口演

5月20日 （水）
Long term follow-up of Segawa disease

Segawa Neurological Clinic for Children
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Object: Segawa disease (SD) is an autosomal dominantly inherited dopa responsive dystonia caused by heterozygous mutation of the GCH1 gene. We present the long term follow-up of SD [Method] Seventy-eight cases of SD seen in this clinic, were subjected to the study. The clinical characteristics were retrospectively analyzed. [Result] SD is clinically classified into two types: postural (P-type) and action (A-type). Among 78 cases, GCH1 gene mutation was found in 60 cases (77.9%), but not found in 18 cases. There were 31 P-type and 47 A-type. Mean ages of onset of P-type was 64.4 ± 30.0 years, and A-type 78.8 ± 36.6 years, excluding 3 older onset cases (28, 35 and 58 years). The mean ages of initial visit was 22.8 ± 18.2 years (ranged 5-71 years), and the last neurological examination was 34.7 ± 18.2 years (ranged 7-90 years). P-type remains the postural dystonia throughout the course. Neuropsychological data of a P-type case died at 90 years showed normal substantia nigra. A-type showed the late onset cases, and focal or segmental dystonia. One case started with parkinsonism at age 58 years where Positron CT were not compatible with Parkinson disease (PA), however, the parkinsonism progressed and DaT scan was compatible with PA at age 72 years. Depression was observed more in A-type (10/47) than in P-type (3/31). [Conclusion] These results suggest the age-related specific descending and ascending output pathways in the basal ganglia involving direct and indirect pathways play role in the pathophysiology of SD, and support our hypothesis of the pathophysiology of the SD.

White matter integrity in the tegmentum area correlates with freezing of gait

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Background and Purpose: Freezing of gait (FOG) is an episodic inability to generate effective stepping and one of the most disabling features of patients with Parkinson’s disease (PD). However, it is still unclear which area is the primary lesion for FOG in PD. In this study, to investigate the primary neuronal underpinning for developing FOG in PD we cross-sectionally examined the correlation between severity of FOG and damage of anatomical connections among area-related neural network using diffusion-tensor imaging-MRI (DTI-MRI).

Methods: We recruited 12 postural instability gait difficulty subtype PD patients with prominent FOG symptom. Multislice, voxel-based, and multilinear regression analysis were performed to reveal the correlation between FOG severity and the white matter integrity. We also performed tractography analysis using the significant cluster, which were found to correlate with FOG, as seed voxels to investigate the anatomical connections with the significant clusters.

Results: Clinical measures revealed that FOG significantly correlated with balance ability, not with cognitive decline. There was significant negative correlation between severity of FOG and white matter integrity in the dorsal postlissencephalic tegmentum area, and probabilistic tractography confirmed tight anatomical connections between the significant clusters and locomotor network.

Conclusion: Our findings suggested that reduced local anatomical connectivity in the dorsal tegmentum area might contribute to FOG in PD.

Urgent hospital admission in Parkinson’s disease

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Objective: Parkinson's disease (PD) is a progressive neurodegenerative disease. During the later stage of their illness, patients experience dysphasia, falls, psychiatric symptoms, and cognitive impairments. Such patients occasionally need medical treatment in hospitalization. The present study focused on urgent hospital admission in PD patients.

Methods: Medical records were retrospectively reviewed in a consecutive series of PD patients recorded in a database at a neurology department. All of the patients included in this study satisfied the clinical diagnostic criteria for PD.

Results: Three hundred twenty-five PD patients with available medical records were identified. Among these, there were 55 (17%) patients who had experienced urgent hospital admission at some point during the course of their illness. The most common cause of the hospitalization was infectious diseases (n=28), including aspiration pneumonia and urinary tract infection. Other causes included malignant syndrome (n=1), cerebrovascular disease (n=6), psychiatric symptoms (n=3), dysphasia (n=3), and delirium (n=3). Most patients needed urgent admission at advanced stage of the disease. The mean disease duration at the admission was approximately 10 years.

Conclusion: Infectious disease, especially aspiration pneumonia was the most common cause for urgent hospital admission for PD patients in a single neurology department. Collaborative researches with other departments such as psychiatric and orthopedic surgery departments are needed to clarify the entire cause of urgent hospitalization in PD.

Effect of rotigotine on 32 patients with Parkinson’s disease for 24 weeks

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Background: Rotigotine is a non-ergot dopamine agonist formulated in a transdermal delivery system. Long-term objective effect of rotigotine was not well examined in Japan.

Purpose: The present study was to investigate the objective efficacy and safety of the rotigotine transdermal patch in the treatment of Parkinson’s disease (PD).

Methods: 32 patients were treated with rotigotine transdermal patch for 24 weeks. All rotigotine were add-on to other antiparkinsonian drugs, L-DOPA/DLL dopamine receptor agonists COMT inhibitors and MAO-B inhibitors. Efficacy of rotigotine was evaluated by UPDRS PART 3 scores, taking animations and freezing index measured by using the rythmogram. Freezing index is the ratio of the number of freezing gait / number of gait in the patients with PD during 2 or 3 whole days.

Results: The average dose of rotigotine was 244 mg ± 67.4 mg/24h. The mean decrease from base line in UPDRS Part 3 score was -3.9 ± 3.7 after 24 weeks. We also observed improvement of bradykinesia and freezing gait by animation after treatment of rotigotine. Freezing index, which was objective and digitized data, was examined in 6 patients whose freezing of gait was improved in UPDRS Part 3 score and animation. Freezing index was decreased in 85%, 31%, 13.4%, 56.6% and 24% in each patient after 24 weeks.

Conclusion: We detected effectiveness of rotigotine transdermal patch against to the patients with PD in UPDRS 3 Part and objective data, animation and freezing index. Freezing index might be a useful evaluation method in evaluation of antiparkinsonian drugs.

Characterization of the spectrum of autonomic autonomous ganglionopathy in Japan

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[Background] Autonomic dysfunction (AD) occurs in patients with autonomic dysreflexia (AD) at the plexus where sympathetic neural circuit is involved. Our previous study indicated that AD was present in 31.2% of SD and 35% of PD. We investigated the prevalence of AD in various conditions.

[Method] 1242 patients which were attended between 2000 and 2011. SD (n=775) and PD (n=467) that were diagnosed with autonomic dysreflexia were evaluated.

[Conclusion] The prevalence of AD was higher in patients with PD compared to SD. The prevalence of AD was higher in patients with PD compared to SD.

Autobodies to vinculin in patients with CIDP

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Objective: Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune disorder of peripheral nervous system. Current hypothesis is that humoral immune factors contribute to the autoimmune mechanisms. The aim of this study was to identify the immunological target antigens in subgroups of CIDP by proteomic-based approach.

Methods: Target molecules of autoantibodies in the patient’s sera were investigated among extracted proteins from pig cilia equine by ageose 2DIE and immunohotting. The candidate molecules were validated by immunoflotting, immunoblotting and Biochemistry.

Results: We found that two of 31 patients with CIDP had anti-vinculin autobodies. Vinculin exists ubiquitously and plays a role in the cell adhesion. Both two patients with anti-vinculin autoantibodies had symmetric weakness, distal pattern of demyelination and glove and stocking distribution. Immunohistochemistry analysis revealed that vinculin was localized at the myelin sheath where serum samples of the patients with CIDP reacted. Vinculin in Schwann cells were also immunostained by the patient’s sera with characteristic patterns.

Conclusion: Our results suggested that vinculin could be a possible immunological target of autobody in a few patients with CIDP.
0.03.2 ApoE polymorphism distribution among Filipino elderly community dwellers

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Introduction. Apolipoprotein E (ApoE) gene, which on chromosome 19 and has three allelic variants (2,3,4) and five common genotypes (2/3,3/2,3/4,4/3,4/4). ApoE polymorphic alleles are the main genetic determinants of Alzheimer disease risk. Purpose. The main objective of this study is to determine ApoE genotypic and allelic distribution among Filipino community dwellers. Methods. Subjects who meet the inclusion criteria underwent screening, memory testing, and genomic DNA extraction. We estimated allelic and genotypic frequencies of ApoE isoforms for the different groups by counting alleles and genotypes and calculating sample proportions. Results. In this study, 464 adults met inclusion criteria. The most frequent genotype in this cohort of Filipinos was $e_3/e_3 (60.37\%)$ and the most frequent allele was $e_3 (71.8\%)$ which were similar to western population; however, the least common was $e_4$, which was contrary to the least frequent $e_2$ in other countries. Conclusion. This study implies that Filipinos have a different genetic background than western population and this justifies the fact that we need more population-based studies that explores on genetic make-up of a certain well-defined group of people. A significantly low number of subjects (only 30% of the cohort members) volunteered to have genotypic analysis. The main barrier as to this low outcome was Filipino community dwellers’ perception on unacceptability of a genotype examination. Nationwide efforts on information dissemination on this issue should be done in order to increase the number of genotypic research in our country.

0.03.3 Risk of Alzheimer’s disease in relation to diabetes

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Purpose. Detailed information on the age and sex specific relationships between diabetes and Alzheimer’s disease (AD) is scarce. This study aims to prospectively investigate the age and sex specific incidence density and relative hazards of AD in relation to diabetes. Method. A total of 615,329 diabetic patients and 614,871 age and sex matched random controls were linked to the claim data from 2000 to 2008 to identify the first occurrence of a primary or secondary diagnosis of AD. Incidence density was calculated under the Poisson assumption. We also assessed the age and sex specific risk of AD in relation to diabetes with the Cox proportional hazards regression model. Results. Over nearly 9 years of follow up, a total of 4615 diabetic subjects developed AD, representing a cumulative incidence rate of 0.75% (n = 3873.063% in controls). The overall incidence densities of AD for diabetic men and women, respectively, were 0.82 and 1.15 per 1,000 person years, which were higher than those for control men and women 0.73 and 0.90 per 1,000 person years, respectively. Diabetic patients had a significantly higher hazard ratio (HR) of AD (1.45) Diabetic women above 65 years had a higher HR (1.52) than diabetic women less than 65 years. Conclusion. Diabetes may increase the risk of AD in both sexes and in all ages. A higher HR of AD was especially notable in older diabetic women.
LRP4は重症筋無力症の1種である。

【目的】本研究では、低密度リポ蛋白受容体4（LRP4）抗
体Glyceraldehyde 3-Phosphate Dehydrogenase (GAPDH)を
免疫組織化学法で検討し、LRP4抗ボディの有無及び量
による筋無力症の発症の可能性について検討した。

【方法】対象は、重症筋無力症症例を対象に、GAPDHを
用いた免疫組織化学を行い、LRP4の発現状態を評価した。

【結果】LRP4の発現は、重症筋無力症の症例において
有意に高発現を認めた。また、LRP4の発現は、症例の重症
度に関連し、重症筋無力症の重症度が高いほど、LRP4の
発現が顕著であった。

【結論】LRP4は重症筋無力症の発症に重要な役割を
果たしていることが示唆された。今後、LRP4の発現が重症
筋無力症の発症に関与しているかどうかの詳細な検討
が必要である。
O-05-3
Incidence and characteristics of injuries due to falls in Neurological diseases
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【目的】従来の脳血管障害の研究においては、脳卒中の発症疾患や原因について十分に検討されていない。そこで本研究では、脳卒中の発症疾患において実際に発症する疾患の状態を把握し、脳卒中の発症疾患の特徴について検討する。

【方法】2015年4月から2018年3月までの間、脳卒中発症の患者を対象に、発症疾患の状態を把握し、脳卒中の発症疾患の特徴について検討する。脳卒中の発症疾患を以下の3つに分類し、脳卒中の発症疾患の状態を把握する。脳卒中の発症疾患の特徴について検討する。

【結果】脳卒中の発症疾患の状態を把握し、脳卒中の発症疾患の特徴について検討する。脳卒中の発症疾患を以下の3つに分類し、脳卒中の発症疾患の状態を把握する。脳卒中の発症疾患の特徴について検討する。

【結論】脳卒中の発症疾患の状態を把握し、脳卒中の発症疾患の特徴について検討する。脳卒中の発症疾患を以下の3つに分類し、脳卒中の発症疾患の状態を把握する。脳卒中の発症疾患の特徴について検討する。

O-05-4
4 cases of nasogastric tube syndrome: a life-threatening larvalygeal obstruction
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【目的】音声麻痺は様々な原因により生じることがあり、その時治療の選択肢を主な目的とするため、音声障害を有する患者に対する治療の必要性について検討する。

【方法】音声麻痺の原因を含む患者的検査結果を対象に、音声障害を有する患者の治療の必要性について検討する。

【結果】音声麻痺は様々な原因により生じることがあり、その時治療の選択肢を主な目的とするため、音声障害を有する患者に対する治療の必要性について検討する。

【結論】音声麻痺は様々な原因により生じることがあり、その時治療の選択肢を主な目的とするため、音声障害を有する患者に対する治療の必要性について検討する。
p62 plays a protective role in neurodegenerative diseases model of mice

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Objective: Oligomer formation and accumulation of pathogenic proteins are key events in many neurodegenerative diseases, such as Alzheimer’s disease (AD), amyotrophic lateral sclerosis (ALS), and polyglutamine (pQ) diseases. Although p62 plays a physiological role in selective autophagy, whether p62 contributes to degradation of such pathogenic proteins is still unknown. In this study, we aimed to elucidate the role of p62 in various neurodegenerative disease model mice, especially the role in degrading such pathogenic proteins in vivo.

Methods & Results: To investigate the role of p62 in neurodegenerative diseases, we crossed the transgenic p62RNAi mice with the various neurodegenerative disease model mice. p62 knockout exacerbated eye degeneration in the pQ7 disease and ALS model mice. Meanwhile, p62 knockdown did not cause any exacerbation in the AD model mice. Furthermore, p62 overexpression contributes to polyQ protein degradation, we examined the p62 protein turnover in the polyQ disease model mice bearing p62 or Agp6p mutation. Western blotting showed that loss of p62 function clearly delayed the degradation of both monomeric and oligomeric polyQ protein, similarly to loss of Agp6p function.

Conclusion: Our study identifies that p62 plays a protective role against polyQ-induced neurodegeneration by the autophagic degradation of polyQ protein, indicating its therapeutic potential for the polyQ diseases, and possibly for other neurodegenerative diseases.

Establishment of transgenic marmoset models of a polyglutamine disease

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Objective: Although various models of neurodegenerative diseases have been developed, they have limited utility in the translational research because of different strain structures and genetic backgrounds. Therefore, a new model system is needed to evaluate whether p62 overexpression in human primary models of neurodegenerative diseases have been effectively inhibited. In this study, we aimed to establish a transgenic marmoset model of Machado-Joseph disease (MJD) expressed in the human polyQ disease model mice.

Methods: Lentiviral vectors carrying human mutant MJD 94LL aged 6-8 weeks under CMV promoter were injected into MF1 embryos, and a total of 18 MF1 mice were delivered.

Results: Lentiviral vector expression was confirmed to carry the transgene integration. Although all offspring showed no symptoms at birth, MJD2 and 4 weeks, which expressed the mutant human transgene at higher levels, gradually developed progressive neurological symptoms such as motor impairment, ataxia, and choreoathetosis at 12-13 weeks of age. MRI showed enlarged head and phase delay at 13-15 weeks of age. Neuropathological examinations revealed significant neurodegeneration accompanied by polyglutamine inclusion in the brains of MJD2 and 4 weeks, which partially morphed marmoset patients' features.

Conclusion: Our success in modeling human neurodegenerative diseases in non-human primates will accelerate our understanding of the pathophysiological mechanisms and development of clinically applicable therapies for neurodegenerative diseases.

SCA31-linked UGAAxep RNA causes progressive neurodegeneration in Drosophila

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Background: Spinocerebellar ataxia type 31 (SCA31) is a dominantly inherited neurodegenerative disease caused by insertion consisting of complex pentanucleotide repeats containing TGGAG, TGGAA, TGAATGG in an array of 17,912 putative repeats in SCA31-affected patients. We aimed to elucidate the molecular pathological pathways of SCA31 by generating a transgenic model of SCA31 in Drosophila.

Objective: We aimed to elucidate the molecular pathological pathways of SCA31 by generating a transgenic model of SCA31 in Drosophila.

Methods: We generated transgenic flies expressing UGAAxep RNA and showed that UGAAxep RNA causes neurodegeneration. Expression of UGAAxep resulted in dramatic decrease of eye morphology in larvae and female diapause and normal morphology in males. We determined whether the intronic TGGAG repeat was alternatively transcribed into pre-mRNA (pre-RNA) protein, which contributed to polyglutamine expression in Drosophila.

Conclusion: Drosophila data suggested that expression of UGAAxep increased toxicity in flies in respect length and profound development manner accompanied with accumulations of both RNA isoforms and UGAAxep-encoded pre-mRNA (pre-RNA). Min Gb repeat.

A search for novel causative gene for hereditary spastic paraplegia

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Effects of anti-AQAP and co-existing autoneutolysis in neuroimyelitis optica

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[Background] Neuroinflammatory optic neuritis (NO), an autoimmune inflammatory optic neuropathy, is caused by antibodies to the astrocyte water channel aquaporin 4 (AQP4), which is expressed exclusively on astrocytes. The IgG plasma fraction of NO patients (NO-IgG) contains AQP4 antibodies. 30% of NO patients also have coexisting autoantibodies (such as antiphospholipid antibody). It remains uncertain how NO-IgG and these autoantibodies affect the blood-brain barrier.

[Aim] We examined effects of anti-AQAP and co-existing autoantibodies on endothelial cells and astrocytes.

[Method] We prepared the total NO-IgG (T-NO-IgG) and individual NO-IgG (I-NO-IgG) T-NO-IgG is separated from IgG pool as therapeutic plasma exchange from 16 NO patients and 11 I-NO-IgG came from each NO patient without other autoantibodies (N=30 NO-IgG). IgG prep. Conditionally immortalized human brain microvascular endothelial cell line (EC) or human astrocyte cell line with AQP4 expression (A4) were cultured in the slide chamber. After exposing NO-IgGs, we evaluated ICAM1 expression of EC by qPCR and immunocytochemistry, IC6 expression of EC and A4 by ELISA. We also demonstrated immunochemistry with T-NO-IgG or I-NO-IgG as primary antibodies.

[Result] T-NO-IgG increased ICAM1 of EC and IC6 of EC and A4 and recognized unknown molecules in EC although T-NO-IgG elevated IC6 in A4. These results indicate that 1) coexisting autoantibodies exerts various effects, causing upregulation of ICAM1 and IC6; and 2) Anti-AQAP IgG itself induces IC6 in astrocytes via AQP4.

Clinicalopathological features of anterior visual pathway involvement in NMO

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Background: Neuroimyelitis optica (NMO) and multiple sclerosis (MS) are autoimmune disorders in the CNS. In spite of a frequent site of their injury, the details of pathomechanisms in anterior visual pathway (AVP) remain unclear. Objective: To elucidate the clinicalopathological features of AVP in NMO. Methods: A clinical retrospective study was performed on 17 NMO spectrum disorder (NMD) patients (28 attacks) and 16 MS patients (25 attacks) with history of visual impairments. Pathological analysis was conducted on tissues from 12 patients with NMD and 5 patients with MS and 8 patients with other diseases. Result: The mean visual acuity (VA) and mean deviation of visual field at ON attacks were significantly worse in eyes of NMD than those of MS. Optical coherence tomography (OCT) analysis in NMD demonstrated a shrinked retinal fovea fiber layer than MS. Importantly, on eyes with NMD had more prolonged time from ON onset to achieving VA to 10 logMAR than those with MS suggesting poorer visual outcome in NMD patients. Pathological findings of AVP in NMD were identical to those of spinal cord, demonstrating extremely active demyelination of MS and 8 patients with other diseases. The results were in accordance with our previous data on MS. Conclusion: These data suggest that AQP4-mediated autoneutolysis with more widespread axonal damage is important in AVP involvement of NMO.
Astrocyte injury in AQP4 and MOG antibody positive CSF: a multicenter study

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Objective: To evaluate astrocyte injury in the cerebrospinal fluid (CSF) of patients with antibodies against aquaporin 4 (AQP4) or myelin oligodendrocyte glycoprotein (MOG). Methods: We compared 30 AQP4 and 30 MOG-positive seropositive patients with stored CSF samples from Japan, Brazil, France, South Korea, and Thailand. CSF samples were blindly tested for anti-AQP4 and anti-MOG using validated assays. Astrocyte damage was evaluated using glial fibrillary acidic protein (GFAP)-like levels with a commercial ELISA kit. Results: Among the patients, 30% of the AQP4 group and 20% of the MOG group had elevated GFAP-like levels. Astrocyte damage was more pronounced in the AQP4 group compared to the MOG group. Most AQP4 and MOG antibody-positive patients had detectable GFAP-like levels in their CSF. All antibody results in their CSF identified the same antibody present in serum 28% of anti-AQP4 and 20% of anti-MOG. CSF samples were positive for both antibodies. The mean GFAP-like level in the CSF was significantly elevated in the anti-AQP4 group (57 ± 27 pg/mL in comparison to anti-MOG group 38 ± 14 pg/mL, P = 0.001). The concentration of GFAP correlated with anti-AQP4 levels in the CSF (P = 0.19; R² = 0.80). Conclusion: Astrocyte damage is evident in anti-AQP4 and anti-MOG CSF and is correlated in the CSF with GFAP-like levels. The absence of detectable GFAP suggests a distinct underlying mechanism in anti-MOG cases.

Astrocyte injury and secondary demyelination in intracranial injection NMO model

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Objective: To determine the role of secondary demyelination in the cerebrospinal fluid (CSF) of patients with antibodies against aquaporin 4 (AQP4) or myelin oligodendrocyte glycoprotein (MOG). Methods: We compared 30 AQP4 and 30 MOG-positive seropositive patients with stored CSF samples from Japan, Brazil, France, South Korea, and Thailand. CSF samples were blindly tested for anti-AQP4 and anti-MOG using validated assays. Astrocyte damage was evaluated using glial fibrillary acidic protein (GFAP)-like levels with a commercial ELISA kit. Results: Among the patients, 30% of the AQP4 group and 20% of the MOG group had elevated GFAP-like levels. Astrocyte damage was more pronounced in the AQP4 group compared to the MOG group. Most AQP4 and MOG antibody-positive patients had detectable GFAP-like levels in their CSF. All antibody results in their CSF identified the same antibody present in serum 28% of anti-AQP4 and 20% of anti-MOG. CSF samples were positive for both antibodies. The mean GFAP-like level in the CSF was significantly elevated in the anti-AQP4 group (57 ± 27 pg/mL in comparison to anti-MOG group 38 ± 14 pg/mL, P = 0.001). The concentration of GFAP correlated with anti-AQP4 levels in the CSF (P = 0.19; R² = 0.80). Conclusion: Astrocyte damage is evident in anti-AQP4 and anti-MOG CSF and is correlated in the CSF with GFAP-like levels. The absence of detectable GFAP suggests a distinct underlying mechanism in anti-MOG cases.

SIP1R agonist exert a neuroprotective effect via enhancing collagen growth

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Background: The leptomeningeal collateral circulation is established by increase of shear stress after an acute occlusion of intracranial artery. We recently found that the expression of sphingosine-1-phosphate receptor 1 (SIP1R) in endothelial cells of collaterals markedly increased after cerebral hypoperfusion. This study aimed to investigate the effect of SIP1R agonist on collateral growth and subsequent ischemic damage after focal ischemia.

Methods: CSTB mice underwent left common carotid artery occlusion (CCAO), and were assigned to one of the following groups: 1) Control, 2) CCAO and SIP1R agonist administration, 3) CCAO and DMSO administration, 4) CCAO and SIP1R agonist administration after DMSO administration. In each group, the percentage of CCAO-induced infarct volume was measured. SIP1R agonist significantly reduced CCAO-induced infarct volume.

Conclusion: SIP1R agonist selectively enhanced collateral growth in cerebral hypoperfusion model and may exert a neuroprotective effect after subsequent MCAO.

RANKL-RANK signaling is a novel anti-inflammatory signaling system in ischemic brain

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Background & Purpose: Although several clinical studies showed that the high serum osteoprotegerin (OPG) decoy receptor for RANKL level was associated with unfavorable outcome in ischemic stroke, its mechanism is unknown. Since OPG/RANKL inhibitor activated macrophage-like B lymphoma 10 (BMDM) and RANK-receptor for RANKL system has critical roles in immune systems, we examined their expression and functions in mice.

Methods: The expression and function of OPG/RANKL-BMDM were analyzed in transient middle cerebral artery occlusion in mice: BMDM culture medium (RANKL: 200 ng/mL, OPG: 100 ng/mL, M-CSF: 0.5 ng/mL, TNF-α: 100 ng/mL). IL-6 was measured from BMDM conditioned medium after treatment of LPS.

Results: Expression of RANK, RANKL, and OPG mRNA was increased from 4.5 h after ischemia and changed the activated macrophage-like BMDM to M2 phenotype. The combination of OPG and RANKL treatment treated WT mice showed reduced infarct volume, whereas the mice treated with RANKL & OPG showed increased infarct volume. The expression of IL-6, TNF-α, and IL-1 β was less in OPG mice and RANKL treated mice. Additionally, LPS-stimulated macrophage cultures showed less neuronal death in the group of RANKL-treatment cultures through inhibition of inflammatory cytokines production.

Conclusion: RANKL-RANK signaling might work as anti-inflammation in ischemia brain through inhibiting TLR signaling pathways. High serum OPG in clinical situations might inhibit RANKL-RANK signaling and exacerbate the post-ischemic inflammation, resulting in poor recovery.

SIP1R expression and endothelial cell proliferation after focal ischemia in mice

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Background: After acute cerebral ischemia, the leptomeningeal collateral circulation correlates with smaller infarction volume in stroke patients. The leptomeningeal arterioles are dilated by altered shear stress but its detailed mechanism is unknown. Sphingosine-1-phosphate receptor 1 (SIP1R) is one of the key molecules regulating arterial development in response to altered arterial flow. This study aimed to investigate the temporal profile of SIP1R expression and cell proliferation in leptomeningeal arterioles after stroke.

Methods: C57/ Bl6 mice (n = 35) underwent left middle cerebral artery occlusion (MCAO). The expression of SIP1R was analyzed with EdU (endothelial differentiation gene 1) antibody immunostaining after surgery, and a set of mice was administered BrdU (5-bromo-2-deoxyuridine) to label mitotic nuclei.

Results: In control mice, the expression of EdU signals was not detected. In MCAO mice, the expression of EdU signals were observed in endothelial cells of the intraparenchymal leptomeningeal arterioles and neurons in peri-infarct region, with a peak from 12hrs and 4 days after surgery, and late phase expression was detected in astrocytes. The number of BrdU-positive cells in endothelial cells was significantly increased compared to the control group (3.8 ± 0.9 vs 3.2 ± 0.4; P < 0.01).

Conclusion: In MCAO mice, SIP1R expression in endothelial cells and neurons mainly around ischemic region increased early after the onset, which was associated with endothelial cell proliferation. SIP1R signaling may promote collateral growth by cell proliferation and neovascularization after stroke.

3- and 4-repeating tau is phosphorylated and cleaved by transient cerebral ischemia

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Background: We have shown that tau phosphorylation and cleavage is observed in both ischemia stroke and traumatic brain injury models. In the current study, we hypothesized that 3- and 4-repeat tau is phosphorylated and cleaved in rat models of traumatic brain injury.

Methods: 3-week-old male Wistar rats were subjected to 90 min of focal cerebral ischemia followed by 8h, 12h, 24h, 48h or 72h of reperfusion (n = 5/condition). Tau1, B-III, EDI, and AT8 antibody were used for immunohistochemical studies and western blot analyses.

Results: The full-length EDI and EDI were decreased and the 17kDa band of EDI and the 24kDa band of both indicative of tau fragment was observed after MCAO. The phosphorylated 3R and 4R tau were increased after MCAO by the separation of phosphorylated forms using Phos-tag. Fluorescence immunohistochemistry revealed increased EDI and EDI staining in neuronal perikarya in peri-infarct area and accumulation of EDI and RDI immunoreactive granules in ischemic core. Some Tau-positive neurons represented partial overlapping expression of AT8 in the peri-infarct area. On Gallyas-Braak staining, argyrophilic neurons were present in the ischemic lesion.

Conclusion: We showed the evidence of 3- and 4-repeat tau phosphorylation as well as cleavage of both 3-repeat and 4-repeat tau isomers in transient cerebral ischemia. The pathological alteration in transient ischemic area was comparative to that of AD in terms of modification and accumulation of tau protein.
臨床神経学第55巻別冊（2015）S5：S212

O-10-4  慢性頭痛症候群に対するMelatonin Intoxication Therapy 日本の効果

O-10-3  Lesions in the left precentral gyrus were associated with Bucofacial apraxia

O-10-1  Functional connectivity change within syntax-related networks in glioma patients

O-11-1  Duchenne型筋ジストロフィに対するエクソンスプリッタ治療の早期臨床試験

O-11-2  Development of exon-skipping therapy by hetero-chimera-duplex oligonucleotide

Objective: Splitting-switching oligonucleotide (SSO) mediated exon-skipping therapies for treating Duchenne muscular dystrophy (DMD) show great promise from preclinical studies. However, recent failure of clinical trials highlights the importance of identifying more effective SSOs. We developed a new structure of oligonucleotide, hetero-chimera-duplex oligonucleotide (HCDO) and showed that HCDO including locked nucleic acid (LNA)-based microRNA inhibitor achieved enhancement of in vivo efficacy of the therapeutic oligonucleotide. In the present study, we assessed efficacy of HCDO using LNA-based SSO for exonskipping (HCDO) 5' UAG 3', and 5' UCA 3' for 5'\xrightarrow{AAUUCU}3' and 5'\xrightarrow{UACUUU}3' targeting p53, respectively. In this study, we evaluated the ability of inducing exon skipping or revert to wild-type p53 using RT-PCR, quantitative real-time RT-PCR and a murine reporter expressing exons 51-59 of the human dystrophin gene. Results: HCDO demonstrated potent and dose-dependent exon-skipping which was better than the original SSO. We revealed effect on the efficacy of the tiny size of SSO into integrating into HCDO and chemical modification of HCDO. Conclusions: We developed a new molecule technology of oligonucleotide structure for splicing-blocking therapy.

Materials and Methods: We designed a series of HCDO, including LNA-doped miRNA/mixed-modified phosphorothioate SSO complementary to the human dystrophin exon 58 and 59. We evaluated the ability to induce exon skipping or revert to wild-type p53 using RT-PCR, quantitative real-time RT-PCR and a murine reporter expressing exons 51-59 of the human dystrophin gene.

Results: HCDO-SSEO demonstrated potent and dose-dependent exon-skipping which was better than the original SSO. We revealed effect on the efficacy of the tiny size of SSO into integrating into HCDO and chemical modification of HCDO.
O.113
Fukita is prerequisite to ameliorate muscular dystrophy by LARGE expression

O.114
Mioastatin/protein domain core is ligand-receptor complex to regulate

O.121
Abnormal neuronal activity in natural motion perception in DYT1 dystonia

O.122 Diagnostic Significance of Cortical Superficial Siderosis in Alzheimer Disease

O.123 安静時MRIによるパーキンソン病および進行性核上性麻痺の機能的ネットワークの検討

1. Fukita in prerequisite to ameliorate muscular dystrophy by LARGE expression

2. Mioastatin/protein domain core is ligand-receptor complex to regulate

3. Abnormal neuronal activity in natural motion perception in DYT1 dystonia

4. Diagnostic Significance of Cortical Superficial Siderosis in Alzheimer Disease
O-13.1 The comprehensive study of genetics of Parkinson’s disease

[Background] Parkinson’s disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopamine-producing neurons in the substantia nigra. This loss leads to the characteristic symptoms of PD, which include tremor, rigidity, bradykinesia, and postural instability. The genetics of PD are complex, and while the majority of cases are considered sporadic, approximately 10% of PD cases are inherited as familial disorders.

[Objective] The objective of this study was to investigate the genetic factors contributing to PD by conducting a comprehensive genetic analysis of a large cohort of PD patients.

[Methods] The study enrolled 1400 PD patients, who were clinically defined PD patients based on data from JUN 1996 to JUN 2011. The genetic analysis included the assessment of SNCA multiplication, PARK2, and PARK7.

[Results] The frequency of each gene was calculated, and the association between the genes and PD was evaluated. The results showed a significant association between PD and SNCA, PARK2, and PARK7.

[Conclusion] These findings suggest that genetic factors play a role in the development of PD, and understanding these genetic contributions may lead to new therapeutic strategies for this disease.

O-13.2 A Japanese family of hereditary geniospasm (chin trembling)

[Background] Geniospasm is a neurological disorder characterized by involuntary contractions of the chin. It is often associated with stress or anxiety and can lead to significant discomfort for affected individuals. The disorder can be hereditary or acquired.

[Objective] The objective of this study was to investigate a Japanese family with hereditary geniospasm.

[Methods] A family history and neurological examination were conducted to identify symptomatic members of the family.

[Results] The family history revealed a pattern of inheritance, indicating a genetic basis for the disorder.

[Conclusion] The findings support the hypothesis that hereditary geniospasm is a genetically inherited disorder, and understanding the underlying genetic mechanisms could lead to new treatment strategies.

O-13.3 Clinical genetic study of beta-propeller protein-associated neurodegeneration

[Background] The beta-propeller protein (BPP) associated neurodegeneration is a rare genetic disorder characterized by progressive cognitive decline, motor dysfunction, and psychiatric symptoms.

[Objective] The objective of this study was to investigate the genetic basis of BPP associated neurodegeneration.

[Methods] Participants were assessed using a standardized battery of cognitive, motor, and psychiatric tests. Genetic analysis included the assessment of BPP mutations.

[Results] The results showed a significant association between BPP mutations and the clinical manifestations of the disorder. The most common mutation was a frameshift mutation, which led to a premature stop codon and a truncated protein.

[Conclusion] These findings suggest that BPP mutations are a significant contributor to the development of BPP associated neurodegeneration, and targeted genetic testing could be useful for diagnosis and treatment planning.

O-13.4 New gene therapy strategy for neurodegenerative disease with migration of BMDCs

[Background] BMDCs (bone marrow-derived cells) have been used in neurodegenerative diseases, but their migration and therapeutic efficiency remain challenging.

[Objective] The objective of this study was to develop a new gene therapy strategy that improves BMDC migration and therapeutic efficiency.

[Methods] BMDCs were engineered to express a chemokine receptor that enhances their migration to the CNS. The engineered BMDCs were administered to mouse models of neurodegenerative disease, and the therapeutic effects were assessed.

[Results] The results showed improved BMDC migration and therapeutic efficacy in the mouse models of neurodegenerative disease.

[Conclusion] These findings suggest that the new gene therapy strategy could be a promising approach for the treatment of neurodegenerative diseases.
口演

5月21日（木）
抗AChR抗体陽性における神経システムの多様性についての検討

【目的】

当院ではAChR抗体陽性による神経症状を認めた症例を検討し、その神経症状をどのように理解してよいか、その治療法をどのように考えべきか、などの問題を検討することを目的とした。当院での神経症状の発症の原因については、AChR抗体陽性による神経症状を様々な観点から検討した。

【結果】

AChR抗体陽性の神経症状を認めた症例に、多様性を有する神経症状を認めた症例が見られた。これらの症例は、多様性を有する神経症状を認めた症例が多く、その原因については、AChR抗体陽性による神経症状を様々な観点から検討した。

【結語】

AChR抗体陽性の神経症状を認めた症例に、多様性を有する神経症状を認めた症例が見られた。これらの症例は、多様性を有する神経症状を認めた症例が多く、その原因については、AChR抗体陽性による神経症状を様々な観点から検討した。

【参考文献】


Amyloid imaging of dementia using the radioligand 18F-AV45 (Florbetapir F 18)  

Position emission tomography (PET) to detect Alzheimer's disease (AD). The availability of PET scanning is becoming more widespread. In this study, we investigated the amyloid burden in a large cohort of cognitively healthy elderly subjects using the radioligand 18F-AV45. The purpose of this study was to determine the feasibility of using 18F-AV45 to quantify amyloid burden in cognitively healthy elderly subjects. The results showed that the 18F-AV45 PET scan is a feasible and reliable method for quantifying amyloid burden in cognitively healthy elderly subjects.

Functional mapping of praxic network: Electrical cortico-stimulation study

Anesthesia-induced impairment of the praxic network: A feasibility study

Olfactory bulbectomy-induced impairment of the praxic network: A feasibility study

Clinical conundrum of medically intractable seizures - A prospective study

Olfactory bulbectomy-induced impairment of the praxic network: A feasibility study

Characteristic p57/kip2 expression in balloon cells in focal cortical dysplasia

Characteristic p57/kip2 expression in balloon cells in focal cortical dysplasia

Olfactory bulbectomy-induced impairment of the praxic network: A feasibility study

Clinical conundrum of medically intractable seizures - A prospective study

Characteristic p57/kip2 expression in balloon cells in focal cortical dysplasia

Olfactory bulbectomy-induced impairment of the praxic network: A feasibility study

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Olfactory bulbectomy-induced impairment of the praxic network: A feasibility study

Clinical conundrum of medically intractable seizures - A prospective study

Characteristic p57/kip2 expression in balloon cells in focal cortical dysplasia

Olfactory bulbectomy-induced impairment of the praxic network: A feasibility study

Clinical conundrum of medically intractable seizures - A prospective study
O-17.1
Loss of FUS affects adult neurogenesis by modulating Tau isoforms

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Objective: To clarify the regulation of hippocampal adult neurogenesis by FUS. Methods: We generated hippocampal specific FUSknockout mice by injecting AAV expressing shRNA against FUS. The mice exhibited abnormal behaviors including aberrant anxiety, disorientation, and hyper activity which mimicked FTLD-like behavioral impairments. Using this mouse model, we investigated the effect of FUS silencing and subsequent change of Tau isoform ratio on adult neurogenesis in the hippocampus. Results: We observed a decrease of doublet (DCX) positive neurons and at subgranular zone (SGZ) in the hippocampus in FUS knock-down mice. The BrdU incorporation assay revealed that decreased number of BrdU positive cells at SGZ in FUS knock-down mouse. These aberrant adult neurogenesis caused by FUS silencing was rescued by co-silencing of 4-repeat (TDP). Next, we investigated whether the suppressive effect of a FUS silencing on adult neurogenesis was cell-autonomous using a neurosphere formation assay and found that FUS silencing negatively affects the proliferation of neuronal progenitors via increase of R4A in a cell-autonomous fashion. Conclusion: Our findings suggest a pathological link between FUS and Tau in ALS/FTLD through the regulation of R4A/TDP isoforms accompanied with altered adult neurogenesis.

O-17.2
Effect of dietary conditions in Drosophila models of neurodegenerative diseases

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1Objective Neurodegenerative diseases are considered to share a common molecular pathogenesis which involves protein misfolding and aggregation. Recently, increasing evidence suggests a relationship between metabolic syndrome and neurodegenerative disease. The purpose of this study is to explore whether the protein misfolding-related neurodegeneration is generally influenced by nutritional conditions and to examine underlying molecular mechanisms. [Methods] Disease model flies expressing Abeta, tau, alpha-synuclein, MJ, TDP-43 and FUS proteins were fed a high-nutrient diet or a nutrient-restricted diet, and compound eye degeneration was evaluated for screening. The effect of diet on locomotor ability and lifespan was further analyzed in the selected model flies, and protein aggregation was examined by immunohistochemistry and immunoblotting. [Results] Nutrient-restricted diet improved compound eye degeneration of alpha-synuclein, MJ- and TDP-43-expressing flies, while it exacerbated that of tau- and FUS-expressing flies. The nutrient-restricted diet also improved locomotor dysfunction and shortened lifespan of the MJ- and TDP-43-expressing flies, which is accompanied by reduced accumulation of MJ protein inclusion bodies and high-molecular-weight oligomeric TDP-43 protein. [Conclusion] The effect of nutritional condition is not commonly shared among the neurodegenerative disease model flies. The nutrient-restricted diet improved MJ- and TDP-43-induced neurodegeneration through suppression of the misfolded and aggregated protein accumulation in the host tissues.

O-17.3
Loss of FUS causes a decrease in brain volume accompanied with neuronal loss

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Background: FUS is a neurotoxic gene for familial ALS and FTLD. FUS aggregates are recognized as a pathological hallmark of both familial and sporadic ALS/FTLD. In ALS/FTLD, distinct samples are major characteristics in the brains with FTLD pathology.

Aim: To determine whether FUS binding does occur normal brain and brain steaple by using FUS antibody in normal mouse model established by injecting transgenic animals carrying ALS/FTLD disease and normal counterparts and examining the FUS immunostaining in these animals, which could identify FUS behavior.

Methods: We injected APP mice (C57BL/6-Tg(APPxSV2P) 89A6B1F1) or Tg mice (C57BL/6-Tg(APPxSV2P) 89A6B1F1 X LBD human tau) with AAV expressing FUS. The tau transgenic mice were also used to verify the results of imaging study.

Results: We found the APP mice expressing FUS in the motor cortex, hippocampus, and thalamus. In the APP mice expressing FUS, the FUS pathology was also ventrally similar to the results of imaging study.

Conclusions: Our results indicated a significant decrease in hippocampal volume in APP mice compared with their corresponding control mice, whereas no apparent difference was observed between Tau mice expressing FUS and their control counterparts. The tau transgenic mice expressing FUS showed a decrease in amyotrophic lateral sclerosis (ALS) and FTLD in the motor cortex and hippocampus, but no decrease was observed in APP mice. In APP mice, the FUS pathology was also ventrally similar to the results of imaging studies.

O-17.4
Interaction of TDP-43 with NF-kB in MCI with Episodic Memory Deficits

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1Introduction: Transcriptive response DNA binding protein 43 (TDP-43) is detected in pathological inclusions in many cases of Alzheimer’s disease (AD) and mild cognitive impairment (MCI), but its pathological role in AD and MCI remains unknown. TDP-43 was reported to contribute to pathogenesis in amyotrophic lateral sclerosis through its interaction with p65 nuclear factorκ B (NF-κB) resulting in abnormal hyperphosphorylation of this signaling pathway. Methods: Here, we investigated the interaction of TDP-43 with p65 in the temporal cortex of subjects with a clinical diagnosis of MCI in (AD = 12) or AD (n = 32) as well as in age-matched controls with no cognitive impairment (MCI, n = 32). Results: Immunoprecipitation and immunofluorescence approaches revealed a robust interaction of TDP-43 with p65 in the nucleus of temporal lobe neurons in four individuals with MCI (mean MCI p). The analysis of cognitive performance tests showed that MCI individuals presented intermediate deficits of global cognition and episodic memory between those of AD cases and MCI cases. Conclusion: From these results, we propose that enhanced NF-κB activation due to TDP-43 and p65 interaction may contribute to neuronal dysfunction in MCI individuals with episodic memory deficits.

O-18.1
Immunohistochemical analysis of ErbB4 in sporadic ALS patients

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[OBJECTIVE] ErbB4 was recently identified as a novel causative gene for familial ALS (ALS/FR). No immunohistochemical analysis (IHC) of ErbB4 has been reported in sporadic ALS (SALS) patients. This study aims to investigate the relevance of ErbB4 to the pathogenesis of SALS (MEETHRO) autopsy specimen from 16 SALS patients. 14 normal subjects, and 2 patients with spinocerebellar ataxia type 30 (SCA30) using IHC with an anti-ErbB4 polyclonal antibody (Santa Cruz Biotechnology). [RESULTS] In the spinal cord and normal subjects, ErbB4 immunoreactivity (IR) was specifically observed in the cytoplasm of motor neurons. In SALS patients, striking variability of IR was noted motor neurons with enhanced or profoundly reduced IR were encountered. Conversely, IR was unambiguously observed in the cytoplasm of neurons in the caudal nucleus of olives and caudal parts of the nucleus. Selective localization was altered in some of the residual motor neurons including localization in nucleus, anterior or posterior dendrites. Spheroids were intensely immunostained. IR was also detected in glial cells in the anterior horn or the lateral column. In the advanced stage, the majority of residual spinal motor neurons displayed loss of IR. In contrast, in SCA30 patients, residual spinal motor neurons exhibited normal IR patterns. [CONCLUSIONS] This study demonstrated the aberrant expression of ErbB4 in SALS patients, raising the possibility that ErbB4 is relevant to the pathogenesis of SALS IIC in SCA30 did not support the idea that the observation is a non-specific phenomenon following motor neuron dysfunction.

O-18.2
Matrin3 is a component of neuronal cytoplasmic inclusion of motor neuron in SALS

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[OBJECTIVES] Mutations in the MATR3 gene have been identified as a cause of familial amyotrophic lateral sclerosis. The purpose of this study is to elucidate the involvement of matrin 3 in sporadic amyotrophic lateral sclerosis (SALS) patients. [Methods] We analyzed the brains and the spinal cords from ten SALS and five control autopsy cases. For immunohistochemical analysis, we used anti ubiquitin (Ub) antibody, anti phosphorylated TDP-43 (p-TDP-43) antibody and anti-matrin 3 (MATR3) antibody. [Results] All SALS cases showed Ub-positive and pTDP-43-positive neuronal cytoplasmic inclusion (NCI) in the anterior horn cells of the lumbar spinal cord. We observed MATR3-positive NCIs in six out of ten SALS cases. None of Ub- or pTDP-43- or MATR3-positive NCIs were seen in control cases. 15% of Ub- and TDP-43-positive NCIs were seen in the anterior horn cells of the lumbar spinal cord. We observed MATR3-positive NCIs in six out of ten SALS cases. None of Ub-, pTDP-43- or MATR3-positive NCIs were seen in control cases. The pTDP-43-positive NCIs were not observed in the anterior horn cells of the lumbar spinal cord. We observed MATR3-positive NCIs in six out of ten SALS cases. None of Ub-, pTDP-43- or MATR3-positive NCIs were seen in the anterior horn cells of the lumbar spinal cord.

[Conclusion] Matrin3 is a component of neuronal cytoplasmic inclusion of motor neuron in SALS.
O-18-3 Nuclear translocation of cytoplasmic 1C2 and TDP-43 in anterior horn of SCA2

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Backround: SCA2 is one of the polyglutamine diseases caused by the trinucleotide CAG expansion in the ataxin-2 resulting in a neuronal loss in the cerebellum, spin, and spinal cord. SCA2 has been reported to exhibit a phenotype combining cerebellar symptoms and upper and lower motor neuron anomalies mimicking amyotrophic lateral sclerosis. Objectives: We examined the neuropathological findings of the anterior horn in SCA2 to investigate the protein components of polyglutamine aggregates and evaluate the subcellular distribution of pathologically altered proteins.

Materials & Methods: Genetic analysis confirmed the clinical diagnosis in all of the three SCA2 patients by demonstrating the expanded CAG repeat sequences in the mutated SCA2 alleles. Brain tissues of three SCA2 patients from unrelated families were obtained postmortem. Immunohistochemistry was performed using antibodies against I2C and TDP-43.

Results: Interestingly, the cytopathology of the anterior horn in SCA2 was classified into three types by immunostaining: These types are as followings: Type A: cytoplasmic staining of I2C and nuclear staining of TDP-43, type B: focalized nuclear staining of I2C and I2C with NLI type C: type cytoplasmic staining of I2C.

Conclusion: Sequential alteration of nuclear translocation pattern of I2C and TDP-43 in anterior horn, i.e., from type A to B and from type B to C, observed in this study, strongly suggests that TDP-43 might play a role in neurotrophic pathogenesis of SCA2.

O-18-4 Clinicopathological study of autosomal familial ALS cases with optineurin mutation

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Aim: Optineurin (OPTN) was reported as a causative gene in familial amyotrophic lateral sclerosis (FALS). Here, we report clinicopathological features of ALS cases with mutations of OPTN. Methods and clinical features Case 1: A 66-year-old woman noticed right arm weakness followed by weakness in extremities and died of pneumonia at age 76. Case 2: A 38-year-old woman noticed visual changes followed by weakness in extremities and died of pulmonary fibrosis at age 41. Case 3: A 46-year-old woman showed right arm weakness followed by weakness in extremities and resting tremor and died of heart failure at age 61. All cases were characterized with dementia and dysarthria. We performed genetic analysis of OPTN and neuropathological examination. Results: Case 1: heterozygous E44G mutation. There were mild motor neuron degeneration, TDP-43-positive neuronal cytoplasmic inclusions (NCIs) in the motor neurons, and neuronal intranuclear tangles (NITs) in the hippocampus. Case 2: homozygous F694S mutation. There were degeneration in motor neurons, the basal ganglia, and the substantia nigra and TDP-43-positive neuronal inclusions throughout the nervous system. Case 3: heterozygous E44G mutation. There were mild motor neuron degeneration, degeneration of SM, TDP-43-positive NCIs, NITs positive NCIs, and a spinocerebellar-tying lesion in the brainstem. Conclusion: OPTN was detected as an autophagy receptor in selective autophagy. Our results support the idea that mutant OPTN would cause abnormal accumulation of TDP-43 thus a synergism through dysregulation of selective autophagy.

O-18-5 Multiple therapeutic effects of pranbolin on experimental ischemic stroke

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Shun Nakamura, Masanori Tanaka, Tohru Kiyota, Shigemi Kojima, Toshiro Nishimura, Hiroko Watanabe, Kuranosuke Ohno

Introduction: In central nervous system, a growth factor protein (GPG) is considered to play crucial roles in maintaining physiological functions, and mutations in GPG cause Type 2 congenital stationary blader degeneration. Methods: We determined the temporal changes of expression and localization of PGRN after ischemia as well as therapeutic effects of PGRN on ischemic brain injury. Results: We demonstrated a dynamic change of PGRN expression in ischemic Sprague-Dawley rats, including increased levels of PGRN expression in microglia within the ischemic core, and those in survived neurons as well as induction of PGRN expression in endothelial cells within the ischemic penumbra. We observed that PGRN could protect against acute focal cerebral ischemia by variety of mechanisms including attenuation of blood brain barrier disruption via vascular endothelial growth factor, suppression of neurtunamidase via anti-inflammatory interleukin-10 and microglia, and neurogenesis in part by inhibition of cytoplastic reduction of TDP-43 using PGRN knock-out mice. Finally, we demonstrated the therapeutic potential of PGRN against acute focal cerebral ischemia using a rat autologous thromboembolic model with delayed tissue plasminogen activator treatment. Intravenously administered recombinant PGRN significantly reduced volumes of cerebral infarct and edema, suppressed hematoma formation, and improved motor outcome.

Conclusion: PGRN may be a novel therapeutic target that provides vascular protection, anti-neutunamidase, and neuroprotection.

O-19-1 Therapeutic window on transplanted auto-mono-uncellular cells into stroke mice

1Okayama University Medical School, 2Okayama University Medical School, 3Okayama University Medical School

Shuji Hara, Norio Nakamura, Yuji Hashimoto, Kenji Yasuda, Hiroshi Nishijima, Noriyuki Ueda, Masato Yamasaki, Ken-ichi Uchida

Purpose: Embryonic Progenitor Cell (EPC) was reported to enhance repairing and preventing neurovascular units. So far many papers have reported repairing and regenerating experiments using EPC derived from bone marrow, spleen, or peripheral blood. However, the results were not always satisfied. Recently, we succeeded in autotransplantation of EPC including higher grade quality EPC using a novel colony assay system which we have developed (Hara et al. 2010). In the present study, we used novel EPC colony assay system, and evaluated EPC effects on ischemia stroke model in mice.

Methods: We made 89 ischemic stroke model mice (10 weeks male C57BL/6J) with permanent middle cerebral artery occlusion (MCAO). We injected 7E5 as control (20×10⁴, MCAO, intraperitoneal blood + 20×10⁴, MCAO, intracranial EPC), or with control needles at 0, 1, 3 days, 5 days, and 7 days after MCAO (10×10⁴, MCAO, 15×10⁴, MCAO, 10×10⁴, MCAO). (1) We took the brains and investigated time-course physiological parameters including cerebral blood flow and immunochemistry against some anti-angiogenic factor antibodies.

Results: In the stroke model mice on day 1 and 3 days MCAO injection after MCAO the stroke volume was decreased, however the positive cells were increased with immunohistochemistry of EPC. The cerebral blood flow tended to increase as all stroke mice models.

Conclusion: These results indicate that the mice’s EPC including EPC could promote repairing and preventing neurovascular units after ischemic stroke, and the better EPC injection timing might be 1 day and 7 days after MCAO.

O-19-2 Impact of antithrombotic therapy on intracerebral hemorrhage onset after stroke

1Okayama University Hospital, 2Okayama University Medical School

Ryo Tanaka, Hiroshi Kusaka, Tatsuo Nakamura, Minoru Yamasaki, Satoru Matsuda, Akio Takeda, Masato Yamasaki, Ken-ichi Uchida

Background and purpose: Antithrombotic therapy carries a certain risk of bleeding events. We therefore investigated the incidence of uncontrolled hemorrhage (UOIH) in patients taking antithrombotic agents for secondary prevention.

Methods: We examined 437 ischemic stroke patients (67% males, mean age, 72.4 ± 12.5 years) registered in the Fukushima Stroke Registry (FUSR) from June 2007 to May 2013. Clinical characteristics and kinds of antithrombotic agents being administrated at discharge were assessed, and the clinical course of all patients was followed. Patients were classified into the following three groups according to antithrombotic treatment Group 1: antithrombotic agents (78%) (Group 2: antithrombotic (52%) and Group 3: antithrombotic plus antiplatelet agents (48%) We assessed cumulative risks of UOIH using the Kaplan-Meier method, and calculated hazard ratios (HR) and 95% confidence intervals (95% CI) using Cox proportional hazards modeling.

Results: Total ischemic events (71 patients, 16.9%) occurred during follow-up (0.5 - 38.4 days). The Kaplan-Meier method revealed that cumulative recurrence rates of UOI in the three groups differed significantly (p = 0.01, 0.01, 0.05 vs. 0.08) by log rank test). On Cox proportional analysis with adjustments for multiple confounding factors, HR (95% CI) for Group 2 and Group 3 were 0.310 and 0.004 (95% CI 0.019-0.213) vs. Group 1. Conclusion: In stroke patients who take as an antithrombotic plus antiplatelet agent for secondary prevention, the risk of UOI is increased significantly.

O-19-3 Gut microbiota in patients with ischemic stroke

1Okayama University Medical School, 2Okayama University Medical School

Kohei Tanaka, Akiko Futsuji, Katsunori Uemura, Takayuki Suzuki, Tatsuo Fujita, Ken-ichi Uchida

Background: Systemic inflammation is associated with an increased risk of stroke. However, little is known about the cause of systemic inflammation in stroke patients. It has been recently reported that gut dysbiosis is associated with obesity, type 2 diabetes and systemic inflammation. We therefore investigated whether the composition of gut microbiota is altered in patients with ischemic stroke.

Methods: We investigated the bacteria counts and short chain fatty acid levels in feces, and serum inflammatory cytokines in 25 patients with acute ischemic stroke and in 25 control subjects.

Results: The counts of the Aplongobium cluster were significantly higher, while those of L. sakei subgroup were significantly lower in focal samples of stroke patients than in the control subjects. The local concentrations of total organic acids and acetic acids were significantly lower in stroke patients than in the control subjects. Frequency of detection of inositol and concentrations of valeric acid were significantly higher in stroke patients than in the control subjects. The concentration of interleukin-1β was significantly higher in stroke patients than in the control subjects.

Conclusions: Our study showed alteration of gut microbiota composition and increased systemic inflammation in patients with ischemic stroke. Further studies are needed to elucidate the mechanisms of ischemic stroke by gut dysbiota.
O-2-18
Association of CSF Levels of LOTUS with Disease Activity in Multiple Sclerosis

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Keita Takahashi,1 Yuji Kurihara,1 Yumie Suzuki,1 Yoshio Goda,1 Kohtaro Takeda,1 Fumiaki Tanaka1

Objectives
Although multiple sclerosis (MS) is generally considered as autoimmune disease resulting from an autoimmune mechanism, there is no current clinical practice accepted as an immunological gold standard. The present study aimed to clarify the clinical significance of CSF levels of LOTUS in MS patients compared with healthy controls.

Methods
CSF samples were collected from 28 MS patients (14 relapsing-remitting MS and 14 secondary progressive MS) and 18 healthy volunteers. CSF levels of LOTUS were determined using a sandwich enzyme-linked immunosorbent assay (ELISA).

Results
The relationship between MS disease activity and CSF levels of LOTUS was analyzed using the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) score. The CSF levels of LOTUS were higher in relapsing-remitting MS patients than in healthy controls (P = 0.001). In patients with secondary progressive MS, no significant differences were observed in CSF levels of LOTUS compared with healthy controls.

Conclusions
Our results suggest that CSF levels of LOTUS may be a promising biomarker for the clinical assessment of disease activity in MS patients.

O-2-19
Inversion of multiple sclerosis model by superior dominant peptide

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Youhei Lin1,2, Sashiko Miyake1, Takashi Yamamura1

Objective
Recently developed disease-modifying agents dramatically improved the therapeutic efficiency in multiple sclerosis (MS). However, they might have risk of severe adverse effects and some of them could completely ablate the disease activity. Focusing on experimental autoimmune encephalomyelitis (EAE), we previously demonstrated that the thymic hormone interleukin-7 induced a protective effect in EAE model with different levels of induce severity. In the current study, we tried to test the protective effect of IL-7 in the chronic phase of EAE.

Results
We analyzed an anti-peptide antibody against a superior dominant peptide. The antibody was specifically detected in CD4+ T cells in the EAE model with IL-7 treatment. The results were also directly confirmed by the thymic hormone interleukin-7 in the chronic phase of EAE.

Conclusions
Our results suggest that IL-7 treatment could improve the therapeutic efficiency in multiple sclerosis (MS).

O-2-20
Gene expression of autoimmunity-related genes in mini-brains from patients with autism spectrum disorder

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BACKGROUND: Although interferon-beta (IFN-β) is the first-line therapy in relapsing-remitting multiple sclerosis (MS), one-third of MS patients do not respond to IFN-β therapy. We previously reported that immune serum sickness is increased in the MS patients who did not respond to IFN-β therapy. Therefore, we investigated the gene expression profile of the IFN-β response in MS patients.

METHODS: The subjects for the investigation were 20 patients with MS in our hospital with high IFN-β level and 20 patients with IFN-β level in healthy controls. In addition, the gene expression profile of the IFN-β response was also investigated in the immortalized B-cells (K562) and the human neural stem cells (NSC-34).

RESULTS: The gene expression levels of IFN-β were significantly higher in patients with high IFN-β levels compared to healthy controls. In addition, the gene expression levels of the IFN-β response were also significantly higher in the immortalized B-cells (K562) and the human neural stem cells (NSC-34) compared to healthy controls.

CONCLUSIONS: Our results suggest that the IFN-β response may be a promising biomarker for the clinical assessment of disease activity in MS patients.

O-2-21
De novo Parkinson’s disease and the blood pressure in a clinical cohort

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Hirotaka Arai,1,2,3 Hiroshi Mori,1,2 Takeshi Ono,1,2,3 Kazuaki Ono1,2,3

Objective
Parkinson’s disease (PD) is a neurological disorder characterized by dopaminergic neuronal loss, which is associated with genetic factors. In this study, we aimed to investigate the relationship between PD and blood pressure in a clinical cohort.

Methods: A total of 100 PD patients were recruited from the Neurology Department of our hospital. We measured the blood pressure of each patient at the time of their first visit. The blood pressure was recorded as systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Results: The mean SBP and DBP of PD patients were significantly higher compared to healthy controls (P = 0.001 and P = 0.002, respectively). The higher blood pressure was associated with an increased risk of PD development.

Conclusions: Our results suggest that blood pressure plays a significant role in the development of PD.
O.2.2

**Autothpy dysregulation in amyotrophic lateral sclerosis**

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**Objective:** TDP-43 has been linked to the pathological features of FTLD/ALS, but the precise mechanism of TDP-43-mediated neurotoxicity is still open to debate (i.e., toxic gain of function vs. loss of function, cell-autonomous neuronal death vs. non-cell-autonomous neuronal death). To elucidate these issues, we developed TDP-43 loss of function model for FALD/ALS using the neuronal-specific, drug-inducible DREADD (GPR55) knockout mice.

**Methods:** The neuronal-specific, tetracerin inducible TDP-43 knockout mice were generated using Thy1-CreERT2 system. To ablate TDP-43 expression, mice (10–12 weeks old) were given 5 mg/kg/day tamoxifen by gavage for 5 consecutive days. To inhibit glial excitotoxicity, mice were intraperitoneally injected with 20 mg/kg of NPS371 (β3R permeable gap junction blocker) every other day 3 weeks after tamoxifen treatment (n = 11 in each group).

**Results:** After ablation of neuronal TDP-43, mice exhibited behavioral abnormalities, cognitive deficit, and rapid progressive motor paralysis associated with neuronal loss and massive gliosis, which resembles FTLD/ALS phenotypes. Intraperitoneal treatment suppressed CSF glial limitans, gliosis, and neuronal loss, and improved the disease symptoms.

**Conclusion:** Our findings suggested that the loss of function of neuronal TDP-43 can cause neuronal death different from TDP-43-mediated neurotoxicity.

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O.2.3

**Autophagy dysregulation in amyotrophic lateral sclerosis**

1Center for Translational Research of Neurodegenerative Disease, 1st Affiliated Hospital, Dalian Medical University. 2Institute of Health Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences.

**Objective:** Amyotrophic lateral sclerosis (ALS) is an adult-onset devastating neurodegenerative disease. Although the causes in most cases of ALS are not yet delineated, it is believed that a toxic gain of function resulting from abnormal protein aggregation is probably one of the mechanisms contributing to this disease. To investigate if there is any autophagic alteration in ALS we used SOD1-G93A mutant mice, a model of ALS mice at early stages, including an accumulation of LC3-II and p62 in the MNs, an increase of autophagic vacuoles (AVs) in the myelinated axons of MNs, an activation of mTOR-dependent autophagic pathway, aggregation of ubiquitin and SQSTM1 (p62) proteins associated with LC3-II depilation. In addition, we have demonstrated that autophagy enhancer rapamycin treatment in the ALS mice increases accumulation of AVs, but fails to reduce the level of mutant SOD1 aggregates, indicating the possibility of abnormal autophagic flux in ALS. On the contrast, we found that MTOR independent autophagy enhancer trehalose prolongs the MNs survival and ameliorates autophagic flux defect in a mouse model of amyotrophic lateral sclerosis. These studies indicate that defect in autophagic flux and proteasome dysregulation is the critical pathogenetic mechanisms of ALS.

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O.2.4

**Ablation of neuronal TDP-43 causes non-cell autonomous neuronal death in mice**

1Department of Neuroimmunology, Research Institute of Environmental Medicine, Nagoya University, Japan. 2Future Environmental Systematic Research Institute, Research Institute of Environmental Medicine, Nagoya University. 3Center for Neurodegenerative Disease Research, the Hospital of Pennsylvania University, Pennsylvania, U.S.A.

**Objective:** TDP-43 has been linked to the pathological features of FTLD/ALS, but the precise mechanism of TDP-43-mediated neurotoxicity is still open to debate (i.e., toxic gain of function vs. loss of function, cell-autonomous neuronal death vs. non-cell-autonomous neuronal death). To elucidate these issues, we developed TDP-43 loss of function model for FALD/ALS using the neuronal-specific, drug-inducible DREADD (GPR55) knockout mice.

**Methods:** The neuronal-specific, tetracerin inducible TDP-43 knockout mice were generated using Thy1-CreERT2 system. To ablate TDP-43 expression, mice (10–12 weeks old) were given 5 mg/kg/day tamoxifen by gavage for 5 consecutive days. To inhibit glial excitotoxicity, mice were intraperitoneally injected with 20 mg/kg of NPS371 (β3R permeable gap junction blocker) every other day 3 weeks after tamoxifen treatment (n = 11 in each group).

**Results:** After ablation of neuronal TDP-43, mice exhibited behavioral abnormalities, cognitive deficit, and rapid progressive motor paralysis associated with neuronal loss and massive gliosis, which resembles FTLD/ALS phenotypes. Intraperitoneal treatment suppressed CSF glial limitans, gliosis, and neuronal loss, and improved the disease symptoms.

**Conclusion:** Our findings suggested that the loss of function of neuronal TDP-43 can cause neuronal death different from TDP-43-mediated neurotoxicity.

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O.2.5

**The mouse CSQRF72 ortholog is enriched in neurons known to degenerate in ALS/FTD**

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**Purpose:** Recently, expansion of a noncoding hexanucleotide repeat in CSQRF72 was identified as a common cause of both amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). The normal physiological function of CSQRF72 and its expression pattern in the developing and adult nervous system have not been explored. We produced mice harboring a LacZ reporter gene targeted to the mouse ortholog of CSQRF72 and used them to study the gene's expression pattern. Method: Using 7–8 week-old heterozygous mice (n = 9), we studied the expression pattern of 31H000201Rik using X-galactosidase staining. To determine the identity of X-gal-positive cells in the CNS, we performed co-immunostaining with antibodies to beta-tubulin (beta-tub) and antibodies labeled relevant classes of neurons (cerebellar neuronal cell type). Results: In the brain, we found X-gal activity in the hippocampus, dentate gyrus, striatum, thalamus, brainstem nucleus, cerebellum and throughout the cortex. In the spinal cord, X-gal activity was distributed throughout the gray matter, with the highest levels being observed in the ventral horn. We found that most beta-tub+ cells of the cortex expressed NeuN. Two thirds of beta-tub+ cells in layer V further co-stained with antibodies specific to CTIP2. In cortical layers II and III, most beta-gal+ cells expressed CUX1. In the spinal cord, cells expressing beta-gal+ colabeled with GABAT.

**Conclusion:** The CSQRF72 ortholog was highly transcribed in the neuronal populations that are sensitive to degeneration in ALS and frontotemporal dementia.
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O.2.3.1 Nicotine receptor and amyloid burden for frontal affection in Alzheimer disease

O.2.3.2 Viability of basal forebrain in AD: a longitudinal FDG-PET study

O.2.3.3 DATスキャン・MBGと新シネシニを共に行ったパーキンソン病とその関連疾患の臨床検討

O.2.3.4 Progressive supranuclear palsy患者における臨床検討と11C-PB207 PETの関係

O.2.4.1 A Placebo-Controlled Exploratory Study of Zonisamide for Parkinsonism in D LB

O.2.4.2 Pharmacokinetic factors and levodopa-induced dyskinesia in Parkinson disease
Effect of Lee Silverman Voice Treatment in Filipino Parkinson's Disease Patients

St. Luke's Medical Center, Philippines
○ Juan Miguel P. Bautista, Carla Krishan A. Cuadra, Roland Dominic G. Janora

Purpose. Lee Silverman Voice Treatment (LSVT) is an intensive course focused on improving speech, swallowing and respiratory function in Parkinson’s disease patients. Several studies have been done on LSVT and the Filipino PD patient. Aim of study is to determine the effect of LSVT on these patients based on vocal intensity and length of time of sustained phonation. Another objective is to correlate the Subject PD profile to their response to treatment.

Methods. This is a cross-sectional pilot study of PD patients in a single institution in the Philippines. Records of PD patients independent of disease severity who completed the course were retrieved. Vocal intensity and time of sustained phonation at different vocal pitches were measured at baseline and during all 16 sessions. Baseline data and the mean of all 16 sessions were statistically analyzed.

Results. 7 patients completed the LSVT course. For vocal intensity, 5 of 7 subjects showed louder vocal intensity compared to baseline on at least 1 vocal pitch. 3 of the 7 subjects showed longer time of sustained phonation. For vocal pitch, 5 of 7 subjects had longer sustained phonation on at least 1 vocal pitch. Improvement was seen more in patients with mild PD.

Conclusion. Among Filipino PD patients who completed LSVT, majority showed improvement in either vocal intensity or length of time of sustained phonation. Improvement was seen more on the patient’s habitual pitch. Most improvement was seen in patients with mild PD and mild speech disorder. This implies that LSVT may have most benefit in this category of patients.

The Effectiveness of the Parkinson's disease rehabilitation using tai chi

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○ Yoshishara Ara1, Kazuichi Kawamura1, Toshio Ima1, Yukio Sawada2, Mayumi Od3, Itsuzo Hashi1, Takao Mitsui

【目的】近年、大腸癌のがん放射線治療の症例に重篤な放射線障害を示すことが報告され、多くの研究が大腸癌の放射線治療効果を追求しているが、本論文では、放射線治療を受けてから再発することを示す細胞の再発症例を経験している。放射線治療を受けてから再発することが示す細胞の再発症例を経験している。

【方 法】対象：放射線治療後2年以内に再発を示す細胞の再発症例をもつ患者を対象とした。対象：放射線治療後2年以内に再発を示す細胞の再発症例をもつ患者を対象とした。

【結果】初回再発症例31型の自覚症候・多施療法前向検討

1九州大学医学部附属病院消化器内科、2九州大学医学部神経精神科学研究所、3九州大学医学部附属病院放射線科、4九州大学医学部附属病院放射線科、5NHK、6九州大学医学部放射線科、7九州大学医学部放射線科、8九州大学医学部放射線科、9九州大学医学部放射線科、10九州大学医学部放射線科、11九州大学医学部放射線科
○中村常勤1、吉田明宏2、松村晴3、中村伸4、佐藤幸之5、矢野礫之6、森田正7、大場慎8、池田修9、塚本和也10

【目的】放射線療法前再発症例31型の遠隔再発症例および放射線療法前再発症例の一部を対象とした。

【方 法】放射線療法前再発症例31型の遠隔再発症例および放射線療法前再発症例の一部を対象とした。
口演

5月22日（金）
筋萎縮性側索硬化症（ALS）における治療研究

1. イブメシジンの効果

イブメシジンは、ALS患者の症状を改善する可能性があるとされている。特に筋萎縮の進行を抑制する効果が期待されている。

2. 他の治療法

これまでに、ALSに対する様々な治療法が提案されている。その中には、神経保護剤の使用、運動・栄養指導、精神的ケア、家庭で行う自己訓練などが含まれる。

3. 今後の方向

今後は、これらの治療法がより効果的なものとなることが期待されている。また、新しい治療法の開発も進めていく予定である。

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O-26.1 アトロピン使用と抗運転動作 眼科検査室

O-26.3 完全性脳卒中患者の再発予防 眼科学会

O-26.4 盲導器をもとに症例数を症例数に換算する

O-26.2 特異的異常検査に 臨床検査科学研究会

O-26.2 罕見例の脳神経疾患に関する新たな精密画像検査の検討：PROMISE-TIA一連

O-27.4 FACILITATION OF EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS BY PERIPHERAL ASPHYXIA

O-27.2 Mechanistic insight into I6-L signal blockade therapy for multiple sclerosis

O-27.1 Department of Neurology, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP), 2 Multiple Sclerosis Center, National Center Hospital, NCNP, 3 Department of Neurology, National Center Hospital, NCNP, 4 Neurological Institute, Graduate School of Medicine, University of Tokyo, 5 Masaki Suzuki, M.D., Ph.D.

Phenolic compounds prevent the oligomerization of α-synuclein

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2Systematic Science, Graduate School of Medicine and Pharmaceutical Science, University of Toyama.
3Faculty of Pharmaceutical Sciences, University of Toyama.
4Department of Neurology, National Hospital Organization Joshi Hospital.
5Kensyo Takamura.

Objective: We evaluated the in vitro and in vivo effects of 5 polyphenols on the oligomerization of α-synuclein. The effects of polyphenols on the neuroprotective effects were also evaluated.

Methods: We used a FRET sensor and a secondary structure conversion assay, using the methods of photo-induced cross-linking of modified proteins, circular dichroism spectroscopy, the electron microscope, and the atomic force microscope. Treatment with 5 polyphenols (naringenin, curcumin, resveratrol, luteolin, and fisetin) was applied to the assay. The effects of polyphenols on the oligomerization of α-synuclein were evaluated by using the FRET sensor and the electron microscope.

Results: Polyphenols, especially curcumin and fisetin, reduced the size of the oligomers by inhibiting the FRET signal and secondary structure conversion. NMR experiment showed that the chain length of α-synuclein was reduced in the oligomers when α-synuclein was treated with polyphenols.

Conclusion: These results suggest that curcumin and fisetin are effective for inhibiting the oligomerization of α-synuclein, which may be a promising new drug for treating Parkinson’s disease.

Dopaminergic influences on functional neural connectivity in Parkinson’s disease

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Objective: We investigated the functional changes in the dopaminergic system using a novel method of functional connectivity analysis.

Methods: We used a whole-brain functional connectivity analysis using fMRI data obtained from healthy volunteers. We analyzed the functional connectivity of the dopaminergic system using voxel-based statistics and cluster analysis.

Results: We found that the functional connectivity of the dopaminergic system was altered in Parkinson’s disease patients compared to healthy controls.

Conclusion: These results suggest that alterations in the dopaminergic system contribute to the functional connectivity changes observed in Parkinson’s disease.
急性期頭痛患者に対する治療の重要性

急性期頭痛治療における脳神経科学の進歩とその応用

小野和彦

急性期頭痛治療における脳神経科学の進歩とその応用

目的：

急性期頭痛治療における脳神経科学の進歩とその応用について

急性期頭痛の治療は、脳神経科学の進歩とその応用により大きく進歩している。これにより、急性期頭痛の治療率は著しく向上し、患者の生活質の改善に寄与している。

急性期頭痛の治療法として、脳神経科学の分野では、薬物療法が主に使われている。

急性期頭痛の薬物療法は、 NSAIDs、COX-2 阻害薬、非キシミン抗ヒスタミン薬、抗発汗薬、抗不安薬、抗うつ薬、アミノグリコシド系菌薬、レベリン系薬物などが用いられている。

急性期頭痛の薬物療法の効果の検証

急性期頭痛の薬物療法の効果は、臨床試験によって検証されている。臨床試験によると、NSAIDs、COX-2 阻害薬、非キシミン抗ヒスタミン薬、抗発汗薬、抗不安薬、抗うつ薬、アミノグリコシド系菌薬、レベリン系薬物が効果的であることが示されている。

急性期頭痛の薬物療法の副作用

急性期頭痛の薬物療法の副作用は、NSAIDs、COX-2 阻害薬、非キシミン抗ヒスタミン薬、抗発汗薬、抗不安薬、抗うつ薬、アミノグリコシド系菌薬、レベリン系薬物が用いられている場合に生じる可能性がある。

急性期頭痛の薬物療法の経済性

急性期頭痛の薬物療法の経済性は、NSAIDs、COX-2 阻害薬、非キシミン抗ヒスタミン薬、抗発汗薬、抗不安薬、抗うつ薬、アミノグリコシド系菌薬、レベリン系薬物が用いられている場合に検討されている。

急性期頭痛の薬物療法の将来の可能性

急性期頭痛の薬物療法の将来の可能性は、NSAIDs、COX-2 阻害薬、非キシミン抗ヒスタミン薬、抗発汗薬、抗不安薬、抗うつ薬、アミノグリコシド系菌薬、レベリン系薬物が用いられている場合に示唆されている。

急性期頭痛の薬物療法の新薬研究

急性期頭痛の薬物療法の新薬研究は、NSAIDs、COX-2 阻害薬、非キシミン抗ヒスタミン薬、抗発汗薬、抗不安薬、抗うつ薬、アミノグリコシド系菌薬、レベリン系薬物が用いられている場合に進められている。

急性期頭痛の薬物療法の現状

急性期頭痛の薬物療法の現状は、NSAIDs、COX-2 阻害薬、非キシミン抗ヒスタミン薬、抗発汗薬、抗不安薬、抗うつ薬、アミノグリコシド系菌薬、レベリン系薬物が用いられている場合に示されている。

急性期頭痛の薬物療法の問題点

急性期頭痛の薬物療法の問題点は、NSAIDs、COX-2 阻害薬、非キシミン抗ヒスタミン薬、抗発汗薬、抗不安薬、抗うつ薬、アミノグリコシド系菌薬、レベリン系薬物が用いられている場合に生じる可能性がある。

急性期頭痛の薬物療法の解決策

急性期頭痛の薬物療法の解決策は、NSAIDs、COX-2 阻害薬、非キシミン抗ヒスタミン薬、抗発汗薬、抗不安薬、抗うつ薬、アミノグリコシド系菌薬、レベリン系薬物が用いられている場合に示されている。

急性期頭痛の薬物療法の今後の展開

急性期頭痛の薬物療法の今後の展開は、NSAIDs、COX-2 阻害薬、非キシミン抗ヒスタミン薬、抗発汗薬、抗不安薬、抗うつ薬、アミノグリコシド系菌薬、レベリン系薬物が用いられている場合に示されている。

急性期頭痛の薬物療法の今後の課題

急性期頭痛の薬物療法の今後の課題は、NSAIDs、COX-2 阻害薬、非キシミン抗ヒスタミン薬、抗発汗薬、抗不安薬、抗うつ薬、アミノグリコシド系菌薬、レベリン系薬物が用いられている場合に生じる可能性がある。
Purpose: To elucidate independent risk factors of falling of Parkinson’s disease (PD) patients. Methods: Subjects were 103 PD patients aged from 40 to 90 years old (mean age was 72.7). We defined patients who experienced falling once or more during6 consecutive months forming the falling group. Intellectual activity was evaluated by MMSE. Subjective walking difficulty was measured by freezing of gait questionnaire (FOG). Severity of motor symptoms of PD was evaluated by UPDRS part 3. Grade of atrophy of hippocampus was evaluated by T1WI MRI using Voxel-Based Specific Regional Analysis System for Alzheimer’s disease (VSRA). We asked all subjects whether they had lower back pain or not, and whether they experienced halucination in one year or not. In addition to these variables, we included age and duration of PD for analysis as potential risk factors of falling. Results: Falling were experienced by 29 patients (28%). Comparing with no-falling group by un-ivariate analysis, falling group had higher MMSE (25.4 vs 28.3), higher VOR score (17 vs 12), higher FOG (110 vs 4.3) and higher UPDRS part 3 (238 vs 14) significantly. Falling group also experienced lower grade panic (5%) or hallucinations (55.2% vs 20%) more frequently than no-falling group significantly. Logistic correlation analysis revealed that VOR score and FOG were independent correlation factor of falling. Conclusion: Results of this study suggest that atrophy of hippocampus is an independent risk factor of falling of PD patients.

O3-34

Genetic and neuropathological analyses of a pedigree with familial PSP

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Background and Objectives: Progressive supranuclear palsy (PSP) is a sporadic neurogenetic disorder, but there are rare pedigrees with PSP. We experienced a family with autosomal dominant PSP and conducted a case of autopsy. Here we report on neuropathological and genetic analyses conducted to clarify the pathology of this disorder.

Clinical presentation: The proband was a 62 years old male. Forgetfulness started from 43 years old, and was gradually exacerbated. Bradykinesia and a tendency to fall appeared at 55 years old. Although his brain MRI showed loss of the mass in addition to the signs of mild neuronal loss, his movement disorder was consistent with the signs of mesencephalic tegmentum, he was diagnosed with PSP. Similar family histories were found in his mother and elder brother. Autopsy of the brother was performed after he died at the age of 64 years.

Results: Tangle astrocytes were observed in the striatum as a neuropathological finding, that is compatible with PSP. Fifty disease-causing mutations including MAPT, EP30, TARDBP and C9ORF72, previously reported as genes responsible for inherited PSP, were analyzed, but no causative variations were observed. However, a novel mutation assessment, which is specifically expressed in the patients that developed PSP was found in one of the genes expressed in the system nerve by linkage analysis and whole exome sequencing.

Discussion: This newly discovered candidate gene is involved in translation of proteins related to the release of neurotransmitters from presynaptic locations. Currently, a neuroimmunological study is underway using antibody to this protein.

O3-35

Muscle biopsy findings predictive of cancer in rare infiltrative dermatomyositis

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Objective: The characteristic pathological muscle findings of polymyositis (PM) and dermatomyositis (DM) have been shown to reflect their different pathogenesis. Here, we characterized the muscle biopsy findings of 23 consecutive PM and DM patients with or without malignancy.

Methods: We evaluated the muscle biopsy findings of 23 consecutive PM and DM patients (16, 7) who met either the ‘definition’ or ‘probable’ category of Bohan-Picart’s criteria and moreover underwent muscle biopsy between 1975 and 2008. Patients showing rimmed vacuoles on pathological examination, and others showing other characteristic clinical features were excluded. Patients with myositis associated with auto-signal recognition particle (ASPs) antibodies, exposure to statins, and corticosteroids were also excluded. Pathology of the lesion biopsy sections was classified into three types: endomysial infiltration-type, perivascular infiltration-type, and rare-infiltrative-type.

Results: The mean age of DM was 58.8 ± 15.4 years and that of PM patients with malignancies (n=9) was 58.6 ± 10.8 years. The mean age of all DM was 50.5 ± 18.5 years, and that of DM patients with malignancies (n=11) was 59.5 ± 8.9 years. There was no difference between the muscle pathology of PM patients with and without malignancy. However, the incidence of rare-infiltrative type muscle pathology in DM patients with malignancy was significantly lower than those without such malignancies.

Conclusion: The incidence of rare-infiltrative type muscle pathology may be a predictive marker of DM with malignancy.
O-35-1
Influence of glycemic control on stroke recurrence in transient ischemic attack
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Background and purpose: In transient ischemic attack (TIA) patients, diabetes mellitus is a risk factor for subsequent ischemic stroke. We investigated whether the glycemic control in acute phase TIA patients affects stroke recurrence.

Methods: Among 234 TIA stroke patients registered to the Fukuoka Stroke Registry from June 2004 to July 2013, participants completed TIA TIA patients (60 years or more: 8-11 years). Clinical characteristics of patients were assessed in admission, and the clinical course of all patients was followed. With regard to glycemic control, we divided patients into the following three groups according to their initial glucose level after admission: G1: 130-180 mg/dL, G2: 120-170 mg/dL, G3: <120 mg/dL. We then compared the risk of stroke recurrence within 1 year after TIA between groups.

Results: Of the 185 patients, 104 (56%) suffered stroke recurrence during the first year after TIA. The Kaplan-Meier method revealed that the cumulative recurrence rates of ischemic stroke was significantly higher in the patients of G3 than in those of G1 (0.5% vs. 0.1% for the log rank test). Multiple conditioning factors adjusted (peri-proportional hazards modeling showed that risks of stroke recurrence in the first year for patients G2 and G3 compared to patients G1 were indicated by a hazard ratio (HR) of 1.16 (95% confidence interval (CI): 1.11-1.21, p = 0.01) and 1.83 (95%), CI 1.06-1.62, p = 0.006 respectively).

Conclusions: A high CGI in the acute phase TIA tends to increase the risk of stroke recurrence.

O-35-2
Evaluation of ischemic stroke risk based on the aortic plaque characteristics
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Purpose: Atherosclerotic aortic plaques (AP) are one of the risk factors of ischemic stroke. Especially in mobile or ulcerated aortic plaques (MUPs), we have been attended to high risk of cerebral embolism. We evaluated the relationship between the aortic plaque characteristics and the markers for platelet activation, both of which may reflect intraplaque hemorrhage and atherosclerotic changes.

Methods: We enrolled 85 patients with first-ever ischemic stroke undergoing transesophageal echocardiography. We measured the markers for platelet activation in 60 patients who did not receive antiplatelet therapy, nor had significant stenosis in carotid arteries. We checked aortic plaque imaging (APAI) and pathological analysis of aortic plaques (APAP).

Results: Platelet activating markers were not significantly different between APAs <4mm group and APAs ≥4mm group. In addition to MUPs and APAs group, significantly higher in MUPs and APAs group than in APAs <4mm group (P = 0.01; 0.01; 0.001; 0.001; 0.001; 0.001).

Conclusion: Our results suggests the positive correlation between the aortic plaque characteristics and platelet activation. We emphasize the stratification of risk including not only APAs but also characteristics in this study.

O-35-3
Clinical Features and Risk Factors of Primary IVH In Filipino Patients
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O-Rica Monica S. Asuncion, Jose C. Navarro

Introduction: Spontaneous primary IVH in non contrast CT scan or MRI studies is extremely rare. 0.3% of all stroke cases and about 3% of all hemorrhagic strokes. The study was significant in raising awareness regarding the initial presentation and gave the clinician a high index of suspicion for quick diagnosis and early intervention. This study aims to discuss the clinical manifestation, risk factors and clinical outcome on discharge and on 1 year follow up.

Methodology: Patients were collected from the Stroke Database from 2010-2012. The clinical data, risk factors and review of cranial CT scan and cranial MRI was done. A review of imaging of intracranial vessels (MR-CTA and 4V) was done also if available. Clinical outcome on discharge and on 1 year follow up was done using mRS.

Results: Eighty (20.5%) of ICH patients with IVH was collected, only 7 satisfied this study’s criteria for primary IVH. Patient complaints included headache, nausea, vomiting, and alteration in sensorium. Focal deficits were absent or mild which may be due to lack of parenchymal involvement and damage. Risk factors included hypertension (80.7%), diabetes (62%), dyslipidemia, smoking, alcohol use and use of OCPs.

Conclusion: Primary IVH present clinically with headache, nausea/vomiting and alteration in sensorium with minimal or no focal deficit. Hypertension is the most significant risk factor, however, in cases of young patients, structural abnormalities has to be investigated. Mortality is predicted by the amount and location of the hemorrhage and concomitant hydrocephalus.

O-35-4
Risk scores on severity and outcomes in acute stroke with atrial fibrillation
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Background: We aimed to elucidate the association between pre-admission risk scores and severity and functional outcome in acute ischemic stroke with atrial fibrillation (AF). Methods: Between September 2011 and April 2014, we retrospectively extracted consecutive patients with ischemic stroke with AF and pre-admission modified Rankin Scale (mRS) <3 from our prospective database. Pre-admission CIEADS, CHA2DS2-VASc, and R-CHADS 2-score were calculated in each patient and associations between these scores and mRS score on admission or unfavorable outcome (mRS≥3) at 3 months were assessed.

Results: A total of 255 patients (men: 71, 71:1000; CHA2DS2-VASc: +2.1:1000; and R-CHADS 2-score: +2:1:1000, p = 0.086). ROC curve analysis revealed pre-admission CIEADS, CHA2DS2-VASc, and R-CHADS 2-score were positively correlated with the pre-admission CHADS 2-score (p = 0.01), CHA2DS2-VASc (p = 0.01), and R-CHADS 2-score (p = 0.01). The mRS score was higher (p <0.05), sensitivity: 8% specificity: 46%; AUC: 0.85, CHA2DS2-VASc: 0.85, sensitivity: 85% specificity: 85%; AUC: 0.85, and R-CHADS 2-score: sensitivity: 63% specificity: 68%) were associated with unfavorable outcome. The CHA2DS2-VASc score was better than the CHADS 2-score to predict outcome (p <0.05). In multivariate analysis, cutoffs of these scores female sex, higher NIHSS score and internal carotid artery occlusion were associated with unfavorable outcome.

Conclusions: Pre-admission risk scores were associated with severity and functional outcome in acute ischemic stroke with AF.

O-35-5
Toward the First in Human Clinical Trial of Medical Chaperone for Prion Diseases
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Kazu Mikiwata, Hidehiro Mizusawa

A medical chaperone (MC) is a molecule that stabilizes the native conformation of a protein. Here we applied the MC strategy for prion diseases. MC was initially designed to stabilize the prion protein (PrPSc). We optimized a lead compound, GN, in terms of anti-prion activity, delivery to the brain, and safety. The lead compound was successfully synthesized according to the GMP guidelines. For the first time in academia, we constructed an exposure-proof organic synthesis facility in conformity with GMP. Non-clinical studies required for the first-in-human clinical trial were conducted in conformity with GLP. The lead compound was successfully synthesized according to the GMP guidelines. For the first time in academia, we constructed an exposure-proof organic synthesis facility in conformity with GMP. Non-clinical studies required for the first-in-human clinical trial were conducted in conformity with GLP. The lead compound was successfully synthesized according to the GMP guidelines. For the first time in academia, we constructed an exposure-proof organic synthesis facility in conformity with GMP. Non-clinical studies required for the first-in-human clinical trial were conducted in conformity with GLP. The lead compound was successfully synthesized according to the GMP guidelines. For the first time in academia, we constructed an exposure-proof organic synthesis facility in conformity with GMP. Non-clinical studies required for the first-in-human clinical trial were conducted in conformity with GLP. The lead compound was successfully synthesized according to the GMP guidelines. For the first time in academia, we constructed an exposure-proof organic synthesis facility in conformity with GMP. Non-clinical studies required for the first-in-human clinical trial were conducted in conformity with GLP.
Jott accretion of headache in patients with suspected meningitis

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Objectives: We aimed to clarify the diagnostic sensitivity and specificity of jott accretion of headache in meningitis.

Methods: We prospectively investigated the diagnostic accuracy of jott accretion of headache in patients in whom meningitis was suspected on the basis of 2 or more classic symptoms (headache, fever, nuchal rigidity, and altered mental state). We performed the jott accretion maneuver in 249 patients hospitalized for suspected meningitis and calculated the sensitivity and specificity for the diagnosis of meningitis. This result was compared to the sensitivity and specificity of other classic symptoms.

Results: Among the 249 patients in whom meningitis was suspected, the CSF pleocytosis was confirmed and diagnosis of meningitis was made in 109 patients. Sensitivity of jott accretion of headache for the diagnosis meningitis was 51.4%, and specificity was 52.9%. Sensitivity of headache was 83.5%, and specificity was 166%. Sensitivity and specificity of fever (<37.9°C) were 94.5% and 129%, respectively, and those of fever (≥38°C) were 46.6% and 59.3%, respectively. Sensitivity of nuchal rigidity was 66.8%, and specificity was 52.9%. Sensitivity of altered mental state was 29.4%, and specificity was 81.4%.

Conclusions: Sensitivity and specificity of jott accretion of headache were not superior to those of nuchal rigidity for the diagnosis of meningitis. Neurologists should take into consideration the rarity of diagnostic value of jott accretion of headache when using this maneuver.
O-38-4
Modeling Charcot-Marie-Tooth disease using patient iPSCs

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Purpose
Charcot-Marie-Tooth Disease (CMT) is the most common inherited neuropathy. There has been a therapeutic drug for CMT. CMT is classified as axonal and demyelinating types. CMT2A is the most common form of the axonal type of CMT, which is an autosomal dominant trait in a gene encoding a mitochondrial basic protein, MFN2. Our purpose was to model CMT using induced pluripotent stem cells (iPSCs) from CMT2A patients for pathology elucidation and drug development.

Methods
We generated iPSCs from peripheral blood mononuclear cells from 2 healthy controls and 2 CMT2A patients. Motor neuron cells were generated from iPSCs derived from CMT2A patients by serum-free hanging culture of embryonic body-like aggregates with quick re-aggregation (SBFE) method. Then we analyzed the cellular phenotypes of motor neurons.

Results
MFN2 mutation was preserved in CMT2A iPScs. These iPSCs showed normal karyotype by staining of Y and SRE- 
4 at each of 46 normal layers. Immunohistochemical analyses with MAP1B (marker neurons) and SMN1 (marker motor neuron) revealed no differences in differentiation properties between control and CMT2A iPScs.

Conclusion
We generated CMT motor neurons using CMT2A patient iPSCs. This model may be useful for pathology elucidation and drug development.

O-38-2
The Axonal Property in Prediabetes Patients

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Purpose
Whether or not the axon excitability changes in prediabetic patients.

Method
Ten patients diagnosed as prediabetics at least for 2 years were enrolled to receive the nerve excitability test. Prediabetes is defined by American diabetes association (ADA) as one of the three following criteria: I. HbA1C 5.7% to 6.4%, or fasting glucose 100mg/dl to 125mg/dl, or 2 hour oral glucose tolerance test 140 to 199mg/dl. Age-matched healthy subjects were also received nerve excitability test. Subjects with radicalopathy, myopathy, entrapment neuropathy such as carpel tunnel syndrome, and polyneuropathy were excluded.

Result
Among all parameters in nerve excitability test, superfasciculation and strength-duration time constant (SDTC) showed significant difference (p < 0.05) to the Healthy control (HC). These findings are similar to those diabetic patients with normal nerve conduction study (NCs) cohort that has been reported before.

Conclusion
The results suggest that nodal and paranodal ion permeability was affected in the early stage of prediabetic patients. These results can hint us to evaluate the early treatment or protective treatment for the diabetic neuropathy.

O-38-3
Elucidation of the cervical sudomotor pathway based on hemifacial dysarthrosis

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Objective: The present study was performed to elucidate the cervical intramedullary sudomotor pathway in patients with hemifacial dysarthrosis. Patients and Methods: We analyzed 14 patients aged 37-74 years with hemifacial hyperhidrosis compensatory to the anhidrotic area caused by cervical disc hernia. A qualitative sweat test (Minor's method) and infrared thermography were conducted to evaluate the lesion in an artificial climate chamber at 40°C and 50% relative humidity. Neurological examination and magnetic resonance imaging (MRI) were also performed. Results: Hemilateral and segmental sudomotor distribution patterns were specified. MRI showed disc protrusion near the midline (median type) in the hemilateral sweat pattern and approximately 3 mm lateral to the midline (paramedian type) in the segmental sweat pattern with no intramedullary lesion. In 80% of the later cases, the disc protrusion was ipsilateral and corresponded to the segment of axonorrhesis. Discussion: In patients with the median type, the protruded disc may compress the central artery and cause insufficient peripheral perfusion of the sudomotor pathway around the anterior horn, resulting in ipsilateral anhidrosis without motor or sensory disorders. In patients with the paramedian pattern, the disc may compress the sympathetic premotor neuron in the dorsolateral funiculus and spare the upper segments synapsing the spinal segmental autonomic intramedullary sudomotor neuron and the intermedullary nucleus. Conclusion: Analysis of hemifacial hyperhidrosis could help to clarify the cervical intramedullary sudomotor pathway.

O-38-1
The importance of clinical features in nunchין/chek syndrome

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Introduction: Focal numbness in the face is a rare neurological condition which origins in the absence of trauma. However, physicians are needed to be aware of the relationship between malignancies and paresthesia or complete loss of sensation in the trigeminal nerve territory, more specifically the mandibular and maxillary branch territory. They are known as numb chin syndrome and numb cheek syndrome.

Patients and Methods: We report eight cases of numb chin syndrome and three cases of numb cheek syndrome who presented our hospital between February 2003 and November 2011. We studied their age, gender, onset of numbness, associated neurological deficits, underlying causes (final diagnosis), and prognosis.

Case presentation: The patient was a 27-year-old woman who presented with numbness of her right cheek for 7 months. Her laboratory tests, head MRI, whole body CT scan showed no remarkable findings. However, FPG-PE-T/CT detected abnormal accumulation in the left breast. Tissue biopsy revealed breast cancer.

She was performed operation and radiotherapy. Fortunately, she discharged with fully recovered.

Conclusion: We described cases of numb chin syndrome and numb cheek syndrome. We would like to highlight these rare and unusual conditions, because we should consider them as differential diagnoses for early intervention of malignancies and improve the prognosis.
O-39.3
レム睡眠行動異常症におけるDATスキャンによるドパミン作動神経機能の評価

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【目的】パーキンソン病（PD）あるいはレビー小体型認知症（DLB）では、その疾患に前駆あるいは合併するレム睡眠行動異常症（RBD）が高率に存在する。ドパミン作動神経機能評価は、DATスキャンが有用であると報告されている。本研究ではPD 30例、DLB 30例、RBD 26例を対象にDATスキャンによる視床基底核の病変について検討した。

【方法】当院通院中のPD 30例（70歳±38歳）、DLB 30例（74歳±33歳）、RBD 26例（69.7歳±4.4歳）を対象にDATスキャンを施行した結果を調査した。運動機能はUPDRS-III、認知機能の評価にはMMSEを用いた。さらに嗅覚同定検査（OB）を施行した症例では視床基底核の病変との関係を調べた。

【結果】視覚的な検討で視床基底核の病変が、PDでは部分的基底体側頭葉から、DLBでは基底体全体が高縮し、RBDでは部分した基底核ではPDとDLBの2パターンがみられた。その定量評価の指標として使用したspecific binding ratio（SBR）はPD 1.8±0.7、DLB 1.2±0.6、RBD 1.3±0.9であり、PDとDLBではRBDと比べ有意に集積低下を認めた。RBDにおいてSBRは年齢と負の相関を示し、OBとの間には相関を示さなかった。

【結論】RBDでは嗅覚同定検査よりもドパミン作動神経の評価によって、神経変性疾患への進展方向性が予測できる可能性が示唆される。

O-39.4
片頭痛の慢性化と大脳基底核の銅沈着

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【背景と目的】近年、片頭痛病名が注目されており、頭痛病分類第3版改訂（ICHD-3）で片頭痛の関連疾患で一つのサブタイプとして再分類された。臨床的治療や病態の追究のため大脳基底核の銅沈着像を標的として解析するため、片頭痛の慢性化における銅沈着像の検討が重要である。片頭痛の慢性化の定義は未だ明らかであるが、反復性頭痛症候群と診断されたものに該当すると考えられる。

【対象】当院通院中にICHD-3で診断されたEM（38名、53.7±7.2歳）、CM（43名、46.1±7.9歳）、224名で薬物乱用頭痛のMOHを含む全て。女性、対象群として反復性頭痛症候群（1例）、22名（平均7.5±38歳）。

【方法】血清銅を測定し、15T-MRI（GE healthcare）により、Proton density画像とT2強調画像を取得し1mmスライスで画像、ワークステーション上で、神経放射線科専門医がブラインド下に検査、頭蓋線骨、緊張帯、尾状核、尾状核、尾状核体、尾状核体、尾状核体、耳核でRCHを設定し、PDとT2の信号値を測定することで、銅沈着を反映するT2値を計算した。

【結果】CM群（12人、62.7±6.3歳）と前頭葉、尾状核体、頭頂辺縁野、赤核で銅沈着が検出された。CM群（12人、62.7±6.3歳）と前頭葉、尾状核体、頭頂辺縁野、赤核で銅沈着が検出された。CM群（12人、62.7±6.3歳）と前頭葉、尾状核体、頭頂辺縁野、赤核で銅沈着が検出された。

【結論】頭痛のCMおよびMOHの大脳基底核において、銅沈着の先進がみられ、病態と関連の可能性が示唆された。
口演

5月23日（土）
O-4.13
非聴覚難聴アルツハイマー病患者における認知機能と末梢インスリン代謝の解析
(九州大学大学院医歯学総合研究科 神経内科)

1. 九州大学病院脳神経疾患センター, 2. 私立調理師協会
1. 九州大学病院脳神経疾患センター, 2. 私立調理師協会

O-4.22
抗MAG抗体陽性ニューロパーキーにおけるアドヒステロフィー周辺分子の分布異常
(名古屋大学大学院 医学部 腎臓内科学)

1. 名古屋大学大学院医学部 腎臓内科学
2. 甲府市立市民病院

O-4.42
慢性炎症性脱性多発神経炎におけるヘルペスウイルス・ケモカイン受容体による研究
(山口大学大学院 医学研究科 神経内科)

1. 山口大学大学院 医学研究科 神経内科
2. 甲府市立市民病院
3. 甲府市立市民病院

O-4.23
Sera from CIDP patients disrupt blood–nerve barrier via activation of rho-kinase
(和歌山大学大学院 医学研究科 神経内科)

1. 和歌山大学大学院 医学研究科 神経内科
2. 和歌山大学大学院 医学研究科 神経内科
3. 和歌山大学大学院 医学研究科 神経内科

O-4.12
合成GM1dimerに対する抗GM1抗体の反応性の解析Guillain-Barré syndromeにおける検討
(岐阜大学医学部 神経内科)

1. 岐阜大学医学部 神経内科
2. 岐阜大学医学部 神経内科
CSF derived exosomal microRNA profiles in patients with Parkinson's disease

1Division of Neurology, Department of Neuroscience & Sensory Organs, Tokushima University Graduate School of Medicine. 2Department of Neurology, Sendai Nishitaka Hospital. 3Tokufuji Hasegawa1, Naoto Sagawa, 4Aki Kikuchi, 5Ryu Oshirina, 6Shun Yoshida1, 7Atsushi Takeda, 8Masashi Aoki

Objective: The clinical diagnosis of Parkinson's disease (PD) entirely relies on medical history, neurological findings and the response to dopaminergic replacement therapy. However, for development of disease-modifying therapy, early diagnosis by objective laboratory test is urgently needed. The aim of this study is to characterize the CSF derived, exosomal microRNA (miRNA) profiles in PD patients and healthy controls, to determine its usefulness as biomarkers for PD.

Methods: The study cohort consisted on sex and age matched healthy controls (n=3; mean age 67.7, 2 males and 1 female) and patients (n=8; mean age 63.9; 3 males and 2 females) who fulfilled clinical diagnostic criteria of PD. Exosomes were isolated from frozen samples of CSF using ExoQuick kit (BioSciento). After purification of miRNA from exosome, Agilent human microRNA Microarray v20 (Agilent Technologies) was used to identify miRNAs expressed at high level in CSF derived exosome in PD patients versus control. Total RNA (100 ng per sample) was hybridized to the microarrays. Predicted miRNA-mRNA interactions were taken from TargetScan 4.1 and miRDB ver 3.3 and DIANA LAB. Results: We identified that the expression of hsa-miR-21, which specifically binds the miRNA of poly-like kinase (PLK2), a known ε-synuclein disease, was significantly higher in PD patients compared to controls. Conclusion: CSF derived, exosomal miRNA expression profiles may provide supplemental biomarkers for diagnosing PD.

Cerebrospinal fluid cytokine levels in multiple system atrophy patients

1Department of Neurological Therapeutics, Neurological Institute, Graduate School of Medical Sciences, Kyushu University. 2Department of Neurology, Tokyo Medical and Dental University School of Medical Sciences, Kyushu University. 3Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University. 4Ryo Yamashita1, Hiroshi Yamaguchi, 5Akio Hikawa, 6Takaya Matsushita, 7Jun-ichi Kira

Purpose: To discover cytokines that have influences on disease activity and brain atrophy in the cerebrospinal fluid (CSF) of multiple system atrophy (MSA) patients. [Methods] We measured 27 cytokine/chemokines among 20 patients with cerebellar dysfunction subtype of MSA (MSA-C) and 12 patients with hereditary spinocerebellar degeneration (hSCD) by multiplexed fluorescence bead-based immunoassay. We also measured the size of CSF and cerebrospinal from MRA. [Results] MSA-C patients were older than hSCD patients (MSA-C: 59.1 yrs vs. hSCD: 44.7 yrs) and the disease duration were shorter in MSA-C than hSCD (MSA-C: 25.2 months vs. hSCD: 125.9 months). Among 27 cytokines, IL-1β (p=0.0034), IFN-γ (p=0.0034) and IL-8a (p=0.0001) were increased in MSA-C patients compared with hSCD patients. Interestingly, there was no negative correlation between CSF MCP-1 levels and disease duration in MSA-C patients (r=0.008, R=0.07). Brain MRI also revealed positive correlation between the size of putamine bases and CSF IL-6 levels in MSA-C patients (p=0.0074, R=0.49). [Conclusions] These data suggested the involvement of inflammatory mechanisms in the early course of MSA-C. Anti-inflammatory therapy for early MSA-C patients may be useful to attenuate the neuronal damages.

Hypoxia might be linked to inferior temporal thickness in Parkinson’s disease

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Objective: Severe hypoxia is thought to be a prodromal symptom of cognitive decline in Parkinson's disease (PD). Recently, several evidences have suggested that the early presence of mild cognitive impairment (MCI) in PD patients with PD is associated with a faster rate of grey matter thinning in various cortical regions, including the inferior temporal lobe and medial occipital lobe. In this study, we aim to reveal the correlation between cortical thickness and hypoxia in PD.Methods. We enrolled 28 patients with PD, without any cognitive decline (age 63.8 ± 8.6, Males:17). Participants olfactory performance was assessed using the OSIT-J. We performed 3-T crani-MRI and examined the relationship between olfactory impairment and global and regional gray matter atrophy, thickness, diffusion tensor imaging (DTI), and in order to estimate white matter integrity using quantitative neuromatological approaches. Results. Correlating the rate of changes of cortical thickness and white matter integrity with the results of OSIT-J scores, revealed significant thinning of left inferior temporal lobe (β = 0.14385, p = 1.05-13.484) decrement of fractional anisotropy at the left hippocampus white matter (β = 0.090.95, CI = 85.277) were associated with olfactory dysfunctions, as similar to those of PD patients with MCI.Conclusions. These results indicated that the presence of severe hypoxia in PD patients is associated with abnormalities in various lesions, including inferior temporal lobe and hippocampus white matter; this is also evident in PD patients with MCI.

Patterns of cognitive decline in Parkinson’s disease

1Department of Behavioral Neurology & Cognitive Neuroscience, Tokushima University Graduate School of Medicine. 2Department of Neurology, Tokushima University Graduate School of Medicine. 3Department of Occupational Therapy, Yamagata Prefectural University of Health Sciences. 4Department of Clinical Neuroscience, Yamagata University Graduate School of Medical Sciences. 5Department of Diagnostic Radiology, Tokushima University Graduate School of Medicine. 6Department of Nuclear Medicine and Radiology, Institute of Development, Aging and Cancer, Tokushima University. 7Sendai Nishitaka National Hospital. 8International University of Health and Welfare. 9Tokushima Pharmaceutical University. 10Fumi Kida, Yohisuki Fukushima, 11Yoshida Nakai, 12Akio Kikuchi, 13Takuma Hasegawa, 14Kazuhiro Hirayama1, 15Kiyoko Suzuki, 16Masashi Aoki, 17Yasuto Inoyama, 18Shoki Takashita, 19Hiroshi Fukuda, 20Atsushi Takeda, 21Etsuko Mori

Objective: Cognitive impairment is common in patients with Parkinson’s disease (PD). The Movement Disorders Society (MDS) published the criteria for PD with mild cognitive impairment (PD-MCI), but longitudinal evidence for the applicability of this criteria is limited. We performed this study to clarify whether the MDS-MCI criteria is suitable for longitudinal assessment of cognitive DN in PD.

Methods: Data of 80 PD patients who did not have dementia at baseline and completed 3-year follow-ups were retrospectively analyzed. To validate the applicability of the PD-MCI criteria, we performed one-way ANOVA of the cognitive status in the PD-TTC data.

Results: At baseline, 20 patients were classified as cognitively normal PD, and 17 patients fulfilled PD-MCI level criteria. At follow-up, 28 patients were classified as cognitively normal group, 12 patients were classified as PD-MCI, and 6 patients were classified as PD. Dementia conversion rate was much higher in the PD-MCI group compared with that in the cognitively normal PD group (33% vs 17%) at 3 years. 12 of 17 patients similarly diagnosed as PD-MCI returned to cognitively normal group at follow-up although cortical metabolites abnormalities in these patients were maintained. Conclusion: Current PD-MCI criteria may be useful in predicting dementia in PD. However, careful attention to cognitive reversion phenomenon; probably reflecting regression effect is needed.

Long-term follow-up of microbleeds in patients with acute cerebral infarction

1Dept. of Neur. Japanese Red Cross Nagoya Diai Hosp. 2Kazunori Yashuri, Tatsuo Ueda, Chisato Ogawa, 3Kento Ohji, Koutaro Oiwa, Mari Miyagawa, Kuniyuki Endo, Koyo Tsujikawa, Sao Morozumi, Shigenori Kato, Yasuhiro Hasegawa

【目的】 微小出血の再発予防で抗血栓療法を使用すると頭蓋内出血が起こることがある。これは、疾病によるものか薬物療法によって誘発された病痛なのかを判断するためには、microbleedsのMIBSは脳深部血栓症の映像を伴わない病態であり、その長期経過を観察する技術を明らかにした。

【方策】 2009年当院に入院治療した急性脳梗塞患者48名のうち28名でMRIで強調画像撮影で病变を全例検査し、疫学的に入院後25名のMRIの数を変動を検討する。微小出血の再発は、前回と同様に無変化群4例、5例に変化が増加して3例 viz3%の頭盖内出血を25例中4例に認め、頭蓋内出血の再発のリスクを明確にし、再発リスクの新たな予防と治療の新しい視点を示すと考える。

【結果】 5年後のMIBスコアの増加群は29例で、5年後においてMIBスコアの増加群は25例中4例に認め、頭蓋内出血の再発のリスクを明確にし、再発リスクの新たな予防と治療の新しい視点を示すと考える。

【考察】 微小出血5年後のMIBスコアの増加速度を換算して、抗血栓療法非使用者では増加したため、抗血栓療法使用者にはDAPTをようやくで微小出血を誘発する症例があると考える。

【結論】 微小出血の再発予防で抗血栓療法を使用すると頭蓋内出血が起こることがある。これは、疾病によるものか薬物療法によって誘発された病痛なのかを判断するためには、microbleedsのMIBSは脳深部血栓症の映像を伴わない病態であり、その長期経過を観察する技術を明らかにした。
CYP2C19 polymorphisms and adjunctive clopidogrel in patients taking clopidogrel

Saitama Medical University International Medical Center, Department of Neurology and Cerebrovascular Medicine

[1] Dr. Кролфлорив Расселла Хеверсона было названо. Кроме того, CYP2C19 и CYP2C9 используются в 2D5 и 2D6 фермах, которые участвуют в метаболизме стрессов.


[3] Genotype-phenotype correlation with FUS-TLS-linked familial ALS cases in Japan

東北大学医学部 神経内科

[4] Objective: To describe the properties in Japanese case series with familial ALS (FALS) carrying fusion. In a study of CYP2C19 genotypes and FUS-TLS gene expression as a marker for pharmacological methods. This study included more than 134 unrelated Japanese autonormal familial (AD) FALS pedigrees. For all probands, we screened copper/zinc superoxide dismutase 1 (SOD1) gene and found 31 SOD1-linked pedigrees. We then screened all exons of the FUS-TLS gene out of cases without SOD1 mutations. Clinical data including age at onset, site of onset, duration of symptoms, and cognitive function were collected. Results: We found 9 different mutations in 11 independent families with FUS-TLS mutations were the second most common in this cohort (9%). Most of the FUS-TLS-linked cases in this cohort showed early onset, predominantly onset from bolivar to upper spinal, and short duration of the disease. Both of two probands with pRS212 mutation exhibited late onset, predominantly lower limb onset, and long disease duration. These results were consistent with only a few cases with FUS-TLS mutations. The case with pG497Alx527 mutation also showed unusual phenotypes: extremely early onset and complicated mental retardation. The case with pRS212 presented ALS with frontotemporal dementia. Conclusion: Since FUS-TLS gene occupies the second most common mutational gene in AD FALS cases in Japan, screening of this gene is highly recommended, especially in cases without SOD1 mutations. Although early-onset and rapid progression are the characteristics of our overall cases, there are some cases with mild phenotype or mental retardation.

[5] Chronic Metformin Preconditioning Provides Neuroprotection in Ischemia Reperfusion

Department of Neurology, Qindao Medical University, Nanjing Medical University, China

Purpose: Accumulating evidence suggests that chronic metformin preconditioning offers potent neuroprotective effects against ischemic stroke. However, the underlying mechanisms remain largely unknown. We tested the hypothesis that chronic preconditioning with metformin conferred neuroprotection via suppression of nuclear factor kappa B (NF-кx)-mediated inflammatory pathways. Methods: Eighty male Sprague-Dawley rats were treated with vehicle or metformin (50 mg/kg, daily; p) for 3 weeks and were subjected to permanent middle cerebral artery occlusion (pMCAO). At 24 h (acute phase) and 96 h (subacute phase) after pMCAO, the infarct volume and neurological deficits were evaluated. The activity of NF-кx and the levels of its downstream proinflammatory cytokines were detected at 24 h after pMCAO. Results: Our results showed that chronic metformin preconditioning significantly reduced infarct volume and improved neurological deficits compared to the control group. The suppression of NF-кx activity, which was accompanied by a reduction in tumour necrosis factor-α, interleukin (IL)-1β, IL-6 and induced nitric oxide synthase in the peri-infarct regions at 24 h, after pMCAO. The microglia and astrocytes induced by pMCAO were also ameliorated by chronic metformin preconditioning. Conclusions: We provide the first evidence that suppression of NF-кx-mediated inflammatory pathways may represent one potential mechanism underlying the neuroprotective effects of chronic metformin preconditioning. And, metformin may have a practical clinical use for stroke prevention and treatment.

Chronic Metformin Preconditioning Provides Neuroprotection in Ischemia Reperfusion

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[6] 筋膜性狭帯状硬化症患者における次世代シーケンサーサービスを用いた構築異常解析

東京大学病院 神経内科

Objective: The major clinical-phenotypic, molecular and neuropathological profiles were suggested between wildtype mice and amyotrophic lateral sclerosis (ALS) patients. A randomized double-blind trial of methylphenothiazine (MPO) is under analysis in Japanese ALS patients. We aimed to examine whether MPO treatment improved wildtype mouse motor neuron disease.

METHODS: After the symptom onset at postnatal 34 weeks, wildtype mice received MPO (or 30 mg/kg, 100 mg/kg or 200 mg/kg) vehicle (or 100 mg/kg) daily for 4 weeks in intraperitoneal administration in a blind fashion. Symptomatic and neuropathological changes were compared among 3 groups. Vitamin B12 deficiency was used in the experiments, the skeletal muscle and the spinal cord were measured in 3 experimental groups and untreated normal littermates (5=5).

RESULTS: Higher dose MPO treatment delayed progression of hindlimb muscle weakness (P<0.001) and hindlimb muscle weight (P<0.001). Furthermore, preserved degeneration atrophy in the hindlimb muscle (P<0.001) and autophagic degradation in the muscleatocnautic nerve (P<0.001) compared to vehicle. The mean number of cervical motorneurons was increased at 20% in the high-dose MPO group compared to vehicle. Vitamin B12 levels were elevated 6-fold in the serum, 5-fold in the kidney muscle and 4-fold in the spinal cord of high-dose MPO-treated wildtype mouse compared to vehicle and untreated littermates.

CONCLUSIONS: This study is expected to provide supportive neuroprotective effects of ultra-high dose MPO on neurodegenerative degenerations of motor neuron in wildtype mouse. This method might have disease-attenuating benefits in ALS patients.
高齢者の軽度パーキンソン病の割検の検討

【目的】
高齢者の軽度パーキンソン病患者の脳の組織検査を行ない、生前の病状と一致する生前の現状を明らかにすることを目的とした。

【対象】
生前の診断を高齢の軽度パーキンソン病とする1例。

【方法】
1. 1.1 生前の診断を高齢の軽度パーキンソン病とする1例。
1.2 生前の診断を高齢の軽度パーキンソン病とする1例。

【結果】
1. 生前の診断を高齢の軽度パーキンソン病とする1例。
2. 生前の診断を高齢の軽度パーキンソン病とする1例。

【考察】
1. 生前の診断を高齢の軽度パーキンソン病とする1例。
2. 生前の診断を高齢の軽度パーキンソン病とする1例。

【まとめ】
生前の診断を高齢の軽度パーキンソン病とする1例。

O-46-2
パーキンソン病患者における姿勢異常と運動障害の関連

日本医科大学病院 神経内科
○石井利子, 森田真由, 林原由美, 坂本伸弘, 松本隆生

【目的】
パーキンソン病患者における姿勢異常と運動障害の関連を検証する。

【方法】
1. パーキンソン病の診断 методの研究
2. パーキンソン病の診断方法の研究

【結果】
1. パーキンソン病の診断方法の研究
2. パーキンソン病の診断方法の研究

【考察】
1. パーキンソン病の診断方法の研究
2. パーキンソン病の診断方法の研究

【まとめ】
パーキンソン病の診断方法の研究

O-46-3
パーキンソン病患者における姿勢異常と運動障害の関連

日本医科大学病院 神経内科
○石井利子, 森田真由, 林原由美, 坂本伸弘, 松本隆生

【目的】
パーキンソン病患者における姿勢異常と運動障害の関連を検証する。

【方法】
1. パーキンソン病の診断方法の研究
2. パーキンソン病の診断方法の研究

【結果】
1. パーキンソン病の診断方法の研究
2. パーキンソン病の診断方法の研究

【考察】
1. パーキンソン病の診断方法の研究
2. パーキンソン病の診断方法の研究

【まとめ】
パーキンソン病の診断方法の研究

O-46-4
ドライビングアシスト離脱状態(DDAW)とドライビングの検討

【目的】
ドライビングアシスト離脱状態(DDAW)の検討

【方法】
ドライビングアシスト離脱状態の検討

【結果】
ドライビングアシスト離脱状態の検討

【考察】
ドライビングアシスト離脱状態の検討

【まとめ】
ドライビングアシスト離脱状態の検討

O-47-1
脳卒中上肢麻痺に対する反復治療磁気刺激療法(TMS)の有効性の検討

【目的】
脳卒中上肢麻痺に対する反復治療磁気刺激療法(TMS: transcranial magnetic stimulation)の有効性を検討する。

【方法】
1. 対象: 脳卒中上肢麻痺患者
2. 平均年齢: 65歳
3. 平均体重: 65kg
4. 平均BMI: 25
5. 平均TMS療法: 3回

【結果】
1. 反復治療磁気刺激療法(TMS)の有効性を示す。
2. 反復治療磁気刺激療法(TMS)の有効性を示す。

【考察】
反復治療磁気刺激療法(TMS)の有効性を示す。

【まとめ】
脳卒中上肢麻痺に対する反復治療磁気刺激療法(TMS)の有効性を示す。

O-47-2
Dual electrical stimulation improved upper limb paresis of patients with stroke

目的: Objective. We recently developed a dual electrical stimulation system that stimulates sympathetic muscles during shoulder flexion, elbow extension, wrist extension, and finger extension to improve motor functions of hemiparetic upper limbs. Here we investigated the effectiveness of this system in chronic stroke patients.

方法: Participants. The eight patients (male: female, 5: 3, mean age: 68.9 years) with chronic stroke received dual electrical stimulation.

Interventions. The patients undergoing dual electrical stimulation system underwent upper limb training for 60min per day, 5 days per week for 3 weeks.

Main Outcome Measures: Quantitative measures were assessed using the upper extremity component of Fugl-Meyer assessment (FMA), Wolf Motor Function Test (WMFT), Modified Ashworth Scale (MAS), Motor Activity Log (MAL) before and after intervention. Two sets of samples were obtained before and after the intervention to perform pre- vs. post-treatment comparisons of the FMA, WMFT, MAS, and MAL.

結果: All patients completed the training successfully using this system without any incidents or complications. The FMA score increased from 219.3 to 289.3 (p<0.05), the WMFT score decreased from 1059.3 to 779.3 (p<0.05). The mean MAS did not show the difference, and the MAL increased from 87 to 127 (p<0.05).

結論: In this study, our dual electrical stimulation system may be effective for upper limb paresis of patients with chronic stroke.
A survey of difficulties in taking medicine

Introduction: Patients with cerebrovascular disorders (CVDs) are sometimes unable to consume oral medications, resulting in inaccurate determinations about the effectiveness of treatment. This study aimed to analyse data on taking medicine through medical professionals, and extract the clinical problems in taking medicine.

Methods: Inhabitants taking medicine were defined as difficulties in swallowing medicine, especially needing it dissolving, and remaining medicines in the oral cavity and pharynx. A total of 90 car cases on CVDs were collected in different 9 cities. This study was supported by JSPS KAKENHI.

Results: Among the CVD patients with difficulties in taking medicine, drug remained were observed in the oral cavity in 60% patients, and in the pharynx in 30% Remaining drugs included orally disintegrating tablets, biologics, capsules, and powdered medicine. Of these patients, 28% required assistance in taking medicine. 65% reported partial assistance in 30 min. 62% patients took a 1500-mixed fluids. A number of swallowing was observed during prescribing in 46% of CVD patients with difficulties in taking medicine.

Conclusions: Even for the patients taking oral medication independently, they led difficult in taking medicine or drug remained in their oral cavity or pharynx. It is critical to observe the patients taking medicine regularly.

Cerebral artery dissection as a cause of convexity subarachnoid hemorrhage

Purpose: Convex subarachnoid hemorrhage (cSAH) defined as intraventricular bleeding restricted to the hemispheric convolutes, has several etiologies: reversible cerebral vasospasm syndrome, cerebral amyloid angiopathy, and internal carotid artery stenosis/occlusion. However, it remains uncertain whether cerebral artery dissection causes cSAH. The aim of this study was to clarify the association between cSAH and cerebral artery dissection.

Methods: We retrospectively investigated patients diagnosed with ischemic stroke or transient ischemic attack caused by cerebral artery dissection and admitted to our hospital between 2006 and 2013. Participants were selected from those presenting with spontaneous cSAH. Data referring to demographics, medical history, symptoms, imaging analysis, and treatment were collected.

Results: Eight-two patients were diagnosed with ischemic stroke caused by cerebral artery dissection. The affected arteries were the internal carotid artery in 9 patients, anterior cerebral artery (ACA) in 12, middle cerebral artery (MCA) in 12, vertebral artery in 3, posterior cerebral artery in 2, and posterior inferior cerebellar artery in 4. The dissected vessel was MCA in 4 cases and ACA in the remaining 2 with a cSAH frequency of 37% (4/11) and 17% (2/12) in ACA dissection cases, respectively. Artery dissection in the vertebrobasilar arterial system was not responsible for the cSAH (8/48).

Conclusion: SAH occurring intracranial artery dissection in the anterior circulation is not a rare but a self-limiting process.
Percygenosis in spinal cord microvasculature of a rat model of ALS

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Objective: We have utilized telemetry fish to model human neurological disorders. In this study, we described the similarity and difference between teletest and human by examining dopamine system, cerebellum, red nucleus and cerebrospinal fluid (Method). We compare neuroanatomy and neurophysiology of teletest and human. Furthermore, we examine the possibility to model human neurodegenerative disorders and other diseases by using these teletest. (Result) The anatomy of dopamine system was already described, but the existence of neuronal cluster that corresponds to the substantia nigra is not clear. We have produced a lot of Parkinson’s models by medaka and zebrafish, and we found a cluster that is vulnerable to various toxins and genetic manipulation. Thus this cluster may correspond to human substantia nigra. Teletest cerebellum lacks deep cerebellar nucleus. However, by using optogenetics, we disclosed the existence of similar functional map between teletest and human. The presence of red nucleus has been not confirmed in teletest. We revealed a structure that received contralateral afferent from the cerebellum and projected contralateral afferent to the spinal cord. This structure anatomically fulfills the demand of red nucleus. (Conclusion) Small teletest species are small but as vertebrates they share very similar neuroanatomy and neurophysiology with us human. Furthermore, there have been a lot of disease models that mimic human diseases. By utilizing the great merit of telemetry system and small size, these animal models will be developed further in the future.

The novel mutations of the CLCN1-1 and SCN4A in non-dystrophic myotonia

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Purpose: We aimed to examine the molecular, clinical and histopathological characteristics of 13 patients with NMDS. Methods: We collected information on the clinical characteristics and detailed skeletal muscle biopsy features of 13 patients with NMDS. Sequencing results of CLCN1 gene in patients, having clinical features and muscle pathology indicative of NMDS. Results: CLCN Mutations were identified in 9 patients, encompassing 2 missense (p.C277R, p.A287T), 3 nonsense (p.R254X, p.Q386X, p.R233X), 2 deletions mutations (c.233delG and c.214_215delAG). Mutations c.1262insC, p.R338X, p.C277R and p.A208T were detected in our study were reported. Two patients were homozygote and six patients were compound heterozygote. We detected 3 novel missense mutations (p.182R, G716R, R6198H) occurred in exon 24 and 1 missense mutation (V1228D) in exon 22 in SCN4A, which were located in hot-spot region and associated with PMD. In contrast to the previous researches, secondary dystonia, joint contracture and accompanied with cardiac abnormal were showed in some patients. In routine pathological examination, ATPase of fibre subtypes demonstrated a predominance of type 2A fibres, a complete absence of type 2B muscle fibres in patients with CLCN1 mutations. Conclusion: Skeletal muscle biopsy is an essential tool for making a definite and differential diagnosis of NMDS. Novel mutations in CLCN1-1/SCN4A were detected, and the spectrum of CLCN1-1/SCN4A mutations known to be associated with NMDS was expanded.
O-50.3
Long-term outcome of chronic progressive neuro-Behçet's disease

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Objective: Chronic progressive neuro-Behçet’s disease (CPNB) is characterized by progressive deterioration leading to disability and death. The purpose of the patients treated with high doses of steroids, immunosuppressants, or cyclophosphamide has been mainly focused on the prevention of relapses. There is limited evidence that CPNB patients treated in the long-term outcome remain stable. We therefore explored the effects of various treatments on the prognosis.

Methods: Thirty-five patients, who met the international classification criteria for BD and developed chronic progressive neurologic manifestations after flare were followed up. The duration of illness at the time of presentation in patients with severe disability or severe disability of brainstem state examined by English-Miller analysis and Cox proportional hazard model.

Results: Twenty-five of 35 patients with CPNB had the re-treatment. Among 25 patients, seven died and 16 patients reached to be stable. By contrast, among the 8 patients without re-treatment, six patients died and 2 patients reached to be stable.

Conclusion: The re-treatment of CPNB, not high doses of steroids, immunosuppressants or cyclophosphamide is effective to prevent the progression of CPNB.

O-50.4

PBF and hyperthermia of 17 cycles in 20 patients

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Purpose: The effect of prostatic brachytherapy (PBF) and hyperthermia of 17 cycles in 20 patients was to report the effectiveness and safety of this treatment.

Methods: Twenty patients with prostate cancer were treated with PBF and hyperthermia of 17 cycles. The effectiveness of the treatment was assessed by the changes in the PSA level and the safety of the treatment was assessed by the occurrence of adverse events.

Results: The PSA level decreased significantly after the treatment and the adverse events were mild and well managed.

Conclusion: PBF and hyperthermia of 17 cycles is an effective and safe treatment for prostate cancer.

O-51.1
Transcription factor 4 variants in schizophrenia: Investigation of age at onset

University Tunusi Abdul Rahman

Purpose: Age at onset (AAO) is a known prognostic indicator for schizophrenia and is correlated to the age at which symptoms develop. The purpose of this study is to investigate whether certain transcription factor (TCF) gene variants are associated with schizophrenia or AAO remains to be elucidated. The current study examines the effect of TCF4 variants on AAO of schizophrenia.

Methods: This study consisted of 322 patients with schizophrenia meeting the DSM-IV criteria. Six TCF4 single nucleotide polymorphisms (rs296647, rs5766, rs2958182, rs996676, rs1041120 and rs753286) were genotyped using Taqman® SNP Genotyping by Assays method. Association of AAO with each variant was investigated using analyses of variance (ANOVA).

Results: There was an interaction between TCF4 variants with AAO. Among the six variants rs296647 (p = 0.024) and rs7666 (p = 0.021) were significantly associated with earlier AAO. Patients with AA genotype of rs296647 and CT genotype of rs7666 were demonstrated to have lower average AAO. Our finding suggested an age-dependent influence of specific variants. Individual risk genotype may influence cognitive performance in schizophrenia in an age-specific manner.

Conclusions: This finding suggests that TCF4 variants rs296647 and rs7666 are associated with AAO owing to the role of TCF4 in cognition. Future studies incorporating cognitive performance assessment could provide unique insights.

O-51.2
Long-term effects of botulinum toxin type A on hemifacial spasm

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Objective: To evaluate the long-term effects of botulinum toxin type A (BTX-A) on hemifacial spasm (HFS). The BTX-A treatment efficacy was assessed at 1 and 2 years after treatment.

Methods: Forty-two patients with HFS were enrolled in this study. The duration of HFS was 2-15 years. The treatment was repeated every 3 months. The patients were followed-up for 1 and 2 years after the last injection.

Results: The treatment efficacy was evaluated by subjective and objective criteria. The treatment efficacy was sustained for more than 2 years in most patients. The mean duration of symptom improvement was 15 months.

Conclusion: BTX-A is an effective and safe treatment for HFS. The treatment efficacy is sustained for more than 2 years in most patients.

O-51.3
Predictive risk factors for neurologic sequelae after carbon monoxide poisoning

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Objective: To identify the predictive risk factors for neurologic sequelae after carbon monoxide (CO) poisoning.

Methods: This study was a prospective, observational study. The study period was between November 2016 and September 2018. The patients were classified into two groups: those with neurologic sequelae and those without.

Results: The predictive risk factors for neurologic sequelae included age, gender, and the duration of hypoxia exposure.

Conclusion: The predictive risk factors for neurologic sequelae after CO poisoning include age, gender, and the duration of hypoxia exposure.

O-51.4
Mitochondrial Polyporphosphinylphosphorylated by PINK1 Promotes Parkinnon relocalization

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Background: The kinase PINK1 and the E3 ubiquitin ligase Parkin participate in mitochondrial quality control. The phosphorylation of Ser63 of Parkin’s ubiquitin-like domain by PINK1 stabilizes Parkin activation and translocation to damaged mitochondria, which induces mitochondria generating polyubiquitin chain. However, Parkin phosphorylation is insufficient for Parkin mitochondrial translocation. Phosphorylation of Ser63 of Parkin’s ubiquitin-like domain by PINK1 stabilizes Parkin activation and translocation to damaged mitochondria, which induces mitochondria generating polyubiquitin chain. However, Parkin phosphorylation is insufficient for Parkin mitochondrial translocation. Phosphorylation of Ser63 of Parkin’s ubiquitin-like domain by PINK1 stabilizes Parkin activation and translocation to damaged mitochondria, which induces mitochondria generating polyubiquitin chain. However, Parkin phosphorylation is insufficient for Parkin mitochondrial translocation. Phosphorylation of Ser63 of Parkin’s ubiquitin-like domain by PINK1 stabilizes Parkin activation and translocation to damaged mitochondria, which induces mitochondria generating polyubiquitin chain. However, Parkin phosphorylation is insufficient for Parkin mitochondrial translocation. Phosphorylation of Ser63 of Parkin’s ubiquitin-like domain by PINK1 stabilizes Parkin activation and translocation to damaged mitochondria, which induces mitochondria generating polyubiquitin chain. However, Parkin phosphorylation is insufficient for Parkin mitochondrial translocation. Phosphorylation of Ser63 of Parkin’s ubiquitin-like domain by PINK1 stabilizes Parkin activation and translocation to damaged mitochondria, which induces mitochondria generating polyubiquitin chain. However, Parkin phosphorylation is insufficient for Parkin mitochondrial translocation. Phosphorylation of Ser63 of Parkin’s ubiquitin-like domain by PINK1 stabilizes Parkin activation and translocation to damaged mitochondria, which induces mitochondria generating polyubiquitin chain. However, Parkin phosphorylation is insufficient for Parkin mitochondrial translocation. Phosphorylation of Ser63 of Parkin’s ubiquitin-like domain by PINK1 stabilizes Parkin activation and translocation to damaged mitochondria, which induces mitochondria generating polyubiquitin chain. However, Parkin phosphorylation is insufficient for Parkin mitochondrial translocation.