), a rare and severe variant of Stiff-person syndrome. A role of GlyR-Ab in the pathogenesis of PERM remains to be determined and the treatment strategy is under debate. Here, we report a 71-year-old male patient with GlyR-Ab-positive PERM who presented chronic neurodegenerative-disease mimicking course and favorable response to steroid therapy. He presented with sleep-relieving board-like rigidity and painful cramps in extremities at 68-year-old, followed by startle-induced myoclonus (hyperekplexia). Extrapyramidal degenerative disorders were initially suspected because the rigidity slowly worsened and generalized in the whole body. Before long lymphoplasmacytic lymphoma (LPL) was diagnosed and rituximab treatment was initiated in view of the possibility of paraneoplastic conditions, with no efficacy. Somnolence, brainstem dysfunction such as ptosis and disturbed eye movements, dysautonomia, respiratory failure, and gastroparesis appeared subacutely at 71-year-old. Cerebrospinal fluid findings and brain MRI were uninformative. The autoantibody survey identified GlyR-Ab in his cerebrospinal fluid and serum, but not any antibodies to GAD65, amphiphysin, VGKC, or DPPX. GlyR-Ab-associated PERM was diagnosed and intravenous immunoglobulin and plasma exchange were administered, with little efficacy. Subsequent intravenous methylprednisolone pulse and oral prednisolone produced improvement of symptoms. Our patient is unique in that subacute brainstem symptoms and hyperekplexia followed chronic rigidity and corticosteroids were most effective for the disorder.

Circulating follicular helper T cells decrease with pathological condition improvement by immunotherapy in myasthenia gravis

Akihiro Kubota and Kyoichi Nomura
Saitama Medical Center, Saitama Medical University, Saitama, Japan

Objectives: To characterize the participation in MG condition of the follicular helper T (Tfh) cells by measuring a change of the Tfh cells in the treatment of the oral steroid, immunosuppressant.

Methods: We defined the Tfh cells as lymphocytes of surface marker CD4+ CXCR5+. Peripheral heparinized blood samples (2 mL) were obtained in the morning from MG patients upon enrollment for assessment of circulating Tfh cells by flow cytometry. Whole blood was incubated with the surface markers (all BD Biosciences), and erythrocytes were hemolyzed, and analyzed on a FACS Canto II cytometer (BD Biosciences). The results are shown in ratio per number of total lymphocytes.

Results: Tfh cells were 6.76 ± 2.74% (n = 32) in the group of before start of immune therapy, 5.33 ± 2.02% (n = 44) in the group of stable state after immune therapy start, 5.77 ± 3.22% (n = 15) in the group of exacerbation state after immune therapy start. Tfh cells were lower in the group of stable state after immune therapy start than in the group of before start of immune therapy (P < 0.05).

Conclusion: The condition of MG patient is stable, meanwhile, Tfh cells decrease by a treatment of the oral steroid, immunosuppressant.

Upregulation of vascular adhesion molecules and downregulation of BBB and lymphatic markers lead to chronic CNS inflammation in progressive multiple sclerosis model

Seiichi Omura,1,2 Fumitaka Sato,1,2 J. Steven Alexander,2 Phillip C.S.R. Kilgore,2 Urska Cvek,2 Marjan Trutschl2 and Ikuo Tsumoda1,2
1Kindai University, Osaka, Japan, 2Louisiana State University, Baton Rouge, LA, USA

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). MS has also been proposed to be a vascular disease, since the expression levels of vascular adhesion molecules have been demonstrated in association with disease activity. Recently, we reported that serum lymphatic markers associated with MS, while Louveau et al. proposed the presence of CNS lymphatics. Theoretically, upregulated vascular adhesion molecules and downregulated blood-brain barrier (BBB)-related molecules contribute to inflammatory cell entry into the CNS, while lymphatics contribute to inflammatory cell exit from the CNS. Although the precise cause(s) of MS is/are unknown, viral infections have been associated with MS. Theiler’s murine encephalomyelitis virus (TMEV) can cause inflammatory demyelinating disease (TMEV-IDD) with viral persistence in the spinal cord of mice. TMEV-IDD has been used as a viral model of MS. We aimed to clarify the involvement of BBB, lymphatics and blood vessels, using the RNA sequencing (RNA-seq) transcriptome data of TMEV-infected mice. We found upregulation of several vascular adhesion molecules and their ligands on T cells in the spinal cord. Principal component analysis (PCA), using the RNA-seq data of these molecules, suggested that upregulation of vascular adhesion molecules as well as downregulation of BBB-related molecules led to lymphocyte entry into the CNS. Downregulation of lymphatic markers could reflect dysfunction of lymphatics, leading to failure of clearance of inflammatory cells, which prolongs inflammation.