AO-01-1 New therapeutic strategy for multiple sclerosis by DNA/RNA heteroduplex oligonucleotide technology

Masaki Ohyagi, Tetsuya Nagata, Kensuke Ibara, Rieko Nishi, Yo Mabuchi, Chihiro Akazawa, Takanori Yokota

1 Department of Medical Genetics, National Defense Medical College, Saitama, Japan. 2 Department of Biochemical Pharmacology, National Defense Medical College, Saitama, Japan. 3 Department of Clinical Pharmacology, National Defense Medical College, Saitama, Japan. 4 Department of Clinical Genetics, National Defense Medical College, Saitama, Japan.

Introduction: The oligonucleotide drugs such as antisense oligonucleotide (ASO) have been shown to be effective in many diseases, but the safety and efficacy of these drugs in clinical practice are not yet fully established.

Methods: We generated several lines of mice carrying a bacterial artificial chromosome (BAC) targeting the familial amyotrophic lateral sclerosis (ALS)-associated G93A SOD1 mutation. We performed pathological studies and genetic analyses on transgenic mice generated by electroporation (i.e., electrotransfer) into the early embryonic stage of mice.

Results: We found that the transgenic mice overexpressing the familial ALS-associated G93A SOD1 mutation showed symptoms of ALS, including periventricular heterotopia (PVH) and hyper-phosphorylation of 4R-tau in the migrating neurons in vivo. The brains of the twins showed 4R-tau aggregation consistent with PSP and several neurodevelopmental malformations including subependymal gliosis. The number of DA neurons in the SNc, nigra pars compacta (SNc), dorsal motor nucleus of the vagus nerve, and myenteric plexus.

Conclusion: Our findings suggest that the development of disease-modifying therapies (DMT) for multiple sclerosis (MS) is an important goal. The development of oligonucleotide drugs targeting the familial ALS-associated G93A SOD1 mutation is a promising strategy for the treatment of MS and other neurological diseases.

AO-01-2 Filamin-A promotes four-repeat tau aggregation and is associated with progressive supranuclear palsy

Koyo Tsujikawa, Kentaro Sahashi, Yuki Hattori, Kohei Hamaoka, Shinshke Ishigaki, Yuichiro Kikuchi, Yohsei Iuchi, Mayumi Katoh, Takashi Miyata, Mari Ishida, Ken Sobue, Naomi Michishimoto, Masahiko Kasunaka

1 Department of Neurology, Nagoya University Graduate School of Medicine, Japan. 2 Department of Biomedical Research and Innovation, Institute for Medical Research, National Hospital, Japan. 3 Research Division of Dementia and Neurodegenerative Disease, Nagoya University Graduate School of Medicine. 4 Department of Neuroscience, Institute for Medical Research, National Hospital, Japan.

Introduction: Progressive supranuclear palsy (PSP) is a tauopathic neurodegenerative disease with four-repeat tau (4R-tau) aggregation in neurons and astrocytes. The pathogenesis of this disease is not fully understood. We hypothesized that Filamin-A (FLNA) plays a role in the aggregation of 4R-tau tau.

Methods: We performed immunohistochemical and biochemical analyses on the brains of patients with PSP, including the examination of tau filament formation and phospho-tau expression. We also performed in vitro and in vivo experiments on cell lines and transgenic mice.

Results: We found that FLNA colocalizes with 4R-tau tau in the neurons and astrocytes of the brain, and that overexpression of FLNA enhances the aggregation of 4R-tau tau. These findings suggest that FLNA plays a role in the pathogenesis of PSP.

Conclusion: Our results provide new insights into the role of FLNA in the aggregation of 4R-tau tau and the pathogenesis of PSP.

AO-01-3 A therapy using peripheral blood cells preconditioned by oxygen-glucose deprivation against ischemia

Masahiro Hatakeyama, Masato Kanazawa, Itaru Ninomiya, Kao Shihomi, Kin Koyama, Tetsuya Takahashi, Osamu Onodera, Masanori Fukushima, Takayoshi Shimohata

1 Department of Neurology, Brain Research Institute, Niigata University, Japan. 2 Biomedical Research Center for Musculoskeletal Innovation, Foundation for Biomedical Research and Innovation at Kobe, 3 Department of Neurology, Gifu University Graduate School of Medicine.

Objectives: To determine the effects of administration of peripheral blood mononuclear cells (PBMCs) preconditioned by oxygen-glucose deprivation (OGD-PBMCs) for ischemic stroke.

Methods: We prepared PBMCs from rats and human by centrifugation. We treated therapeutically and prophylactically with HDO targeting VLA-4, and EAE mice were treated therapeutically and prophylactically with HDO targeting VLA-4-4, and EAE mice were treated therapeutically and prophylactically with HDO targeting VLA-4.

Results: Our findings suggest that HDO targeting VLA-4 remarkably suppressed adoptive transfer EAE. The data showed that HDO targeting VLA-4 could be a potential therapeutic strategy for EAE.

Conclusion: Our findings provide new insights into the potential therapeutic strategy for EAE.

AO-01-4 A53T mutant human-alpha-synuclein BAC transgenic mice exhibit RBD-like behavior and hyposmia

Tomoyuki Taguchi, Masaki Isumi, Masato Ishio, Katsutoshi Matsuzawa, Takeshi Yoda, Kohei Hamana, Dai Yagihara, Yuki Abe, Shohei Beppu, Shinya Ito, Naoki Ogata, Katsutoshi Tsunoda, Takashi Nishizawa, Takamiya J. Nakamura, Yuko Kobayashi, Yukihiro Kita, Naoki Takagi, Katsutoshi Taguchi

1 Department of Neurology, Kobe University Graduate School of Medicine, Japan. 2 Department of Neurobiology, The University of Tokyo, Japan. 3 Department of Neurology, Gifu University Graduate School of Medicine, Japan. 4 Department of Neurology, Kyoto University Graduate School of Medicine, Japan. 5 Department of Neurology, International Institute for Integrative Sleep Medicine (WPI-IISM), Shiga University of Medical Science. 6 Department of Neurology, Nagoya University Graduate School of Medicine, Japan.

Objectives: Parkinson’s disease (PD) is characterized by motor and non-motor symptoms associated with dopaminergic (DA) neurotransmission. DA neurons are affected early in the disease, leading to motor symptoms such as tremor and rigidity.

Methods: We used a mouse model of PD induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to study the effects of HDO targeting VLA-4 on motor and non-motor symptoms.

Results: Our findings suggest that HDO targeting VLA-4 could be a potential therapeutic strategy for PD.

Conclusion: Our findings provide new insights into the potential therapeutic strategy for PD.

AO-01-5 SCA31 transgenic mice show pathologic features similar to human patients

Miwa Higashi, Michi Okita, Nounana Sato, Meiko Asaka, Takashi Ishii, Hanako Aoki, Toru Ishihara, Masahiro Hatakeyama, Takunori Yokota, Kinya Ishikawa

1 Department of Neurology and Neurosurgery Science, Graduate School of Medical Science, Kobe University, Japan. 2 Department of Life Sciences, Graduate School of Arts and Sciences, The University of Tokyo, Japan. 3 Department of Pharmaceutical Sciences, Nagoya University School of Pharmaceutical Sciences, Japan. 4 Department of Biomedical Research and Innovation, Foundation for Biomedical Research and Innovation at Kobe, 5 Department of Neurology, Gifu University Graduate School of Medicine.

Objectives: Spinocerebellar ataxia type 31 (SCA31), one of the most common types of autosomal-dominant cerebellar ataxia in Japan, is caused by the presence of a pentanucleotide repeat containing long TGGGA repeats in introns of brain expressed gene 1 (BEAG1) and thymidine kinase 2 (TK2). Previous studies have shown that RGMa to ALS model mice (transgenic mice overexpressing the familial ALS-associated G93A SOD1 mutation) showed morphological changes in astrocytes, with RGMa aggregation. CONCLUSIONS: Filamin-A induces RGMa aggregation and is a potential driver for PS.
**AO-01-7** Depletion of microglial TAK1 exacerbates neuroinflammation in the mouse model of tauopathy

○ Atsuko Katsumoto,1,2 Hideyuki Takeuchi,1 Keita Takahashi,1 Misako Kunii,1 Mikiko Tada,1 Hiroshi Doi,1,2 Guixiang Xu,1 Bruce Lamb,1 Fumiaki Tanaka1

1 Department of Neurology and Stroke Medicine, Yokohama City University Hospital, Japan. 2 Stark Neuroscience Research Institute, Indiana University, USA

[Objective] The pathophysiology of Alzheimer’s disease (AD) is likely strongly influenced by inflammation mediated through microglia. Depletion of microglial TGF-β activated kinase 1 (TAK1) has been reported to reduce autoimmune inflammation of the central nervous system such as in multiple sclerosis. Using microglia-specific TAK1 knockout mice (Cx3cr1Cre/+; TAK1fl/fl or TAK1 ko) and human microtubule-associated protein tau-overexpressing mice (hTau), we aimed to elucidate the involvement of TAK1 to the progression of tauopathy, a pathological hallmark of AD, as mediated by inflammasome.

[Methods] Transgenic hTau;TAK1 ko mice, hTau mice and TAK1 ko mice were analyzed for tau pathology, microglial activation, and NLRP3 inflammasome activation by immunohistochemistry at 4 and 12 months of age.

[Results] Contrary to what we expected, strong morphological changes were observed in hTau;TAK1ko microglia, whereas microglia in other groups showed minor changes at 4 months. In addition, inflammasome protein NLRP3 and ASC were markedly increased in hTau;TAK1ko mice. Microglial activation had been sustained in hTau;TAK1ko mice at 12 months along with RIPK1 activation. Furthermore, hTau;TAK1ko mice had severe ventricle enlargement that indicates cortical atrophy.

[Conclusions] The deficiency of microglial TAK1 led to continuous inflammasome activation through RIPK1 in mouse model of tauopathy. Because TAK1 depletion itself induced less microglial activation compared to hTau;TAK1ko mice, tau burden might facilitate neurodegeneration under TAK1-deficient conditions with unknown mechanisms.

**AO-01-8** Intrathecal injection of patient-derived anti-Plexin D1-IgG induces neuropathic pain in mice

○ Takayuki Fujii, Yukino Miyachi, Kyoko Iinuma, Ryo Yamasaki, Jun-ichi Kira

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

[Objective] Anti-Plexin D1-IgG associated with neuropathic pain (NeP) binds to small dorsal root ganglion (DRG) neurons. As the pathomechanism of anti-Plexin D1-IgG remains unclear, we aimed to elucidate its pathogenicity by passive transfer of patient-derived anti-Plexin D1-IgG to mice.

[Methods] We intrathecally injected female ICR mice (10 to 12 weeks) with patient-derived purified IgG (20 μl) obtained from two NeP patients with anti-Plexin D1-IgG (Patients 1 and 2) and one healthy control (HC) and assessed mechanical and thermal hypersensitivity using von Frey test and hot-plate test 24 hour after injection. Additionally, we evaluated phosphorylated extracellular signal-regulated protein kinase (pERK) immunoreactivity in DRG neurons from passive transfer mice as a marker for activation of DRG neurons.

[Results] Purified IgG from Patients 1 and 2 induced mechanical hypersensitivity in mice significantly more strongly than HC IgG (n = 7 each group). Moreover, purified IgG from Patient 1 also produced thermal hypersensitivity in hot-plate test significantly more strongly than HC IgG (n = 7 each group). Immunohistochemical analysis revealed that the percentages of the pERK-labeled neurons relative to total DRG neurons in mice treated with purified IgG from Patients 1 and 2 were significantly higher than that in HC IgG-treated mice (12.4 ± 4.7%, 15.4 ± 5.8%, and 0.18 ± 0.4%, respectively, n = 4 each group, p < 0.05).

[Conclusions] Anti-Plexin D1-IgG can induce NeP via ERK activation in DRG neurons.
Clinical features of at-risk subjects for Lewy body disease

Makoto Hattori, Katsunori Yokoi, Yuki Satake, Yasuyuki Tanaka, Makiko Nakamura, Kazuhiko Kawashima, Akiko Suzuki, Tomio Shimizu

Department of Neurology, Nagoya University Graduate School of Medicine, Japan.

Objective: Clinical features of at-risk subjects for Lewy body disease.

Methods: We performed an open-label, long-term drug study in subjects with parkinsonism plus syndrome (PPS) and patients with multiple system atrophy (MSA) in order to evaluate the development of clinical and imaging features associated with the PPS-MSA spectrum.

Results: A total of 31 PPS patients and 21 MSA patients were enrolled. The clinical characteristics of the PPS group included depression, autonomic dysfunction, cognitive impairment, and gait disturbance, while the MSA group had ataxia, postural instability, and cognitive impairment. The PPS group showed a higher prevalence of autonomic dysfunction and depression compared to the MSA group. The PPS-MSA spectrum was characterized by a progressive decline in cognitive function and an increased risk of dementia.

Conclusion: Our findings suggest that the clinical features of PPS-MSA spectrum are heterogeneous and may overlap with those of PPS and MSA. Further studies are needed to clarify the clinical and genetic differences between these two conditions.

Drug screening using urine-derived cells obtained from patients with Duchenne muscular dystrophy

Yota Ichinose1, Hiatani Nai2, Kishin Koh2, Masaki Tanaka3, Hiyoriyuki Ishihara1, Jun Mitsui1, Heisuke Muzikami1, Masafumi Morimoto1, Shunji Ohkawa2, Shoji Tsujii3, Kazumasa Shindo3, Yoshitaka Takiyama1

1Department of Neurology, University of Yamanashi, Japan; 2Institute of Medical Science, International University of Health and Welfare, Tokyo, Japan; 3Kyoto Prefectural University of Medicine, Department of Neurology, University of Yamanashi, Japan; 4Institute of Medical Science, International University of Health and Welfare, Tokyo, Japan; 5Department of Neurology, Chiba University, Japan

Objectives: Duchenne muscular dystrophy (DMD) is a severe muscle disorder characterized by mutations in the DMD gene. We aimed to develop a high-throughput screening system to identify potential therapeutic targets for DMD using urine-derived cell models.

Methods: We established urine-derived cell models from 10 DMD patients and 10 age-matched healthy controls. The cells were cultured and treated with siRNA in a high-throughput manner. We performed a siRNA screening to identify genes associated with muscle regeneration and function.

Results: We identified several genes that were downregulated in DMD cells compared to healthy controls. These genes included MYO5D, RYR1, and ACTA2, which are involved in muscle regeneration and function.

Conclusion: Our findings suggest that urine-derived cell models can be used to identify potential therapeutic targets for DMD. Further studies are needed to validate these findings in preclinical and clinical settings.

The age of onset of multiple system atrophy has become older in the last 50 years

Shinya Oginezawa1, Takuya Konno1, Hiroshi Shimizu2, Mari Tada1, Akiyoshi Kakita3, Akihiro Hori1, Shobha Dhadda1, Masafumi Morimoto1, Hiroshi Doi1, Lars Lannfelt2, Shun Hamada3, Yoshitaka Takiyama1

1Department of Neurology, Brain Research Institute, Niigata University, Japan; 2Department of Pathology, Brain Research Institute, Niigata University, Japan; 3Department of Clinical Neurosciences, University of Cambridge, UK

Objectives: Changes in the age of onset of multiple system atrophy (MSA) over the last 50 years were investigated.

Methods: We performed a retrospective analysis of MSA cases collected from neurology clinics in Japan from 1970 to 2013. We compared the age of onset among patients diagnosed in different decades.

Results: The median age of onset of MSA increased from 60.5 years in the 1970s to 63.1 years in the 2010s. The proportion of patients over the age of 70 at onset also increased from 17% in the 1970s to 33% in the 2010s.

Conclusion: The age of onset of MSA has become older in the last 50 years. This may be due to changes in lifestyle or other environmental factors.
Liquid biopsy in lymphoma associated CNS involvements: a potential tool for the early diagnosis

Kenichiro Murate1, Chisako Iriyama2, Kazutaka Hayashi1, Fumihiko Banno1, Kunihisa Kato1, Atsuhiro Higashiyama1, Koichi Kukuchi1, Ryosuke Nagai3, Toshiki Miyazaki1, Tomoki Ishikawa1, Yoshiki Nino1, Tomoki Muzami1, Satoshi Ita1, Akira Okamoto1, Sayuri Shirai1, Akihiro Ueda1, Hideyuki Yamamoto1, Tatsuro Muto1, Akihiro Tomita1, Hirohisa Watanabe1

1 Department of Neurology, Fujita Health University School of Medicine, Japan, 2 Department of Hematology, Fujita Health University School of Medicine

[Objective] Early diagnosis of lymphoma associated central nervous system (CNS) involvements can be still challenging. Brain biopsy is a gold standard for the diagnosis but invasive. Flow cytometry (FCM) is available only when increasing the number of cells evident in the cerebrospinal fluid (CSF). We aim to elucidate the usefulness of the liquid biopsy of CSF for the diagnosis of CNS lymphoma.

[Methods] This study included 7 cases with lymphoma associated CNS involvements (3 cases of primary CNS lymphoma (PCNSL), 3 cases of diffuse large B cell lymphoma (DLBCL) infiltrating CNS, and 1 case of intravascular large B cell lymphoma). We performed genetic analysis of cell-free DNA (cfDNA) from CSF using droplet digital (dd) PCR focusing on mutations of MYD88L265P and CD79BITAM, those were recurrently observed in patients with DLBCL and PCNSL.

[Results] 6 of 7 cases demonstrated a significant increase of the components which were positive for MYD88L265P mutation irrespective of cell number in CSF. In 1 case, the mutation in the CSF could be detected about four weeks before abnormality in FCM was confirmed. In 6 patients, genetic mutations could be detected at the time point of diagnosis. Conclusions] Liquid biopsy targeted to the CSF cfDNA using ddPCR may become a highly sensitive strategy detecting genetic mutations in CNS lymphoma prior to the presence of abnormal findings of the cytology and FCM. Further studies should be required to establish the sensitivity and specificity of this procedure. It is also necessary to investigate other gene mutations related to DLBCL.

Natural history of gait characteristics in patients with SCA6, SCA31, and MSA-C

Akira Matsushima1, Kunihiro Yoshida2

1 JA Nagano Koseiren Kakeyu-Misayama Rehabilitation Center Kakeyu Hospital, Japan, 2 Department of Brain Disease Research, Shinshu University School of Medicine

[Objective] To reveal a natural history of gait characteristics in patients with SCA6, SCA31, and MSA-C.

[Methods] The subjects were instructed to repeat 10-meter walk 6 or 12 times, with a triaxial accelerometer put on the median of the waist. The velocity, step length, cadence, regularity, symmetry, and body sway were calculated as gait parameters. SARA score was also measured on the same day. Chronological data were measured repeatedly at about 6-month interval, and analyzed by the mixed model.

[Results] Among 61 patients (SCA6, 19; SCA31, 24; MSA-C, 18) who completed the first measurement, 42 (SCA6, 11; SCA31, 15; MSA-C, 16) were measured chronologically. The maximum length of follow-up was 4.8 years in SCA6, 4.9 in SCA31, and 2.3 in MSA-C. The annual deterioration speed of SARA score and gait velocity was -0.8 and -0.02m/s in SCA6, -0.9 and -0.04m/s in SCA31, 3.3 and -0.17m/s in MSA-C, respectively. Statistical models showed that SARA score changed linearly with disease duration in SCA31, but the change was quadric in SCA6. The change of gait velocity with disease duration was quadric in both SCA6 and SCA31. The deterioration speed of gait velocity was relatively high in the early stage compared with the late stage in SCA6 whereas it was relatively slow in the early stage in SCA31. The models could not be applied to MSA-C due to the shortness of disease duration (~2 years). Conclusions] Chronological change of gait characteristics in SCA6, SCA31, and MSA-C was quantified. Those data provided the basic information on how gait function would deteriorate in these subtypes.
**AP-01-1** Whole-exome sequencing of recessive hereditary leukoencephalopathy

**Kei Yasuda, Tomokatsu Yoshida, Ikuo Mizuta, Masashi Watanabe, Ryutaro Sata, Masakazu Nakano, Kei Tashiro, Lilliagam, and Toshio Mizutani**

1Department of Neurology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan; 2Department of Neurology, Ehime Prefectural Hospital, Ehime, Japan; 3Department of Genomic Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan; 4Department of Neurology, National Medical Center, Kyoto Prefecture of Medical University

**Objective**

The identification of genetic cause in patients with leukoencephalopathy is important for a proper diagnosis and appropriate management. We performed an exome sequencing in patients with leukoencephalopathy for the identification of genetic cause.

**Methods**

Whole-exome sequencing was performed in 15 Japanese patients with leukoencephalopathy. Exome sequencing data were analyzed using the GEM software (version 4.0).

**Results**

We identified 4 novel and 4 known genetic cause in 12 patients. The molecular genetic diagnosis rate was 80%.

**Conclusions**

Whole-exome sequencing is a useful tool for the molecular genetic diagnosis of leukoencephalopathy.

---

**AP-01-2** Utility of modified Awaji criteria for diagnosis of amyotrophic lateral sclerosis

**Kazuo Takahashi,1 Yuichi Hamada,2 Masahiro Sono**

1Department of Neurology, Teikyo University School of Medicine, Japan; 2Department of Neurology, Kochi Medical School, Japan

**Objective**

In order to have an efficient diagnostic test of amyotrophic lateral sclerosis (ALS), we developed a modified Awaji criteria for ALS.

**Methods**

A total of 787 patients were enrolled at our hospital from 2000 to 2019. We assessed the clinical features of patients with ALS and modified Awaji criteria using the Awaji criteria and the National Institutes of Health (NIH) criteria.

**Results**

The modified Awaji criteria had a sensitivity of 92.8% and a specificity of 81.8%. The modified Awaji criteria were superior to the NIH criteria.

**Conclusions**

The modified Awaji criteria are useful for the diagnosis of ALS.

---

**AP-01-3** Reclassification based on muscle pathology and specific antibodies in idiopathic myopathies

**Ai Yamakana, Nobuyuki Eura, Tomo Shiotia, Minako Yamakama, Yuka Katakai, Naoki Iwasa, Takao Kiriyama, Tessa Ikumi, Hiroki Kataoka, Kazuma Sugie**

1Department of Neurology, Nara Medical University, Japan

**Objective**

The classification of idiopathic myopathies is challenging due to the lack of a definitive diagnostic test. We aimed to reclassify idiopathic myopathies based on muscle pathology and specific antibodies.

**Methods**

We performed muscle biopsies and immunostainings in 30 patients with idiopathic inflammatory myopathy. Specific antibodies were determined using a panel of 15 antibodies.

**Results**

We reclassified 8 patients from the originalidiopathic inflammatory myopathy to a different category based on muscle pathology and specific antibodies.

**Conclusions**

Muscle pathology and specific antibodies can be useful for reclassifying idiopathic myopathies.

---

**AP-01-4** Distinction of Brainstem MRI Lesions Between MOG and AQP4 Antibody Associated Diseases

**Yuki Matsumoto, Tatsuro Misu, Shunjirugi Kikuchi, Yoshiaki Taike, Isobuyuki Takahashi, Yumimori, Ichiro Nakashima, Kazufusa Fujihara,**

1Tokushima University Graduate School of Medicine, Department of Neurology, Japan; 2Tokushima University Graduate School of Medicine, Department of Diagnostic Radiology, Sendai, Miyagi, Japan; 1National Hospital Organization Yonezawa Hospital, Department of Neurology, Yonezawa, Yamagata, Japan; 2Tokushima Medical and Pharmaceutical University, Department of Neurology, Sendai, Miyagi, Japan, Fukushima Medical University, Department of Multiple Sclerosis Therapeutics, Southern Tokushu Research Institute for Neuroscience, Multisecneuritis & Neuromyelitis Optica Center, Fukushima, Japan

**Objective**

The purpose of this study is to clarify the difference of brainstem manifestations and MRI lesions between MOG-Ab and AQP4-Ab positive patients. We enrolled consecutive cases of MOG-Ab (n=16) and AQP4-Ab (n=10) patients who were referred to three centers. In these cases, we picked up cases with brainstem lesions and compared brainstem signs and lesion localizations between two diseases. We also tried to clarify the difference of brainstem lesions in each area and evaluated brainstem signs. All MRI assessments were performed by two independent neurologist and neuroradiologist. Statistical analysis was done by Mann-Whitney U test with Bonferroni correction with significance level as p value less than 0.05. Results: A total of 28 MOG-Ab and 44 AQP4-Ab patients were enrolled. Clinical symptoms were divided into two groups: MOG-Ab vs. AQP4-Ab. MOG-Ab patients showed more frequent brainstem lesions than AQP4-Ab patients. Furthermore, MOG-Ab patients showed more frequent brainstem symptoms than AQP4-Ab patients.

**Conclusions**

The results of this study demonstrated that MOG-Ab and AQP4-Ab patients have different clinical symptoms and MRI lesions of the brainstem.

---

**AP-01-5** Analyses of immunolabeling patterns using tissue-based assay can predict anti-NMDAR encephalitis

**Makoto Harra, Kenta Tasaki, Natoshi Oshita, Natsuo Kataori, Satoshi Hirose, Tomotaka Mizoguchi, Takayuki Akimoto, Yuka Yokota, Masaki Ishihara, Akhiko Morita, Katsuhiko Ogawa, Satoshi Kamei, Hideki Nakajima**

Division of Neurology, Department of Medicine, Nihon University School of Medicine, Japan

**Objective**

The screening of neuronal surface antibodies (NSAbs) in the cerebrospinal fluid (CSF) of patients is performed via an immunohistochemical assay using mouse brain tissue sections (tissue-based assay: TBA). However, the significance of immunolabeling patterns in the TBA is unclear. The aim of this study was to evaluate whether NSAbs exhibit specific immunolabeling patterns in the TBA in patients with anti-NMDAR encephalitis. We enrolled 17 patients with anti-NMDAR encephalitis with a mean age of 43 years (range: 18-78 years) and compared the immunolabeling patterns with normal controls (n=20) with a mean age of 41 years (range: 16-63 years).

**Methods**

The immunohistochemical assay using mouse brain tissue sections was performed using the tissue-based assay system. The cellular structures analyzed included pyramidal neurons, astrocytes, and oligodendrocytes. The immunohistochemical assay using mouse brain tissue sections was performed using the tissue-based assay system. The cellular structures analyzed included pyramidal neurons, astrocytes, and oligodendrocytes.

**Results**

We observed specific immunolabeling patterns in the TBA in patients with anti-NMDAR encephalitis. However, there were no significant differences in the immunolabeling patterns between patients with anti-NMDAR encephalitis and normal controls.

**Conclusions**

The analysis of immunolabeling patterns using tissue-based assay can predict anti-NMDAR encephalitis.

---

**AP-01-6** Usefulness of olfactory test and pseudoaesthesia test in diagnosis of dementia with Lewy bodies

**Yuza Inagawa, Seichiro Shimizu, Naoto Takeshita, Akito Tsugawa, Daiskue Hirose, Hirohiko Sakurai, Haruo Hanami**

Department of Geriatric Medicine, Tokyo Medical University, Japan

**Objective**

A reduction uptake in DaSPECT and MBIG mycocardial scintigraphy were defined as indirect biomarkers in the 4th revised clinical diagnosis of dementia with Lewy bodies (DLB). Other factors may also be useful in diagnosing DLB such as a decrease in olfactory perception as supportive clinical features and the presence of hallucinations as core clinical features. The purpose of this study was to determine the efficacy of olfactory and pseudoaesthesia test in distinguishing between DLB and Alzheimer's disease (AD). The usefulness was compared with indicative biomarkers of DLB: MethA. Method: A total of 40 DBL and 24 AD patients were enrolled. Decline in olfactory function was determined with the use of DaSPECT and MBIG. The usefulness of olfactory test and sensory test were compared with the DaSPECT and MBIG data on the illusion reaction rate. The values of the left-right specific binding ratio were used in DaSPECT; the heart-to-mediastinum ratio on the delay phase of MBIG was used in MBIG. The results were analyzed using two groups: high-hypocampal region (hipp) and cerebellar cortex (Cb). The specific antigens of the NSAbs were confirmed using a cell-based assay. Results: The CSF samples of 10 (16%) patients showed a specific immunolabeling pattern in the TBA with DaSPECT. The DaSPECT and MBIG were compared with the MethA. The olfactory test and pseudoaesthesia test were compared with the DaSPECT and MBIG. The results showed a significant difference between the two groups: high-hypocampal region (hipp) and cerebellar cortex (Cb).

**Conclusions**

The usefulness of olfactory test and pseudoaesthesia test in diagnosis of dementia with Lewy bodies is useful in distinguishing between DLB and AD. This suggests that these tests may be useful in determining whether to perform a nuclear medicine test, and offer an alternative in facilities not equipped to perform that.
AP-01-7 Characteristic of Perry disease in Japan
○Takayasu Mishima1, Shinsuke Fujioka1, Kazunori Sato2, Hideki Houzen3, Ichiro Yabe1, Kazutaka Shiomi1, Kenya Nishio3, Taku Hatano4, Nobutaka Hattori5, Yoshiho Tsuibo1
1Department of Neurology, Fukuoka University School of Medicine, Japan, 2Department of Neurology, Hokkaido University Graduate School of Medicine, 3Department of Neurology, Ohkio Kosei General Hospital, 4Division of Neurology, Respiratory, Endocrinology and Metabolism, Department of Internal Medicine, University of Miyazaki, 5Department of Neurology, Juntendo University School of Medicine

[目的] Perry病はパーキンソニズム、うつ・アパシー、原因不明の体重減少、中枢性呼吸障害を認め、同疾患の自律神経障害の生物学的マーカーになりうる。Perry病はL-dopaやドパミンアゴニスト投与による衝動制御障害を来しやすい取り込みが低下し、便秘や排尿障害、起立性低血圧などが合併していた。〔結論〕過去の我々の報告と同様にL-dopaやドパミンアゴニスト投与後に衝動制御障害K68E, G71Vであり、発症者はPerry病の診断基準を満たしていた。1症例では、2家系 (北海道家系、宮崎家系) の存在が確認され、2家系の遺伝子変異はそれぞれPerry病の国際診断基準を作成し、Perry症候群からPerry病への名称変更を提

AP-01-9 Magnetoencephalogram analysis of epilepsy patients with amygdala enlargement
○Naoki Takegami1, Satoshi Kodama1, Yuichiro Shirata2, Takayuki Tamura1, Kaori Sakushi1, Naoto Kuni1, Harushi Mori1, Masato Yumoto1, Masashi Hamada1, Tatsumi Toda1
1The Department of Neurology, Graduate School of Medicine, The University of Tokyo, Japan, 2The Department of Neurosurgery, Graduate School of Medicine, The University of Tokyo

Background and objective: Amygdala enlargement (AE) is associated with temporal lobe epilepsy (TLE). However, its occurrence, dysplasia, encephalitis, or seizure-related secondary changes. We investigated whether the distribution pattern of epileptic discharges detected with magnetoencephalogram (MEG) is related to clinical phenotype. Methods and patients: We retrospectively analyzed MEG findings in AE-TLE patients. Of 27 consecutive patients who underwent MEG from January 2017 to June 2019, MEG findings for AE were screened by two neurologists (SK and NT) and later confirmed by a neuroradiologist (BM). Three neurologist-neuropsychologists (MV, SK, and NT) visually inspected distribution of the equivalent current dipoles (ECDs) with the MEG Result. We found 16 cases of AE-TLE and were able to classify the ECD pattern into three categories medial temporal ECD type, lateral temporal ECD type, and diffuse ECD type. Nine showed unilateral medial ECDs and AE on the same side (four left, five right). Three more patients had medial ECDs, two of whom had left ECDs and bilateral AEs while the other bilateral ECDs and bilateral AEs. These patients were relatively older. Lateral ECDs were found in two, and both were bilateral with right AE. These two showed emotional changes. The other two had diffuse ECDs on the left side and left AE associated with atypical epilepsy and secondary generalization Conclusion ECD distribution pattern in AE-TLE patients could be categorized into three groups, each related to a specific clinical phenotype.
AP-02-1  Chronic cerebral hypoperfusion induces Alzheimer’s pathology and mitochondrial form change in mice

Namiko Matsumoto, Tian Feng, Toru Yamashita, Yun Zhai, Jingwei Shang, Yumiko Nakano, Ryuta Morihara, Yusuke Fukui, Nozomi Hishinuma, Yutaka Ohhashi, Katsunori Oda
Okayama University, Department of Neurology, Japan

Objective: We investigated the changes of mitochondrial fission and fusion proteins in AD with chronic cerebral hypoperfusion (CHP) in a novel mouse model. Methods: To clarify the impacts of hypoperfusion (HP) on mitochondrial dynamics, reactive oxygen stress in the pathogenesis of AD, and protective effect of galantamine, the novel AD with HP mouse model (APP23 + HP) was applied in this project. Male mice were randomly divided into the APP23 group (APP23 + sham surgery, n = 17), HP group (chronic hypoperfusion group (APP23 + HP, n = 12), and galantamine treated group (APP23 + HP + Gal, n = 10). Results: Compared with APP23 mice, APP23 + HP mice significantly enhanced the number of Ab oligomer-positive/phosphorylated tau (pTAU) cells, the expression of mitochondrial fission proteins (Drp1 and Fis1), and decreased the expression of mitochondrial fusion proteins (Opal and Mfn1) in the cerebral cortex (CTX) and thalamus (TH) at 12 month (M) of age. Moreover, the expression of peroxiredoxin products (4-HNE and 8-oxo-dG) showed a significant increase in CTX and TH of APP23 + HP mice at 12 M. However, above neuropathological characteristics were retrieved by galantamine (Gal) treatment, detected through immunohistochemical analyses.

Conclusions: The present study demonstrates that cerebral HP shifted the balance in mitochondrial fission from fusion to fission with increasing Ab oligomers and phosphorylated tau in APP23 mice, and such neuropathologic changes were strongly attenuated by Gal treatment.

AP-02-3  A new method of radiological-pathological comparative study using micro-MRI for small vessel disease

Hidehiro Ishikawa, Atsushi Nishi, Yuichi Il, Akhiro Shindo, Yamatani Nishiyama, Masayuki Maeda, Yuusho Kato, Yoshio Hashizume, Hidekazu Tomimoto
1 Mie University, Department of Neurology, Japan, 2 Mie University, Department of Advanced Diagnostic Imaging, 3 Mie University, Radiosotope Facilities for Medical Science, 4 Chou Medical Institute, Fukusihuma Hospital

Objective: Small vessel diseases (SVDs) have a crucial role in stroke and dementia. Although a high-resolution MRI can partly detect SVDs, the exact underlying pathology remains uncertain. It has been difficult to verify small lesions with pathology. In this study, we aimed to gain more insight into the pathological basis of MRI-defined SVDs using a new method with ex vivo micro-MRI (exM-MRI). Methods: Brain samples from four cases with ex vivo MRI-defined SVDs were subjected to ex vivo 3T micro-MRI histopathology corresponding to cerebral microbleeds (CMB), cortical microinfarct (CMI), and white matter hyperintensity (WMH). In the both side of ex vivo MRI and in vivo MRI were examined using paraffin sections with HE staining and immunohistochemistry. (Results) SVDs such as CMB, CMI, and WMH on in vivo MRI were clearly detected on ex vivo micro-MRI. Further, CMIs smaller than 4mm were detected clearly on ex vivo micro-MRI. These lesions were regarded as histopathologically confirmed in CMB with CMI and detected as low intensity lesion on T2-weighted image on ex vivo micro-MRI turned out to be agenouscious on histopathology. (Conclusion) We revealed the histopathological findings about MRI-defined SVDs. Our new method with ex vivo MRI is useful to clarify the exact pathology of SVDs on in vivo MRI.

AP-02-5  Coagulation Mechanism of BRCA1 and Tau

Masanori Kurihara, Tatsuo Mano, Shigeo Murayama, Atsushi Iwata, Tatsushi Toda
1 Department of Neurology, Graduate School of Medicine, The University of Tokyo, Japan, 2 Japan Society for the Promotion of Science (Research Fellow DK21), 3 Department of Neurophatology (the Brain Bank for Aging Research), Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology

Objective: We previously reported in Alzheimer’s disease (AD) that tau aggregation induces coaggregation of DNA repair protein, BRCA1, and that subsequent dysfunction of DNA repair in neurons may be important in AD. Since preventing this coaggregation may improve neuronal dysfunction in AD, we investigated the coaggregation mechanism. Methods: To investigate the property of tau aggregates important for coaggregation with BRCA1, we tested whether the same phenomena occur in other human tauopathies with different tau isoforms and strains. We evaluated in vitro coaggregation of tau with DNA repair proteins and 4-kDa and 2-kDa tau of F9 and other human tauopathies. Results: BRCA1 coaggregated with tau but did not aggregate with both DNA repair proteins and tau. BRCA1 was observed in all examined cell lines with full length or 4 deletion mutants of BRCA1 and tau aggregation was induced. Conclusion: Coaggregation of BRCA1 and tau aggregates were seen in not only AD but also in PD and FTD. However, BRCA1 was observed in AD and PD from brains in which BRCA1 was not available. In the cellular model, the BRCA1 mutant lacking the C-terminal BRCT domains was the only mutant without signs of BRCA1 aggregation. Conclusion: Tau aggregation with BRCA1 occurs in AD and the nature of BRCA1 and tau aggregation was critical for the coaggregation mechanism. We will further study the precise mechanism and aim to prevent the coaggregation of BRCA1 and tau.

AP-02-6  Identification of blood-based exosomal biomarkers for Alzheimer’s disease by using an animal model

Tomohiro Imamura, Hirohisa Asai, Yuki Yamasaki, Jun-ichi Kira
1 Department of Neurology, Neurological Institute Graduate School of Medical Sciences, Kyushu University, Japan, 2 Department of Neurology, Graduate School of Medicine, Kyoto University, Japan

Objective: Alzheimer’s disease (AD) is one of the major causes for dementia. Although reliable biomarkers for AD are highly needed, validated peripheral biomarkers for AD diagnosis are not available. To identify exosomal miRNA biomarkers for AD diagnosis using an animal model. Methods: Six-month-old APP-KI mice (APP23 mice) and wild-type mice were used as control. The mice were treated with β-secretase inhibitor (BACE1 inhibitor) Kit (Kit. Quence, Valencia, CA, USA). MicroRNAs in exosomes were quantified by the Illumina HiSeq sequencing platform. We used TargetScanMouse v7.1 to generate lists of predicted target genes. To extract the biological meaning associated with these large gene lists we used the bioinformatics database, DAVID. Result: A next generation sequencing analysis revealed differential miRNA expression profiles in APP-KI and wild-type mice. Only one miRNA was significantly up-regulated and 10 miRNAs were down-regulated. The up-regulated miRNA was reported to be associated with neurodegenerative diseases. The most significantly down-regulated miRNA was one of the miRNAs which has been indicated to be a target of AD progression. 

Conclusions: We could identify miRNA signatures that might serve as potential blood biomarkers for AD. These potential blood-based biomarkers may lead to earlier diagnosis as well as new targets for AD treatment. Further analyses on human samples are now underway.
A pericyte-macrophage axis induces myelin debris clearance and tissue repair after ischemic stroke

Tomoya Shibahara, Tetsuro Ago, Masaki Tachibana, Kuniyuki Nakamura, Yoshinobu Wakisaka, Junya Kuroda, Takanari Kitazono

Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Japan

Background and Purpose-Both macrophage-mediated clearance of myelin debris and pericyte-mediated fibrotic response within infarct area are important processes in tissue repair and functional recovery after ischemic stroke. We aim to study the post-stroke intercellular interaction between pericytes and macrophages in these processes. Methods-We performed permanent occlusion of the middle cerebral artery (pMCAO) in wild-type and PDGFRβ heterozygous knockout (Pdgfrb+/-) mice in which pericyte functions are deficient. We examined post-stroke histological changes by immunohistochemistry and quantitative PCR, and evaluated neurologic functions. We also examined the effects of culture medium (CM) of cultured pericytes on functions of bone marrow-derived macrophages (BMDMs). Results-Intra-infarct accumulation of macrophages was significantly attenuated in PDGFRβ+/- mice from day 7 to 28. Pericytes within infarct area expressed CCL2 and CSF1, representative molecules involved in macrophage migration and proliferation. Quantitative PCR demonstrated that the intra-infarct expression of CCL2 and CSF1 was significantly lower in PDGFRβ+/- mice. Furthermore, PDGFRβ+/- mice exhibited suppressed clearance of myelin debris and attenuated functional recovery after pMCAO. CM of cultured pericytes significantly enhanced migration, proliferation and phagocytosis of myelin debris in BMDMs. Conclusions-Pericytes may enhance macrophage recruitment and clearance of myelin debris within infarct area, thereby contributing to tissue repair and functional recovery after ischemic stroke.
APe-01-1 withdrawn

APe-01-2 withdrawn

APe-01-3 Endothelial cells regulates cognitive function through communication with hippocampal neurons

○ Feng Han, Ya-ping Lu, Ying-mei Lu
College of Pharmacy, Nanjing Medical University, China

Objective: The proper interactions between blood vessels and neurons are critical for maintaining the strength of neural circuits and cognitive function. However, whether vascular cells can directly regulate neural circuits through intercellular signaling in the central nervous system remains largely unknown.

Methods: We used the mice of the selective knockout of semaphorin 3G in endothelial cells. Extracellular field recordings and Whole cell recordings combining with optogenetics were used to determine the mechanisms that underlie synaptic plasticity and transmission. Y-maze task and contextual-dependent memory were examined.

Results: In this study, we used a database mining strategy with three inclusion criteria to find a critical gene Sema3G. We showed that knockout of Sema3G specifically in ECs impairs hippocampal dependent memory in mice. Furthermore, we uncovered a Sema3G/Nrp2/PlexinA4 signaling cascade that activates intracellular Rac1 to promote excitatory glutamatergic synapse density and synaptic function.

Conclusion: These results provide the first evidence that, in the central nervous system, Sema3G, a vascular endothelium derived synaptic organizer, plays a critical role in regulating synaptic plasticity and hippocampal dependent memory.

Our findings highlight the role of vascular endothelial cells in regulating cognitive function through intercellular communication with neurons in the hippocampus.

APe-01-4 Results of thirty-six-month amyloid PET: continuous reduction in amyloid burden with gantenerumab

Gregory Klein1, Paul Delmar2, Geoffrey A. Kerchner2, Carsten Hofmann1, Danielle Allen2, Andrew Davis1, Nicola Voyle3, Hironori Tatsuda4, Monika Baudler1, Pablo Fontoura1, Rachelle Doody1
1Roche Pharma Research and Early Development, Switzerland, 2Roche Genentech Product Development, Ltd., 3Chugai Pharmaceutical Co., Ltd., 4Genentech, Inc.

Objectives To report the effects of high-dose gantenerumab (1,200 mg/month (mo)) on amyloid PET at 36 mo of ongoing treatment in the XcetReAD (SR) and MarquopReAD (MR) open-label extension (OLE) studies. Methods Patients (pts) were assigned to one of five titration schedules (ranging from 2 to 10 mo). Due to differences in titration schedules and time between DB and OLE dosing, the analyses divided pts into three cohorts: MR DB placebo (MR-Pbo), MR DB pretreated with gantenerumab (MR-Gant), and SR DB assigned to placebo or gantenerumab (SR). Change from OLE baseline in amyloid burden was assessed via global and regional standard uptake value ratio analysis of florbetapir PET scans acquired at OLE baseline: Mo 12 (Year 1), Mo 24 (Year 2), and Mo 36 (Year 3). Results Preliminary pooled analyses of 23 pts (MR-Pbo, 8; MR-Gant, 6; SR, 9) who had a 36-mo scan by May 30, 2019 showed continued amyloid reduction between the 24- and 36-mo scans. Seventeen of 23 pts (73.9%) were below the amyloid-positive threshold of 24% at 36 mo of gantenerumab treatment. An additional - 8 pts are expected to have their OLE 36-mo PET scan by December 2019. The safety profile of gantenerumab remained unchanged compared with prior reports. Conclusion Updated findings are expected to confirm preliminary results and show continued reduction in amyloid burden with ongoing gantenerumab treatment for 36 mo. These data support the ongoing investigation of the clinical efficacy of gantenerumab in two Phase III trials in pts with early (prodromal-to-mild) AD (GRADUATE I, II). Updated, 2019.

APe-01-5 withdrawn

APe-01-6 Wnt signaling is associated with hemorrhagic transformation after intravenous thrombolysis

○ Junlei Chang1, Song Ta2, Zhen-ni Gao1, Hang Jin2, Peng Zhang2, Feng Li3, Chengqiu Zeng1, Qingquan Gu4, Yuan Zhang4, Wenlan Liu1, Yi Yang1, Xian-fang Rong1
1Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, China, 2Dept of Neurology, The First Hospital of Jilin University, 3Shenzhen RealOms Biotech Co., Ltd., 4Shenzhen Second People’s Hospital

Objective: The Wnt signaling is essential to blood-brain barrier function in animals. Here we explored the implication of the Wnt signaling in hemorrhagic transformation (HT) after intravenous thrombolysis in acute ischemic stroke (AIS) patients. Methods Blood samples are collected at admission prior to thrombolysis and HT is detected with CT scans 24 hours later. Serum Wnt signaling biomarkers were measured, and SNPs or exon sequences for 28 Wnt signaling genes were determined with a customized sequencing chip. Gene mutations were further studied in zebrafish in cellular models. Results 124 patients including HT patients (n = 54, consecutively enrolled) and Non-HT patients (n = 70, age- and sex-matched) were enrolled. Serum DKK3 was decreased in HT patients (p=0.001), whereas serum DKK2 was selectively increased in HT patients with parenchymal hematoma (PH) (p=0.015). FVIIIa SNP rs2383101 and rs1224488, and FVIII:VIIa SNP rs60606462 were increased in HT patients (p<0.05) GPR124 SNP rs5306900 (missense variant, c.357G>C-A1) was selectively enriched in PH patients (p=0.0088). A higher proportion of PH patients than Non-HT patients had multiple copies of these HT risk SNPs (4 copies/patient, 18.2% vs. 7.6%). Furthermore, the c.357G>C mutation of GPR124 substantially reduced Wnt signaling by dissociating DVL1 from GPR124 intracellular domain in cell culture. Conclusions Wnt signaling serum biomarkers and genetic variations are associated with increased risk of HT following thrombolysis in AIS patients, suggesting a key role of Wnt signaling in thrombolysis induced intracerebral hemorrhage.
CRTC1-regulated microRNA-132/212 plays a vital role in stroke mediated by vascular function

Objective MicroRNAs (miRNAs) play critical roles in post-transcriptional regulation of gene expression. Among the miRNAs involved in central nervous system diseases, miR-132/212 cluster was demonstrated to regulate the process of synaptogenesis, neuroinflammation and brain vascular integrity. However, the mechanism of miR-132/212 in cerebral ischemia remains unrevealed. This study therefore aims to investigate the role of miR-132/212 in ischemic stroke.

Methods Neuronal cultures were prepared from the cortex of embryonic day 16 (E16) mice embryos. Oxygen glucose deprivation (OGD) was performed as in vitro ischemia. MiR-132/212 qPCR expression assay was taken. As CRTC1 was predicted to be an upstream regulator of miR-132/212 by statistics analysis, we generated CRTC1-/- mice and subjected them to 60min-middle cerebral artery occlusion (MCAO). Neurological functions were examined. BBB damage was evaluated by Evans Blue injection. Moreover, miR-132/212 target proteins were assayed.

Results The neuronal death was remarkably aggravated in neuronal cultures isolated from CRTC1-/- mice after OGD. Likewise, the infarct volume and BBB damage in CRTC1-/- mice were significantly aggravated than wild-type (WT) mice. MiR-132/212 expression was obviously decreased in CRTC1-/- mice after stroke. Neurological function deficits of CRTC1-/- mice were evidently worse than WT mice.

Conclusion These findings suggest that miR-132/212 cluster is modulated by CRTC1, and it could associate with functional recovery after ischemia by enhancing neuronal survival and vascular integrity.