2015年  口演部門 トピックス
基礎部門
AO-I-1

Gaucher disease model in medaka displays axonal accumulation of alpha-synuclein

Objective: Recent genetic studies have revealed that mutations in glucocerebrosidase (G Latinos), a causative gene of Gaucher disease (GD), are a strong risk for Parkinson’s disease (PD). However, its pathological mechanism leading to PD remains largely unknown. To investigate how GD mutations cause PD, we generated GD mutant medaka and analyzed their phenotype.

Methods: We generated GD mutant medaka by screening targeted artificial lesions in genes (TASL2G) library and identified beta mutant medaka by transgenic animals like edf (LATS2G). Results: We generated GD nonsense mutant (G Latinos) medaka completely deficient in glucocerebrosidase (G Latinos) activity. In contrast to the partial toxicity of human and mouse knockout (G Latinos) activity, G Latinos medaka survived for months, enabling us to analyze disease progression. G Latinos medaka displayed neurodegeneration in the dorsal root ganglia, neuronal cell death, and axonal accumulation in the peripheral nerves. Furthermore, the current study demonstrates that a G Latinos accumulation has minimal contribution to the pathogenesis of neurological GD in medaka.

AO-I-2

Sialylated IgG-Fc: A Novel Biomarker of CIDP

Department of Neurology, Hokuohkaki Neurological Hospital. Department of Medicine, National University of Singapore. Department of Neurology, Dokkyo Medical University.

Objective: Sialylation in Fc portion of IgG plays a crucial role in the pathogenesis of autoimmune diseases and the working mechanism of intravenous immunoglobulin (IVIG). We aimed to test whether IgG-Fc sialylation is a biomarker of disease activity for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Methods: By specific lectins for sialylation, galactosylation and agalactosylation, lectin enzyme assay and lectin blotting with pre-treatment of IDE were performed to compare the glycosylation levels of serum IgG-Fc in between patients of untreated CIDP (n=170) and normal control. In each group, 25 (n=25) were treated with untreated CIDP of different clinical severities, and ii) before and after IVIG treatment of patients with CIDP (n=12).

Results: Sialylation and galactosylation of IgG-Fc were significantly reduced in patients with CIDP than normal control subjects (p<0.001). Moreover, after IVIG treatment, levels of sialylated IgG-Fc significantly increased (p<0.001).

Discussion: Sialylation of IgG-Fc is reduced in CIDP. It is level correlated with clinical severity and increased after IVIG treatment. Sialylation as well as ratio of sialylated/agalactosylated IgG-Fc could be new biomarkers to monitor the disease severity and treatment status in CIDP.

AO-I-3

A new drug delivery system across the blood-brain barrier into brain

Department of Neurology and Neurological Science, Tokyo Medical and Dental University. Graduate School of Engineering, The University of Tokyo. Graduate School of Medicine, The University of Tokyo.

Objective: The development of a drug delivery system across the blood-brain barrier (BBB) into brain is a challenging problem to achieve effective target therapy in the central nervous system. We aim to develop an efficient BBB-crossing delivery system by utilizing a physiological glucose transport pathway.

Methods: We constructed a self-assembled supramolecular micelle integrated with glucose on its surface (Gc-micelle). We injected fluorescent-labeled Gc-micelle intravenously to BALB/c mice (female, 6-week old) and examined systemic distribution by fluorometric determination and immunohistochemical analysis in vivo. Moreover, we investigated the localization of Gc-micelle in mouse brain by intravital real-time confocal microscope and two-photon excitation microscope.

Results: Gc-micelle rapidly decreased from blood circulation and highly accumulated in brain (about 4% dose/gbrain in three days) in response to an increase of blood glucose concentration after a prior fasting condition. Gc-micelle was not accumulated in brain when we did not induce any change of blood glucose concentration. We observed the transport of Gc-micelle from blood vessel into brain parenchyma and identified the microglia and astrocytes.

Conclusion: Glucose-integrated micelle, a well-organized drug carrier, can efficiently cross the BBB upon intravenous administration at fasting condition and a subsequent increase of blood glucose concentration. Our BBB-crossing delivery strategy may enable to achieve an effective targeted therapy in the central nervous system.
2015年 口演部門トピックス
臨床部門
AO2-1

球状頭節症候群患者に対するリブプロリン酸塩経口剤長期使用の効果

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2. 名古屋大学高等研究院
3. JASMITT study group.
4. 横浜市立大学 医学科

結論

1. 背景 背景頭節症候群 (以下, SDMA) は過剰進行性の神経疾患であり、現在で確立された治療法はなく、緩髄性頭節症に対する薬剤のみの臨床研究において治療効果は観察されていない。軽症の症例においては、リブプロリン酸塩経口剤の有効性が示されている。本研究グループは、SDMAに有用なリブプロリン酸塩経口剤の治療法を提案する。

2. 方法 本研究は、SDMAに対するリブプロリン酸塩を用いた治療実験を目的とし、治療群、比較群を設定し、1年間の治療期間を想定した。治療群は、リブプロリン酸塩を経口投与し、比較群は、通常の病院での治療を行う。治療期間中、患者の日常生活をより良好とするために、リブプロリン酸塩を経口投与した。

3. 結果 約4年間の治療期間を経た後、比較群の生存率は10%を上回り、リブプロリン酸塩の経口投与により、死亡率が大幅に改善された。さらに、発病10年後の無発症期間における分野集団の治療法を検討した。早期治療介入のある治療法を用いた場合、治療開始後2年での生存率は61.2%であり、経口投与されたリブプロリン酸塩を用いた治療群の生存率は比較群の2倍以上であった。

AO2-2

Neurofascin 155 antibodies related to juvenile-onset CIDP with ataxia and tremor

1. Departments of Medicine, National University of Singapore, Singapore.
2. Departments of Physiology, National University of Singapore, Singapore.

Yuki Fukumoto, Yumako Miura, Anna Hu Yi Wong, Nobuhito Yuki

Background: We aimed to describe the clinical features of Japanese patients with chronic inflammatory demyelinating polyneuropathy (CIDP) associated with autoantibodies to neurofascin 155 (NF-155).

Methods: Enzyme-linked immuno-sorbent assay (ELISA) was used to identify antibodies to NF-155. Clinical features was obtained retrospectively and compared with antibodies-negative CIDP patients.

Results: Sera from 288 of 533 (57%) CIDP patients contained anti-NF-155 IgG4 antibody. However, ELISA, whereas neither patients with Guillain-Barré syndrome, multiple sclerosis, nor normal control subjects did (p < 0.001). Six patients (16%) had the onset under 20 years of age and were significantly younger than another 87 patients (p = 0.048). Twelve patients (52%) showed the acute-onset CIDP. Thirty-four percent of the patients had tremor and 77% had sensory ataxia (p = 0.002, < 0.001, respectively). Two patients showed multiple sclerosis-like lesions on brain MRI. Four of 17 (24%) antibody-positive patients had poor response to IVIG (p = 0.008).

Conclusions: Our results indicate that anti-NF-155 IgG4 antibodies are associated with a subgroup of juvenile-onset CIDP patients with sensory ataxia and tremor. Autoantibodies to NF-155 are thus potential biomarkers to differentiate typical CIDP, and characterized by a poor response to IVIG.
2015年  ポスター部門トピックス
基礎部門
AP-01-1 Passive transferred NMO rat model with high affinity mouse anti-AQP4+ antibody
1Department of neurology, Tohoku University Graduate School of Medicine.
2Department of Multiple Sclerosis Therapeutics, Tohoku University Graduate School of Medicine.

Background We previously reported the passive transferred model with anti-AQP4 Abs passed from SD rats to mice is an NMO model but the astrocyte pathology was quite mild. The purpose of this study was to evaluate the pathological feature of passive transferred NMO rat model with high affinity mouse anti-AQP4 antibody in NMD rat model.

Methods To determine the pathological feature of passive transferred NMO rat model with high affinity mouse anti-AQP4 antibody in NMD rat model.

Results NMD rat model was confirmed by lack of myelination and demyelination in brain and spinal cord at E18. Gallyas silver-stained brains were stained for NMD rat model and the characteristics of NMD rat model were observed.

Conclusion Passive transferred model with high affinity mouse anti-AQP4 antibody in NMD rat model is a useful model for NMO research.

AP-01-2 Effects of STN and GPi stimulation to primate striatal interneuron
1Department of Neurology, Juntendo University School of Medicine.
2Department of Research and Therapeutics for Movement Disorders Juntendo University School of Medicine.

Background The effect of STN and GPi stimulation to primate striatal interneuron is not well known. The object of this study is to investigate the effect of STN and GPi stimulation to primate striatal interneuron.

Methods and Results In vivo single-unit recordings were performed in the primate striatum in the presence of STN and GPi stimulation. Single unit activity of the interneurons was recorded in the presence of STN and GPi stimulation. The effect of STN and GPi stimulation to the interneurons was observed.

Conclusion The results of this study showed that STN and GPi stimulation to the primate striatal interneuron is effective for the treatment of movement disorders.

AP-01-3 Distinct patterns of neuronal and glial TDP-43 inclusions in motor cortex of ALS
1Department of Pathology, Brain Research Institute, University of Niigata.
2Department of Neurology, Brain Research Institute, University of Niigata.

Background TDP-43 is a major disease protein in ALS. Two distinct distribution patterns of TDP-43 immunoreactive inclusions in brains of patients with ALS have been noted. One type I inclusions are mainly localized to the pyramidal motor system, whereas in type II brains widespread occurrence of the inclusion is evident. To clarify TDP-43 pathogenicity in the motor cortex of both types of ALS we performed morphological analysis.

Methods We used histology sections of the motor cortex of autopsied 8 and 10 patients with ALS in whom the inclusions were distributed as the types I and II patterns, respectively. We performed double labelling of in situ hybridisation for TDP-43 mRNA and immunohistochemistry for TDP-43.

Results There were no differences in the density per unit area of both patterns in ALS patients. The density of TDP-43 mRNA was higher in type II patterns than in type I patterns.

Conclusion TDP-43 mRNA in type II is involved much frequencies in TDP-43 cellular pathology than those in type I pattern, even though glia in both types are involved equally. This evidence indicates notwithstanding when considering the variability of the protein propagation mechanism underlying ALS.

AP-01-4 Astrocye-derived TGF-beta1 accelerates disease progression in ALS mice
Department of Neuroscience and Pathobiology, Research Institute of Environmental Medicine, Nagoya University.

Background TGF-beta1 is a pleiotropic cytokine that is involved in the progression of neurodegenerative diseases. Our previous study demonstrated that TGF-beta1 accelerates disease progression in ALS mice.

Methods We generated TGF-beta1 transgenic ALS mice and evaluated the effect of TGF-beta1 on disease progression in these mice.

Results TGF-beta1 transgenic ALS mice showed more rapid disease progression than wild-type ALS mice.

Conclusion TGF-beta1 accelerates disease progression in ALS mice and may be a potential therapeutic target for slowing disease progression in ALS.

AP-01-5 Development of tau imaging probes using the mouse model of taupathy
1Chiba University Department of Neurology.
2National Institute of Radiological Sciences.

Background Tauopathy is a misfolded protein disorder that is associated with various neurological diseases. The objective of this study was to develop tau imaging probes using the mouse model of taupathy.

Methods We generated a tauopathy mouse model using a transgenic mouse overexpressing mutated tau protein and evaluated the suitability of the tau imaging probes using this mouse model.

Results The tau imaging probes showed high specificity for the tauopathy mouse model and were useful for the diagnosis and monitoring of tauopathy.

Conclusion The tau imaging probes developed in this study are promising tools for the early detection and treatment of tauopathy.
2015年 ポスター部門トピックス 臨床部門
AP02.2  
筋萎縮性側索硬化症患者の発症・進展様式の検討

【目的】筋萎縮性側索硬化症（ALS）の発症は様々である。ALSの発症・進展様式を自覚症状にて調査し、その後の自然進行をみた。

【方法】ALS患者14例を対象に、発症・進展様式の調査を行った。

【結果】発症時年齢39±18歳、発症から診断までの期間11±7年、発症から進展までの期間12±7年であった。発症時症状は、難聴、筋力低下、運動神経障害、小脳症候群、意識障害など多種多様であった。

【考察】ALSの発症・進展様式は個体差が大きく、発症から進展までの期間は10年以内から数十年までと幅広い。

AP02.4  
高齢者のてんかん発作状態-臨床的症状と背景因子について

【目的】発症の原因やてんかん発作状態の改善をめざして、高齢者のてんかん発作状態を検討することを目的とした。

【方法】高齢者120名を対象に、てんかん発作状態の背景因子や治療の有効性を検討した。

【結果】高齢者のてんかん発作状態は、発症部位や治療の有効性が異なることがわかった。

【考察】高齢者のてんかん発作状態の改善には、個々の背景因子を考慮することが重要である。

AP02.5  
Facilitating SMA using a NIRS-mediated neurofeedback improves postural stability

【目的】SMAにおける動的支持動作の改善にNIRS-mediate neurofeedbackを行うことで改善するかを検討した。

【方法】SMA患者10名を対象に、NIRS-mediated neurofeedbackを用いて動的支持動作の改善を評価した。

【結果】NIRS-mediated neurofeedbackを用いることで、動的支持動作の改善が見られた。

【考察】NIRS-mediated neurofeedbackは、SMA患者の動的支持動作の改善に有効であることが示唆された。

AP02.3  
A novel familial prion disease with autonomic/sensory neuropathy

【目的】新たな家族性プリオン病（FPrP）の発症を検討した。

【方法】100例の患者を対象に、FPrPの発症を検討した。

【結果】FPrPの発症は、年齢20代から70代までと幅広く、発症部位は脳や脊髄に多かった。

【考察】FPrPの発症は、家族歴や発症部位により異なることが示唆された。

AP02.6  
The analyze of three pedigrees with MAPT N279K mutation accompanying DAT-scan

【目的】MAPT N279K突変が三世代家族に見られるとき、DAT-scanを用いて検討した。

【方法】MAPT N279K突変を有する家族3代を対象に、DAT-scanを用いて検討した。

【結果】MAPT N279K突変が家族3代に見られるとき、DAT-scanで異常を検出すことが示唆された。

【考察】MAPT N279K突変が三世代家族に見られるとき、DAT-scanを用いて検討することが有用であることが示唆された。
Introducing the Glucose Metabolism to Amyloid Deposition Ratio Image

OBJECTIVE: Alzheimer’s disease (AD) is characterized by increased cortical amyloid deposition in the prodromal stage and subsequent decrease of cerebral glucose metabolism with disease progression. The present study introduces voxel-wise metabolism into amyloid deposits ratio (MAR) imaging in order to evaluate its reliability in the diagnosis of AD. METHODS: 324 consecutive subjects with 143 AD and 181 normal subjects were included in this study from the Alzheimer’s disease neuroimaging initiative (ADNI) database. The MAR image was created by dividing each FDG-PET image by corresponding AV-45 PET image using voxel-wise inter-image computation. We examined voxel-wise comparison in the MAR images between AD subjects and normal subjects and compared the diagnostic performances between the MAR image and FDG-PET and AV 45 image. RESULTS: MAR images of AD subjects exhibited severe and extensive decreases compared with normal subjects in the affected region in AD. The highest t-value was equivalent to the FDG-PET and the voxel extent was much greater than the other images. The diagnostic accuracies were 82.6%, 80.7%, and 76.8% for the MAR image, FDG-PET, and AV-45, respectively. AUC for the MAR image was 0.904, and was larger than those for FDG-PET (AUC 0.884), and AV-45 (AUC 0.847). CONCLUSION: MAR image reflects not only amyloid deposition, but cerebral hypometabolism and can successfully classified subjects with AD. MAR imaging techniques might be a more appropriate marker for monitoring disease progression of AD.