AO-01-1 A single Intrathecal injection of OPC expressing scFv against misfolded SOD1 improved ALS model rats

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[Objective] Approximately 20% of familial ALS cases are caused by mutations in the Cu/Zn superoxide dismutase1 (SOD1). Many lines of evidence suggest that cytotoxicity of misfolded SOD1 and the existence of secretory pathways for SOD1.The antibody to inhibit extracellular misfolded SOD1 spreading is a promising option for ALS treatment and several studies showed the efficacy of antibody therapy against misfolded SOD1. In ALS, oligodendrocyte precursor cells (OPCs) are shown to exhibit excessive proliferation with impaired functions. Then we tested a combination therapy of cell transplantation and antibody by injection of OPC expressing antibody to ALS model rats. [Method] We generated a monoclonal antibody (antibody X) recognizing misfolded SOD1 specifically. Tandem single chain of the antibody X (scFv-X) was subcloned into a Borna disease virus vector, named RNA virus-based episomal vector (REVec), which multiply episomally in the recipient cells. Primary OPCs from postnatal rats were infected by the REVec carrying scFv-X (scFv-X-OPC). We injected intrathecally to SOD1H46R rats antibody X, OPCs alone or scFv-X-OPCs and investigated their motor function and survival time. [Result] Four weeks injection of full length antibody X delayed onset and extended life span of rats, while the efficacy of single injection of scFv-X-secreting OPCs was higher than antibody X alone. Motor neuronal loss and gliosis in the spinal cords were also ameliorated. [Conclusion] Our combination therapy of OPCs and scFv showed the effect to ameliorate SOD1-mediatied ALS.

AO-01-2 Distribution Discrepancy of alpha-synuclein oligomers and Lewy bodies in Parkinson's disease brain

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[Objective] To examine the distribution of alpha-synuclein (aSYN) oligomers in Parkinson's disease (PD) brains and compare the distribution of aSYN oligomers and Lewy bodies. [Background] Lewy bodies, the late-stage aSYN aggregation, have been considered as the pathological hallmark of PD. However, the presence of incidental Lewy bodies in elderly individuals without Parkinsonism and the absence of Lewy bodies in some of the familial PD patients with Parkinsonism have been reported. Whether Lewy bodies drive neurodegeneration remains controversial and aSYN oligomers, the early-stage aSYN aggregation, may play the pathogenic role. [Methods] We examined autopsied brains from 5 PD patients and 9 control cases. We conducted phosphorylated-aSYN immunostaining to detect Lewy bodies and adopted a proximity ligation assay (PLA) to examine the distribution of aSYN oligomers. [Results] As well as the punctate staining in remaining neurons in the substantia nigra, PD patients showed widespread aSYN-PLA signals in the putamen, pontine nuclei, and the frontal cortex, whereas such signals were rarely found in control cases. Among PD patients, the Braak stage was 3 in 2 patients, 5 in 1 patient, and 6 in 2 patients. We found punctate staining of aSYN oligomers in cortical neurons even in patients with Braak stage 3, who showed no Lewy bodies in cortical neurons. [Conclusions] We found a widespread distribution of aSYN oligomers in PD brains. aSYN oligomers may distribute widely throughout the brain even in the earlier pathological course of PD.

AO-01-3 SynGAP variant from ALS cohort causes spine abnormality by excessive recruitment of FUS and hnRNPK

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[Objective] FUS is one of the common pathogenic RNA-binding proteins for amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). We reported that FUS stabilizes SynGAP mRNA at its 3'UTR and this mechanism is important for spine maturation and cognitive function in mice model. To elucidate whether SynGAP might be pathogenic for ALS, we validate this mechanism in sporadic ALS cohort and confirm in human induced pluripotent stem cells (hiPSC)-derived motor neurons. [Methods] We explored the exome data of JaCALS cohort to find SynGAP 3'UTR variant at the binding site of FUS. Identified variant was introduced in hiPSC (201B7) by CRISPR/Cas9. Motor neurons were differentiated from edited hiPSCs and were cultured for 4 weeks. [Results] We identified 5 patients who had SynGAP 3'UTR variant at the binding site of FUS. The number of spines decreased in motor neurons with SynGAP variant. SynGAP variant increased SynGAP isoform alpha1 and decreased isoform gamma, which were both coincident to a decrease of spines. Pull-down assay revealed that SynGAP 3'UTR variant excessively recruited FUS and hnRNPK.In knockdown experiments, the change in SynGAP expression was similar to that in SynGAP variant, especially in hnRNPK knockdown. [Conclusions] The SynGAP 3'UTR variant caused spine abnormality, suggesting that the variant might be pathogenic for ALS. Moreover, excessive recruitment of RNA binding proteins by SynGAP variant caused aberrant expression of SynGAP isoforms, which could be the novel mechanism for the pathogenesis of ALS.

AO-01-4 The roles of oligodendrocyte lineage cells on the pathogenesis of Alzheimer's disease

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[Objective] Neuron-centric view cannot explain all aspects of Alzheimer's disease (AD). Among non-neuronal cells, dysfunctional oligodendrocytes (OLGs) and demyelination are reported to be observed in AD model mice and patients. Given that oligodendrocyte precursor cells (OPCs) regulate neurovascular function by interacting with neuronal, vascular, glial, and immune system, pathological OPCs/OLGs (OLs) could be involved in the onset and progression of AD. However, the mechanisms by which OLs exert effects in AD remain elusive. Therefore, the aim of this study is to examine the roles of OLs on the pathogenesis of AD.[Methods] For *in vitro* studies, we examined the influence of Aβ oligomers on OLs as well as the expression levels of Aβ and its related proteins in primary cultured OLs. For *in vivo* studies, we examined the behaviour of OLs in AD model mice (Tg-SwDI) and postmortem human brains with AD.[Results] *In vitro* studies showed that Aβ oligomers caused cytotoxicity in OPCs in a dose-dependent manner. In addition, OLs themselves produced Aβ40/42, which are pathogenic proteins in AD, via amyloidogenic pathway, and secreted sAPPα, which has neuroprotective and neurogenic functions, via non-amyloidogenic pathway. In AD model mice and patients, OPCs were located in close proximity with Aβ accumulation.[Conclusions] The present study suggest the bi-directional relationship between APP processing and OLs in AD. Further studies are warranted to elucidate the pathological shift in OLs from beneficial non-amyloidogenic process to harmful amyloidogenic process during AD progression.

AO-01-5 Thalamic functional profiles and connector hubs

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[Objective] The thalamus is not just a relay station in the sensory signal flow but has crucial integrative hub functions associated with attention, arousal, motor, sensory processing, and cognition. It has recently attracted attention as a therapeutic target for various neurological diseases, including essential tremor or Parkinson's disease. We aimed to elucidate functional hubs in the thalamus using a novel measure called functional connectivity overlap ratio (FCOR) that we have developed. [Methods] We used resting-state fMRI data from 101 healthy participants, aging 20 to 40 years old, scanned with a 3T-MRI scanner. All images were preprocessed and used to generate the FCOR maps for canonical resting-state networks (RSNs) in the thalamus per participant. [Results] We identified that core-neurocognitive networks (i.e., default mode networks, executive control networks) were localized predominantly in the anterior and medial thalamus, such as areas of the anteroventral and mediodorsal nuclei. The sensorimotor network was located around the lateral pulvinar nucleus, but the extent was limited. The visual network-related regions existed in the dorsal lateral thalamus around the lateral geniculate nucleus. The anteroventral, ventral lateral, and mediodorsal nuclei are prominent as connector hubs with connections to not just one but multiple RSNs. [Conclusions] FCOR maps showed the local functional topography and important connector hubs in the thalamus. These findings can serve as the basis for understanding the role of the thalamus in aging or neurodegenerative disorders.

AO-01-6 Zonisamide can ameliorate the conduction of the mutant CaV3.1 that causes spinocerebellar ataxia

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[Background] Spinocerebellar ataxia (SCA) 42 is caused by a mutation in *CACNA1G*, which encodes the low voltage-gated calcium channel $Ca_V3.1$ (T-type). Patients with SCA42 exhibit a pure form of cerebellar ataxia. We encountered a patient with SCA42, suffering from intractable resting tremor, particularly head tremor. This symptom improved with the administration of low-dose of zonisamide (ZNS), a T-type calcium channel blocker. Previous electrophysiological studies showed that the voltage dependence of this mutant $Ca_V3.1$ was shifted toward the positive potential. This abnormal shift was considered a factor related to disease onset and symptoms. The aim of this study is to clarify whether ZNS ameliorate the voltage-dependence alteration of the mutant $Ca_V3.1$. [Methods] We performed whole-cell recordings of GFP-expressing HEK293T cells that expressed wild-type or the mutant $Ca_V3.1$ with ZNS or efonidipine, which is another T-type calcium channel blocker and had no effect on tremors in our patient with SCA42. [Results] ZNS in an amount equivalent to the patient's internal dose significantly ameliorated the abnormal shift in the mutant $Ca_V3.1$. Whereas, efonidipine did not. [Conclusions] These results indicate that ZNS is distinct from other T-type calcium channel blockers in terms of modulation of the voltage dependence of the mutant $Ca_V3.1$. Because $Ca_V3.1$ is known to be involved in tremogenesis, modulation of the voltage dependence of the mutant $Ca_V3.1$ by ZNS might have contributed to improvement in the intractable tremor of our patient with SCA42.

AO-02-1 Complications and pregnancy in GNE myopathy patients: A nationwide repository survey in Japan

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[Background] GNE myopathy is an autosomal recessive adult-onset distal myopathy. Little is known about the complications and there are only a few case reports about pregnancy. [Objective] This study is aimed to reveal systemic and psychiatric complications, maternal complications and the impact of pregnancy on disease progression in GNE myopathy patients. [Methods] We conducted a questionnaire survey of GNE myopathy patients registered in a national registry in Japan. [Results] The response rate was 62.4% (126/198). Of the respondents, 4.1% (5/123) had a diagnosis of idiopathic immune thrombocytopenia (ITP), 16.3% (8/49) of males and 6.6% of females (5/76) had a diagnosis of sleep apnea syndrome (SAS). In total, 14.7% (16/109) had psychiatric disease. Of the female respondents, 61.1% (44/72) had pregnancy experience. The frequency of threatened abortion was 26.9% (7/26) among post-onset pregnancies. No other complications were commonly observed. Over 80% were unaware of changes in disease progression, while 19.0% experienced disease exacerbation within a year after delivery. Six patients developed myopathy within a year after delivery. [Conclusions] GNE myopathy patients were more likely to experience ITP or SAS. Platelet counts and evaluation of sleep-disordered breathing should be considered in the examination. Regarding to pregnancy, there were no serious complications and subjective progression did not differ in the majority of the respondents. However, possibility of threatened abortion and disease progression after delivery should be kept in mind.

AO-02-2 LGI4 is a novel autoantigen for nodopathy type chronic inflammatory demyelinating polyneuropathy

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Objective: IgG4 antibodies to nodal proteins such as neurofascin 155 (NF155) and contactin-1 (CNTN-1) were recently reported in a fraction of chronic inflammatory demyelinating polyneuropathy (CIDP) patients showing unique features. However, CIDP patients with similar features were occasionally negative for these antibodies. Therefore, we aimed to discover novel autoantibodies in such seronegative CIDP patients with similar features. **Methods:** We screened autoantibodies that bind to mouse sciatic nerves and dorsal root ganglions (DRG) by tissue-based indirect immunofluorescence assays (IFA) in 159 CIDP patients who were seronegative for anti-NF155 and anti-CNTN1 antibodies. Western blotting (WB) and cell-based RNA interference assay were used to identify the target antigens. **Results:** Sera from four CIDP patients selectively bound to juxta-paranodal regions of the sciatic nerves and satellite glia in DRG. The main IgG subtype is IgG4. The patients' IgG commonly stained a 60 kDa protein band on WB using mouse DRG and sciatic nerve lysates. Based on these features, we hypothesized Leucine Rich Repeat LGI Family Member 4 (LGI4) as a candidate antigen. Commercial anti-LGI4 antibodies showed similar staining patterns of DRG and sciatic nerves. All four patients' IgG bound to LGI4-overexpression lysates. LGI4 siRNA effectively down-regulated LGI4 in LGI4-expressing melanoma cells and reduced the patients' IgG binding. Anti-LGI4 antibody-positive patients had very high cerebrospinal fluid protein amounts. **Conclusion:** Anti-LGI4 antibody is a novel autoantibody for nodopathy type CIDP.

AO-02-3 Longitudinal analysis of at-risk cohort of 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。ハイリスク者の臨床的特徴と自然歴を明らかにし、先制治療法の開発へつなげる。【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4月から2020年10月までにのべ31,480名の健診受診者にアンケートを配布し、新規回答者は9,878名（男性5,464名、女性 4,414名）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370名（50歳以上の健診受診者の6.6%）であった。ハイリスク者59名に二次精査を実施したところ、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、20名（33.8%）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。ハイリスク者19例の縦断的検討では、1年の経過でDaT SBR値が急速に低下する症例が存在したが、レビー小体病へphenoconversionした者は見られなかった。【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。2020年2月から、画像異常を有するハイリスク者に対し、DaT SBR値を主要評価項目とし、ゾニサミドを用いた先制治療の有効性を検証する特定臨床研究を実施する。

AO-02-4 Establishment of diagnostic system for progressive supranuclear palsy using in vivo tau imaging

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[Objective] We aim to establish a diagnostic system for progressive supranuclear palsy (PSP) by tau positron emission tomography (PET) with ^{18}F-PM-PBB3. **[Methods]** We employed the data of 24 healthy controls (HC; age 67.5 ± 5.1 [mean ± SD] y, 9 males); 30 PSP (71.4 ± 8.2 y, 21 males, PSP rating scale [PSPRS] 41.1 ± 17.7) who met the MDS-PSP criteria and showed a typical topological pattern of ^{18}F-PM-PBB3 PET observed in PSP. All data were corrected by age and sex, and standardized for analysis. Standardized uptake value ratios using the cerebellar cortex as reference region were obtained in 112 volumes of interests (VOIs) by the multi-atlas method. The Elastic Net cross validation analysis was applied to the set of VOIs to determine the VOIs useful for discriminating PSP from HC. The obtained coefficients were applied to each individual data to calculate and define as PSP score. We tested PSP score for validation to 10 HC (68.9 ± 7.4 y, 7 males) and 5 PSP cases (73.0 ± 7.8 y, 3 males, PSPRS 46.6 ± 11.3) in a new cohort. We also evaluated association between PSP score and disease severity measured by PSPRS. **[Results]** Globus pallidus, putamen and midbrain were selected as pivotal VOIs calculating PSP score. PSP score for training and validation data showed accuracy of 94.4% and 80%, precision of 93.3% and 100%, and recall of 96.6% and 62.5%. Moreover, PSPRS correlated well with PSP score (Spearman's $r_s = 0.56$, $p < 0.001$). **[Conclusions]** Automated analysis system of tau PET with ^{18}F-PM-PBB3 would be a promising tool both for diagnosing and predicting disease severity in PSP.

AO-02-5 The clinical features of small fiber neuropathy patients with anti-Plexin D1 antibodies

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[Objective] Anti-Plexin D1 antibodies (Plexin D1-IgG) associated with neuropathic pain (NeP) specifically binds to small dorsal root ganglion (DRG) neurons. In this study, we assessed the prevalence of Plexin D1-IgG in patients with idiopathic small fiber neuropathy (iSFN). [Methods] We screened 38 patients with probable iSFN (24 Koreans and 14 Japanese) and 55 healthy controls (HCs) (30 Koreans and 25 Japanese) for serum Plexin D1-IgG using indirect enzyme-linked immunosorbent assay (ELISA) with recombinant human Plexin D1. The results were confirmed by a tissue-based assay with mouse DRG. Moreover, we retrospectively reviewed their demographic data, neurological findings, comorbidities, and SFN Symptom Inventory Questionnaire (SFN-SIQ).[Results] The frequency of Plexin D1-IgG was higher in iSFN patients than in HCs [15.8% (6/38) vs. 0.0% (0/55), $p = 0.0036$]. Correlation analysis showed a significant positive correlation between the corrected optical density value and disease duration in iSFN patients with Plexin D1-IgG (Spearman's rank correlation; $r_s = 0.971$, $p = 0.0012$). In subclass analysis of Plexin D1-IgG, three had only IgG2, two had predominant IgG2 and weak IgG1, and one had only IgG1, which indicates IgG2 predominance (83.3%). iSFN patients with Plexin D1-IgG showed late-middle age onset (mean ± SD = 60.2 ± 9.5 years), chronic disease course (100%), and burning feet (80%) in SFN-SIQ. Their NeP was characterized by burning (66.7%) and pricking (66.7%). [Conclusions] We have demonstrated the presence of Plexin D1-IgG in a fraction of classical iSFN patients.

AO-02-6 Respiratory event distribution predicts phenoconversion in idiopathic REM sleep behavior disorder

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[Objective] Idiopathic REM sleep disorder (iRBD) can precede the onset of α-synucleinopathies. On polysomnography (PSG), severity of REM sleep without atonia (RWA) is considered as a potential predictor of phenoconversion; however, inconsistency and complexity of RWA calculating methods hinder its clinical application. Inspired by the fact that RWA ameliorates obstructive sleep apnea (OSA) in REM sleep, we hypothesized that distribution of respiratory events over REM and NREM sleep can be an easily applicable biomarker of phenoconversion. **[Methods]** Consecutive 108 PSG-confirmed iRBD patients were included. To remove the effect of posture on OSA, we compared apnea-hypopnea index in supine position (AHI-sup) during REM sleep with that during non-REM (NREM) sleep to divide iRBD patients into REM-dominant OSA (REM-OSA) and NREM-dominant OSA (NREM-OSA) groups. **[Results]** After iRBD patients with AHI-sup of zero were excluded, REM-OSA and NREM-OSA groups consisted of 37 and 57 iRBD patients, respectively. Kaplan-Meier analyses revealed that the REM-OSA group had significant longer conversion time than the NREM-OSA group (median conversion time; 10.3 vs. 5.3 years; $P < 0.01$). The REM-OSA group has significantly lower amounts of tonic RWA than the NREM-OSA group ($P < 0.05$). If analyses were restricted to iRBD patients with AHI ≧ 5, differences became more prominent. **[Conclusion]** Distribution of respiratory events is associated with the severity of tonic RWA and, therefore, has a great potential as an easily applicable PSG-based biomarker of phenoconversion in iRBD.

AP-01-1 TDP-43-specific aptamer rescues ALS phenotype in TDP-43 transgenic mice

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Objective: TAR DNA-binding protein 43 (TDP-43) is an RNA and DNA-binding protein, which was identified as the major component of the cytosolic inclusion in amyotrophic lateral sclerosis (ALS). TDP-43 contains two tandem RNA recognition motif (RRM) domains, which bind UG or TG-rich sequences with high affinity. Recent studies suggest that the imbalance of quality and quantity in crosstalk between TDP-43 and nucleotides leads to TDP-43 proteinopathy. Therefore, we hypothesized that the introduction of the aptamer, TDP-43- binding oligonucleotide, to neurons could mitigate TDP-43 pathology. Methods: We used in vitro shaking-induced aggregation model to explore the high affinity sequence and chemical modification of TDP-43 aptamer, potential inhibitor of TDP-43 aggregation. Then, we evaluated the efficacy of the aptamer on human-TDP-43 -transgenic mice. The aptamer was administered intracerebroventricularly. We evaluated life span, weight loss, and motor function with rotarod. Results: With administration of TDP-43-specific aptamer, all of life span, weight loss and motor function were significantly improved. Conclusion: Our data have shown a robust neuroprotective effect on this ALS mouse model and suggest that the use of TDP-43-specific aptamer is a new therapeutic approach for ALS.

AP-01-2 Hippocampal dominant-variant of multiple system atrophy

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[Objective] Patients with multiple system atrophy (MSA) who display abundant neuronal inclusions out of striatonigral or olivopontocerebellar pathways have occasionally been reported as variants of this disease. We studied cases of atypical MSA with abundant neuronal inclusions in the hippocampus. [Methods] We reviewed the clinical and neuropathological findings of 194 consecutively autopsied, pathologically confirmed MSA cases. Among the 146 eligible, included cases, semi-quantitative analysis of neuronal cytoplasmic inclusions (NCIs) using a 3-point scale in the hippocampus, parahippocampal gyrus, and amygdala revealed 12 cases (8.2%) with a severe neuronal alpha-synuclein burden in two or more of the evaluated regions. [Results] The 12 cases showed a higher proportion of women (9 women / 3 men), longer disease duration (13.1 ± 5.9 years, range: 2-25), higher prevalence of cognitive impairment, and lower brain weight (1070.3 ± 168.6 grams, range: 700-1390) than the other 134 cases. The granule cells of the dentate gyrus and the CA1/subiculum were the most vulnerable regions to NCIs. Among the 12 cases, 3 had Pick body-like NCIs and showed severe atrophy of the medial temporal lobes. The frequencies of Lewy bodies, neurofibrillary tangles, amyloid phases, and argyrophilic grains did not differ between the 12 cases and the remaining 134 cases. [Conclusions] We identified a neuropathological variant of MSA with abundant NCIs in the hippocampus. Neuronal inclusions may play an important role in the degenerative process of MSA in addition to glial inclusions.

AP-01-3 Treatment of Muscular Dystrophy Caused by Pseudoexon Insertion

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[Objective] The recent advancement in next generation sequencing technology revealed the great impact of splicing mutations in disease pathogenesis. Fukuyama congenital muscular dystrophy (FCMD) is the most common form of congenital muscular dystrophy in Japan. Recently, a deep intronic mutation *FKTN* c.647+2084G>T was discovered as the second most mutations among Japanese FCMD patients. This mutation induces pseudoexon inclusion within intron 5, which produces a non-functioning shorter FKTN protein. In this report, we attempted to restore normal FKTN by modifying splicing patterns by small molecule compounds. [Methods and Results] Splicing reporters of *FKTN* (c.647+2084G>T) was created to pick up small molecule compounds that can skip the pseudoexon and restore the normal splicing pattern. By using this reporter, splicing factor 3b, subunit 1 (SF3B1) inhibitors and Cdc2-like kinases (CLKs) inhibitors were identified as the possible splicing modifiers for this mutation. [Conclusions] We have found several candidate molecules that can induce pseudoexon skipping of the splicing reporter. Currently we are investigating their therapeutic potential on patient-derived myoblasts. We believe that our approach would be a novel clinical role in treating FCMD patients.

AP-01-4 Transitional pathology of TDP-43 from nucleus to cytoplasm: An observation of 23 ALS autopsy cases

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[Objective] In amyotrophic lateral sclerosis (ALS), it is estimated that TDP-43 expression is disappeared from nucleus of motor neurons, then aggregated in cytoplasm, and finally skein and round inclusions are formed. But the transitional mechanism of TDP-43 from nucleus to cytoplasm remains unclear. In this study, we focused on "TDP-43 overlapped immunoreactivity neuron (TDP-43-OIN)" having TDP-43 immunoreactivity in both nucleus and cytoplasm, which was estimated as transitional pathology of TDP-43 from nucleus to cytoplasm. [Methods] We investigated 23 continuous autopsy cases pathologically diagnosed as ALS. TDP-43 immunohistochemistry was performed on every segment of the spinal cords, formalin fixed and paraffin embedded sections, and the appearance frequency of spinal segments with TDP-43-OINs was evaluated. [Results] The 23 cases included 14 men and 9 women, and the median disease duration was 20 months (6-132 months). TDP-43-OINs were observed in 15 out of 23 cases. The case with 18 months of disease duration showed maximum appearance frequency of TDP-43-OINs. The appearance frequency of TDP-43-OINs tended to decrease along with the expansion of disease duration, and were never observed in the 4 cases with over 60 months of disease duration. [Conclusions] We confirmed that TDP-43-OINs are not existed in the cases with long duration. TDP-43-OIN is estimated to be the transitional pathology of TDP-43 from nucleus to cytoplasm, and indicate the continuity between elimination of the normal nuclear expression and cytoplasmic aggregation of TDP-43.

AP-01-5 A development of novel vaccine targeting galectin-3 for Alzheimer's disease

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[Background]Alzheimer's disease (AD) is the major cause of dementia and one of the intractable neurodegenerative diseases. There are many reports that neuroinflammation is related to the pathomechanism of AD and microglia have an important role in neuroinflammation of central nervous system. [Objective] We focused on galectin-3, which is known to be a pro-inflammatory regulator. In this study, we examined the relationship between microglia and galectin-3, and developed a galectin-3 vaccine using virus-like particle (VLP) platform technology. [Methods] We activated BV2 cells by stimulation with lipopolysaccharide (LPS) and measured secretory galectin-3 by ELISA. We also designed galectin-3 epitopes on the surface of VLP and immunized SAMP8 mice intramuscularly with 10 micrograms of VLP three times in one week (n=5). Two weeks after the immunization, we obtained serum samples from mice and measured anti-galectin-3 antibody titer by ELISA. Then, we also examined serum galectin-3 level by ELISA. [Results] Levels of galectin-3 in the supernatant of BV2 cell cultures increased by stimulation with LPS. All immunized SAMP8 mice showed high titer of anti-galectin-3 antibody. Serum galectin-3 level decreased compared to saline injected mice. Moreover, our preliminary data suggested that galectin-3 vaccination may have improved cognitive impairment of AD model mice.[Conclusions] Our data suggest that galectin-3, which appeared to be secreted by activated microglia, can be the target of AD and we succeeded the development of a galectin-3 vaccine.

AP-01-6 Ablation of interleukin-19 improves motor function in a mouse model of amyotrophic lateral sclerosis

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[Objective] Neuroinflammation by activated microglia and astrocytes plays a critical role in the disease progression of ALS. Interleukin-19 (IL-19) is a negative-feedback regulator to limit pro-inflammatory response of microglia in autocrine/paracrine manners, but it remains uncertain how IL-19 contributes to ALS pathogenesis. Here, we investigated the role of IL-19 in ALS using transgenic mice carrying human superoxide dismutase 1 with G93A mutation ($SOD1^{G93A}$ Tg mice). **[Method]** We generated IL-19 deficient $SOD1^{G93A}$ Tg ($IL\text{-}19^{-/-}/SOD1^{G93A}$ Tg) mice by crossing $SOD1^{G93A}$ Tg mice with $IL\text{-}19^{-/-}$ mice and evaluated disease progression, motor function, and survival rate as well as pathological and biochemical alternations. ($SOD1^{G93A}$Tg, n = 29; $IL\text{-}19^{-/-}/SOD1^{G93A}$Tg, n = 30) In addition, the effect of IL-19 on glial cells were assessed using the primary microglia and astrocyte cultures from the embryonic brains of $SOD1^{G93A}$ Tg mice and $IL\text{-}19^{-/-}/SOD1^{G93A}$ Tg mice. **[Result]** Expression level of IL-19 was upregulated in the primary microglia and the lumbar spinal cords of $SOD1^{G93A}$ Tg mice compared to those of wild type mice. Unexpectedly, $IL\text{-}19^{-/-}/SOD1^{G93A}$ Tg mice showed a partial improvement of motor function. Ablation of IL-19 in $SOD1^{G93A}$ Tg mice increased expression levels of both neurotoxic and neuroprotective factors such as TNF-α, IL-1β, GDNF, and Tgf-β1 in the lumbar spinal cords. The primary microglia and astrocytes from $IL\text{-}19^{-/-}/SOD1^{G93A}$ Tg mice showed TNF-α upregulation, which induced GDNF release from astrocytes. **[Conclusion]** These findings suggest that inhibition of IL-19 signaling may alleviate ALS symptoms.

AP-02-1 Whole-exome sequencing of leukoencephalopathy without NOTCH3 mutation (CADASIL mimics)

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【目的】CADASILは最も頻度の高い遺伝性脳小血管病であり，若年性脳梗塞や頭部MRIにおける側頭極の白質病変を特徴とする．一方で臨床的にCADASILが疑われるが，その原因遺伝子*NOTCH3*に変異を認めない症例が多く存在している．これらの症例に対してエキソーム解析を行い，*NOTCH3*以外の遺伝性脳小血管病の原因遺伝子を同定することを目的とした．【方法】2009年から2017年にCADASILの疑いでサンガー法による遺伝子検査を行い，*NOTCH3*に変異を認めなかった266症例のうち，①頭部MRIで側頭極病変を認める，②発症年齢が60歳以下，③神経精神症状の家族歴を有する，の3条件を満たした19症例を"CADASIL mimics"として選出し，エキソームシーケンスを行った．同定したバリアントからアミノ酸同義置換など病原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，単一遺伝性脳小血管病の原因として確立している8遺伝子（*NOTCH3*，*HTRA1*，*COL4A1*，*COL4A2*，*CTSA*，*TREX1*，*GLA*，*POLG*）のバリアントに着目した．【結果】6症例において5遺伝子に7個のバリアントを認めた．ACMGガイドラインに準拠すると，*HTRA1*，*POLG*，*GLA*のミスセンス変異はlikely pathogenicに該当し，このうち*HTRA1*，*POLG*は同一変異を持つ他家系例の文献報告があった．*COL4A1*イントロン変異，*COL4A2*ミスセンス変異は同ガイドラインでvariants of unknown significanceに該当した．【結論】CADASIL mimicsにおいて*NOTCH3*以外の病原性あるいは感受性遺伝子の関与を明らかにした．遺伝性脳小血管病における遺伝的多様性が示唆された．

AP-02-2 Usability of the Gold Coast criteria ,the new diagnostic criteria of Amyotrophic Lateral Sclerosis

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【目的】2020年に筋萎縮性側索硬化症（ALS）の新しい診断基準である、Gold Coast診断基準（Shefner et al. *Clin Neurophysiol.* 2020）が公表された。この診断基準の主要項目として、1. 進行性の経過があること、2. 身体1部位以上に上位および下位運動ニューロン徴候（あるいは筋電図での脱神経所見）を認めること、あるいは身体2部位以上に下位運動ニューロン徴候（あるいは筋電図での脱神経所見）を認めること、3. 他疾患が除外できること、が挙げられている。この診断基準の有用性を検討するため、改定El Escorial診断基準およびAwaji診断基準、Updated Awaji診断基準との比較検討を行う。【方法】2016年から2020年にかけて当院当科を受診し、ALSが疑われ系統的な筋電図検査が実施された連続321症例を対象とし、最終受診時の診断を参考に改定El Escorial診断基準およびAwaji診断基準、Updated Awaji診断基準、Gold Coast診断基準の感度と特異度を算出し、偽陽性、偽陰性となった患者背景を解析した。【結果】最終診断がALSであった患者234名で、その他疾患87名（頚椎症性筋萎縮症22名、パーキンソンニズム15名、脳血管障害4名等）であった。改定El Escorial診断基準probable以上は感度68.4%、特異度94.3%、Awaji診断基準probable以上は感度81.6%、特異度94.3%、Updated Awaji診断基準probable以上は感度87.6%、特異度94.3%、Gold Coast診断基準は感度98.7%、特異度74.7%であった。Gold Coast診断基準でも当てはまらなかった偽陰性3症例のうち2例は後に診断基準を満たした。その他疾患であるもGold Coast診断基準でALS診断にあてはまった偽陽性患者は、頚椎症性筋萎縮症10名、パーキンソニズム4名、その他8名であった。【結論】Gold Coast診断基準は、改定El Escorial診断基準やAwaji診断基準、Updated Awaji診断基準と比べて感度が高く早期診断が可能となる一方で、特異度が低く除外診断をより厳密に行う必要がある。

AP-02-3 In vivo direct relation of tau pathology with neuroinflammation in dementia with Lewy bodies

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[Objective] The presence of misfolded proteins such as tau and alpha-synuclein together with neuroinflammation and neurodegeneration is considered key pathophysiological events in dementia with Lewy bodies (DLB). However, those mutual relations are still unknown in vivo. Then, we examined the relationships among tau deposition, microglial activation and glucose metabolism in DLB patients using PET with [^{11}C]DPA713, [^{11}C]PBB3 and [^{18}F]FDG, respectively. **[Methods]** Sixteen DLB patients (73.4y, MMSE 19.8, CDR 0.8 in average) underwent PET scans with the triple tracers. The binding potential (BP_{ND}) was estimated using the simplified reference tissue model or SUVR. Regional values of BP_{ND} were calculated using region of interest (ROI) analysis. Multiple correlation analyses by SPM were performed to determine the associations of [^{11}C]PBB3 BP_{ND} with NPI hallucination (NPI-h) scores and the [^{18}F]FDG SUVR in the occipital cortex. **[Results]** The [^{11}C]PBB3 BP_{ND} was greater in the occipital cortex in DLB, and a similar pattern of [^{11}C]DPA713 BP_{ND} was observed. Positive correlation was found between [^{11}C]PBB3 BP_{ND} and [^{11}C]DPA713 BP_{ND} in the occipital cortex. The SPM analysis showed significant correlation between NPI-h scores and [^{11}C]PBB3 BP_{ND} in the frontal-temporal regions. Occipital [^{18}F]FDG SUVR had a positive correlation with the occipital [^{11}C]PBB3 BP_{ND}. **[Conclusions]** The direct positive correlation of tau pathology with neuroinflammation in the occipital cortex suggests that tau-linked neuroinflammation in the occipital cortex is characteristic of the pathophysiology of DLB.

AP-02-4 10-year survival rate of subthalamic nucleus DBS in Parkinson's disease

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[Background] Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a therapeutic option for advanced Parkinson's disease (PD). There is abundant evidence on the short and middle term efficacy and safety, but there is a paucity of evidence in the long term effectiveness and safety of STN-DBS. We investigated the 10-year survival rate of STN-DBS. **[Methods]** A retrospective database analysis was conducted. To investigate the 10-year survival rate of STN-DBS, PD patients who underwent bilateral STN-DBS from 2006 to 2009 in our hospital were included in this study. The primary outcome is the 10 year survival rate, and the secondary outcome includes the Unified Parkinson's Disease Rating Scale (UPDRS) score and the total amount of levodopa equivalent dose (LED) at baseline and 10 years after surgery. **[Results]** 35 patients underwent STN-DBS during the investigation period. 32 patients were followed for ten years, and 20 patients were available to investigate the changes in UPDRS part 3 scores and the total amount of LED for 10 years. No patient died in the first 5 years, but 5 patients died of irrelevant causes to PD between 5 to 10 years. The Kaplan-Meier survival curve revealed the standardized mortality ratio for the total patient group was 2.61 (95% CI, 2.23-3.07). The UPDRS part 3 scores in on-medication and on-stimulation significantly declined for 10 years, whereas the total amount of LED was significantly lower than baseline even after 10 years. **[Conclusions]** This study provides evidence of long term safety and benefit of bilateral STN-DBS for 10 years.

AP-02-5 Ultra-High Field 7 Tesla Magnetic Resonance Imaging in the study of Transient Global Amnesia

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【目的】一過性全健忘（TGA）は突然の記憶障害を呈する疾患で、通常は24時間以内に症状が回復することが特徴である。画像診断的には、急性期に高分解能3T MRIを用いた拡散強調像(DWI)で一過性に海馬に点状高信号を認め、確定診断に役立つ。しかしながらTGAの病因については未だに解明されていない。より高解像度の情報が得られる7テスラMRI（7T MRI）を用いて、TGAの急性期画像所見を検討した。【方法】Hodgesの診断基準を満たすTGAの2症例で、急性期および回復期（2週間後）に3T MRIと7T MRIを撮影した。症例1は67歳男性で、発症翌日に3T, 7T MRIを撮影した。症例2は57歳女性で、発症翌日に3T MRIを第４病日に7T MRIを撮影した。DWIを含む通常プロトコールに加えて、7T MRIでは、高解像度のデータが得られるT2WI（冠状断、軸位断）を撮影した。【結果】急性期の3T, 7T DWIで症例1は右側、症例2は左側の海馬に高信号域を認め、ADC値は低値であった。同所見は、7T MRI T2WIでも高信号域として検出され、海馬の層構造の変化を捉えた。いずれの症例も、回復期に3T, 7T MRIを撮影したが、DWIでみられる異常信号は消失し、7T MRI T2WIで認めた海馬の層構造の変化も回復した。【結論】TGAの急性期に7T MRIを撮影した。調べた限り、同様の報告はなかった。発症早期に7T MRIのT2WIで認めた海馬の層構造の一過性の変化は、発症15日目には両症例とも消失していた。DWI高信号に対してADCは軽度低下しているのみであり細胞傷害性浮腫よりも軽度な可逆性浮腫性変化であると考えられた。脳梗塞のような虚血状態とはことなり、既に指摘されている静脈圧上昇などに合致する所見と考えられた。

AP-02-6 Impact of dyskinesia onset on non-motor symptoms and quality of life in Parkinson's disease patients

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[Objective] J-FIRST was a first-in-Japan, large-scale, prospective, 52-week observational study evaluating non-motor symptoms (NMSs) and quality of life (QoL) in 996 Parkinson's disease (PD) patients with wearing-off phenomenon (WO). This *post hoc* analysis aimed to establish if dyskinesia onset impacts NMSs and QoL. **[Methods]** NMSs and QoL were evaluated throughout the study using the Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part I (MDS-UPDRS I) and 8-item PD Questionnaire (PDQ-8), respectively. In this analysis, patients who developed dyskinesia during the study were assessed for change from baseline in MDS-UPDRS I and PDQ-8 scores. Baseline was defined as one timepoint before dyskinesia was observed. A mixed effect model, adjusted for baseline variables, was used for analysis. **[Results]** Of the 996 patients, 546 did not have dyskinesia at study entry, of which 133 developed dyskinesia during the study. These patients showed a significant increase in MDS-UPDRS I and PDQ-8 scores after 26 weeks vs baseline, indicating worsening NMSs and QoL. Of MDS-UPDRS I sub-items, significant score changes were observed for cognitive impairment, constipation problems, and lightheadedness on standing. No significant changes from baseline were observed in daily levodopa or levodopa equivalent dose. **[Conclusions]** This is the first large-scale Japanese observational study assessing the impact of dyskinesia onset on NMSs and QoL in advanced PD patients. The results show that NMSs and QoL deteriorate after dyskinesia onset in PD patients exhibiting WO.

APe-01-1 Altered peripheral clock genes and sleep and wakefulness disturbances in Parkinson disease

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Objective: There is a growing number of studies that revealed a link between Parkinson's disease (PD) and circadian clock system dysregulation, but the investigations at the molecular level are rare, especially in a large population-representative PD cohort. To evaluate the altered expression of peripheral clock genes and their correlation with the sleep-wake phenotypes including rapid eye movement sleep behavior disorder (RBD) symptoms in a relatively large population of PD patients. **Methods:** We determined the expression profiles of five principal clock genes, *BMAL1*, *CLOCK*, *CRY1*, *PER1*, and *PER2*, in the peripheral blood mononuclear cells (PBMCs) of the patients with PD (n=326), and healthy controls (HC, n=314) using real-time quantitative PCR. Then we performed comprehensive association analyses on the sleep characteristics and the PBMCs clock gene expression.**Results:** Our data showed that the expression levels of *BMAL1*, *CLOCK*, *CRY1*, *PER1,* and *PER2* were significantly decreased in the PBMCs of PD as compared with that of HC ($P<0.05$). Statistical analyses revealed that a combination of five clock genes could reach a high diagnostic performance (areas under the curves, 92%) for PD comorbid probable RBD, as well as the risk predictive of sleep and wakefulness disturbances in PD patients. **Conclusions:** Our study demonstrates that peripheral *BMAL1*, *CLOCK*, *CRY1*, *PER1,* and *PER2* levels are altered in PD patients and may serve as endogenous predictors for sleep and wakefulness disturbances of PD.

APe-01-2 Astroglial Connexin 43 Is A Novel Therapeutic Target for Chronic Multiple Sclerosis Model

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Objectives: Connexin (Cx) 43 gap junction channel proteins are overexpressed in chronic plaques of multiple sclerosis (MS) and its animal model, experimental autoimmune encephalitis (EAE), at chronic phase, reflecting astrogliosis. We aimed to elucidate the role of overexpressed Cx43 in MS by therapeutic administration of a novel Cx43 blocker, INI-0602, in chronic EAE. *Methods:* EAE was induced by immunizing myelin oligodendrocyte glycoprotein peptide$_{35\text{-}55}$ in 35 C57BL6 mice. Following the peak of acute EAE, INI-0602 (40mg/kg) or saline was intraperitoneally administered every other day from Day postimmunization (dpi) 17 to dpi 50. *Results:* The clinical signs of EAE were significantly attenuated at chronic phase and demyelinated areas were reduced in INI-0602-treated mice compared with saline-treated mice. Infiltration of $CD3^+$ T cells, $Iba1^+$ microglia, $F4/80^+$ macrophages and $C3^+GFAP^+$ A1 astroglia was significantly less in the lumbar spinal cord lesions in INI-0602-treated mice than saline-treated mice. Flow cytometry analyses of $CD4^+$ T cells isolated from the central nervous system tissues revealed significant decrease in Th17 and Th17/Th1 cells at dpi 24 and Th1 cells at dpi 50. Furthermore, $Cx43^+GFAP^+$ astroglia areas were significantly decreased in INI-0602 treated mice compared with saline-treated mice. **Conclusion:** These results suggest that the overexpressed astroglial Cx43 in chronic EAE and MS lesions exacerbate neuroinflammation. Thus, astroglial Cx43 is a novel promising therapeutic target for chronic progressive MS, in which no highly efficient drugs are available.

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APe-01-6 Transferability and sustainability of tDCS on sleep quality and cognition in preclinical dementia

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Objective: We aimed to investigate the effects of transcranial direct current stimulation (tDCS) on sleep quality and cognition in mild neurocognitive disorder due to Alzheimer's disease (NCD-AD) patients. Methods: A 12-week, double-blind, randomized controlled trial (Registration ID: ChiCTR-TRC-14005036) was conducted in 201 mild neurocognitive disorder due to Alzheimer's disease (NCD-AD) patients. All subjects were randomly assigned to receive a 4-week intervention of either a combination of tDCS and cognitive training, sham tDCS, or tDCS. Primary outcomes included sleep quality (measured by PSQI) and global cognition (measured by ADAS-Cog) at 4th week, 8th week and 12th week. Results: Compared to combined modality, mild NCD-AD patients who received tDCS only demonstrated prominent enhancement on sleep quality at 12th week ($F=9.5$, $p=0.003$). Within the tDCS group (n=62), we defined poor sleepers as baseline PSQI total score larger than 5 and good sleepers as PSQI total score less than 5. After a 4-week course tDCS treatment, poor sleepers showed significantly enhanced sleep quality than good sleepers at 4th week ($t=-2.41$, $p=0.02$), 8th week ($t=-2.7$, $p=0.01$) and 12th week ($t=-4.38$, $p<0.001$). Meanwhile, poor sleepers had more cognitive gains than good sleepers across the follow-up observations, including global cognition measured by ADAS-Cog (4th week, $t=-2.42$, $p=0.019$; 8th week, $t=-2.19$, $p=0.031$). Conclusions: A 4-week course tDCS has significant positive effects on sleep quality and cognitive function in mild NCD-AD patients with or without sleep disturbances.