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

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[Introduction] The oligonucleotide drugs such as antisense oligonucleotide (ASO) have remarkably progressed over the last few years with the recent approvals and promising developments; however, effective delivery of oligonucleotides to lymphocytes *in vivo* remains a major challenge. Here, we report that a heteroduplex oligonucleotide (HDO), comprised of an ASO and its complementary RNA, can regulate lymphocytes function *in vivo*. We also define the therapeutic application of HDO in EAE, a mouse model of multiple sclerosis (MS). [Methods] We evaluated the target gene and protein expression in wild-type mouse lymphocytes after intravenous injection of ASO and HDO by qRT-PCR and flow cytometry. We analyzed endocytic pathways of HDO in cultured lymphocytes by pharmacological inhibition. We then evaluated the clinical score in active EAE mice treated therapeutically and prophylactically with HDO targeting *VLA-4*, and EAE mice induced by adoptively-transferred MOG_{35-55}-primed T cells which were treated with HDO *ex vivo*. [Results] Intravenous administration of HDO could effectively silence the lymphocyte endogenous gene expression with higher potency, efficacy, and longer retention time than ASO. We demonstrated the distinct mechanisms of HDO cellular uptake. Both therapeutic and prophylactic inhibition of *VLA-4* using HDO ameliorated EAE symptom and pathology. HDO targeting *VLA-4* remarkably suppressed adoptive transfer EAE. [Conclusions] HDO-mediated gene silencing technology based on manipulating lymphocyte functions will provide a new therapeutic platform to treat MS and EAE.

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

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BACKGROUND: Progressive supranuclear palsy (PSP) is a fatal neurodegenerative disease with four-repeat tau (4R-tau) aggregation in neurons and astroglial cells. The mechanism that drives wild-type 4R-tau aggregation in PSP has not been elucidated. METHODS: We performed pathological studies and genetic analyses on monozygotic twins concordant for PSP without tau mutations. We added protein expression analyses on 34 human brains, cell-based biochemical assays and animal experiments utilizing *in utero* electroporation (IUE) [n ≧ 3 in each group]. RESULTS: The brains of the twins showed 4R-tau aggregation consistent with PSP and several neurodevelopmental malformations including periventricular heterotopia (PVH). Our whole exome sequence and high-resolution microarray identified duplication of *filamin-A* in the twins. The brain tissues from the twin and sporadic PSP showed significantly increased protein levels of filamin-A in sarkosyl-insoluble fractions ($p < 0.05$) and co-localization of filamin-A with aggregated tau in their neurons and astroglial cells. In rat primary astroglial cells expressing human 4R-tau, filamin-A induced hyper-phosphorylation and further aggregation of 4R-tau. Mice overexpressing filamin-A in neural progenitors by IUE at embryonic day 14 showed the phenotype of PVH and hyper-phosphorylation of 4R-tau in the migrating neurons *in vivo*. The extracted primary cortical neurons overexpressing filamin-A showed morphological changes in actin cytoskeleton with 4R-tau aggregation. CONCLUSIONS: Filamin-A induces 4R-tau aggregation and is a potential driver for PSP.

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

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[Objective] 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 compared levels of vascular endothelial growth factor (VEGF) and cytokines in conditioned media under normoxic and OGD conditions. Then, we performed microscopic analyses to assess the expression level of remodeling factors, angiogenesis, and axonal outgrowth by administration of PBMCs after ischemic stroke in rats. Finally, we examined the therapeutic benefits of intra-arterially administered OGD-PBMCs after cerebral ischemia. [Results] We confirmed marked secretion of remodeling factors *in vitro*. First, while VEGF levels were found in the conditioned media of OGD-PBMCs, the same was not valid for PBMCs under the normoxic condition ($P = 0.03$). Expression of transforming growth factor-β (TGF-β), was twice higher after OGD compared with a normoxic condition ($P = 0.04$). We also found that intravascular administration of OGD-PBMCs caused increased expression of VEGF and TGF-β in the brain parenchyma. This treatment promoted angiogenesis and axonal outgrowth in the ischemic penumbra. Finally, we demonstrated that administration of OGD-PBMCs at 7 days after ischemia prompted functional recovery at 28 days after cerebral ischemia compared to control therapies. [Conclusions] Intravascular administration of PBMCs preconditioned by OGD might be a novel therapeutic strategy against ischemic stroke.

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

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[Objective] Parkinson's disease (PD) is characterized by motor and non-motor symptoms associated with dopaminergic (DA) cell loss and the accumulation of pathological α-synuclein (α-syn). To develop disease-modifying therapies (DMT), an animal model that recapitulates the early phase of the disease is indispensable. The aim of this study is to create mouse model that reproduces the early stage of PD.[Methods] We generated bacterial artificial chromosome transgenic (BAC Tg) mice harboring the entire human α-syn gene and its gene expression regulatory regions with the A53T mutation and risk polymorphisms. [Results] A53T-BAC Tg mice showed phosphorylated α-syn accumulation in the olfactory bulb, cerebral cortex, substantia nigra pars compacta (SNc), dorsal motor nucleus of the vagus nerve, and myenteric plexus. Behaviorally, these mice exhibited RBD-like behavior at as early as 5 months and hyposmia at 9 months, coupled with phosphorylated α-syn accumulation in olfactory pathway and RBD-related regions such as the sublaterodorsal tegmental nucleus. The number of DA neurons in the SNc was decreased in an age-dependent manner by up to 17.1% at 18 months, although the mice did not show locomotor dysfunction. [Interpretation] A53T-BAC Tg mice recapitulated the prodromal symptoms and related pathologies of PD. This novel transgenic mouse model can provide an opportunity to understand the prodromal changes of the disease and to start DMT for PD.

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

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[Objective] Spinocerebellar ataxia type 31 (SCA31), one of the most common types of autosomal-dominant cerebellar ataxia in Japan, is caused by the presence of complex pentanucleotide repeats containing long TGGAA stretch in introns of brain expressed associated with NEDD4-1 (*BEAN 1*) and thymidine kinase 2 (*TK2*). Previous study showed that RNA foci containing UGGAA repeats were observed in Purkinje cell (PC) nuclei of SCA31 patients, and that UGGAA repeats caused progressive neurodegeneration in *Drosophila*. This study aimed to investigate the pathological role of UGGAA repeat of SCA31 through generating a transgenic mouse model. [Methods] We generated several lines of mice carrying a bacterial artificial chromosome (BAC) containing the entire human *BEAN1* derived from a homozygous SCA31 patient. Thus, the pentanucleotide repeat containing TGGAA is introduced in mice with the flanking human genomic context. We investigated their histopathological and genetic changes. [Results] Several lines were successfully maintained. Among those, we confirmed that at least two lines faithfully expressed human *BEAN1* including messenger RNA isoforms with extended coding exons. We found RNA foci containing UGGAA repeat in PC nuclei of BAC transgenic mice. Similar foci were never observed in wild type (WT) mice. Some of these RNA foci were seen co-localized with TDP43 as in human patients and *Drosophila*. [Conclusion] Expressing SCA31 genomic region in mice leads to RNA foci formation and TDP43 co-localization. This will be a valuable model in studying SCA31 pathobiology and therapy.

AO-01-6 Role of Repulsive guidance molecule A (RGMa) in amyotrophic lateral sclerosis (ALS)

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[Object] RGMa was originally identified as a molecule that has a repulsive effect on axon growth, but, recent evidence indicates that it plays significant role in neuronal apoptosis. The aim of this study is to reveal the role of RGMa in ALS. [Method] We first measured RGMa levels in cerebrospinal fluid (CSF) and compared ALS patients with controls. Next, we performed western blot analysis for CSF to confirm the isoform of RGMa. Finally, in order to reveal the function of RGMa in ALS, we administered neutralizing antibodies against RGMa to ALS model mice (transgenic mice overexpressing the familial ALS-associated G93A SOD1 mutation). [Results] The levels of soluble RGMa were significantly increased in the CSF of ALS patients. Western blot analysis revealed that isoform containing receptor binding site was increased in the CSF of ALS patients. Of note, the soluble RGMa levels were correlated with the severity of respiratory status and the administration of neutralizing antibody against RGMa to ALS mice significantly extended survival and motor symptoms. [Conclusion] These data suggest that RGMa play an important role in the pathogenesis of ALS

AO-01-7 Depletion of microglial TAK1 exacerbates neuroinflammation in the mouse model of tauopathy

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[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 ($Cx3cr1^{Cre/+}$;$TAK1^{fl/fl}$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

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

AO-02-1 The Phase 2 study of BAN2401 (anti-amyloid beta protofibril antibody) in early Alzheimer's disease

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Background: BAN2401 is a humanized monoclonal antibody that binds with high selectivity to amyloid-beta (Aβ) protofiblils. We have conducted a Phase 2 study in subjects with early Alzheimer's disease (AD) in order to evaluate efficacy, safety, and tolerability of BAN2401 (NCT01767311). **Methods:** This study was an 18-month, placebo-controlled, double-blind, parallel-group, multicenter, and multinational study of BAN2401 in 856 subjects diagnosed as early AD with confirmed brain amyloid pathology including 53 Asian subjects (34 Japanese and 19 Korean). This study assessed the changes from baseline to 18 months in both clinical symptoms (ADCOMS, ADAS-Cog, CDR-SB) and biomarkers (CSF, amyloid PET). **Results:** BAN2401 demonstrated slowing disease progression on clinical outcome measures at 18 months at the top two doses (10 mg/kg biweekly and monthly). The efficacy in Asian population was a same tendency with that in whole population. BAN2401 demonstrated a dose-dependent and significant reduction in brain amyloid plaques as measured by amyloid PET, and a dose-dependent increase in CSF Aβ[1-42] level. **Conclusion:** This Phase 2 study of BAN2401 was the first large clinical study of anti-Aβ treatment which supported the amyloid cascade hypothesis of AD pathophysiology and demonstrated an alteration on the underlying AD pathology led to sustained clinical benefits compared with placebo. Currently, a global Phase 3 trial (CLARITY AD) is underway based on the result of this Phase 2 study to confirm the efficacy of BAN2401 in multiple countries including Asia.

AO-02-2 A clinical and genetic study of SPG80, the new type of hereditary spastic paraplegia

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[Objective] To find a new causative gene, exome sequencing of genomic DNA from hereditary spastic paraplegia (HSP) patients recruited from the Japan Spastic Paraplegia Research Consortium (JASPAC) was carried out. [Methods] We performed exome sequencing of juvenile-onset sporadic SP patient and her parents. Western blot analysis was conducted in COS7 cells transfected with GFP-tagged UBAP1-WT and UBAP1-mutant (c.425_426delAG) plasmids.Fluorescence images were acquired in primary cultures of rat hippocampal neurons transfected with the same plasmid as above. [Results] Heterozygous de novo mutation of *UBAP1* was identified in the first patient, and we extracted additional 4 families (6 patients) with heterozygous mutation of *UBAP1* from JASPAC and in-house samples. All mutations were loss-of-function mutations (p.K143Sfs*15, p.S105Pfs*46 and p.E179*), and all 7 patients showed similar clinical features of a pure type of juvenile-onset HSP. Functional studies on rat hippocampal neurons revealed that the C-terminal deletion UBAP1-mutant of our disease model had lost its ability to bind ubiquitin in vitro. Overexpressed wild type UBAP1 interacted directly with ubiquitin on enlarged endosomes, while the UBAP1-mutant cannot be recruited to endosome membranes. Loss of UBAP1 function may perturb endosomal fusion and sorting of ubiquitinated cargos. [Conclusion] We found *UBAP1* gene as a new causative gene of HSP (SPG80). Our study demonstrated that mutations in the *UBAP1* gene cause SPG80 and elucidated its pathogenesis. We will continue to find undiagnosed SPG80 patients in Japan.

AO-02-3 Clinical features of at-risk subjects for Lewy body disease

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【目的】健常者におけるレビー小体病のprodromal症状のスコア分布を明らかにし、ハイリスク群を抽出する。また、ハイリスク者の臨床的特徴と自然歴を明らかにする。【方法】共同研究機関の健診受診者に対して、PASE（身体活動量）、SCOPA-AUT（自律神経障害）、RBDSQ（レム期睡眠行動異常症）、SAOQ（嗅覚障害）、BDI-Ⅱ（うつ）、ESS（日中の眠気）を施行する。ハイリスク群と正常群の2群に分け、両群に対してレビー小体病に関する二次評価を前向きに施行する。【結果】2017年度に12,378名の健診受診者にアンケートを配布し、回答者は4,953名（男性：女性＝2641：2312）、年齢は51.1±10.4歳であった。50歳以上かつSCOPA-AUT、SAOQ、RBDSQの2つ以上で上位10%の異常値を示したハイリスク者は155名（50歳以上の健診受診者の5.7%）で、年齢は61.4±7.1歳、PASEは123.1±79.5、SCOPA-AUTは12.5±5.2、SAOQは82.4±19.8%、RBDSQは5.0±2.7、BDI-Ⅱは12.0±8.3、ESSは9.6±5.0であった。ハイリスク者41名に二次評価を実施したところ、ほとんどのハイリスク者で運動・認知機能に異常を認めなかったが、13名（31.7%）でDaT SPECTとMIBG心筋シンチグラフィの1つ以上で集積低下を認めた。また、男性のハイリスク群は正常群に比べHb（14.8±1.3 vs. 15.0±1.1, p=0.032）とLDLコレステロール（114.5±30.3 vs. 123.0±28.9, p=0.004）が低値であった。【考察】50歳以上で複数のprodromal症状を有する健診受診者の中に、神経症状を有しないDaT SPECT・MIBGの集積低下例が存在し、prodromal期のレビー小体病であることが示唆された。

AO-02-4 The age of onset of multiple system atrophy has become older in the last 50 years

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【目的】多系統萎縮症（multiple system atrophy; MSA）の平均発症年齢は50歳代とされてきたが、しばしば高齢発症例を経験する。本研究では、MSAの発症年齢が高齢化しているという仮説を立て、自験例をもとに検証することを目的とした。【方法】1970年1月から2018年12月までに当科に入院したMSA臨床診断例と、1976年1月から2014年12月まで当施設で病理解剖を行ったMSA病理診断例について、診療録から性別、発症年齢、臨床病型を抽出した。発症年代別の平均発症年齢を、一元配置分散分析で解析し、TurkeyのHSD検定を用いて多重比較を行った。【結果】MSA臨床診断例は297例（男性180例、女性117例）であった。発症年代毎の発症年齢（平均±標準誤差）は、54.0±1.3歳（1970年代発症、40例）、55.6±1.0歳（1980年代発症、77例）、57.8±1.2歳（1990年代発症、50例）、60.6±1.0歳（2000年代発症、74例）、61.5±1.1歳（2010年代発症、56例）で、有意な群間差を認めた（p<0.0001）。多重比較を行うと、1970年代発症群に比して2010年代発症群は有意に高齢発症化していた（p=0.0003）。臨床病型では、MSA-Cの発症年齢が有意に高齢化していた（60.1±1.4歳［2010年代発症］vs 54.2±1.6歳［1970年代発症］、p=0.0447）。MSA病理診断例は81例（男性47例、女性34例）であった。発症年代別発症年齢（平均±標準誤差）は、55.0±2.4歳（1970年代発症、9例）、60.5±1.4歳（1980年代発症、28例）、61.8±1.5歳（1990年代発症、24例）、62.2±1.6歳（2000年代発症、20例）で、高齢発症化の傾向はあるが有意な群間差を認めなかった（p=0.0738）。【結論】本邦のMSAの発症年齢は過去50年のうちに高齢化しており、現在の平均発症年齢は60歳代である。高齢発症化の理由は不明だが、50年間で生活環境が大きく変化したことを鑑みると、環境因子が関与する可能性がある。神経変性疾患の発症年齢が高齢化している事実は、その成因を考えるうえで興味深い。

AO-02-5 Iron leakage owing to blood-brain barrier disruption in small vessel disease CADASIL

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[Objective] To evaluate blood-brain barrier (BBB) integrity and brain iron accumulation and their relationships to disease activity in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). [Methods] We enrolled 21 patients with *NOTCH3* mutations and 21 age-matched healthy controls in this cross-sectional study. All participants underwent global physical and cognitive assessments and brain MRI, using dynamic contrast enhanced MRI (DCE-MRI; BBB permeability measure) and voxel-based quantitative susceptibility mapping (QSM; iron deposition measure). We compared behavioral and imaging data between the groups and analyzed the correlations in each group. [Results] Among 21 *NOTCH3* mutation carriers, 10 were symptomatic and 11 asymptomatic. Voxel-based QSM analysis revealed that the symptomatic group had higher QSM values than did the asymptomatic group in the caudate nucleus, temporal pole, and external capsule. These QSM values were positively correlated with regional BBB permeabilities (caudate nucleus: r = 0.512, p = 0.019; temporal pole: r = 0.486, p = 0.030; external capsule: r = 0.471, p = 0.038) and negatively with Montreal Cognitive Assessment scores (caudate nucleus: r = -0.531, p = 0.012; temporal pole: r = -0.562, p = 0.008). [Conclusions] This study showed that cerebral iron burden was associated with regional BBB permeability and cognitive dysfunction in patients with CADASIL, highlighting the potential of these imaging techniques as auxiliary biomarkers to monitor the course of small vessel disease.

AO-02-6 Drug screening using urine-derived cells obtained from patients with Duchenne muscular dystrophy

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[Objective] Duchenne muscular dystrophy (DMD) is a severe muscle disorder characterised by mutations in the *DMD* gene. Now we are developing the morpholino antisense targeting exon 53 and 44. For drug screening, immortalized human skeletal muscle cell line, such as rhabdomyosarcoma (RD) cells, are often used, but we cannot evaluate the recovery of dystrophin protein using RD cells because they express this protein endogenously. Recently, we have established an *in vitro* model of DMD using MyoD, one of the muscle regulatory factors, -transduced urine-derived cells (MyoD-UDCs). The purpose of this study is to establish an *in vitro* drug screening system using MyoD-UDCs instead of RD cells. [Methods] We collected UDCs from DMD patients with exon 45-50, 48-50, or 49-50 deletion, expected to be restored their open reading frame by exon 51 skipping, and produced MyoD-UDCs. We performed exon 51 skipping using various antisense oligonucleotides (ASOs) in RD cells and these MyoD-UDCs. [Results] We clearly detected exon skipping after treatment with ASOs both in RD cells and MyoD-UDCs, and found that MyoD-UDCs had high resolution to detect exon skipping when treated with low dose of ASOs. Furthermore, we detected higher exon skipping efficiency in MyoD-UDCs with exon 49-50 deletion than that of with exon 48-50 after exon 51 skipping, suggesting response may be variable after exon skipping depending on their mutation pattern in the DMD gene. [Conclusions] We newly established an *in vitro* drug screening system using MyoD-UDCs, leading to development of mutation-specific medicine for DMD.

AO-02-7 Liquid biopsy in lymphoma associated CNS involvements: a potential tool for the early diagnosis

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[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 *MYD88*^{L265P} and *CD79B*^{ITAM}, 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 *MYD88*^{L265P} 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.

AO-02-8 Natural history of gait characteristics in patients with SCA6, SCA31, and MSA-C

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[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

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【目的】白質脳症の原因は多岐にわたり診断に苦慮することが少なくない．本研究では劣性遺伝が疑われる白質脳症家系を対象にエキソーム解析を行い，原因遺伝子を同定することを目的とした．【方法】発端者は37歳女性，両親がいとこ婚であり，30歳代で歩行障害が出現し，両下肢痙性と頭部MRIでびまん性白質病変を認めた．患者と母親の血液から抽出したDNAを用いてSureSelect Human All Exon V5 (Agilent Technologies) でターゲットキャプチャーを行い，HiScanSQ (Illumina) でエキソームシークエンスを行った．同定したバリアントからアミノ酸同義置換など重要性の低いバリアントを除外し，当施設のin-house data 54例中に認めたバリアントを除外したうえで発端者と母親に共通のバリアントを選出した．【結果】患者において415個の候補バリアント中に白質脳症と関連が報告されている遺伝子が3個あり，うち遺伝子Xのみがホモ接合性変異（ミスセンス変異）であった．両親はいずれも神経学的異常所見を認めず，サンガーシークエンス法にて遺伝子Xのヘテロ接合変異が確認できた．この変異は多型データベースに登録がなく，in silico解析では複数の予測ツール（SIFT，PolyPhen-2, Mutation Taster，PROVEAN，CADD）で病原性ありと判定された．遺伝子Xは基底膜の構成成分をコードし，ホモ接合性のナンセンス変異で乳児期発症の重度精神発達遅滞，ナンセンス変異とミスセンス変異の複合ヘテロ変異では幼児期発症のてんかん等を呈することが報告されている．【結論】本研究により劣性遺伝性白質脳症の原因として遺伝子Xの新規変異を同定した．同遺伝子変異による成人発症例の報告は初めてであり，ナンセンス変異ではなくホモ接合性のミスセンス変異であったことが比較的軽症の表現型に関連している可能性がある．

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

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【目的】現在、ALSの診断基準として改訂El Escorial基準（R-EEC）とAwaji基準が広く用いられている。AwajiはR-EECと比較し、線維束自発電位を評価基準に加えたこと、下位運動ニューロン徴候（LMN）において臨床徴候と筋電図所見を同等に扱うとしたことが改訂点である。しかし、AwajiではR-EECにおけるclinically probable laboratory supported（PRLS）カテゴリーが削除されたため、上位運動ニューロン徴候（UMN）が2領域以上ないとClinically probableに達せず、confirmed（study eligible）の診断をくだすのに障害となることが指摘されている。そのため、Awaji基準においてUMN1領域でも、臨床的あるいは筋電図基準でLMN2領域を満たす場合をPRLSと定義してconfirmed ALSに含めるupdated Awaji基準が提唱された（Geevasinga et al., 2016）。ただしこれはこの論文の本文中の記載であって、同論文中の各診断基準の要約の表においては、UMN1領域で筋電図基準のみにおいて2領域を満たすものをPRLSと定義している。PRLSという用語はむしろ後者に対応するとも解釈される。我々は前者でPRLS、正確にはprobableを定義するのをmodified Awaji、後者でPRLSを定義するのをupdated Awajiとして、ALS診断におけるそれぞれの感度をR-EECとAwajiも併せて比較した。【方法】対象は、ALSが疑われ針筋電図検査を施行した患者220名である。(男性127例、女性93例：26～94歳)。臨床所見、針筋電図所見を後ろ向きに検討し、R-EEC、Awaji、updated Awaji、modified Awaji、それぞれのconfirmed以上の感度を比較した。【結果】各診断基準でconfirmed ALSと診断される感度は、R-EEC 34.3%、Awaji 29.0%、updated Awaji 43.5%、modified Awaji 52.2%であった。【結論】ALSの診断においてはmodified Awajiが最も感度が高く、ALSの早期診断に有用であると考えられる。ただし、これでも半数近くのALSはconfirmedと診断できないのが今後の課題である。

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

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【目的】近年、封入体筋炎（IBM）を除く特発性炎症性ミオパチー（IIM）は、筋病理所見を重視した2014年European Neuromuscular Centre（ENMC）基準により皮膚筋炎（DM）、多発筋炎（PM）、免疫介在性壊死性ミオパチー（IMNM）、非特異的筋炎（NS）、抗合成酵素症候群（ARS）に分類される。一方、筋炎特異的自己抗体（MSA）はIIMの臨床所見や予後予測に有用だが、ENMC分類との関連について詳細に研究されたものは少ない。本研究では、IIM患者をENMC基準の下に再分類し、筋炎特異的自己抗体と臨床病理像との関連性を検討した。【方法】2008年1月1日から2018年12月31日までに筋生検を施行されたIIM患者の臨床情報、筋病理所見をカルテより抽出した。【結果】IBMを除く87例のIIM症例（DM 40、IMNM 25、NS 5、PM 3、ARS 14）が得られた。男女比は26：61、平均年齢は61歳であった。MSA陽性例はDM 20（50%）（TIF1-γ 10、Mi-2 4、MDA5 3、SRP 2、HMGCR 1）、IMNM 22（88%）（SRP 12, HMGCR 8, ミトコンドリアM2 2）、NS 1（20%）（ミトコンドリアM2 1）、PM 0、ARS 14（100%）であった。血清CK値（IU/L）の平均は、DM 2,370、IMNM 6,148、NS 1,366、PM 1,081、ARS 3,552であった。間質性肺炎の合併はDM 17（43%）、IMNM 8（32%）、NS 3（60%）、PM 0、ARS 13（93%）であり、悪性腫瘍はDM 15（38%）、IMNM 6（24%）、NS 0、PM 1（33%）、ARS 3（21%）であった。治療前mRSはDM 2.4、IMNM 2.2、NS 1.8、PM 2、ARS 1.9であり、免疫抑制剤はDM 13（33%）、IMNM 6（24%）、NS 1（20%）、PM 1（33%）、ARS 8（57%）で投与された。【結論】IMNMに関連するといわれる抗SRP抗体、抗HMGCR抗体はDMでもみられ、治療抵抗性であった。合併症検索や治療方針決定は特定の分類に基づいて画一的に行われるのではなく、病理所見やMSAを加味し、個々の症例に応じてなされるべきである。

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

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Objectives: The aim of this study is to clarify the difference of brainstem manifestations and MRI lesions between MOG-Ab and AQP4-Ab positive patients. Methods: We enrolled consecutive cases of MOG-Ab (n=216) and AQP4-Ab (n=197) positive patients who were referred to three centors. In those cases, we picked up cases with brainstem lesions and compared brainstem signs and lesion localizations between two diseases. The region of brain was divided into 13 parts for comparison and we assessed brainstem lesion 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 52 MOG-Ab positive and 35 AQP4-Ab positive patients were enrolled. In clinical symptoms,cerebellar ataxia is most frequently observed in MOG-Ab positive patients, while intractable hiccups and vomiting were dominant in AQP4-Ab positive patients. In MRI, the incidence of cerebellar peduncle lesions in MOG antibody patients was higher than that in AQP4 antibody patients (P =0.00028). In addtion, the dorsal medullary lesions were found in a higher proportion of AQP4-Ab positive patients than MOG-Ab positive patients (P <0.000001). There was no statistically significant difference in lesions of the other parts of brain and brainstem. Conclusions: We revealed a unique feature of brainstem lesions in MOG-Ab-positive cases mainly exist in lateral aspects of pons and cerebellar peduncle.

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

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[Objective] The screening of neuronal surface antibodies (NSAbs) in the cerebrospinal fluid (CSF) of patients is performed via an immunohistochemical assay using frozen rat brain 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. [Methods] All adult patients with encephalitis treated at our institution from July 2017 to October 2019 (n = 62) were enrolled in the study. An in-house TBA was used to screen NSAbs in CSF. The regional labeling of rat brain tissues was assessed in detail in TBA-positive samples. Immunolabeled brain sections were divided into two groups: hippocampal region (Hp) 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 positive neuropil pattern in the TBA (six with NMDAR, one with AMPAR, two with LGI1, and one with $GABA_BR$ Abs). The sample-subdivision analyses showed that the Hp was involved in the patients with NMDAR, AMPAR, LGI1, and $GABA_BR$ Abs, whereas those with NMDAR, AMPAR, and $GABA_BR$ Abs exhibited an unstained hilus of the dentate gyrus (DG). All patients but those with NMDAR Abs showed involvement of the Cb. [Conclusions] CSF positivity for NSAbs in the neuropil of the Hp and negativity in the hilus of the DG accompanied by unstaining of the Cb in the TBA can predict anti-NMDAR encephalitis.

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

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<Objective> A reduction uptake in DaT-SPECT and MIBG myocardial scintigraphy were defined as indicative 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 decline in olfactory function as supportive clinical features and the presence of hallucination as core clinical features. The purpose of this study was to determine the efficacy of olfactory and pareidolia tests in differentiating between Alzheimer's disease (AD) and DLB, and their usefulness was compared with indicative biomarkers of DLB. <Methods> A total of 40 DLB and 25 AD patients were enrolled. Decline in olfactory function was determined with the OSIT-J test. The pareidolia test was used to obtain data on the illusion reaction rate. The values of the left-right specific binding ratios were used in DaT-SPECT; the heart-to-mediastinum ratio on the delay image was used in MIBG. <Results> In the receiver operating characteristic curve analysis, MIBG: Area Under the Curve (AUC) 0.886, sensitivity 85%, specificity 85%; DaT-SPECT: AUC 0.885, sensitivity 80%, specificity 93%; the pareidolia test: AUC 0.676, sensitivity: 72%, specificity 72% ; OSIT-J:AUC 0.666, sensitivity of 72%, specificity of 58%. <Conclusions> The results of this study demonstrated that the pareidolia and OSIT-J tests were useful in distinguishing between DLB and AD. This suggests that these two tests are 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

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〔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、中枢性呼吸障害の4徴候を特徴とする常染色体優性遺伝の神経変性疾患である。Perry病は*DCTN1*遺伝子変異が原因であり、病理学的にはTAR DNA-binding protein 43（TDP-43）プロテイノパチーに分類される。我々は、国際共同研究により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唱した。日本で発見されたPerry病家系の臨床的多様性を明らかにする。〔方法〕2018年5月までに報告された日本のPerry病症例および未発表症例における臨床症状やMIBG心筋シンチグラフィーを含む画像所見について検討した。〔結果〕新たな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、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がみられた。10症例でMIBG心筋シンチグラフィーが施行され、8症例（80%）で取り込みが低下し、便秘や排尿障害、起立性低血圧などが合併していた。〔結論〕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可能性がある。また、Perry病では高頻度にMIBG心筋シンチグラフィー取り込み低下を認め、同疾患の自律神経障害の生物学的マーカーになりうる。

AP-01-8 Motor and cognitive outcome evaluation 3 years after deep brain stimulation for Parkinson's disease

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[Objective]Deep brain stimulation (DBS) for treatment of Parkinson's disease (PD) motor symptoms is well-established, but cognitive decline and psychoneurological complications are known negative side effects. [Methods]We examined 15 PD patients who had a DBS operation at our hospital from October 2013 to November 2019 with a 3-year follow up. (13 subthalamic nucleus (STN) -DBS and 2 posterior subthalamic area (PSA)- DBS) We evaluated a change of the motor symptoms and neuropsychological batteries. The correlation of changes of the neuropsychological batteries' score and pre-operative ^{18}F-FDG PET result was also evaluated. [Results]Compared to pre-operation, the Unified Parkinson's Disease Rating Scale (UPDRS) Part III of medication-off state improved significantly through the 3rd postoperative year. (mean, S.D.: pre-operation 37.2, 9.6, 3 years after surgery: 20, 9.1). On neuropsychological batteries, the difference between trail making test (TMT) part A completion time and that of B (TMT B-A time) were significantly prolonged after DBS surgery (mean: pre-operation 75.5s, 3 years after surgery 98.4s, p=0.04).Prolongation of TMT B-A time 3 years after surgery had a significant correlation to pre-operative low FDG uptake of medial segments of both side superior frontal gyri (right side: R= -0.85, p= 0.0037, left side: R= -0.90, p= 0.001). [Conclusion] Our patients showed good motor outcomes 3 years after DBS surgery. Reduction of pre-operative FDG uptake at medial segments of superior frontal gyri may predict post-operative decline of executive function.

AP-01-9 Magnetoencephalogram analysis of epilepsy patients with amygdala enlargement

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Background and objective: Amygdala enlargement (AE) is associated with temporal lobe epilepsy (TLE). However, its etiology is heterogeneous: tumors, 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. Patients and methods: We retrospectively analyzed MEG findings in AE-TLE patients. Of 237 consecutive patients who underwent MEG from January 2017 to June 2019, MRI findings for AE were screened by two neurologists (SK and NT), and later confirmed by a neuroradiologist (HM). Three neurologist/neurophysiologists (MY, 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 ECD 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 autoimmune etiology and secondary generalization. Conclusion: ECD distribution pattern in AE-TLE patients could be categorized into three groups, each related to a specific clinical phenotype.

最優秀演題賞候補

AP-02-1 Chronic cerebral hypoperfusion induces Alzheimer's pathology and mitochondrial form change in mice

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【Objective】We investigated the changes of mitochondrial fission and fusion proteins in AD with chronic cerebral hypoperfusion (HP) in a novel mouse model. 【Methods】To clarify the impacts of hypoperfusion (HP) on mitochondrial fission and fusion, related oxidative 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 3 groups: APP23 group (APP23 + sham surgery, n = 17), chronic hypoperfusion group (APP23 + HP, n = 12), and galantamine treated group (APP23 + HP + Gal, n = 10). 【Results】Compared with APP23 mice, APP23 + HP mice greatly 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 (Opa1 and Mfn1) in the cerebral cortex (CTX) and thalamus (TH) at 12 month (M) of age. Moreover, the expression of peroxidation products (4-HNE and 8-OHdG) 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 morphology from fusion to fission with increasing Ab oligomer/pTau accumulations in APP23 mice, and such neuropathologic processes were strongly attenuated by Gal treatment.

AP-02-2 Alpha-synuclein propagation via olfactory pathway in non-human primate model

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Objective: Parkinson's disease (PD) is a neurodegenerative disease characterized by α-synuclein (α-Syn) aggregates. The α-Syn aggregates are believed to propagate in the brain like prion via two major pathways: the olfactory and vagal nerve pathways. Recently the common marmoset (Callithrix jacchus), a new world monkey, has gathered a lot of attention in the field of neuroscience because of its useful characteristics as a non-human primate model (NHP). In this study, we investigated how aSyn pathology spreads from the OB and how the pathology affects brain structure and activity. Methods: Four two-year-old marmosets were anesthetized, and 0.8 ul of fibrils solution (4 mg/ml) was stereotaxically injected at two sites in the unilateral OB. Three or six months after injection, regional brain activity of a marmoset was evaluated with [18F] FDG-PET study, and the brains were immunostained by phosphorylated α-Syn (p-α-Syn). Results: Widespread distribution of p-α-Syn positive aggregation was observed in the ipsilateral OB, amygdala, entorhinal cortex, locus coeruleus and even dorsal motor nucleus suggesting the spreading of α-Syn pathology along with anatomically connected neurons. In addition, [18F]FDG-PET study revealed hemispheric hypoactivity in the injected side. Conclusions: The OB atrophy and hemispheric hypoactivity in this NPH PD model are associated with hyposmia and cognitive dysfunction, both of which are non-motor symptoms of PD. This study demonstrated that these symptoms are presumably attributed to the spread of aSyn pathology from the OB.

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

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【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 unclear. It has been difficult to verify small lesions on MRI 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. 【Methods】Brain samples from four cases with *in vivo* MRI-defined SVDs were subjected to *ex vivo* 3T micro-MRI. Histopathology corresponding to cerebral microbleed (CMB), cortical microinfarct (CMI), and white matter hyperintensity (WMH) in the both *ex vivo* 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* 3T micro-MRI, which remained invisible on *in vivo* 3T MRI. One sample including cortical superficial siderosis (cSS) and WMH on *in vivo* MRI showed CMIs in contact with cSS on *ex vivo* micro-MRI. There were Aβ positive vessels and cells positive for the combination of iron and CD68 around CMIs on histopathological study. One lesion which had been radiologically diagnosed with CMB and detected as low intensity lesion on T2* weighted image on *ex vivo* micro-MRI turned out to be angionecrosis on histopathology. 【Conclusions】We revealed novel pathological findings about MRI-defined SVDs. Our new method with *ex vivo* micro-MRI is useful to clarify the exact pathology of SVDs on *in vivo* MRI.

AP-02-4 In vivo conversion from microglia to neurons reinstates neurological function after ischemic injury

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【Objective】Ischemic brain injury causes neuronal loss, which ultimately results in persistent neurological dysfunction. Although regenerating new neurons in the injured brain could be an ideal approach to replenish the lost neurons for repairing the damage, the adult mammalian brain retains limited neurogenic capability. We have recently revealed that the expression of a single transcription factor, NeuroD1 (ND1), can convert mouse microglia into neurons in the adult mouse striatum. Here, we examined whether microglia-to-neuron conversion at lesion sites can induce functional recovery after ischemic brain injury. 【Methods】Eight-week-old mice were subjected to 30-minute transient middle cerebral artery occlusion (tMCAO) by an intraluminal suture. In order to express ND1 in microglia specifically, we injected the lentivirus expressing ND1 under the control of *CD68* promoter into the lesion site of the striatum at 7 days after tMCAO. 【Results】The expression of ND1 in microglia converged at the injured striatum enabled the conversion into induced neuronal (iN) cells that showed spontaneous action potential of firing and synaptic response. Furthermore, NeuroD1-mediated neuronal conversion significantly improved functional recovery of tMCAO model mice, and the effect was abolished by the following ablation of iN cells. 【Conclusions】Our findings demonstrate that microglia-to-neuron conversion contributes directly to the functional recovery after tMCAO and can be a promising strategy for the treatment of stroke.

AP-02-5 Coaggregation Mechanism of BRCA1 and Tau

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【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 of BRCA1 and tau. 【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 autopsy brains of 4 AD, 2 Pick's disease (PiD), 3 progressive supranuclear palsy (PSP), and 3 corticobasal degeneration using antibodies against phosphorylated tau and BRCA1. We also confirmed the presence of sarkosyl-insoluble BRCA1 by Western blot. To investigate the domain of BRCA1 necessary for the coaggregation with tau, HEK cells were transfected with plasmids with full length or 4 deletion mutants of BRCA1, and tau aggregation was induced. 【Results】Colocalization of BRCA1 with tau aggregates were seen in not only AD but also in PiD and PSP. Insoluble BRCA1 was observed in AD and PSP. PiD frozen brain was unavailable. In the cellular model, the BRCA1 mutant lacking the C-terminal BRCT domains was the only mutant without signs of BRCA1 aggregation. 【Conclusions】Tau aggregates of PiD and PSP also showed coaggregation with BRCA1. BRCT domains of BRCA1 were found to be necessary for the coaggregation. 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

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【Objective】Alzheimer's disease (AD) is one of major causes for dementia. Although reliable biomarkers for AD are highly needed, validated peripheral blood biomarkers for AD diagnosis are not available. We aimed to identify exosomal miRNA biomarkers for AD diagnosis using an animal model. 【Methods】Six-month-old APP-KI mice (APP^{NL-G-F} mice) and wild-type age-matched control mice were used. The serum exosomes were extracted using an exoEasy® Midi Kit (Qiagen, 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. 【Results】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 five miRNAs were significantly 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 have been reported to decrease in response to Aβ. 【Conclusion】We could identify miRNAs 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 using human samples are now under way.

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AP-02-7 withdrawn

AP-02-8 A pericyte-macrophage axis induces myelin debris clearance and tissue repair after ischemic stroke

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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 PDGFR β 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 condition medium (CM) of cultured pericytes on functions of bone marrow derived macrophages (BMDMs). *Results*-Intra-infarct accumulation of macrophages was significantly attenuated in *PDGFR* $\beta^{+/-}$ 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 *PDGFR* $\beta^{+/-}$ mice. Furthermore, *PDGFR* $\beta^{+/-}$ 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 of 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

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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

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Objectives To report the effects of high-dose gantenerumab (1,200 mg/month (mo)) on amyloid PET after 36 mo of ongoing treatment in the SCarlet RoAD (SR) and Marguerite RoAD (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-positivity threshold of 24 centiloids after 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; GRADUATE II).

APe-01-5 withdrawn

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

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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 vitro* 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). *WNT7A* SNP rs2163910 and rs1124480, and *WNT7B* SNP rs67604162 were increased in HT patients (p<0.05). *GPR124* SNP rs75336000 (missense variant, c.3587G>A) was selectively enriched in PH patients (p=0.0088). A higher portion 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.3587G>A 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.

APe-01-7 withdrawn

APe-01-8 CRTC1-regulated microRNA-132/212 plays a vital role in stroke mediated by vascular function

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[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.