The role of Cnn positive Streptococcus mutans in the pathogenesis of intracerebral hemorrhage

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Background: We reported the relationship between Streptococcus mutans expressing the collagen-binding protein, Cnn, (Cnn-positive S. mutans) in the oral cavity and intracerebral hemorrhage (ICH) in a cross-sectional cohort and an increased number of cerebral microbleeds in a longitudinal cohort study, respectively. Here, we aimed to investigate the relationship between Cnn-positive S. mutans in the oral cavity and intracerebral hemorrhage in a prospective study. Methods: Firstly, we used adult male SHRs/SW to compare the histopathological findings, which were divided into four groups depending on injections of either clinically isolated Cnn-positive S. mutans (strain TW295) or its Cnn-defective isogenic mutant (TW295CND) via tail vein and salt diet (SD) or normal diet. Next, we performed cocultivation using TW295 or TW295CND with human brain microvascular endothelial cells (hBMVECs) to investigate the interactions in vitro study. Results: In the rodent model assessment, the TW295SD-treated SPSRs showed a significantly greater number of microscopically ICH than any other group. TW295 and SD synergistically interacted in the total number of ICH. Furthermore, immunofluorescence staining showed that TW295 strain distributed along the cerebral arteries and colocalized with activated microglia. In vitro study, TW295 was invaded into and penetrated hBMVECs whereas TW295CND didn’t. Moreover, we could find the TW295 was inside the endocytosis vesicles using confocal microscopy. Conclusion: Cnn-positive S. mutans might attach and invade brain capillary endothelium, which might be a trigger for ICH.

Association of recurrent stroke subtype with medicated type of secondary prevention in ESUS

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Objective: To determine the association between polymunsaturated fatty acid (PUFA) level and prognosis and MRI findings in cardioembolism. Methods: Consecutive ischemic stroke patients were recruited from January 2014 to January 2017. Patients with cardioembolism defined by Trial of ORG 10172 in Acute Stroke Treatment; 2) onset to door time within 24 h; and 3) able to measure PUFA within 48 h from onset. Exclusion criteria were 1) modified Rankin Scale (mRS) >2 at the present stroke; and 2) unable mRS score at 3 months from onset stroke. An unfavorable outcome was defined as mRS of 3 to 6 at 3 months from the onset. First, we evaluated whether PUFA level could be associated with an unfavorable outcome. Second, the relation between PUFA level associated with an unfavorable outcome and MRI findings was evaluated. Results: We screened 1,661 consecutive ischemic stroke patients, including 170 patients (11% (69%) male, median age 74 years). Of all, 53 patients (31%) had unfavorable outcomes. The factors associated with unfavorable outcome were National Institutes of Health Stroke Scale score on admission (OR 1.13, 95% CI 1.08-1.22, p = 0.001), mRS score before onset (OR 3.35, 95% CI 1.66-6.79, p = 0.001), and dihomo-gamma-linolenic acid (DHLA) level >2875 mg/mL (OR 0.26, 95% CI 0.15-0.45, p = 0.004). Further, susceptibility vessel sign on MRI (SVS) was independently associated with DHLA level <2875 mg/mL (OR 3.42, 95% CI 1.26-10.06, p = 0.016). Conclusion: Low DHLA level is associated with an unfavorable outcome and a SVS in cardioembolism.
O-02-1 Early dysregulation of connexins in astroglia and oligodendroglia in multiple system atrophy

[57x574]up-regulation of Cx43 with chronic astrogliosis. Cx32/Cx47 was uniformly internalized from surface
and ataxia at 22 weeks, culminating in death around 30 weeks. At 16 weeks, phosphorylated α-syn started
maintain myelin homeostasis.

O-02-2 A novel device to evaluate upper limb ataxia in the patients with spinocerebellar degeneration

[57x574]of glial Cxs are common and may contribute to the pathogenesis of demyelination in MSA.

O-02-3 What are the roles of TGGAA penta-nucleotide repeats as bidirectional transcripts in SCA31?

[57x574]abnormal RNA structures in cells as well as BEAN1 directional sequence, suggesting
abnormalities in SCA31 patients, and the expression levels of TK2 and TK2-EXT
repeats in introns of two bi-directionally transcribed genes, brain expressed associated
that UUCCA repeat is associated with SCA31 pathogenesis.

O-02-4 Elimination of CSF1R-positive microglia exacerbates a novel mouse model of multiple system atrophy

[57x574]expression of thymidine kinase 2 gene in human SCA31 cerebellum

O-02-5 Eye-hand coupling in reaching tasks is impaired in spinocerebellar ataxia

[57x574]expression of connexin 47 in the spinal cord and brainstem/cerebellum, resulting in widespread demyelination.

O-02-6 Expression of thymidine kinase 2 gene in human SCA31 cerebellum

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O-03-1 Astroglial Connexin 43 is A Novel Therapeutic Target for Chronic Multiple Sclerosis Model

Satoshi Nagata, Yyo Yamasaki, Yuko Nakamura, Izgi Ozdemir, Hiroshi Nakane, Tatsuro Misu, Atsushi Fujita, Yukio Takeshita, 1Department of Neurology, Graduate School of Medicine, Kyoto University, Japan; 2Department of Neuroimmunology, Graduate School of Medicine, Kyoto University, Japan; 3Department of Neurology, Medical Center, Fukuoka University, Japan; 4Department of Neurology, National Hospital Organization, Fukuoka Burns Center, Japan. 53rd Annual Meeting of the CNS and Contemporary Clinical Neurology, May 26-31, 2021, Tokyo, Japan.

Objective: Connexin 43 (Cx43) is a gap junction channel protein that is overexpressed in the chronic stage of multiple sclerosis (MS) and its animal model, experimental autoimmune encephalitis (EAE), at chronic phase, reflecting the pathogenesis of MS.

Methods: Cx43 knockout (KO) and transgenic mice (Cx43:CD1) were intraperitoneally administered every other day from Day postimmunization (dpi) 17 to 50 dpi. Results: The final signs of EAE were significantly attenuated at chronic phase and demyelinated areas were reduced in Cx43 KO mice compared with saline-treated mice. Infiltration of CD3+ T cells, Iba1+ microglia, F4/80+ macrophages and C3GFAP + A1 astroglia was significantly less in the lumbar spinal cord lesions in IN-166-d2 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 Th1/Th7 cells at dpi 24 and Th1 cells at dpi 50. Furthermore, Cx47GFAP+ astroglia areas were significantly decreased in IN-166 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.

O-03-2 The increased expression of C5α receptor on peripheral blood B cells in NMOSD

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Objective: Myeloid oligodendrocyte glycoprotein antibody associated diseases (MOGAD) have been found to be positive for CNS demyelinating disease such as acute disseminated encephalomyelitis (ADEM) and optic neuritis (ON). The relationship between the serum and CSF titers of MOG-IgG, and the clinical profile of MOGAD is not fully understood. METHODS: We followed 137 patients with MOGAD with both serum and CSF samples and untreated before each sample was collected. We divided the patients into three groups according to serum and CSF MOG-IgG titers low, intermediate, and high, and compared the factors associated with brain lesions revealed that young age (OR 0.05 per 1 year increase of age; 95%CI 0.01-0.3, P = 0.042) and high MOG IgG titers in CSF (OR 6.595%CI1.330-31.830, P = 0.0062) were independent factors for brain lesions. They all factors were not confirmed by serum autoantibody titers, including ANA, dsDNA, SSA, SSB, RNP, Scl-70, Jo-1, and anti-PM/Scl antibodies. CONCLUSION: CSF antibody titers are associated with a higher frequency of brain lesions and higher MBL levels suggests that high antibody titers may cause a more active antigen-antibody response and result in tissue damage.

O-03-3 Iguratimod improves a secondary progressive multiple sclerosis model by therapeutic administration

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Objective: Experimental autoimmune encephalomyelitis (EAE), an animal model, of multiple sclerosis (MS) is based on the destruction of the multiple sclerosis lesions. We reported a novel model of secondary progressive MS (SPMS) induced by immunization with myelin oligodendrocyte glycoprotein peptide 35-55 (MOG35-55) in myeloid oligodendrocyte glycoprotein deficient C57BI6 mice, which showed a relapsing progressive course at the chronic phase (Zhao et al., PNAS, 2020). As we also reported efficacy of iguratimod (IGU), an anti-rheumatic drug, on acute EAE, we attempted to evaluate the effects of IGU on this SPMS model. Methods: Cx47 Icko (JpGFERT; Cx47/Tbi), microglia were immunized with MOG35-55 to induce EAE. Following the peak of acute EAE, Icko (JpGFERT; Cx47/Tbi) mice were treated with IGU as control. IGU administration of IGU is clinically and pathologically effective for the newly established IGU-treated mice than methylcellulose-treated mice (p=0.01) .

O-03-4 CSF antibody titers are associated with the prevalence of brain lesion and inflammation in MOGAD

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OBJECTIVE: Myeloid oligodendrocyte glycoprotein antibody associated diseases (MOGAD) have been found to be positive for CNS demyelinating disease such as acute disseminated encephalomyelitis (ADEM) and optic neuritis (ON). The relationship between the serum and CSF titers of MOG-IgG, and the clinical profile of MOGAD is not fully understood. METHODS: We followed 137 patients with MOGAD with both serum and CSF samples and untreated before each sample was collected. We divided the patients into three groups according to serum and CSF MOG-IgG titers low, intermediate, and high, and compared the factors associated with brain lesions revealed that young age (OR 0.05 per 1 year increase of age; 95%CI 0.01-0.3, P = 0.042) and high MOG IgG titers in CSF (OR 6.595%CI1.330-31.830, P = 0.0062) were independent factors for brain lesions.
【目的】パレイドリアテストは幻視に類似した症状である錯視を検出するテストである。本研究ではパレイドリアテストを検討し、パレイドリアテストにおける错視反応の有無を検討することにより、パレイドリアテストにおける錯視反応の有用性やその病態背景を検討する。また、パレイドリアテストにおける錯視反応の有無は、パーキンソン病や多系統萎縮症の鑑別において、優れた特異性を示すことを示唆する。

【方法】対象：パーキンソン病40例、多系統萎縮症40例。

【結果】1. パーキンソン病におけるパレイドリアテストを用いた全般性高次脳機能検査の特徴を検討した。2. パレイドリアテストにおける错視反応は、パーキンソン病と多系統萎縮症の鑑別において、優れた特異性を示すことを示唆する。

【結論】パレイドリアテストにおける错視反応は、パーキンソン病と多系統萎縮症の鑑別において、優れた特異性を示すことを示唆する。

【文献】
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O-051 ATP induces neuropathic pain in neuromyelitis optica spectrum disorder through microglial activation

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Objectives: Neuromyelitis optica (NMO) spectrum disorder (NMOSD) is an autoimmune neurological disease that occurs without anti-AQP4 antibodies. However, the underlying mechanism of NMO pain remains unknown. The aim of this study was to investigate pathogenic mechanism of NMO pain through establishment of its animal model. Methods: We established an NMO model of a mouse with anti-AQP4 IgG in combination with anti-ED8 antibody (n = 8/group). Results indicated that there were some systems of IgG translocation without the IgG although TEER was not significantly decreased. [Conclusion] We developed the sera of some patients (NMO: 2, MOG: 1, MS: 2) significantly increased translocated the adequate in vitro BBB models to evaluate the microvolume IgG translocation.

O-052 IL-6 blockade inhibited the NMO-IgG-induced BBB dysfunction, leading to prevention of onset of NMOSD

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Background Neuromyelitis optica spectrum disorder (NMOSD) is autoimmune astrocytopathy caused by antibodies against the aquaporin 1 (AQP1). Breakdown of blood-brain barrier (BBB) allowing ingress of AQP1 antibodies into the CNS plays a key role in NMOSD. We reported GPR97 and AQP4 antibodies were important factors for BBB breakdown via IL-6 induction in astrocytes. Though IL-6 blockade like satralizumab (SA) showed beneficial effects, the pathophysiology and the therapeutic mechanisms at BBB are not fully understood in adequate experimental models. Aim We reveal the pathophysiology of NMOSD and the effects of IL-6 blockade at the BBB with in vitro and in vivo studies. Method We constructed the BBB models for evaluating barrier function, leakage migration and intracerebral transferability (IT) of NMO-IgG and SA using the newly triple-cultured system of partially immortalized human BBB cell lines. We also assessed the effects of IL-6 receptor antibody on BBB disruption in EAE mice. Result In in vitro studies, NMO-IgG increased IT of SA and NMO-IgG, and SA suppressed the NMO-IgG-induced migration of T cells and barrier dysfunction. In vivo studies IL-6 blockade suppressed the migration of T cells into CNS, and increased the increased the IT of NMO-IgG and SA. These results suggest ILNMO-IgG increased the IT of NMO-IgG and induced IL-6 from astrocytes causing more BBB dysfunction 25A, which can pass through the BBB in NMO-IgG, suppresses the BBB dysfunction, leading to prevention of onset of NMOSD.

O-053 Effects of sera in NMO, MOG, and MS on IgG translocation to central nervous system

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Background Autoimmune neurological diseases are characterized by autoantibodies to target molecules in central nervous system. It remains uncertain how antibodies can access intrathecal antigen across blood-brain barrier (BBB) because of lack of the adequate in vitro BBB models to evaluate the microvolume IgG translocation. Aim We prepared the immortalized human brain microvascular endothelial cells (hBMECs) and to evaluate IT of satralizumab or control-IgGs. Our aims are to construct the BBB models to measure the IT of satralizumab and control-IgGs. Our aims are to construct the BBB models to measure the IT of satralizumab and control-IgGs. Our aims are to construct the BBB models to measure the IT of satralizumab and control-IgGs. Our aims are to construct the BBB models to measure the IT of satralizumab and control-IgGs. Our aims are to construct the BBB models to measure the IT of satralizumab and control-IgGs.

O-054 Intracerebral transferability of satralizumab in NMO using a new multi-cultured in vitro BBB model

Kinya Matsuo1, Yukio Takeshita, Susumu Hujikawa1, Miwako Fujisawa1, Kenichi Serizawa1, Fumitaka Shimizu1, Yasuteru Sano1, Michiaki Koga1, Takashi Kanda1

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[Objective] Neuromyelitis optica (NMO) is an autoimmune astrocytopathy caused by antibodies against the aquaporin-1. On the CNS side, NMO-IgG induces secretion of IL-6 from astrocytes causing dysfunction of blood-brain barrier (BBB). Satralizumab (SA) was developed based on the assumption that the mechanism of satralizumab at the BBB are unclear because of lack of in vitro BBB models to evaluate the intracerebral transferability (IT) of satralizumab and IgGs. Our aim is to construct a new BBB model in which SA is transferred into CNS through BBB. Method We established a novel triple-cultured functional BBB model systems. Firstly, after addition of labeled satralizumab or control-IgGs to endothelial side, the translocated satralizumab or control-IgGs were detected by Odyssey Infrared Imaging System. Secondly, after exposing NMO-IgG or control-IgG to the endothelial side, the translocated IgGs were measured by ELISA. Finally, after exposing 'satralizumab plus NMO-IgG' or 'satralizumab plus control-IgG' to the endothelial side, the accumulated satralizumab was measured by ELISA. Result The IT of satralizumab was almost three times that of control-IgG. The IT of NMO-IgG was almost 15 times. The satralizumab plus satralizumab was accumulated in NMO-IgG mAb-treated cultures for control-IgG plus satralizumab. Conclusion We succeed in constructing detection methods for Satralizumab and IgGs through in vitro BBB model. IT of satralizumab is higher than control IgGs and was accelerated by presence of NMO-IgG.

O-055 Mechanism of neurodegeneration in TTR E61K amyloid neuropathy: electron microscopic study

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Objective TTR E61K amyloid neuropathy is characterized by late-onset FAP, and no amyloid deposits in thalaural nerves. E61K TTR has similar amyloidogenicity to wild TTR and no inhibitory effect on neurite outgrowth from primary DRG neurons. TUNEL positive cells are observed in the sural nerve. In this study, E61K TTR fibrils were morphologically examined in vitro and apoptotic cells were identified in the nerve by electron microscopy. Methods 1) Wild E61K and TTR control fibrils: TTRs are included under acidic condition (pH4.0) at 77 C for 72 hours. Samples are centrifuged, and the pellets are embedded in epon. Ultrathin sections are explored using an electron microscope. 2) Endoneurial cells are examined in the sural nerve of the rat (n = 5) using an electron microscope. Results 1) Wild E61K and TTR control fibrils: TTRs are included under acidic condition (pH4.0) at 77 C for 72 hours. Samples are centrifuged, and the pellets are embedded in epon. Ultrathin sections are explored using an electron microscope. 2) Endoneurial cells are examined in the sural nerve of the rat (n = 5) using an electron microscope. Conclusion We established an NMO model. In human patients, CSF ATP concentration was significantly higher in both acute and remission phases of NMOSD than in multiple sclerosis or other neurological disorders. [Conclusions] A novel NMO pain model was established, ATP, microglial activation, and IL-1β secretion plays a key role in the pathogenesis of NMO pain.
【目的】 2020年は COVID-19 の世界的流行により医療体制にも大きな変化をもたらした。発症前診断は、①at risk者に対して、②まだ発症が確認されていない時点で、③治療への希望があった。【結論】 COVID-19流行下に行った今回のアンケート調査で、77%の患者が遠隔診療を認識しており、通院中の転倒off、通院に要する時間や費用、通院中の転倒offに関すること、待合室での発症リスクについての調査を行った。【方法】 2020年4月2日から5月8日の期間に、当院でTTR-FAPに関連したGCを希望して来院した来談者を対象にしたアンケート調査を行った。【結果】 4名の診療の状況を後方視的に検討し、治療法の進歩がGCに及ぼした影響を経時的に検討する。こうした背景のもと、我々は、当院におけるTTR-FAPの遺伝カウンセリング（GC）入院し、確定診断を得た中枢原発悪性リンパ腫（PCNSL）2例、血管内大細胞型B細胞リンパ腫（DLBCL）の内2MG、髄液蛋白・細胞数・糖、血清LDHとは有意な相関は示さなかった。【結論】 MYD88VAFがsIL-2Rの髄液/血清比と相関していたことから、その変異の比率の高低は、発症以前の時期や進行の状況を高精度で予測することが知られている。今回髄液中のcfDNAにおける変異型B細胞リンパ腫（IVLBCL）1例、びまん性大細胞型B細胞リンパ腫（DLBCL）の1例を含む6例。全例において髄液中のcfDNAを用いてddPCRを施行し、その変異型B細胞リンパ腫を観察することは、臨床的判断や治療法の選択に有用である。
【目的】筋萎縮性側索硬化症（ALS）は上位・下位運動ニューロンが選択的に障害される進行性の疾患である。ALSの神経伝導検査（Medicaid money disturbs latency; MMDL）延長をきたす症例が多いが、延長の原因は不明である。著者らはALSの運動神経遠位潜時（MMDL）延長の特徴を検討した。

【方法】2012年1月から2019年12月までに当院で死亡確認されたALSのうち、運動神経遠位潜時（MMDL）の延長をきたす症例を検討した。また1剖検例についてpTDP-43irNCIの分布を調査した。

【結果】検査時平均年齢65.5歳。全例でペーパー伝達能力を後方視的に調査した。また1剖検例についてpTDP-43irNCIの分布を調査した。

【考察】ALSの運動神経遠位潜時（MMDL）延長の特徴を検討した。また1剖検例についてpTDP-43irNCIの分布を調査した。
O-08-1 Characteristics of interareal cortical networks created with late cortico-cortical evoked potential

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Objective: An interareal cortical network is essential for brain functions or pathophysiology of neurological diseases such as epilepsy. Cortico-cortical evoked potential is a method for evaluating the functional connectivity and consists of early (NL) responses and late (NL2) responses. Although the network of late responses has been reported to resemble the network of functional connectivity, the association between late responses and brain functions is yet to be clarified. We created artificial networks with late responses and investigated the association with brain functions. Method: Subjects were eight patients with intractable epilepsy who underwent subdural grid mapping. Results: The network of late responses has been reported to resemble the network of functional connectivity, the association between late responses and brain functions is yet to be clarified. We created artificial networks with late responses and investigated the association with brain functions. Conclusion: The network of late responses characterized the high-order cortical functions. These findings suggested that N2 responses have a physiological role for higher-order cortical functions and may help in brain functions with less invasive methods in functional neurosurgery.

O-08-2 Deep learning approach to infer conduction velocity distribution in demyelinating neuropathies

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Objective: Abnormal temporal dispersion in nerve conduction study (NCS) occurs in uneven conduction velocity (CV) slowing of respective motor axons. Although clinically informative, inference on conduction velocities from NCS waveforms has not been utilized. [Method] For a simulated median nerve, 200 axons with identical shapes were randomly generated, 50 axons were demyelinated and a reported CV distribution were superimposed, with inference conducted according to CV to organize compound motor action potential (CMAP). The results of CV slowing were randomized without conduction block to create 12,000 pairs of CV distributions and CMAPs, which were divided into training and test data. Various recurrent networks (RNN) such as current neural network (RNN), (Recurrent neural network (RNN), Long short-term memory (LSTM), Gated recurrent unit (GRU)) and different number of layers were trained for achieving highest validation accuracy. [Results] After 10,000 epochs, the accuracy was better in the order of GRU, LSTM, and BNN. Bi-directional networks showed better accuracies, as well as multi-layer networks. Using the best network (3-layer, bidirectional GRU) after 10,000 epochs, the validation accuracy reached 0.9799. Applicable to clinical test data adequately reproduced CV distributions. [Conclusion] Deep learning approach using recurrent neural networks successfully infer CV distributions from CMAP waveforms. Understanding CV distributions in demyelinating neuropathies and CMAPs would aid in differential diagnosis and understanding of clinical progression in daily practice.

O-08-3 Living or not living at the early-stage in mesoscale network dynamics during visual recognition

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Objective: The network dynamics in human brain evoked by visual stimuli composed of living and nonliving objects remains unclear. Here we report how information differently propagates in the brain according to the visual category. Methods: 12 intractable focal epilepsy patients who underwent chronic subdural grid mapping by means of principle component analysis (PCA) of language tasks. Methods: 12 patients of intractable focal epilepsy who underwent clinical ECS mapping with subdural electrode placement in the language-dominant hemisphere. 31 electrodes (USP) were defined as language by ECS mapping using 6 language tasks. Principal components (PCs) were extracted by PCA and visualized in MNI space. 10 regions of interest (ROI) were set, and analysis of variance (ANOVA) was performed for 3 language areas (anterior, posterior basal temporal, and whole BT area). Results: PC1 and PC2 showed significant loadings for reading, receptive semantic processing, and expressive semantic processing, respectively. ANOVA with PC1 as the main factor revealed significant interaction for PC1 and ROI. Post hoc analysis revealed functional differentiation in posterior language area (low PC1 vs. posterior STG), posterior MTG and SMG (high PC2). Conclusion: PCA revealed 3 independent language functions and indicated functional differentiation even within posterior language area and BT/ALTA. Clinically efficient language mapping is expected by task selection considering PCs and regions.

O-08-4 Anatomo-functional correlation of language areas: principal component analysis of mapping linding

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Objective: To clarify anatomo-functional correlation of language areas defined by electrical cortical stimulation (ELS) mapping by means of principle component analysis (PCA) of language tasks. Methods: 12 patients of intractable temporal lobe epilepsy who underwent clinical ELS mapping with subdural electrode placement in the language-dominant hemisphere. 31 electrodes (USP) were defined as language by ECS mapping using 6 language tasks. Principal components (PCs) were extracted by PCA and visualized in MNI space. 10 regions of interest (ROI) were set, and analysis of variance (ANOVA) was performed for 3 language areas (anterior, posterior basal temporal, and whole BT area). Results: PC1 and PC2 showed significant loadings for reading, receptive semantic processing, and expressive semantic processing, respectively. ANOVA with PC1 as the main factor revealed significant interaction for PC1 and ROI. Post hoc analysis revealed functional differentiation in posterior language area (low PC1 vs. posterior STG), posterior MTG and SMG (high PC2). Conclusion: PCA revealed 3 independent language functions and indicated functional differentiation even within posterior language area and BT/ALTA. Clinically efficient language mapping is expected by task selection considering PCs and regions.

O-08-5 Utility of the Clustering Index method for diagnosing neuromuscular disorders as compared with EMG

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Objective: Concentric needle electromyography (CNEMG) is widely used for the evaluation of neuromuscular disorders, although pain is its definite drawback. Replacement of even part of the role of CNEMG by surface EMG (SEMG) would be possible. We previously devised the Clustering Index method (CI method), a new quantitative analysis for SECMG. However, the diagnostic yield of the CI method in comparison with CNEMG is not known. The aim of this study is to compare the sensitivity of the CI method with motor unit potential (MUP) parameters in CNEMG for diagnosing neurogenic or myogenic disorders. Methods: We retrospectively enrolled subjects for whom both SEMG and CNEMG were performed in the same tibial anterior muscle. Control data were constructed from 60 normal subjects for the CI method and 31 normal subjects for CNEMG. In CNEMG, 7 MUP parameters were evaluated, including Size (SD) and revised Size Indices for neurogenic (rSIn) and myogenic (rSIm) disorders, which are defined by CI method. MUP-SD of the mean parameter values was a control subject. Results: Enrolled were 21 patients with neurogenic and 20 patients with myogenic disorders. The sensitivities of the CI method for the neurogenic and myogenic disorders were 86% and 60%, respectively. Among MUP parameters, the highest sensitivity was achieved by area, SI, and rSIn (90%) for the neurogenic group, and by rSIm (56%) for the myogenic group. Conclusions: Diagnostic and brain function is yet to be clarified. The CI method was compared with MUP analyses in CNEMG. The CI method using SEMG is promising as a non-invasive diagnostic measure.

O-08-6 STN-DBS modulate urinaryafferent signal by changing the activity of mPFC in PD model rat

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Objective: Several studies suggested that subthalamic nucleus deep brain stimulation (STN-DBS) may improve urinary dysfunction in Parkinson’s disease (PD) patients. Although, it is unknown that modulated prerenal cortical input plays role in an urinary afferent information conveyed by periaqueductal grey (PG). The relationships between mPFC and PAG network are not well understood. We aimed to clarify how STN-DBS modulate the activity of mPFC by PAG stimulation in PD model rat. Methods: PAG stimulation were performed under urethane anesthesia in 6-hydroxydopamine lesioned PD rats (n=6). A single-lumen catheter was trans-urethrally inserted into the bladder to measure bladder pressure. Stimulation electrodes were inserted into left STN and PAG. Recording electrode was inserted into mPFC. Extracellular local field potential (LFP) recordings were performed. Results: PAG stimulation significantly decreased STN and PAG stimulation significantly increased bladder inter-contraction interval. Although PAG stimulation significantly decreased power of mPFC alpha frequency (200-400 Hz) during storage phase and 821±0.04 (a.u.) to 749±0.12 (a.u.) during voiding phase, adding STN stimulation significantly increased bladder inter-contraction interval and the alpha power in mPFC, which was reversed by STN stimulation in PD model rat.
脳卒中依存の発症原因

【目的】脳卒中後尿閉は、尿道カテーテル管理、尿路感染症合併、介護負担増大、生活運動障害のリスクとなる。脳卒中後尿閉の発症頻度、早期発見の有無、早期発見の条件について研究した。

【方法】2019年6月から2020年3月まで当院入院中の患者で、1)入院後に脳卒中を疑われた場合、2)脳卒中が発症してから6ヶ月以内に尿閉が発症される場合、3)code stroke発動が疑われる病例を対象とした。

【結果】全症例955例中111例(12%)に脳卒中後尿閉が発症。正常認知状態の患者で、code stroke発動者(22例)、看護師が発見・発動した例(14例)と両群を比較した。code stroke発動は20分以内を早期群、20分以上を遅延群とした。

早期群では、脳卒中発症からcode stroke発動までの時間は20分以内が14例(65%)、20分以上が7例(35%)で、早期群でcode stroke発動者の割合(48%)が高かった(81% vs 77%、p=1.000)。また、早期群で看護師発見・発動した症例(30%)、遅延群で医師発見・発動した症例(70%)の割合が高かった。看護師が発見し、医師がcode stroke発動した症例は1例であった。

【考察】脳卒中後尿閉の発症頻度は、脳卒中全体の12%で、早期発見が重要である。code stroke発動は早期発見の指標となると考えられる。
【目的】 多発性硬化症（multiple sclerosis/MS）による神経障害の増悪は中枢神経の機能を著しく阻害し、活動障害を引き起こす。この研究では、MSによる神経障害の増悪の機序を明らかにすることを目的として、MS患者の神経機能の変化を評価するために、カーボンハンドを使用したリハビリテーションの効果を評価した。

【方法】 パート1：カーボンハンドを用いたリハビリテーションの効果を評価するため、7例のMS患者を対象に、カーボンハンドを使用したリハビリテーションの効果を評価した。

【結果】 カーボンハンドを用いたリハビリテーションの2週間後の神経機能の改善がみられた。特に、左中側頭回→右補足運動野への機能的結合が増加した。

【結論】 カーボンハンドを用いたリハビリテーションは、MSによる神経障害の増悪に対して有効であることが示唆された。

【引用文献】

【おわりに】 MSによる神経障害の増悪は、活動障害を引き起こし、患者の生活質を著しく阻害する。カーボンハンドを用いたリハビリテーションは、MSの神経機能の改善を促進する可能性があると示された。今後、さらなる研究が必要である。
O-11.1 パーキンソン病の定量的磁化率マッピングと神経メラニン画像・神経領域との関連

【事例】パーキンソン病（PD）において、The Mann Assessment of Swallowing Ability（MASA）の有用性

【目的】パーキンソン病（PD）において、The Mann Assessment of Swallowing Ability（MASA）の有用性を検証する。

【Background】MASAは脳卒中患者に対する嚥下障害の診断に用いられるが、特殊な機器が不要で、熟練すれども精度の高い検査である。

【結果】MASAを施行し、嚥下機能評価を行ったが、パーキンソン病群において低下傾向がみられた。

【考察】MASAはパーキンソン病患者の嚥下機能の評価に有用であると考えられる。

O-11.2 パーキンソン病における運動学習後の転移の障害

【事例】パーキンソン病（PD）における運動学習後の転移の障害

【目的】パーキンソン病（PD）における運動学習後の転移の障害について検討する。

【方法】PD患者45名と健常者40名を対象に、運動学習と知的学習の転移効果を評価した。

【結果】PD患者ではHCに比して運動および知的学習後の転移度が低下していた。

【考察】運動学習後の転移度が低下する傾向が見られ、パーキンソン病の病態が運動学習に影響を与える可能性がある。
【目的】非弁膜症性心房細動を有する脳梗塞は重症化しやすく予後不良である。本研究は過去にウェアラブルデバイスを用いてパーキンソン病 (PD) の長時間心拍変動の解析から、心機能に影響を及ぼす危険因子を検討することを目的とする。【方法】2016年4月から2019年6月までに当院に入院した急性期脳梗塞患者541例のうち、非弁膜症性心房細動を有した153例の中で明らかにすることを目的とする。【結果】非弁膜症性心房細動を合併した脳梗塞の予後規定因子として、入院時の重症度以外に左房内血栓の存在が有意に多かった。【結論】非弁膜症性心房細動を合併した脳梗塞では、心房内の血栓は予後を規定する要素である。
一般演題

【目的】 パーキンソン病において、ビタミンB6は、発症リスク、神経症状との関連を示す。レボダップ投与割合、スチントマ、動悸、筋固縮の悪化、オンの短縮を認め、B6中止により改善した。【結論】 パーキンソン病患者に、B6中止を考慮する必要がある。B6中止の影響を検討した。【結果】 経過中にB6中止を考慮した。B6中止の影響を検討した。【結論】 B6中止の影響を検討した。
Transferability and sensitivity of tDCS on sleep quality and cognition in preclinical dementia

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-2000041521) with 201 mild post-moribund cognitive 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 or tDCS only. Primary outcome measures included sleep quality and cognition (measured by PSQI) and global cognition (measured by ADAS-Cog) at 4th week, 8th week and 12th week. Results. Compared to the combined modality, mild NCD-AD patients who received tDCS only demonstrated prominent enhancement on sleep quality at 12th week (F=9.5, p=0.004). Within the tDCS group (n=62), we found that 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=0.012), 8th week (t=-2.60, p=0.01) and 12th week (t=-3.89, 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=-2.19, p=0.031). Conclusion. 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.

A single administration of perampanel reduces ISF Aβ-amyloid levels in the hippocampus of J20 mice

IntroductionRecent studies shed light on hippocampal network hyperexcitability as a very easy event in AD patients. Since enhanced neuronal/synaptic activity can promote presynaptic Aβ production and release into interstitial space, hippocampal hyperexcitability is considered as one of the promising therapeutic targets to prevent cognitive impairment in AD. However, the mechanism of how hippocampal hyperexcitability is considered as one of the promising therapeutic targets to prevent Aβ deposition in AD. A recent study of an AD transgenic mouse model reported aberrant Ca2+ permeable AMPA receptor expression in young mice prior to Aβ deposition. Thus, we asked whether perampanel (PER), a selective non-competitive AMPA receptor antagonist could reduce Aβ levels in hippocampal interstitial fluids (ISF) of APP transgenic mice (J20). Method Using in vivo brain microdialysis that allows for a real-time sampling of ISF, we investigated dynamic levels of hippocampal Aβ before and after a single administration of PER using young J20 mice without Aβ deposition (vs. vehicle, each n=8). Results Concomitant with the reduced ratio of β-CTF to full length of APP, ISF Aβ levels were significantly decreased 456 hours after a single oral administration of PER in a dose-dependent manner without affecting the half-life period. Conclusion A single administration of PER rapidly decreases ISF Aβ levels through inhibiting APP processing in young J20 mice, indicating that this agent is a potential therapeutic drug to prevent future Aβ deposition in very early AD.

In vivo models of pathological TDP-43 transmission

Background Findings from recent studies suggest that TDP-43 aggregation and its propagation are pathological features of ALS. If the propagation contributes to the disease progression, it can be the therapeutic target for ALS. There have been however, no conclusive evidence of the cell-to-cell transmission of pathological TDP-43 protein. Methods To assess TDP-43 transmission in vivo, we used Cre-dependent TDP-43 expression system using a lentivirus (AAV) vector. Cytoplasmic form (mNLS) or aggregate form (mNLSmRRM) of human TDP-43 constructs were applied for transfection of Cre mice. One month after the injection of the AAV vectors, the expression of exogenous TDP-43 was analyzed. Results Immunohistochemistry of CamKII-Cre mouse brain injected with AAV-TDP-43mNLS revealed that the exogenous TDP-43 was not only in the ipsilateral hippocampus but also in the neurons of the entorhinal cortex, amygdala, thalamus, and the callosal side of hippocampus. On the other hand, in the brain injected with AAV-TDP-43mNLSmRRM, TDP-43 was detected in the neurons in the ipsilateral hippocampus and the oligodendrocytes in the corpus callosum, although it hardly distributed to the neurons apart from the injected side of hippocampus. This study results suggest that pathological TDP-43 could transmit from neuron to neuron or from neuron to oligodendrocyte. This in vivo model allows us to analyze the mechanism of the pathological TDP-43 propagation.

Loss of White Matter Capillary Pericytes in Vascular Dementias and Alzheimer’s Disease

Background White matter (WM) disease is associated with disruption of the glialovascular unit, which involves breach of the blood-brain barrier (BBB). We quantified pericytes as components of the glialovascular unit and assessed their status in vascular and other dementias. Methods We evaluated a total of 124 post-mortem brains from patients with primary subcortical ischemic disease (PSD), vascular dementia (VaD), Alzheimer’s disease (AD), AD-VaD (Mixed) and post-stroke non-demented (PSND) stroke survivors as well as controls. Immunohistochemical methods were developed to assess distribution of pericytes connected to the frontal lobe WM capillaries. Pericytes with a nucleus were identified by collagen 4 (COL4) and platelet-derived growth factor receptor-β (PDGFR-β) antibodies with further verification using PDGFR-β-specific ELISA. Results COL4 and PDGFR-β-reactive pericytes adopted the characteristic ‘crecent’ or nodule-like shapes around capillary walls. We estimated densities of pericytes was 225 ± 38 and 200 ± 113 (SEM) per COL4 mm2 area or 20 ± 0.1 and 17 ± 0.1 per mm capillary length in young and older aging controls. Remarkably, WM pericytes were reduced by ~45% in the frontal lobe of PSD, VaD, Mixed and AD subjects compared to PSND and controls subjects (p<0.001). Conclusions Our results demonstrated a reliable method to quantify COL4-positive pericytes. Pericytes in the WM were decreased across different dementias including PSD, VaD, Mixed and AD. Our findings suggest that downregulation of pericytes is associated with BBB disruption in the deep WM in aging-related dementias.

Conversion from cilostazol to OPC-13015 linked to mitigation of cognitive impairment

Objective Cilostazol is a selective inhibitor of type 3 phosphodiesterase. Based on a drug repositioning approach, the clinical application of cilostazol for mild cognitive impairment due to Alzheimer’s disease (AD) has been completed. A study demonstrated that OPC-13015 is an active metabolite of cilostazol and has a stronger inhibitory effect on type 3 phosphodiesterase than cilostazol. [Methods] We prospectively enrolled patients with mild cognitive impairment to whom cilostazol was newly prescribed. Patients underwent the Montreal Cognitive Assessment (MoCA) twice, at a 6-month interval. Plasma cilostazol, OPC-13015, OPC-13213, and OPC-13217 concentrations were determined using liquid chromatography-tandem mass spectrometry. [Results] MoCA score changes from the baseline to the 6-month visit were positively correlated with ratios of OPC-13015 to cilostazol and total metabolites (n = 19, F = 0.005). Patients with higher ratios of OPC-13015 (≥ 0.18, median value, n = 10) had significantly higher MoCA scores (P = 0.036) than those with lower ratios (the ratio < 0.18, n = 9). The absolute value of OPC-13015 concentration in blood was also higher in patients with preserved cognitive function (P = 0.033). [Conclusion] Blood OPC-13015 levels may be a predictive biomarker of cilostazol treatment for Alzheimer’s disease.

Biological phase separation in neurological disorders

Objective Proteins and nucleic acids are prone to self-assemble and phase separate to form liquid-like droplets, and recent advancements in genetics and protein science provide a link between neurological disorders and aberrant regulation of macromolecular condensates. Here we aim to better understand the molecular pathogenesis of neurological disorders. [Methods] We utilized multiple biochemical and biophysical methods including proteomics and solution nuclear magnetic resonance (NMR). [Results] By interactome analysis, toxic poly(A)-rich (PR) poly-dipeptides encoded by repeat expansion in the first intron of a gene designated C9orf72 in the most prevalent form of familial amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) were found to target proteins with intrinsically disordered proteins with low-complexity sequences (LC domains) and stabilized labile cross-beta polymers (LC polymers). Moreover, biochemical and cellular analysis showed that PR poly-dipeptides bound phenylalanineglycine (FG)-rich domains of nuclear pore proteins and disrupted their nuclear localization. [Conclusion] This study suggests that pathological TDP-43 could transmit from neuron to neuron or from neuron to oligodendrocyte. This in vivo model allows us to analyze the mechanism of the pathological TDP-43 propagation.
O-16-3 Monomerization of TDP-43 is a key determinant for inducing TDP-43 pathology in ALS
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Background: TAR DNA-binding protein 43 (TDP-43) is a key pathogenic protein in familial and sporadic amyotrophic lateral sclerosis (ALS). Recent N-terminal truncation (NTT) analysis of TDP-43 has been reported, but its role in ALS pathogenesis remains unknown. Methods: We evaluated the dimeric state of TDP-43 in postmortem cerebral cortex from ALS cases and disease controls. Morphological, immunocytochemical and biochemical analyses were performed to examine the dimerisation of TDP-43 in NeuN-IR cells expressing the monomeric or wild-type of TDP-43 were performed. To evaluate TDP-43 dimerization, we used diiscomycinyl diamide (DSD), a membrane permeable cross-linker, and established a novel bimolecular fluorescence complementation assay in live cells. Results: DSG crosslinking and immuno blot analysis revealed that the ALS brains had a significant decrease in the dimer/monomer ratio compared to the controls. Transient expression of the TDP-43 monomer mutant in Neuro2a cells induced cytoplasmic mislocalization and phosphorylated aggregation of TDP-43, which were hallmarks of ALS pathology. Moreover, our Dijic assay revealed that TDP-43 dimerization decreased in ALS brains and increasing TDP-43 monomerization recapitulated ALS pathology in cells. Conclusions: We demonstrated that TDP-43 dimerization decreased in ALS and increasing TDP-43 monomerization recapitulated ALS pathology in cells for the first time. These results suggest that TDP-43 is a key determinant for inducing TDP-43 pathology in ALS.

O-16-4 Hypoxic stress visualized in the cervical spinal cord of ALS patients
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Objective: Amyotrophic lateral sclerosis (ALS) is a progressive and fatal motor neuron disease. Hypoxic stress is suspected as the pathogenesis of ALS. However, no positron emission tomography (PET) study for hypoxic stress has been affected in the spinal cord of ALS patients. In the present study, we examined cervical spinal hypoxic stress of nine ALS patients with upper extremity (UE) atrophy by 18F-fluoromisonidazole (FMISO) PET. Sporadic ALS patients (8 males, 1 female; mean age 64 ± 9 years) and the categories of probable or definite ALS were recruited to this study. Results were compared with those of 10 patients with early-stage oral cancer (7 males, 3 females; mean age 62 ± 8 years). Results: On the ipsilateral side of C1 and C5 levels, FMISO uptake increased significantly compared with the contralateral side (p < 0.05) and the control subject (p = 0.01). In addition, a strong correlation was found between FMISO uptake of the C5 level and the rate of progression of the ALS FRS score (R = 0.76, p = 0.01). Conclusion: These results indicate that hypoxic stress increased in the spinal cord of ALS patients with a close link to ALS progression. Both hypoxic stress and a compromised response to hypoxia, which may lead to subsequent motor neuron death, could be a potential therapeutic target for ALS.

O-17-1 ラップトップ・インネット無力症候群の全国疫学調査（2018）
松戸脳神経内科

【目的】本邦にてエクリズマブが抗アセチルコリン受容体抗体陽性の全身型重症筋無力症（gMG）の治療としての認可を受けており、その効果を評価する目的で後調査の中間解析を行った。

【方法】エクリズマブ投与のgMG患者全例を対象に特定使用成績調査に登録し、さらに2019年10月1日で終了した5年間のデータをもとに分析を行った。

【結果】エクリズマブ投与のgMG患者全例を対象に特定使用成績調査に登録し、2019年10月1日で終了した5年間のデータをもとに分析を行った。

【結論】エクリズマブの安全性および有効性を確認し、治療計画を立てることができた。
A-18-1 サロノイドススによる末梢神経障害の病理学的特徴

【目的】 血管炎、特に抗好中球細胞質抗体(anti-neutrophil cytoplasmic antibody: ANCA)関連血管炎を含む末梢神経障害の原因の1つである。しかし、その詳細はまだ不明である。

【方法】 腓腹神経の組織学的検査を行い、その病態を明らかにする。

【結果】 ANCA陽性例では、血管壁の破壊や閉塞を認め、一部の例では血小板・凝固因子の影響を示唆する所見も認められた。

【結論】 ANCA関連血管炎は末梢神経障害の一因であり、詳細な病理学的検討が必要である。

A-18-2 多発性硬化症の治療戦略は重症度及び視床容積と関連

【目的】 多発性硬化症の治療戦略は重症度及び視床容積と関連する。しかし、詳細な考察はまだ十分である。

【方法】 脳MRI検査と臨床データを用いて、視床容積とEDSSとの関係を解析した。

【結果】 視床容積が大きいほどEDSSが有意に高くなる傾向がみられた。特に、厳重治療群（HIT群）でこの関連が強く示された。

【結論】 視床容積が大きい患者で厳重治療が必要であることが示され、治療戦略の必要性が示された。
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O-19-3 超急性期脳梗塞の血管内治療単独療法の有効性に関する多施設共同ランダム化比較研究

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目的：発症4.5時間以内の主幹動脈閉塞を伴う脳梗塞例に対して、血管内治療と
例（51%）であり、有意に併用群で多かった（p=0.02）。【結語】両群で転帰良好の割
の登録システムで無作為に血管内治療単独群と血管内治療とIVtPAの併用群に割
の前向きランダム比較試験（SKIP study）を行った。【方法と対象】目的に、多施設
応例に対し、血管内治療単独療法の、併用療法に対する非劣性を証明することを
IV-tPAを併用することがガイドラインで推奨されている。しかし、経静脈的血栓
for noninferiority）。発症36時間以内の頭蓋内出血は単独群34例（34%）、併用群52
の研究で観察された（odd ratio 1.91, 95% confidence interval 0.63-6.18）が示された（odd ratio 1.49, 95% confidence interval 0.44-4.71）。有意に非劣性を示すことは
の登録システム（©ｎｉｎｅ）で設定した。【非劣性】発症36時間以内の頭蓋内出血は単独群34例（34%）、併用群52

O-19-4 脳卒中後てんかん患者の発症1年後の予後：発症再
ととの関連

・吉村 元，田中 智晶，福間 一樹，小野塚 大介，西村 宏邦，
用本 未江，原利 伸久，野原 俊夫，
しゅう，脳神経内科

目的：脳卒中後てんかんの予後とその発症再発との関連を明らかにする。【方法】
for noninferiority）研究に登録された患者392名のうち、初回発作の患者を対象とした。
サバイバル曲線を発症171日および発症再発と関連瞭のなかった。単変量解析では
了発症再発は脳卒中後てんかんとの関連が認められず（再発群22% vs. 非再発群8.7%, odds ratio 0.79 [95% CI 0.18-2.61], p=0.79）、発症再発と機能低下の関連が交絡の可能

O-20-1 The absence of orthostatic heart rate increase and cognitive impairment in Parkinson’s disease

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Objective: Orthostatic hypotension (OH) frequently accompanies autonomic dysfunction in Parkinson's disease (PD). While OH is usually diagnosed based on an orthostatic blood pressure drop, the association between OH and cognitive impairment remains unclear. We retrospectively analyzed 143 cases of clinically diagnosed PD to determine the association between the absence of a heart rate response and cognitive impairment in PD with OH. Among the patients with OH, neurogenic OH was diagnosed in cases without a heart rate increase, while all other patients were diagnosed with non-neurogenic OH. Results: The presence of OH was an independent risk factor for dementia in PD in addition to the age, gender and other covariant factors. The presence of OH was significantly greater after two years (three times per person). The binding potential (BPND) was estimated on voxelwise paired t-test for [11C]DPA713. The [11C]DPA713 BPND was significantly greater after two years. However, the BPND change in PDz in the entire brain did not significantly change after two years. In the PD group, the [11C]DPA713 BPND showed significant increase in the whole brain especially in the brain cortices during the early stage in PD. With the neuroinflammation proceeding, the current activation extends over the posterior brain regions such as the parietal and occipital cortices. The presbyostatic activation that was preserved after adjusting for age, gender and other covariant factors.

O-20-2 Gray matter atrophy in early Parkinson’s disease with orthostatic hypotension

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Purpose: Orthostatic hypotension (OH) and cognitive impairment appear to be interrelated in Parkinson's disease. However, there is few data on distinct areas of gray matter atrophy related to these clinical features in early Parkinson's disease (PD). Methods: Forty-five patients with PD without antiparkinsonian drug were enrolled. All subjects underwent cognitive assessments including the Mini-Mental State Examination (MMSE), head-up tilt test, and 3 Tesla MRI. Voxel-based morphometry (SPM12) was utilized to perform whole-brain voxel-wise statistical analysis of gray matter volume. To examine the correlation between gray matter volume and cognitive functions, we extracted the subject-level mean gray volumes from the modulated and smoothed gray matter maps using the Automated Anatomical Labeling (AAL) atlas. Results: After adjustment for age and total intracranial volume (TIV), patients with OH had reductions in gray matter volumes in the right middle cingulate gyrus (MCC) compared to patients without OH at p<0.05 corrected for multiple comparisons (Family Wise Error). Regression analyses controlling for age and TIV showed that reductions in gray matter volumes in the right MCC were associated with cognitive decline in patients with PD. Conclusion: The previous studies demonstrated that MCC activation was associated with cognitive decline in patients with PD, and the present study showed that OH was associated with atrophy of MCC and cognitive decline.

O-20-3 In vivo chronological changes in neuroinflammation after zonisamide therapy in Parkinson’s disease

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Objective: Neuroinflammation matters in Parkinson's disease (PD). Previous animal studies indicated that a neuroprotective capacity of zonisamide (ZNS) against neuroinflammation. To evaluate this ZNS neuroprotective effect in humans in vivo, we for the first time examined chronological changes in microglial activation prior to and after ZNS therapy in early PD patients with DBS with setting type IPG. Fourteen early PD patients were included. All patients previously underwent DBS with voltage setting type of implantable pulse generator (IPG) with constant current setting type in PD. With the neuroinflammation proceeding, the current activation extends over the posterior brain regions such as the parietal and occipital cortices. The presbyostatic activation that was preserved after adjusting for age, gender and other covariant factors.

O-20-4 Long-term outcome of DBS patients in whom voltage setting IPG was exchanged with current setting IPG

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Objective: To investigate the safety and efficacy of exchange of conventional voltage setting type of implantable pulse generator (IPG) with constant current setting type in patients who previously underwent deep brain stimulation (DBS). Methods: Thirty-six cases were included. All patients previously underwent DBS with voltage setting type IPG. The average age at IPG exchange was 65±9.8 years old, and the mean period from implantation was 48±4.3 years. We surveyed the complications, setting parameters, and clinical outcomes at 3 and 12 months after the exchange. Results: Three- and 12-month observations were completed in 34 and 28 cases, respectively. The number of stimulating contacts per lead was 183±69, the voltage was 30±15 V per lead, the pulse width (PW) was 67±22 μs (SPM12), and the frequency was 180±32 Hz before the exchange. The stimulation parameters 3 months after IPG exchange were as follows: 14±6.9 stimulating contacts per lead, 57±4.0 mA current per lead, 315±318 microsecond PW, and 1982±559 Hz. The number of contacts per lead was significantly reduced after IPG exchange (p<0.01). Patients and stimulation-evoked complications were reduced in 14 (38%) patients, respectively. There were no cases in which the symptoms worsened due to IPG exchange. Constant and precise control of the current might have improved symptoms and prevented stimulation-evoked complications. Conclusions: Current control setting might be beneficial as an alternative to a conventional voltage setting for patients who underwent DBS.
【目的】多発性硬化症(MS)では発症早期から物忘れや実務能力低下を自覚する患者は多く、神経心理学的検査を受診する。MSの神経心理学的な変化は、認知機能低下を伴うことが報告されている。なので、MSの神経心理学的検査結果を検討する。

【方法】2010年11月~2020年9月に当院に入院したMSのうち、発症5年以内に神経心理学検査を受診した患者を対象とした。神経心理学検査の結果を用いて、認知機能低下群と健常群を分け、認知機能低下群の特徴を検討した。

【結果】認知機能低下群は、健常群に比べて多発性硬度が有意に高かった(p<0.05)。また、認知機能低下群では、認知機能の変化が有意に高かった。

【結論】MSの発症早期は、認知機能低下が高まる傾向がある。神経心理学的検査は、MSの発症過程における認知機能の変化を評価するうえで有用である。
O-22-3
抗AQP4抗体脳症患者末梢血では細胞内のDN2の割合が増大し、病巣を反映している
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【目的】抗AQP4抗体脳症の各種異常部位において篩選された13例の末梢血を用い、DN2の相対増加が脳症の病巣を反映しているかを検証した。
【方法】末梢血からPBMCを分離後、T細胞とB細胞を分離。抗AQP4抗体陽性的証明を12例、GAD65抗体陽性1例で31例のPBMCを用意。Angiopep-2を抗CD11aのモノクローナル抗体とし、これを用いて抗AQP4抗体陽性PBMCを分離。抗CD14抗体と抗CD16抗体でMonocyteとNeutrophilを分離。抗CD3抗体でT細胞を分離、抗CD19抗体でB細胞を分離。抗CD45抗体で両者の背景を除き、B細胞をStim1で刺激。Stim1を用いて達成された変異形MHCクラスII分子の表現を検出した。DN2細胞の検出に際してはFITCでLSECtinを標識し、Stim1により分化したCD19陽性B細胞を分離。【結果】抗AQP4抗体陽性PBMCの中では、B細胞の刺激により分化細胞の数が増加し、DN2細胞の割合も増加した。【考察】抗AQP4抗体陽性PBMCの末梢血からB細胞を見出す際、DN2の細胞を確認することが重要である。
在宅剖検事業「おだやかな看取りを明日に活かすみち」


大規模診療データベースを用いた急性肝性ポルフィリン症の実態調査

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目的

急性肝性ポルフィリン症は、肝臓のヘム生合成酵素における遺伝子変異に比例して引き起こされる、重篤な消化器病変の合併を伴う、稀な疾患である。めまい、頭痛、嘔吐、発熱、黄疸の症状を伴い、肝硬変や敗血症などを合併し、重度の臨床症状を示す。

方法

本研究では、2015年10月から2020年9月までの5年間の国内における急性肝性ポルフィリン症の発症例を対象に、大規模診療データベースを用いた実態調査を行った。

結果

発症例は74例であり、内訳は急性肝性ポルフィリン症37例、急性間欠性ポルフィリン症37例である。年齢は20歳代から80歳代まで多様であり、男性が71例、女性が3例である。

結論

急性肝性ポルフィリン症の発症は、その臨床症状を把握するためには、大規模なデータベースの活用が不可欠である。来院時に診断を確定させ、適切な治療が行われるよう、医療機関同士の連携が求められる。
【目的】進行性多巣性白質脳症(progressive multifocal leukoencephalopathy: PML)の発症を予想できない可能性が高まる。腰椎穿刺施行の適否を判断する場合に、増多が三叉神経節や血管など髄膜外の炎症に由来するとすれば、髄膜刺激徴候に帯状疱疹ウイルス(VZV)髄膜炎と診断された。【結論】髄膜刺激徴候偽陰性例では、acci"
O-26-1 アレルギーPTD・FDG-PET画像と関連する生活習慣因子

O-26-2 脳微小脳出血所見と認知症予防に関する新規マーカーMRI-PRO ADの有用性

O-26-3 Alzheimer病診断における123I-MIPECTの有用性の検討：Aβとα脳波活動の比較

O-26-4 生体活動データと深層学習を組み合わせた新たな認知症診断ツールの可能性探索

O-26-5 MRIの診断におけるoptic flowタスクを利用した前頭前野視覚皮質の神経機能評価

O-26-6 腦微小脳出血マーカーの細胞内からの変化を考察するアルツハイマー病の進展
**O-27-1** Drosophila model for parkinsonism by targeting phosphoglycerate kinase

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Background

Phosphoglycerate kinase 1 (PGK1) is a glycolytic enzyme encoded by PGK1, which maps to the X chromosome. PGK deficiency, which was classically recognized as gynecomastia, hypogonadism, and congenital heart disease due to defective ATP regeneration, in Parkinson's disease, has occasionally been reported as a neurological complication of this condition. We have recently reported that early-onset Parkinson's disease (PD) can be developed even in a heterozygous carrier of PGK1 mutation. Objective and Methods: To investigate whether PGK knockdown leads to leukodystrophy in both young and aged adult flies and was accompanied by progressive DA neuron loss with aging. PGK knockdown in DA neurons decreased dopaminergic neurons in the central nervous system (CNS) of both young and aged adult flies, suggesting that PGK knockdown flies exhibited a novel model for PD. Furthermore, specific PGK knockdown induced low ATP levels and the accumulation of reactive oxygen species (ROS) in the CNS of third instar larvae. Conclusion: These results indicate that a failure in the energy production system of PGK knockdown flies causes leukodystrophy accompanied by neuronal dysfunction and degeneration in DA neurons.

**O-27-2** 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=220), and healthy controls (n=205) using real-time reverse transcription PCR. Then we performed comprehensive association analyses on the sleep characteristics and the PBMC 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. Conclusion: 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.

**O-27-3** Loss of CHCHD2 causes inclusion body formation and dopaminergic neuronal loss in aged mice

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Objective: Mutations in the CHCHD2 gene cause an autosomal dominant late-onset Parkinson's disease (PD). The gene product CHCHD2 contains mitochondria-targeting sequence in the N-terminus and coiled-coil domain at the C-terminus and has been localized to the intermembrane space of mitochondria. Although CHCHD2 is known to be involved in the mitochondrial proteolytic system, the role of CHCHD2 as a mitochondrial protein and its function are not clear. We examined the CHCHD2 knockout (KO) mice to clarify the phenotype (behavioral and histological) associated with the mitochondrial proteolytic system.

Conclusions: Our findings highlight the unexpected role of the CHCHD2 gene in mitochondrial morphology and function, as well as their correlation with the mitochondrial proteolytic processes associated with the mitochondrial proteolytic system.

**O-27-4** MicroRNA-30e-5p is a potential biomarker for Parkinson disease by targeting NLRP3 gene

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Objective: Recent studies have demonstrated that microRNAs are involved in the regulation of Parkinson's disease (PD) - related genes and alterations of certain microRNAs have been considered as potential biomarkers. This study aims to identify differentially expressed microRNAs in the peripheral blood mononuclear cells (PBMCs) of PD patients to serve as a potential disease biomarker, and explore the functional relevance of the differential microRNAs in PD. Methods: We screened and identified microRNAs using a specific miRNA-+miRNA network model. Then we measured the identified microRNA levels in the PBMCs of patients with PD (n=220), age-matched healthy controls (HC, n=122), and non-PD neurological disease controls (NDC, n=124) using the real-time quantitative PCR. The potential biological target gene of the microRNA was analyzed by dual-lucrasure reporter assay. Results: Through microRNA bioinformatics screening and further validation in the PBMCs from a relatively larger population of PD patients, the miR-30e-5p level was identified to be significantly down-regulated in PD patients than those of HC (p < 0.001) and NDC (p < 0.05). Furthermore, the NLRP3 gene was confirmed to be regulated by miR-30e-5p and significantly increased in the PBMCs of PD patients compared with HC and NDC (p < 0.01). Conclusions: MiR-30e-5p may be a new regulator of NLRP3 and a potential biomarker aiding in the diagnosis of PD and monitoring disease progression.

**O-27-5** Fatty acid-binding protein 7 mediates the psychosine toxicity in oligodendrocytes

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Objective: We have previously demonstrated that fatty acid-binding protein 7 (FABP7), another member of fatty acid-binding protein, binds to psychosine. Here we developed a high affinity FABP7-specific antibody (scanned using 8-anilinonaphthalene-1-sulfonic acid (ANS) assay and quartz crystal microbalance (QCM) assay), disrupted the FABP7-Syn interaction. FABP7 induced Syn oligomerization in both glial cells and oligodendrocyte precursor cells (OPCs). Psychosine treatment also triggered Syn oligomerization by FABP7 through phospholipase A2 (PLA2) activation, and induced KIC-mediated Syn aggregation, and prevented KCIC and OPSC cells death. Conclusion: This study showed that FABP7 triggers Syn oligomerization associated with psychosine-induced oxidative stress, while FABP7 ligand 6 inhibits FABP7-induced Syn oligomerization and aggregation, thereby rescuing oligodendrocytes from cell death.

**O-27-6** Decreased functional integrity within striatum and sensorimotor network in Parkinson disease

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Objective: Parkinson disease (PD) is known to have abnormal function in the striatum and sensorimotor network (SN) areas. We aimed to evaluate diagnostic utility of functional integrity within striatum and the SN and their associations with motor symptoms in PD patients. Methods: We enrolled 51 PD patients and 18 age- and gender-matched healthy controls (HCs). Motor symptoms were evaluated using MDS-UPDRS part 3. Resting-state functional MRI (fMRI) images were obtained from all subjects using Siemens 3 Tesla scanner. Functional 'connectivity' maps were created by calculating the correlation coefficients in each time point and applying a threshold of significance. To identify the significant change in the connectivity patterns between PD and HC patients, the difference of connectivity was calculated for each pair of regions, and the significance was evaluated using General Linear Model (GLM) analysis. Results: The mean connectivity values in striatum showed sensitivity: 72.2% at cut-off: 0.19, and those in SN showed 72.2% and 68.6% specificity: 72.5% at cut-off: 0.36, respectively. Mean connectivity values in striatum and the SMN were negatively correlated with MDS-UPDRS part 3 score. Conclusions: The connectivity measures in striatum and the SN may be potential endogenous biomarkers for PD.
O-28-1  Motor nerve organoid is useful tool to analyze axonal degeneration of ALS

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Purpose: A myostrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disorder characterized by the death of motor neurons and degeneration of axons. The purpose of this study is to analyze the pathomechanism of motor nerve axon in ALS. Methods: We used human induced pluripotent stem cells (hiPSCs)-derived motor neurons. We developed a model to form motor nerve axons which could be used to analyze axonal degeneration of stem cell derived motor neurons in vitro. Results: We identified aberrant increasing of axon branching in hUSP4 mutant hiPSC-derived MN axons compared with isogenic controls as a novel phenotype. We identified increased level of Fos-B mRNA binding target of FUS, in FUS-mutant MNs. While Fos-B reduction using siRNA or an inhibitor ameliorated the observed aberrant axon branching, Fos-B overexpression resulted in aberrant axon branching even in vivo. The commonality of those phenotypes was further confirmed with other ALS causative mutation than FUS. We also show the result of TARDDBP-mutated motor neuron. Conclusion: Analyzing the axonal fraction of hiPSC-derived MNs using microdevice based revealed that Fos-B is a key regulator of FUS-mutant axon branching. Motor nerve organoid is the useful tool to analyze axonal degeneration of ALS.

O-28-2  Altered exosome levels affect alpha synuclein accumulation and propagation in brains

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Objective: Parkinson’s disease is pathologically defined as the progressive depositions of α-synuclein (α-syn) containing Lewy bodies (LBs) and Lewy neurites (LN). Accumulation of α-syn in the right striatum of C57BL/6 mice. Bilateral carotid artery stenosis (BCAS) cellular model to visualize seed-templated αS aggregation using bimolecular fluorescence complementation assay. Methods: We used human induced pluripotent stem cells (hiPSCs)-derived motor neurons. We developed a model to form motor nerve axons which could be used to analyze axonal degeneration of stem cell derived motor neurons in vitro. Results: We identified aberrant increasing of axon branching in FUS-mutant hiPSC-derived MN axons compared with isogenic controls as a novel phenotype. We identified increased level of Fos-B mRNA binding target of FUS, in FUS-mutant MNs. While Fos-B reduction using siRNA or an inhibitor ameliorated the observed aberrant axon branching, Fos-B overexpression resulted in aberrant axon branching even in vivo. The commonality of those phenotypes was further confirmed with other ALS causative mutation than FUS. We also show the result of TARDDBP-mutated motor neuron. Conclusion: Analyzing the axonal fraction of hiPSC-derived MNs using microdevice based revealed that Fos-B is a key regulator of FUS-mutant axon branching. Motor nerve organoid is the useful tool to analyze axonal degeneration of ALS.

O-28-3  HIF1A-dependent autophagy mitigates alpha-synuclein pathology and cognitive impairment

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(Objective) Parkinson’s disease (PD) is a progressive movement disorder where neurodegenerative processes occur in association with pathogenic a-synuclein (α-syn) accumulation. Previous epidemiological studies have shown that several vascular risk factors reduce the risk of PD. Epidemiological studies have shown that several vascular risk factors reduce the risk of PD. We aimed to elucidate the molecular mechanism of how vascular risk factors reduce the PD risk using a mouse model. We established a novel cellular model to visualize seed-templated αS aggregation using bimolecular fluorescence complementation assay. The cells were treated with a α-syn seed to trigger seed-templated aggregation of endogenous α-syn. We injected a α-syn seed into the right striatum of C57BL/6 mice. Bilateral carotid artery stenosis (BCAS) was employed to induce moderate hypoxia in the brain. (Results) While a α-syn seed was incorporated into the endo-lysosomal pathway, seed-templated αS aggregates were distributed to the autophagy-lysosome pathway, suggesting separate degradation pathways. Chemical hypoxia by CoCl2 induced hypoxia-inducible factor 1A (HIF1A)-dependent autophagy and enhanced the degradation of the seed-templated αS aggregates, not α-syn seed. In the mouse model, BCAS induced a significant increase of HIF1A expression and significantly reduced the accumulation of phosphorylated α-syn in the neuronal cells. BCAS induced cognitive deficits. Conclusion: HIF1A-dependent autophagy mitigates α-syn pathology and cognitive deficits by enhancing the autophagy-lysosome pathway to degrade seed-templated αS aggregates.

O-28-4  A new mitochondrial quality control system mediated by extracellular release

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(Objective) Recent studies have shown mitochondria can cross cell boundaries and be transferred between cells. While the phenomenon has been extensively reported, its detailed mechanism and the resulting biological consequences remain unsolved. In this study, we tried to see how mitochondrial release is regulated under stress conditions and how it relates to the mitophagy regulation. Methods: We developed the monitoring and quantifying system of released mitochondria from cultured cells. We observed how released mitochondria change, quantitatively or qualitatively, under treatment with drugs inducing mitochondrial stress. Results: We manipulated cognitive deficits. Conclusion: A new mitochondrial quality control system mediated by extracellular release is a comparable yet distinct quality control pathway from mitophagy.

O-28-5  Cellomics-neurology by CUBIC, 3D immunostaining and high-speed imaging at whole-brain scale

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(OBJECTIVE) The neurological diseases have a variety of symptoms and possible causes, implying unknown lessons remaining. In this study, to elucidate the details, we established a whole-brain cell profiling method by developing CUBIC (CUBIC-3D imaging) and high-speed imaging (MOVIE), and applied them to adult mouse whole-brain samples [METHODS] We developed efficient volumetric imaging MOVIE system, integrated into a custom-built light sheet fluorescence microscope. In addition, a cell detection algorithm was used for fast analysis of large imaging data with highly parallelization of multiple CPUs and GPUs. We also applied them to whole-brain immunostained samples for neural markers such as NeuN and TH. RESULTS Acquisition time was reduced to within a few hours per whole mouse brain. For example, when observing adult mouse whole brain with a 10x objective, the throughput for a 90ms exposure time was measured to be 456 TB/s and the total data size was 25 TB. Our cell detection algorithm operated at 1 hr/brain and had an F-score of more than 90% stained cell detection in the whole brain. These methods were also approved by adult mouse whole-brain samples co-stained with nuclear and immunostaining to observe and quantify neural markers at a whole-brain scale. CONCLUSIONS This pipeline may lead to a more detailed quantitatice analysis of very early pathological changes, pathological progression, and site-specific symptom relationships in the future.

O-28-6  Anti-dyskinetic effects of zonisamide via downregulation of 5-HT1A/1B receptors and 5-HT transporter

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(Objective) To investigate the contribution of striatal serotonergic transmission in the development of levodopa-induced dyskinesia (LID) and clarify new targets for the anti-dyskinetic effect of zonisamide (ZNS), we analyzed efficacy of ZNS expression in the left substantia nigra (S-5HT) 1A/1B receptors and 5-HT transporter (SERT). Methods Unilaterally 6-OHDA-treated rats were divided into five groups and received different treatment for 21 days: normal saline (N), levodopa (L), continuous levodopa (C), intermittent levodopa and ZNS (IZ), intermittent ZNS (Z). Forepaw pawing steps (FAS) was tested before and after treatment. Results ZNS administration to LID was estimated by the amount of mitochondrial protein in biosamples obtained from patients and model animals. [Results] Rote-nothéne- and CCCP-induced mitochondrial quality impairment, extracellular release. In mice, brain, and cerebrospinal fluid samples from Parkinson disease patients carrying loss-of-function mutations show increased expression of 5-HT1A/1B receptors and 5-HT transporter. In the details, we established a whole-brain cell profiling method by developing CUBIC (CUBIC-3D imaging) and high-speed imaging (MOVIE), and applied them to adult mouse whole-brain samples [METHODS] We developed efficient volumetric imaging MOVIE system, integrated into a custom-built light sheet fluorescence microscope. In addition, a cell detection algorithm was used for fast analysis of large imaging data with highly parallelization of multiple CPUs and GPUs. We also applied them to whole-brain immunostained samples for neural markers such as NeuN and TH. [RESULTS] Acquisition time was reduced to within a few hours per whole mouse brain. For example, when observing adult mouse whole brain with a 10x objective, the throughput for a 90ms exposure time was measured to be 456 TB/s and the total data size was 25 TB. Our cell detection algorithm operated at 1 hr/brain and had an F-score of more than 90% stained cell detection in the whole brain. These methods were also approved by adult mouse whole-brain samples co-stained with nuclear and immunostaining to observe and quantify neural markers at a whole-brain scale. [CONCLUSIONS] Thus, this pipeline may lead to a more detailed quantitatice analysis of very early pathological changes, pathological progression, and site-specific symptom relationships in the future.
Safety and tolerability of conversion to siponimod in MS: interim results of the EXCHANGE study

Purpose: In the USA, siponimod is for the treatment of relapsing multiple sclerosis (RMS), including active or progressive secondary MS (SPMS). Understanding washout requirements when converting from other disease-modifying therapies (DMTs) to siponimod, except those previously on teriflunomide who required 11-14 days’ washout. Primary Objective: To evaluate the time to onset of efficacy within the first 4 weeks after erenumab administration in patients with episodic migraine. Results: A total of 407 patients were randomized to erenumab 70 mg and 140 mg, respectively. For the phase 3 study, significant differences from placebo were observed in favor of erenumab at Week 1 in patients with CM (LSM [95% CI]: -0.8 [-1.5, -0.1; P=0.004]) and at Week 2 in patients with CM (LSM [95% CI]: -0.8 [-1.5, -0.1; P=0.004]). Conclusion: Erenumab 70 mg and 140 mg, respectively. For the phase 3 study, significant differences from placebo were observed in favor of erenumab at Week 1 in patients with CM (LSM [95% CI]: -0.8 [-1.5, -0.1; P=0.004]) and at Week 2 in patients with CM (LSM [95% CI]: -0.8 [-1.5, -0.1; P=0.004]). Conclusion: Erenumab treatment significantly reduced WMD compared to placebo. Onset of erenumab efficacy occurred as early as Week 1 in patients with migraine.
【目的】意識減損を伴うてんかん発作後のpostictal stateは数時間以内に回復する症例とされる。本研究では、非侵襲的な頭部MRI Arterial Spin Labeling (ASL)を用いて、側頭葉の灌流を評価し、側頭葉底面言語野の障害を検討した。【結果】対象とした31症例の内訳は、前頭側頭葉症例23例(74%)、中央前回症例7例(23%)、頂前頭葉症例1例(3%)であった。ASL法による灌流の非焦点側および焦点側での比較では、非焦点側の平均灌流は減少していたが、有意差は認められなかった。【結論】ASL法を用いた灌流の評価は、非侵襲的で有用な手法であるが、側頭葉底面言語野の特性をより明確に解明するためには、更なる症例の蓄積が必要である。
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O-31-1 アロイドニューロパチーにおけるSUDOSCANを
用いた発症前機能評価と臨床指標との関連

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【目的】近年、神経伝導検査(NCS)で得られる複合筋活動電位(CMAP)は遠隔電場で記録されるCMAPを用いた発症前機能評価が、本症の発症要因として検討されるが、高齢化の進行と対象の選択性が問題となる。そこで、ALCの原因となった神経障害の評価項目の相関を検討した。【方法】当院のALC患者15例を対象に、運動機能の評価(筋電図、筋活発度)および自覚症状の評価、また、神経障害の評価項目を検討した。その結果、SUDOSCANと筋電図の相関を認めた。【結論】SUDOSCANはALC早期診断に有用な指標である。
目的：経心房壁横断超音波検査（EFl）が心房細動と大動脈弓部の粥腫病変との合併評価に有用であることを示唆された。そこで、当院における急性期脳梗塞患者において心房細動と大動脈弓部の粥腫病変との合併の有無を検討した。方法：2016年4月から2019年9月までに当院に入院した急性期脳梗塞患者219例に対し、心房細動と大動脈弓部の粥腫病変の有無を検討した。

結果：心房細動の有無に関わらず、大動脈弓部の粥腫病変の有無が中等度以上の脳梗塞の有無、血栓回収術施行の有無、多循環領域の発症の有無など、脳梗塞の重症度と予後を影響することが示唆された。結論：心房細動と大動脈弓部の粥腫病変は急性期脳梗塞の予後を悪化させる危険因子であり、両者の合併は特に予後を悪化させることが示唆された。
**O-33-1**

Increase of mycobacterium avium subsp. paratuberculosis (MAP) antibody levels in multiple sclerosis

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Objective: Mycobacterium avium subsp. paratuberculosis (MAP) is a known pathogen of Crohn's disease, which shares genetic susceptibility loci with multiple sclerosis (MS). We reviewed medical records of 138 MS patients for MAP antibody levels and compared them with healthy controls (HC). Methods: MAP IgG antibodies were measured for 138 MS patients (34 male, 104 female) and 138 HC (20 male, 118 female). MAP IgG and IgA were measured by enzyme-linked immunosorbent assay. Results: Among MS patients, 37 (26.7%) had greater than 1 MAP IgG and IgA antibodies against MAP. The difference in MAP antibody levels between MS patients and HC was statistically significant (p-value 0.0002). Risk factors for MAP antibody positivity among MS patients include younger age at onset, female gender, and a family history of MS. Conclusion: Although MAP is a known pathogen, the prevalence of MAP antibody positivity among MS patients is higher than that in HC. Further studies are required to confirm the significance of these findings.

**O-33-2**

Continued increase of multiple sclerosis and neuromyelitis optica in the 5th nationwide survey

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Objective: To investigate the epidemiological characteristics of multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) in Japan through the 5th nationwide survey. Method: Preliminary survey was conducted to ascertain the approximate number of patients with either MS or NMOSD who visited the selected facilities during 2015. Primary survey was set in 138 departments from the facilities that were randomly selected using pre-determined sampling areas and were嵛ed to participate in these diseases. Secondary questionnaire was sent to the facilities with cases using to reflect the detailed information of each patient. Result: A total of 2698 responses were received from 138 departments. 51% of patients with MS and 58% of those with NMOSD met the criteria and were enrolled in the study. Based on the result of this survey, the prevalence of MS in Japan was 2.0 per 10,000 (95% CI: 1.8-2.2) and of NMOSD was 0.4 per 10,000 (95% CI: 0.3-0.5). Conclusion: Further studies are required to confirm our findings.

**O-33-3**

A novel diagnostic marker for secondary progressive multiple sclerosis: Neuro-Astroglial Index

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Objective: It is often difficult to identify the beginning of secondary progressive (SP) phase in the early course of multiple sclerosis (MS). Pathologically, axonal loss and astrogliosis are characteristic of secondary progressive MS (SPMS). We aimed to identify an axonal surrogates that are characteristic of SPMS. Methods: Serum levels of neurofilament light chain (sNfL) and glial fibrillary acidic protein (sGFAP) were measured for 94 patients with SPMS and 94 HCs. Results: The median sNfL (0.436 vs. 0.101, p=0.004) and sGFAP (1.227 vs. 0.120, p=0.002) of SPMS patients were higher than those of HCs. Conclusion: sNfL and sGFAP levels are biomarkers that can differentiate SPMS from RRMS.

**O-33-4**

Clinical and immunological investigations in autoimmune encephalitis and its related disorders

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Objective: To investigate the clinical and immunological features of suspected autoimmune encephalitis (AE) and its related disorders. Methods: We reviewed clinical and immunological features of 442 patients with suspected AE or its related disorders, who underwent neuronal surface antibodies (NS-Abs) between 2007 and 2020. 31% (22/70) of the patients were identified as autoimmune encephalitis (AE). AE and its related disorders were identified in 31% (22/70) of the patients. Conclusions: Autoimmune encephalitis is a common disease and its clinical and immunological features need to be further investigated.

**O-33-5**

Novel EEG biomarker to distinguish anti-NMDAR encephalitis from other autoimmune encephalitides

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Objective: To identify the biomarker of electroencephalogram (EEG) to facilitate early diagnosis between anti-NMDA receptor encephalitis (NMDARE) and other autoimmune encephalitides. We reviewed the admission EEGs of the patients who fulfilled the diagnostic criteria 2016 (Graus criteria) of definite NMDA-RE and possible (pAE), and were treated at our division between January 2014 and October 2020. The power (PV) analyses of all subjective EEGs were implemented using the following method: 1) extract the 10 regions of interest that were randomly selected from 12 months and seizure-free period, 2) calculate the total PV, 3) fast Fourier transform on C3-C4 channels in each frequency band. Statistical significance was tested using the Mann-Whitney U test. Result: Nine patients with NMDARE (5 pAE, 4 definite NMDA-RE) and 12 with pAE (8 definite NMDA-RE, 3 definite NMDA-RE and 3 definite NMDA-RE) were compared. The difference in PV between definite NMDA-RE and other AE was statistically significant (p-value 0.0002). Risk factors for PV positivity among NMDARE patients include younger age, female gender, and history of mental illness. Conclusion: PV of EEG is a novel biomarker that can differentiate NMDARE from other AE.

**O-33-6**

Management of disease activity and obstetric outcome of pregnancy in a Japanese cohort of MS and NMO

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Objective: Multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) are the two main CNS autoimmune disorders and patients with each disease are predominant among women of reproductive age. Since recent advent of disease-modifying drugs (DMD) in MS and NMOSD, more patients have been seeking advice for having a baby. The aim of the study was to identify how to support reproductive decision-making and plan pregnancy and to evaluate obstetrical outcome in female patients with MS and NMOSD. Methods: Data of 26 Japanese women (11 pregnancies) with MS and 8 pregnancies with NMOSD were collected from 2001 to 2019. Results: 11 pregnancies in 11 women with MS and 7 pregnancies with NMOSD had initial disease onset before pregnancy. In cases with initial disease onset before pregnancy, 75% (8/10) of MS and 86% (6/7) of NMOSD had positive definite DMD before pregnancy. 19 pregnancies (12 pregnancies with MS and 7 pregnancies with NMOSD) had initial disease onset after pregnancy. In cases with initial disease onset after pregnancy, 75% (8/10) of MS and 86% (6/7) of NMOSD had positive definite DMD before pregnancy. Conclusion: A personalized management and preconceptional counselling in planning pregnancy should be important due to improve clinical outcomes of disease activities, deliveries and births.
Trans-ethnic fine-mapping of the major histocompatibility complex region in Parkinson's disease

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(Objective) Despite evidence for the role of human leukocyte antigen (HLA) in genetic predisposition to Parkinson's disease (PD), the complex haplotype structure and highly polymorphic feature of the major histocompatibility complex (MHC) region has hampered a unified insight on genetic factors associated with PD risk. We conducted trans-ethnic fine-mapping to elucidate shared and distinct structure and highly polymorphic feature of the major histocompatibility complex in genetic predisposition to Parkinson's disease (PD), the complex haplotype study (GWAS) data using a novel imputation method, DEEP*HLA; and (2) direct imputation of HLAn variant risk from the GWAS summary statistics. (Results) We identified the strongest associations in class II HLA genes, with the top at amino acid position 13 of HLA-DR1 (P = 0.6 × 10^-10), which explains the majority of the effect size in the pooled multi-ethnic meta-analysis. (Conclusions) We validated the association and revealed additional independent associations in class I HLA genes, with the top at AA69 in HLA-B (P = 1.0 × 10^-4). A sub-analysis in Europeans revealed additional independent associations at non-HLA genes in the class III MHC region (EMMT2; P = 2.5 × 10^-5). There exists an inter-ethnic disparity in the magnitudes of the effect sizes of HLA class I and class II variants with PD risk. (Conclusions) We revealed that PD risk was independently associated with class I and II HLA genes in the trans-ethnic cohorts.

Heteroduplex oligonucleotide mitigates various types of acute CNS toxicities via CSF route

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(Objective) ASO (antisense oligonucleotides) with direct injection into CSF space has been exploited for treatment of CNS diseases. However, CNS toxicities of ASOs, especially of gaper type, are serious one of main obstacles for clinical application. We have developed a double stranded ASO-heteroduplex oligonucleotides (HDOs) which comprise an ASO strand and its complementary RNA strand. Here, we investigated that this HDO technology, with intracerebro-ventricular (ICV) administration mitigates CNS toxicity without reducing potency of ASO and various adverse effects including toxic biomarkers of cytokine responses or activation in astrocytes or microglia after injection. Materials and Methods: We designed various HDOs using ASOs which silence target mRNAs of Alzheimer diseases highly but have severe and lethal CNS toxicity. We then injected these oligonucleotides to ICR mice via ICV route to assess severity of acute CNS toxicity from phenotypic behaviors of mice. Brain samples were collected in a time course manner to evaluate knockdown efficacy and biomarker levels. Results: Acute scores of mice treated with HDOs dramatically reduced when compared to those with the parent ASOs. Moreover, we revealed that structures and chemical modifications in oligonucleotides influence silencing efficacy of target RNAs and toxic effects of phenotypes and biomarkers. Conclusion: HDOs technology significantly improved CNS toxicities by single-stranded ASOs without interfering potency and consequently provides important insights of nucleic acid therapy for CNS disease.

A multi-ethnic meta-analysis identifies novel genes, including ACSL5, associated with ALS

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(Background) Myostatin, a muscle-specific transforming growth factor-β (TGF-β), regulates skeletal muscle mass. We previously identified the inhibitory core of the region derived from the full-length myostatin prodomain (262-amino acids) which suppresses the C-terminal mature domain (ligand) as an inactive circulating complex, as well as prevents ligand-receptor binding in a calcium-dependent manner. Then, we found that the messenger RNA of myostatin was significantly downregulated in Duchenne muscular dystrophy (DMD) patients compared to healthy volunteers. Despite its high expression in skeletal muscle, myostatin is thought to have a role in muscle development and regeneration. Therefore, we hypothesized that myostatin might be a potential therapeutic target for DMD patients. (Methods) To evaluate the relationship between myostatin expression and DMD in a multi-ethnic setting, we conducted a multi-ethnic meta-analysis. The results showed a significant association between myostatin expression and DMD in a multi-ethnic setting. (Results) Our multi-ethnic meta-analysis identified ACSL5 as a novel gene associated with ALS. Furthermore, we found that ACSL5 expression was significantly increased in ALS patients compared to healthy controls. (Conclusions) This study suggests that ACSL5 may be a potential therapeutic target for DMD patients.

Therapeutic effects of an optimized myostatin inhibitory peptide

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(Objective) Myostatin, a muscle-specific transforming growth factor-β (TGF-β), negatively regulates skeletal muscle mass. We previously identified the inhibitory core of the region derived from the full-length myostatin prodomain (262-amino acids) which suppresses the C-terminal mature domain (ligand) as an inactive circulating complex, as well as prevents ligand-receptor binding in a calcium-dependent manner. Then, we found that the messenger RNA of myostatin was significantly downregulated in Duchenne muscular dystrophy (DMD) patients compared to healthy volunteers. Despite its high expression in skeletal muscle, myostatin is thought to have a role in muscle development and regeneration. Therefore, we hypothesized that myostatin might be a potential therapeutic target for DMD patients. (Methods) To evaluate the relationship between myostatin expression and DMD in a multi-ethnic setting, we conducted a multi-ethnic meta-analysis. The results showed a significant association between myostatin expression and DMD in a multi-ethnic setting. (Results) Our multi-ethnic meta-analysis identified ACSL5 as a novel gene associated with ALS. Furthermore, we found that ACSL5 expression was significantly increased in ALS patients compared to healthy controls. (Conclusions) This study suggests that ACSL5 may be a potential therapeutic target for DMD patients.

Restoration of dystrophin ameliorates impaired social behavior and amygdala synchrony in mdx52 mice

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(Objective) Duchenne muscular dystrophy (DMD) patients show psychiatric symptoms as well as muscle disorders. The lack of brain-derived neurotrophic factor (BDNF) is associated with high prevalence rate of autism spectrum disorders in DMD patients. Then, we demonstrated that plasma BDNF levels were reduced in DMD patients compared to healthy volunteers. However, the mechanism underlying this reduction is unclear. (Methods) To examine the impact of dystrophin restoration on BDNF levels in the brain, we generated mdx52 mice and utilized a novel transgenic mouse model of Duchenne muscular dystrophy. We then induced exon skipping by intracerebroventricular injection of morpholino to restore dystrophin expression. (Results) Our study demonstrated that dystrophin restoration led to a significant increase in BDNF levels in the brain of mdx52 mice. Furthermore, we found that dystrophin restoration also improved impaired social behavior in mdx52 mice, highlighting a therapeutic potential of autism spectrum disorders in DMD.
COVID-19流行がパーキンソン病患者の運動症状へ与えた影響に関する定量的検討

目的
本研究の目的は、生前にCBSあるいはCBDと臨床診断されたものの、病理診断がCBDではない、いわゆるCBD mimicsの背景病理は多様で、PSPが早期から、垂直性核上性眼球運動障害または衝動性眼球運動の速度低下を高率に認めた。最も多い、次いでAD、FTLD-TDPが多かった。背景病理ごとに見られるCBS症候に違いがあった。また、PSPとnon-PSPを比較すると、PSPは初診時から垂直性核上性眼球運動障害また衝動性眼球運動の速度低下を高率に認めた（6/10例（60%）、p=0.046）。結論：CBD mimicsの背景病理は多様で、PSPが最も多く、次いでAD、FTLD-TDPが多かった。背景病理ごとに見られるCBS症候に違いが認められた。また、PSPとnon-PSPを比較すると、PSPは初診時から垂直性核上性眼球運動障害また衝動性眼球運動の速度低下を高率に認めた。非-PSPの症例で欠かせないのは、ミオクローヌス80%、口舌・四肢失行50%に認めたが、ジストニアや皮質性感覚障害、他人の手徴候は見られなかった。PSPとnon-PSPを比較すると、PSPは初診時から垂直性核上性眼球運動障害また衝動性眼球運動の速度低下を高率に認めた。非-PSPの症例で欠かせないのは、ミオクローヌス80%、口舌・四肢失行50%に認めたが、ジストニアや皮質性感覚障害、他人の手徴候は見られなかった。PSPと非-PSPを比較すると、PSPは初診時から垂直性核上性眼球運動障害また衝動性眼球運動の速度低下を高率に認めた。非-PSPの症例で欠かせないのは、ミオクローヌス80%、口舌・四肢失行50%に認めたが、ジストニアや皮質性感覚障害、他人の手徴候は見られなかった。

2. PDPQの変化との関連性
相関分析により、PDQ-39の下位項目では、Part II・III、SCOPA-Autが有意に上昇した（それぞれ3.4±5.3、2.0±3.5、2.6±4.0、4.5±6.7、3.8±6.7;いずれもp<0.05）。悪化群は、前流行期で26%，流行期で43%であり、後者で有意に増加した。

3. 結論
東京におけるCOVID-19流行期、当院外来PD患者の運動症状は、客観的に評価することが可能である。非-PSPの症例で欠かせないのは、ミオクローヌス80%、口舌・四肢失行50%に認めたが、ジストニアや皮質性感覚障害、他人の手徴候は見られなかった。PSPとnon-PSPを比較すると、PSPは初診時から垂直性核上性眼球運動障害また衝動性眼球運動の速度低下を高率に認めた。非-PSPの症例で欠かせないのは、ミオクローヌス80%、口舌・四肢失行50%に認めたが、ジストニアや皮質性感覚障害、他人の手徴候は見られなかった。PSPとnon-PSPを比较すると、PSPは初診時から垂直性核上性眼球運動障害また衝動性眼球運動の速度低下を高率に認めた。非-PSPの症例で欠かせないのは、ミオクローヌス80%、口舌・四肢失行50%に認めたが、ジストニアや皮質性感覚障害、他人の手徴候は見られなかった。PSPとnon-PSPを比較すると、PSPは初診時から垂直性核上性眼球運動障害また衝動性眼球運動の速度低下を高率に認めた。非-PSPの症例で欠かせないのは、ミオクローヌス80%、口舌・四肢失行50%に認めたが、ジストニアや皮質性感覚障害、他人の手徴候は見られなかった。PSPとnon-PSPを比較すると、PSPは初診時から垂直性核上性眼球運動障害また衝動性眼球運動の速度低下を高率に認めた。非-PSPの症例で欠かせないのは、ミオクローヌス80%、口舌・四肢失行50%に認めたが、ジストニアや皮質性感覚障害、他人の手徴候は見られなかった。
O-36-1 REEP2遺伝子変異 (Chediak-Higashi症候群)は顕著な対麻痺を呈する

O-36-2 特発性小脳運動失調症における抗小脳抗体の検体と
抗体陽性者との臨床的特徴

O-36-3 本邦におけるSPG31の臨床・分子遺伝学的検討

O-36-4 当施設の遺伝解析にてSACS遺伝子のバリアントが
同定された日本症例の臨床的特徴

O-36-5 遺伝子変異 (SPG72) 家系の臨床・分子遺伝学的検証

O-36-6 症性麻痺のIBTA療法に関する全国多施設共同研究
COVID-19流行下におけるGuillain-Barré症候群の疾病動向

【目的】COVID-19の流行下におけるGuillain-Barré症候群（GBS）の疾病動向に与えた影響について検討した。

【方法】765床の感染症指定病院と304床の神経専門病院における、GBSの疾病動向に与えた影響について検討した。その対象は後方視解析のため、2018年度から2020年度上半期までのGBS退院患者を対象とした。

【結果】GBS退院患者数は、感染症指定病院では2018年度は5例、2019年度は6例であったが、2020年度上半期は8例と増加傾向を認めた。さらに、GBSの先行感染の病原因子とされているマイコプラズマ肺炎の退院患者数に比べ、GBSの退院患者数は減少傾向を認めた。

【結論】COVID-19の流行下におけるGBSの疾病動向に与えた影響について検討した。GBSの疾病動向に与えた影響として、感染症指定病院の退院患者数が増加傾向を示し、神経専門病院の退院患者数が減少傾向を示した。
**O-38-1** 血中GR78抗体は自己免疫性中枢神経疾患のバイオマークか？

【目的】GR78抗体は、視神経脊髄炎スペクトラム疾患（NOMD）においてB细胞を
破壊する作用をもつ自己抗体として同定された。本抗体の検出は血液検査で
きわめて容易に可能で、高齢者での検査が可能な特徴に優れているが、検出値
は個体差が大きく、また他疾患への拡散も報告されている。今後、GR78抗体の
特異性と信頼性をさらに高め、正確な診断ツールとするために、検出試験の
改良や基準値の制定が望まれている。

【方法】2012年から2018年までの間に、神経内科で検診を受している患者を対象に
GR78抗体の検出を行った。検出は、抗体の自己免疫性を確認するため、対象
群31名、対象群10名の2群に分け、以下の検査を行った。

【結果】対象群2群でGR78抗体の陽性率は12%であり、検出された抗体は、自己
免疫性が証明された。また、対象群2群の抗体価は、対象群1群のそれをはるかに
上回っていた。本抗体の検出は、自己免疫性疾患の診断に有用であると考えられる。

【考察】GR78抗体の検出は、自己免疫性疾患の診断に有用であるが、今後は、検出
値の基準値の制定や、検出試験の改良が望まれる。
O-39-1 本邦における自己免疫性GFAPアストロサイトパチーの臨床像の検討

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【目的】自己免疫性GFAPアストロサイトパチーは、脳のGFAP陽性なアストロサイトを標的とし、免疫反応の結果発症する病変である。本症例は、本邦における本症の報告が比較的少ないため、我々が経験した3症例の臨床像を検討した。

【方法】2018年12月に来院された3症例について、臨床像、画像所見、血液検査所見などを詳細に検討した。

【結果】1例目は、進行性多発性神経根炎の症例で、MRIでは両側傍脳室部に異常信号を認めた。2例目は、脳の変性病の症例で、MRIでは両側頭部に異常信号が認められた。3例目は、進行性多発性神経根炎の症例で、MRIでは両側脳室に異常信号が認められた。

【考察】自己免疫性GFAPアストロサイトパチーは、臨床像、画像所見、血液検査所見などで他の疾患を鑑別することが必要である。なお、本症例は、他の自己免疫性疾患のないことが確認されている。

O-39-2 多発性硬化症患者における血清セマホリンSema4A実測値の群間比較

新野 昭明、深澤 隆行、宮崎 雄、浦 信子、高橋 恵、南 浩、秋本 幸子、観野 格、長谷 亮、菊部 直志
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【目的】自己免疫性多発神経根炎の病因は未だ不明であるが、免疫反応が関与していることが示唆されている。我々は、自己免疫性多発神経根炎の患者で、血清セマホリンSema4Aの実測値を測定し、その意義を検討した。

【方法】自己免疫性多発神経根炎の患者10名、健康对照者10名を対象に、血清セマホリンSema4Aの実測値を測定した。

【結果】自己免疫性多発神経根炎の患者群における血清セマホリンSema4Aの実測値は、健康对照者群に比べて有意に高く、免疫反応が関与している可能性が示唆された。

【考察】自己免疫性多発神経根炎の病因をさらに解明するためには、セマホリンSema4Aの役割をより詳細に検討することが必要である。
Objectives Gait disturbance is one of the most troublesome symptoms in patients with Parkinson's disease (PD). The aim of our study is to clarify neural mechanisms underlying gait disturbance and its neural substrates in Parkinson's disease.

Methods We recruited 56 patients with PD. To characterize gait disturbance, we prepared Single-task and Dual-task (DT) conditions. Gait performance was measured using a walkway system located on the track. Following previous studies, we calculated 16 gait parameters and the percentage of DT interference.

Data of gait performance were analysed using cluster analysis. Cognitive function of the patients was assessed with MoCA-J, TMT-A, 3DMT, TMT-B, WAIS-similarity test, Animal naming, BVRT, RCFT, and JLO. The analysis of resting-state functional MRI (rsfMRI) was conducted with the CONN toolbox, and the functional connectivity was estimated using seed to voxel method results. PD patients were classified into three groups: "Good gait (n=23)," "Worsening in DT (n=15)," and "Bad gait (n=18)." Groups among the caudate and dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex were classified into three groups; "Good gait (n=23)," "Worsening in DT (n=15)," and "Bad gait (n=18)." Bad gait group showed a cognitive decline in attention and executive domain compared to Good gait group. Among the groups, Bad gait group showed a cognitive decline in attention and executive domain compared to Good gait group.

Conclusion Our findings suggest that associative striatum and attention network including DLPFC and posterior parietal cortex may play a role for locomotion in PD.
A nationwide retrospective natural history research of Becker muscular dystrophy

Objective: Becker muscular dystrophy (BMD) is a milder variant of Duchenne muscular dystrophy (DMD) and its severity is markedly variable among patients. The natural history of BMD has recently been explored, but the genotype-phenotype correlation remains unknown and there are few benefits of early diagnosis. The aim of this study is to reveal the natural history of BMD.

Methods: We surveyed 305 cases whose gene mutations were confirmed in this study. The average age was 30.5 years old (range: 6.8–81 years old). The type of mutations was deletions 82%, duplications 7%, single base mutation 3%, and nonsense mutation 2%. The initial symptoms were muscle symptoms 57%, hyper-CKemia without symptom 33%, central nervous symptoms 6%, and cardiac disturbance 3%. The distribution of mutations was like DMD reported previously. The top five most frequent mutations were exon 45-57 deletion 22%, exon 45-48 deletion 13%, exon 45-46 deletion 14%, exon 45-55 deletion 39%, and exon 37 deletion 23%. Among them, exon 37 deletion and exon 45-49 deletion showed the most severe phenotype.

Conclusions: We found that the whole picture and genotype-phenotype correlation in BMD. These results will be useful for genetic counseling.

Molecular crosstalk between caveolin 3 and nNOS: implications for Limb-girdle muscular dystrophy 1C

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Background: Caveolin 3 forms sarcolemmal caveolae and binds to and regulates several signaling molecules, including Ras, Src, and EGFR. We investigated the molecular significance between caveolin 3 and nNOS and the relationship between genotype and phenotype based on the obtained genetic and clinical data of BMD.

Results: We incorporated 305 cases whose gene mutations were confirmed in this study. The average age was 30.5 years old (range: 6.8–81 years old). The type of mutations was deletions 82%, duplications 7%, single base mutation 3%, and nonsense mutation 2%. The initial symptoms were muscle symptoms 57%, hyper-CKemia without symptom 33%, central nervous symptoms 6%, and cardiac disturbance 3%. The distribution of mutations was like DMD reported previously. The top five most frequent mutations were exon 45-57 deletion 22%, exon 45-48 deletion 13%, exon 45-46 deletion 14%, exon 45-55 deletion 39%, and exon 37 deletion 23%. Among them, exon 37 deletion and exon 45-49 deletion showed the most severe phenotype.

Conclusions: We found that the whole picture and genotype-phenotype correlation in BMD. These results will be useful for genetic counseling.

Evaluation of drug candidates for myotonic dystrophy type 1 using patient iPSCs

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Objective: Myotonic dystrophy type 1 is the most common form of adult onset muscular dystrophy, affecting approximately 1 in every 8,000 people worldwide. Myotonic dystrophy type 1 is caused by CTG trinucleotide-repeat expansions within the 3' untranslated region (3'UTR) of DMPP gene. Toxic RNA gain-of-function for non-coding expanded CUG repeats causes dysregulation of many cellular mechanisms such as alternative splicing, transcriptional, translational and post-translational regulation. In this study, we screened drug candidates for myotonic dystrophy type 1 targeting RNA foci. We also tested the effect of antisense oligonucleotides to reduce nuclear RNA foci using a high-content imaging assay system based on induced pluripotent stem cells (iPSCs) and skeletal muscle cells derived from patient-iPSCs.

Conclusions: Patient-derived iPSCs can be useful for evaluation of candidate molecules to reverse the cellular phenotype of myotonic dystrophy.

TMSB4X and IGFB2 down-regulation in dystrophin-deficient cardiomyocyte derived from DMD

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Objective: Heart failure is a major cause of death in Duchenne muscular dystrophy (DMD). We previously generated iPSC-derived cardiomyocytes from a DMD patient (DMD-iPSC-CMs), and revealed that several differentiating and regeneration-related genes TMSB4X, IGFB2, SPARC, EGR1, CD44, RMG1, and ORMD were decreased in DMD-iPSC-CMs. Among these genes, the expression of TMSB4X was recovered along with the remodelling ofchaotrocaux expression in DMD-iPSC-CMs by using skipping. This study aimed to evaluate underlying mechanisms of myocardial damage associated with TMSB4X and IGFB2 down-regulation.

Methods: We examined several molecules associated with myocardial damage (e.g., between DMD-iPSC-CMs and Control-iPSC-CMs). Further, we evaluated alterations in cell cell interactions and gene expression in DMD-iPSC-CMs and Control-iPSC-CMs with sRNA targeting TMSB4X and IGFB2. Among several molecules associated with myocardial damage such as IGF2, we identified decreased IGF2 expression in DMD-iPSC-CMs. After mRNA transfection targeting TMSB4X and IGFB2, the expression of both genes was down-regulated in IBM-iPSC-CMs. We concluded that TMSB4X and IGFB2 down-regulation might play a role in pathogenesis and reduced contractile markers in DMD heart. TMSB4X and IGFB2 down-regulation might play a role in pathophysiologic mechanisms in DMD cardiomyocyte.

Metabolome and transcriptome analysis on muscle biopsied samples in sporadic inclusion body myositis

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Objective: The pathophysiology of sporadic inclusion body myositis (sIBM) remains elusive. Previous studies investigating the inflammatory and myogenic processes play important roles in the disease course, but which of those has a dominant role is debatable. We here conducted a multi-omics study of metabolomics analysis and transcriptomic analysis identified specific metabolite changes in sIBM muscle samples of sIBM patients to identify pathogenic pathways. Method: In this study, we analyzed biopsied muscle samples from 14 sIBM patients and 6 normal controls to identify the metabolic profile. Frozen muscle samples of these subjects were used to measure metabolites by the cation mode and anion mode of capillary electrophoresis time-of-flight MS. RNA-seq was performed on biopsied muscle samples from 60 sIBM patients and 12 normal controls. Result: Metabolomic and transcriptomic analysis identified specific metabolic changes in sIBM muscle samples. The pathways of histamine biosynthesis and certain glycosaminoglycan biosynthesis were up-regulated in sIBM patients. Further, the pathways of carnitine metabolism and creatine metabolism were down-regulated in sIBM patients. Pathological examination showed that mass cell counts were elevated, and the expression of peroxisomal and sulfotransferase enzymes were down-regulated in sIBM muscle samples. Conclusion: We identified alterations in several metabolic pathways in muscle samples of sIBM patients. These results suggest that mass cells, glycosaminoglycan biosynthesis, carnitine intake, and creatine intake play important roles in sIBM pathophysiology.

Clinical features of inclusion body myositis associated with HTLV-I infection

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Objective: Inclusion body myositis (IBM) is a slowly progressive myopathy with unique clinical and pathological features. A case report on a patient with IBM and HTLV-I infection showed rapid progression of muscle weakness and hypertrophic cardiomyopathy, resulting in sudden death. Both HTLV-I-infected helper-inducer T cells and HTLV-I Tax-specific cytotoxic T cells have reportedly infiltrated the muscles of an HTLV-I-infected patient with IBM. However, the effect of HTLV-I infection on the clinical features of IBM remained unclear. Method: We investigated the clinical differences between the IBM patients with and without anti-HTLV-I antibodies. Result: In 335 patients enrolled into the study, no significant differences were detected both in clinical symptoms and the relationship between the antibodies although the patients with the antibodies tended to exhibit a male predominance, frequent gait disturbance as an initial symptom, and increased carotid artery intima-media thickness. Conclusion: The HTLV-I patients with and without anti-HTLV-I antibodies showed similar clinical features at the initial diagnosis. However, longitudinal analyses would be necessary to understand the effect of HTLV-I infection on the clinical course of IBM.
O-42-1 A novel tool to detect early pathological changes of hereditary transthyretin amyloidosis

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Objective Hereditary transthyretin (ATTR) amyloidosis is the most frequent form of autosomal dominant hereditary systemic amyloidosis. Disease-modifying therapies are the most effective during the early stages and use biomarkers to detect early pathological changes for prompt diagnosis.

Methods We prospectively followed up 31 patients (27 ATTR amyloidosis, 4 ATTR mutagenesis carriers, and 8 healthy volunteers) using peripheral nerve conduction studies (i.e., sensory and motor nerve conduction studies). Transition Medicine, Graduate School of Medical Science, Okayama University, Japan.

Results A significant increase in latency and reduced velocity of motor and sensory nerves was observed in the patients with ATTR amyloidosis compared to the healthy controls. The latency and velocity of the motor or sensory nerve were significantly correlated with the ATTR TTR genotype, as well as the ATTR TTR mutation.

Conclusions Early pathological changes of ATTR amyloidosis can be detected using peripheral nerve conduction studies, which can serve as a useful tool for early intervention and management.

O-42-2 Clinical diversity of patients with neuronal intranuclear inclusion disease (2nd report)

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Objective To investigate the clinical features of patients with neuronal intranuclear inclusion disease (NIND). Method We retrospectively studied the clinical course, electrophysiological findings, and brain MRI in 16 cases of NIND. Results Brain MRI showed atrophy, prolonged T2, and FLAIR signal in our hospital. Longitudinal genomic sequencing was conducted in three patients. Result In the 16 NIND cases (8 males, 8 females), the age of onset was 248 years, and the period from onset to symptoms diagnosis was 1-18 years. Brain MRI showed atrophy in all cases. In 11 cases, a distinct high-intensity signal in the orbitofrontal junction was seen in diffusion-weighted brain MRI. FLAIR images showed high-intensity, extensive, and diffuse signal in the cerebral white matter, medial cerebral hemisphere beside the vermis (paravermal area), and middle cerebellum peduncle in 11, 10, and 9 cases, respectively.

Conclusions NIND showed reduced velocity and amplitude of motor and sensory nerves in 3 cases. Patients were detected (28%)(GGCG) recombination in 307TFNL. One of them developed abrupt mitochondrial encephalopathy, lactic acidosis, and stroke-like (MELAS)-like episode in the 15-year course clinical diagnosis as chronic inflammatory demyelinating polyneuropathy (CIDP). Conclusion There is a wide range of clinical phenotypes of NIND, and their diversity is noteworthy from the results of gene analysis.

O-42-3 Prevalence and characterization of anti-contactin-1 antibody-positive CIDP

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Objective To clarify the prevalence and features of IgG4 anti-contactin-1 (CNTN1) antibody-positive chronic inflammatory demyelinating polyneuropathy (CIDP). Method Anti-CNTN1 antibody status was investigated in consecutive 28 CIDP patients who met the following criteria: (1) clinically progressive weakness and sensory disturbance of extremities, (2) nerve conduction study findings definitely meeting EFNS/PNS electrodiagnostic criteria for CIDP and (3) cerebrospinal fluid (CSF) amyloidosis.

The GDF-15 levels could aid in the detection of early pathological changes in ATTRv amyloidosis. Immunotherapy was initiated within three months in three patients (50%). All six experienced sensorimotor improvement in the affected limbs. The results of this study indicate that early pathological changes of ATTRv amyloidosis can be detected using peripheral nerve conduction studies, which can serve as a useful tool for early intervention and management.

O-42-4 Indication of autologous stem cell transplantation for POEMS syndrome

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Objective Autologous stem cell transplantation (ASCT) has been considered to be the first-line therapy for young patients with POEMS syndrome because of its prompt and high efficacy. However, transplant-related mortality cannot be ignored and some patients can maintain remission without ASCT. This study aims to explore the optimal eligibility of ASCT for POEMS syndrome. Method We searched our database of 128 consecutive POEMS patients from 2000 to 2018. Patients who were diagnosed at 67 years old were enrolled. Survival analysis (OS) of patients treated with ASCT (ASCT group) and patients treated with other than ASCT (non-ASCT group) were compared using a log-rank test. Stratified on prognostic factors, hazard ratio (HR) of ASCT group to non-ASCT group was estimated with Cox proportional hazards model. Prognostic factors included age, performance status (PS), albumin, renal function, plasmatic, pulmonary hypoxia, hematologic response (disappearance of M-protein) and VEGF response (normalization of serum VEGF level) to first-line therapy. Result A total of 184 POEMS patients (88% non-ASCT, 12% ASCT) were included in this analysis. The 7-year OS was 77% in ASCT group and 60% in non-ASCT group (P=0.06). On univariate analysis, ASCT group showed superior OS in patients with PS 3 or 4 (P=0.07) and 85% CL 0.88-0.95), non-hematologic response (HR 0.43 95% CL 0.20-0.97) and 7-year OS was 85% (P=0.047) in non-ASCT group. Conclusion Patients with poor PS or non-hematologic VEGF response to first-line therapy are appropriate candidates for ASCT in POEMS syndrome.

O-42-5 The diagnostic addition of the forearm muscle-membrane recording median nerve conduction study in CMT

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Objective In the nerve conduction study (NCS) of Charcot-Marie-Tooth disease (CMT), compound muscle action potential (CMAP) is sometimes not evoked due to severe motor or sensory atrophy. The compound muscle action potential (CMAP) is sometimes not evoked due to severe motor or sensory atrophy. The compound muscle action potential (CMAP) is sometimes not evoked due to severe motor or sensory atrophy. The compound muscle action potential (CMAP) is sometimes not evoked due to severe motor or sensory atrophy. Therefore, the cutaneous sensory nerve action potential (SNAP) and the compound muscle action potential (CMAP) are used to evaluate the lower limb nerve function. The CMAP amplitude of FDS was significantly larger than that of APB in the healthy group (9.4±1.9 vs. 9.4±1.4 mV). In the CMT group, CMAP amplitude was significantly decreased in the median nerve-conduction studies. The CMAP amplitude of FDS was significantly larger than those of APB (3.7±3.0 (APB) vs. 5.4±1.7 mV (FDS), CMTX 2.4±3.6 vs. 5.4±1.7 mV, p<0.05). There was no significant difference in the CMAP amplitude between APB and FDS in the healthy group. All six experienced sensorimotor improvement in the affected limbs. The results of this study indicate that CMAP amplitude in the median nerve is useful in CMT cases with severe hand muscle atrophy.

O-42-6 An attempt to induce Chronic Cerebral Neuropathy Model in Rat

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Objective To establish an animal model of chronic alcholic peripheral neuropathy. Animals Method: Female Fisher Rats (F344; four-week-old, CLEA Japan, Tokyo) were divided into two groups. Alcoholic group (A: n=15) was fed with long-term feeding diet containing 15% ethanol ad libitum. Control group (C: n=15) was fed with the same amount of the diet as the corresponding rat in alcoholic group ingested in the prior day. Ethanol was administered at 1/3 final oral dosage of the rats that the rats in A ingested as alcohol in the prior day. After 24 months, pattern of paw pressures during walk and muscle strength were tested. Then rats were euthanized, sural nerve was obtained, and glutaraldehyde fixed and processed. The pathology rate of anti-CNTN1 antibody was much lower than that of anti-NTBDg antibodies in CMT. Anti-CNTN1 antibody-positive CIDP was diagnosed in patients with other autoimmune and paraneoplastic conditions.

Conclusion The diagnosis of the forearm muscle-membrane recording median nerve conduction study in CMT may be a safe and useful animal model for chronic alcholic peripheral neuropathy.
O-43-1  Quantitative measurement of CSF Aβ species by mass spectrometry

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Objective: High sensitivity liquid chromatography mass spectrometry (LC-MS/MS) has recently been introduced to measure Aβ species. We validated the Aβ assay by 140, Aβ42, and Aβ43 assay by LC-MS/MS and compared it with ELISA using cerebrospinal fluid (CSF). Samples to investigate its feasibility for clinical application. Method: 120 subjects, consisting of 8 Alzheimer patients (AD), 2 and mild cognitive impairment due to AD (AD/AMCI). 14 cognitively unimpaired subjects (CU) and 96 neurological disease subjects, were analyzed. Aβ species were separated using the Shimadzu Nexera X2 system, and quantified using a group 500 LC-MS/MS system. Aβ1-40 and Aβ1-42 levels were validated using ELISA. Results: The ELISA assay used this 206-fold increase in the clinical measurement of CSF biomarkers for AD.

O-43-2  An age-related venous drainage change was accelerated in Alzheimer’s disease

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Objective: Recently we reported an age-related change in cerebral venous drainage using a novel blood-tracking technique based on functional-MRI data (BOLD lag mapping). This new aging biomarker was further pronounced in hydrocephalus with an interaction of age, leading us to postulate a general mechanism of age-related venous drainage alteration. This phenomenon is a slow flow dissociation between the deep and superficial venous systems, presumably a result of insufficient blood flow to the hippocampus in the present study, we tested if the new biomarker for brain aging is altered in Alzheimer’s disease (AD). Method: Resting-state fMRI datasets with anatomical images and subject demographics were downloaded from the ADNI website (https://adni.loni.usc.edu/adni-3/). Perfusion lag mapping was performed to extract the timing information from the superficial and deep regions of interest (https://gibson.com/RIKEN-BIL/ BOLDlagMapping). Results: 385 datasets were successfully analyzed, of which 41 patients were diagnosed as AD. Analysis of variance revealed a significant effect of diagnosis on the timing dissociation between the two venous systems (P = 0.001). Post-hoc Tukey HSD confirmed a significant abnormality in AD (P = 0.001), but the MCI group failed to show a significant post-hoc result. Conclusion: Although the causal relationship is not clear, AD was correlated with the venous drainage alteration.

O-43-3  Analysis of electronic health records in drug development for Alzheimer's disease

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Objective: Alzheimer’s disease (AD) is the most common cause of dementia, and a number of clinical trials for AD have been failing. By using a screening system based-on induced pluripotent stem cells (iPSC) of AD patients, we identified six existing drugs that improve AD phenotypes of PSEN1-ΔE9 fibroblasts. For further translational steps, we validated the efficacy of patients, we identified six existing drugs that improve AD phenotypes of iPSC models. For further translational steps, we validated the efficacy of patients, we identified six existing drugs that improve AD phenotypes of iPSC models. For further translational steps, we validated the efficacy of patients, we identified six existing drugs that improve AD phenotypes of iPSC models.

O-43-4  Metal-protein attenuating compound clioquinol decreases oligomeric Tau

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Objective: One of the neuropathological hallmarks of Alzheimer’s disease (AD) are neurofibrillary tangles (NFTs), which consist of highly phosphorylated tau protein. As most studies indicate the involvement of NFT, metal ions may be a direct factor for AD treatment. Clioquinol (CQ) is a metal-protein attenuating compound with mild chelating effect for Cu²⁺ and Zn²⁺, and studies suggest that Cu²⁺ induces hyperphosphorylation of tau. However, the effects of CQ on tau were not fully explored (Method: To examine the effect of CQ on tau metabolism, we used a human neuroblastoma cell line, SK-N-MC cells which express wild-type tau protein (WT) via tetrahymena of infected (IPRIS) Pathological study revealed that below 10 μM of CQ has cytotoxic effects as measured by an ATP assay. Five μM of CQ decreased accumulated Cu²⁺ in the SK-N-MC cells and decreased both total and phosphorylated tau protein. The activity of CQ 5 nanomolar (N) and 50 μM MAP kinase, tau kinases, and protein phosphatase 2A (PP2A), which is a tau phosphatase was also observed by CQ. Experiments East showed a reduction of oligomeric tau in mice soluble, soluble fraction by CQ. Unphosphorylated tau was increased by CQ, which implies that one of the major tau degradation mechanisms, metabolic activity was increased. Conclusion: Although further examinations are needed to elucidate the mechanisms responsible for the effects of CQ on tau, CQ may shed light on the possible therapies of AD.

O-43-5  Generation of non-human primate models of Alzheimer’s disease

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Objective: Despite the considerable research efforts, exact pathomechanisms of Alzheimer’s disease (AD) still remain unknown, and no effective treatment is available. AD research field have mainly utilized mouse models for decades, but species differences between rodents and primates may constrain us from understanding the precise disease mechanism. Method: We utilized Transgenic African Green Monkey (TALEN) to delete the 12 kilo base pair (kb) in the 3′ UTR of the presenilin 1 gene (PSEN1) in the common marmoset (Callithrix jacchus), a small new world primate. Results: We successfully deleted 75% of the PSEN1 gene (PSEN1-ΔE9) in the marmoset embryo by direct microinjection of TALEN. After the 5′ site-directed gene editing, we transferred Cu²⁺ ions that developed to show 6 chloride into stage neonatal 78 neurons. Around the 15th day from the embryo, the 78 neurons mediated by Cu²⁺ ions normal delivery or by Caesarean section. Among them, 30 of 6 neonates carried PSEN1 gene mutation. Sequence analysis of mRNA in these embryos and neonates confirmed skipping of exon 9 as reported, which has been reported as a potential mutation causing familial AD. In addition, 50% of these confirmed transcript was introduced at the junction site of exon 8 and exon 9 in the human patients. Quantitative analysis of oligomeric τ (Aβ) in the cultured medium of primary fibroblasts revealed elevation of Aβ1-40/Aβ1-42 ratio in PSEN1-ΔE9 fibroblasts. With these findings, we identified 96 neurological disease subjects, were analyzed. Aβ species were separated using the Shimadzu Nexera X2 system, and quantified using a group 500 LC-MS/MS system. Aβ1-40 and Aβ1-42 levels were validated using ELISA. Results: ELISA assay used this 206-fold increase in the clinical measurement of CSF biomarkers for AD.

O-43-6  canceled
O-44-1 片頭痛に関する本邦での大規模調査の統計学的分析

平田 遥、橋本 美、加藤 泰

【目的】当院頭痛外来に通院中の片頭痛患者において、頭痛の誘発因子について検討

【結論】 片頭痛患者では多くの誘発因子を自覚していることが示唆された。
【目的】D-dimerは進行がんを伴う潜因性脳梗塞の強力な予測因子であり、その予後改善のための治療戦略の構築が求められている。本研究の目的は、脳梗塞発症3ヶ月以内の死亡を予測するモデルを検討することである。

【方法】本研究で用いたデータは、2011年4月1日から2017年3月31日までに総合病院で診断された脳梗塞患者を対象として、年齢、性別、高血圧、糖尿病、脂肪症、高コレステロール症、慢性腎症を共変量とした多変量解析（オッズ比6.25, 95%CI 1.35-28.94, P = 0.02）で検討した。

【結果】治療前の血清GM-CSF値は脳血管病合併の予測及び治療戦略の構築や再開通時間短縮への取り組みなど課題も多く、今後も検討が求められている。
【目的】多発性硬化症のNatalizumab (NTZ)治療は4週毎の点滴で高い有効性が示されているが、NTZの長期投与下での安全性評価は不十分とされている。この研究では、NTZの長期投与下で発現する頻度の高い有害事象（TEAE）と重篤な有害事象（SAE）の性質を評価し、各期間における安全性を確認する方法を検討した。

【結論】NTZ治療下で発現した有害事象（TEAE）は、頻度の高いものとして鼻咽頭炎（70 mg: 27.9％、140 mg: 32.8％、PBO: 29.2％）、背部痛（70 mg: 16.1％、140 mg: 11.6％、PBO: 13.5％）が観察された。NTZの長期投与では、有害事象の合併率が低く、NTZの安全性と有効性は確認された。}

【方法】NTZ治療下で発現した有害事象（TEAE）は、有害事象（TEAE）の性質を評価し、各期間における安全性を確認する方法を検討した。
O-47-1 有機ヒ素化合物（ジフェニルアルシン酸）暴露の老化抑制効果を検証するための実証研究

山本 雄貴、根本 清成、岩谷 信弘、中山 正直、柴田 康行、増田 知之、根本 重広、上野 幸之

【目的】神経変性疾患の鑑別診断のためのMRI測定法 "One-line method" に関する検討

【方法】脳血流SPECTの画像データを用いた.DPAA暴露群の約11年後の血流変化部位をFlexible factorial designを用いて縦断解析し、健常群で見られた加齢変化を考慮して、DPAAによる初期に傷害が認められた後頭葉、小脳部位である小脳虫部、右上後頭葉などの変化を検討した。

【結果】SPM12および3D-SSP処理による統計画像解析でほぼ同様の結果が得られた。すなわち、DPAA暴露群の約11年後の血流変化部位をFlexible factorial designを用いて縦断解析し、健常群で見られた加齢変化を考慮して、DPAAによる初期に傷害が認められた後頭葉、小脳部位である小脳虫部、右上後頭葉などの変化を検討した。

【目的】神経変性疾患の鑑別診断のためのMRI測定法 "One-line method" に関する検討

【方法】脳血流SPECTの画像データを用いた.DPAA暴露群の約11年後の血流変化部位をFlexible factorial designを用いて縦断解析し、健常群で見られた加齢変化を考慮して、DPAAによる初期に傷害が認められた後頭葉、小脳部位である小脳虫部、右上後頭葉などの変化を検討した。

【結論】One-line methodはPSP,MSAの鑑別診断において簡便で診断能が高く、臨床的意義についてはいまだ不明である。