2015年　口演部門トピックス

基礎部門

AO-1-1　最優秀候補演題

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

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Objective: Recent genetic studies have revealed that mutations in *glucocerebrosidase* (*GBA*), a causative gene of Gaucher disease (GD), are a strong risk for Parkinson's disease (PD). However, its pathological mechanisms leading to PD remain largely unknown. To investigate how *GBA* mutations cause PD, we generated *GBA* mutant medaka and analyzed their phenotype.
Methods: We generated *GBA* mutant medaka by screening a targeting induced local lesions in genomes (TILLING) library and alpha-synuclein deletion mutant medaka by transcription activator-like effector nucleases (TALENs).
Results: We generated *GBA* nonsense mutant (*GBA*$^{-/-}$) medaka completely deficient in glucocerebrosidase (GCase) activity. In contrast to the perinatal death of human and mice lacking GCase activity, *GBA*$^{-/-}$ medaka survived for months, enabling us to analyze disease progression. *GBA*$^{-/-}$ medaka displayed non-selective neuronal cell death accompanied by neuroinflammation, lysosomal abnormalities and alpha-synuclein accumulation in spheroids containing autophagosomes. Unexpectedly, disruption of *α-syn* did not improve the life span, spheroid formation, neuronal loss, or neuroinflammation in *GBA*$^{-/-}$ medaka.
Conclusion: *GBA*$^{-/-}$ medaka display not only the phenotypes resembling human neuronopathic GD but also axonal accumulation of *α*-syn accompanied by impairment of the autophagy-lysosome pathway. Furthermore, the present study demonstrates this *α*-syn accumulation has minimal contribution to the pathogenesis of neuronopathic GD in medaka.

AO-1-2　最優秀候補演題

Sialylated IgG-Fc: A Novel Biomarker of CIDP

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＜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 aim to test whether IgG-Fc sialylation is a biomarker of disease activity for chronic inflammatory demyelinating polyneuropathy (CIDP).
＜Methods＞ By using specific lectins for sialylation, galactosylation and agalactosylation, lectin-enzyme assay and lectin blotting with pre-treatment of IdeS were performed to compare the glycosylation levels of serum IgG-Fc i) between patients of untreated CIDP (n = 107) and normal control subjects (n = 27), ii) among patients with untreated CIDP of different clinical severities, and iii) 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 =0.003 and 0.033, respectively), whereas agalactosylation was increased in CIDP (p = 0.21). Ratios of sialylated/agalactosylated IgG-Fc levels were significantly reduced in CIDP (p＜0.001) and inversely related to disease severity (p = 0.044). After IVIG treatment, levels of sialylated IgG-Fc significantly increased (p = 0.003).
＜Conclusions＞ Sialylation of IgG-Fc is reduced in CIDP. Its level correlated with clinical severity and increased after IVIG treatment. Sialylated as well as ratio of sialylated/agalactosylated IgG-Fc could be new measures to monitor the disease severity and treatment status in CIDP.

AO-1-3　最優秀候補演題

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

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Background: The development of a drug delivery system across the blood-brain barrier (BBB) into brain is a challenging problem to achieve effective targeted therapy in the central nervous system. We aim to develop an efficient BBB-crossing delivery system by utilizing a physiological glucose transport pathway.
Method: We constructed a self-assembled supramolecular micelle integrated with glucose on its surface (Glc-micelle). We injected fluorescent-labeled Glc-micelle intravenously to BALB/c mice (female, 6-week old) and examined systemic distribution by fluorometric determination and immunohistochemical analysis (n=5). Moreover, we investigated the localization of Glc-micelle in mice brain by intravital real-time confocal microscope and two-photon excitation microscope.
Results: Glc-micelle rapidly decreased from blood circulation and highly accumulated in brain (about 4% dose/g-brain in three days) in response to an increase of blood glucose concentration after a prior fasting condition. Glc-micelle was not accumulated in brain when we did not induce any change of blood glucose concentration. We observed the transport of Glc-micelle from blood vessel into brain parenchyma and identified the Glc-micelle localized in neurons and microglia.
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.

AO-1-4　最優秀候補演題

Evidence of a link between TDP-43 and dipeptide repeat protein in c9FTD/ALS

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Objectives: The expansion of the GGGGCC repeat in the *C9orf72* gene is the most common cause of both frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) (c9FTD/ALS). Recently, it was reported that an unconventional mechanism of repeat-associated non-ATG translation arises from *C9orf72* expansion. Translated products of sense and anti-sense transcripts from the expanded *C9orf72* repeat, i.e., the dipeptide repeat protein (DRP) of glycine-alanine (poly-GA), -proline (poly-GP), -arginine (poly-GR), proline-arginine (poly-PR), and -alanine (poly-PA) are deposited in the brains of c9FTD/ALS. However, the pathological significance of DRP remains unknown. **Methods:** We generated synthetic cDNAs encoding 100 repeats of DRP avoiding GGGGCC repeats and evaluated the effects of DRP without RNA toxicity *in vitro* and *in vivo*. **Results:** The poly-GA protein formed highly aggregated ubiquitin/p62-positive inclusion bodies in neuronal cells. In contrast, the highly basic proteins poly-GR and PR formed unique ubiquitin/p62-negative cytoplasmic inclusions, which recruit TDP-43. The evaluation of cytotoxicity revealed that overexpressed poly-GA, GP, and GR impair the ubiquitin-proteasome system (UPS), resulting in an increase of TDP-43 levels, and enhanced the sensitivity to a proteasome inhibitor. **Conclusion:** The present data indicate that DRPs are cytotoxic, possibly via UPS dysfunction and directly lead TDP-43 proteinopathy in c9FTD/ALS.

2015年　口演部門トピックス

臨床部門

AO-2-1　最優秀候補演題

Sequencing of the familial ALS causative genes in Japanese ALS patients

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Purpose

To investigate the frequency and contribution of mutations in major amyotrophic lateral sclerosis (ALS) related genes in Japanese ALS patients from a large ALS cohort, using targeted next generation sequencing.

Methods

We designed a multiplex, PCR-based primer panel to amplify the coding regions of 28 ALS related genes; as follows, *SOD1, ALS2, SETX, SPG11, FUS, VAPB, ANG, TARDBP, FIG4, OPTN, VCP, UBQLN2, SIGMAR1, DAO, NEFH, DCTN1, TAF15, EWSR1, PRPH, GRN, CHMP2B, ZNF512B, PFN1, ATXN2, TFG, C9orf72, RNF19A* and *SQSTM1*. The Ion Torrent PGM sequencer was used to identify variants in the 28 genes. We analyzed 256 ALS patients (217 sporadic ALS, 39 familial ALS patients). To determine if any sequence variations were novel or known variants, all non-synonymous variants were compared with dbSNP and HGVD. We picked up known ALS pathogenic variants, and then, the functional consequences of the non-synonymous novel variants were predicted in silico.

Results

Pathogenic mutations which have been previously reported were identified in 18 patients among the 39 FALS patients and in 14 patients among the 217 SALS patients. Nine SALS patients had one or more novel non-synonymous variants which were classified as Probably Damaging in PolyPhen2 or Damaging in SHIFT.

Conclusions

We presented that 18 FALS patients and 14 SALS patients have mutations of known causative genes of ALS in a Japanese ALS cohort. Nine SALS patients had one or more novel variants in the ALS related genes. These results would contribute to clinical practices and genetic counselling for Japanese ALS patients.

AO-2-2　最優秀候補演題

球脊髄性筋萎縮症患者に対するリュープロレリン酢酸塩長期使用の効果

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[目的] 球脊髄性筋萎縮症（以下，SBMA）は緩徐進行性の神経筋疾患であり現時点で確立した治療法はない．緩徐進行性疾患に対する薬剤の疾患修飾効果を短期間の臨床試験で検出することは非常に困難である．本研究では，リュープロレリン酢酸塩（以下，本剤）長期投与例と自然歴データを比較し，本剤長期投与の有用性を評価する．[方法] 長期投与例には，SBMAに対する第Ⅲ相二重盲検比較試験および継続投与試験において3年間継続して本剤を投与された長期投与群98例のデータを，比較対照として，SBMAの自然歴研究における自然歴群34例のデータを用いた．有効性の発現時期を推定するため，長期投与群における評価指標の変化量は，投与開始後1年目（以下，1期）と，2年目及び3年目（以下，Ⅱ期）に分けて算出した．さらに，発症10年未満の被験者に対する部分集団解析を行い，早期治療介入の意義を推定した．[結果] 背景因子について，全体集団では発症からの経過年数に群間差を認めた（自然歴群9.0±4.9年，長期投与群12.5±8.4年，以下同順）が，発症10年未満の部分集団では差を認めなかった（5.5±2.1年，6.1±2.4年）．有効性について，6分間歩行距離において，全体集団では自然歴群の1年あたりの平均変化率が-14.6m/年であるのに対し，長期投与群のⅠ期では-24.2m/年，Ⅱ期では-11.4m/年であり，治療介入開始2年目以降で変化率が緩やかになる事が示唆された．発症10年未満の部分集団解析では，自然歴群で-13.8m/年であるのに対し，長期投与群のⅠ期では-14.8m/年，Ⅱ期では-9.5m/年であり，同様の傾向がより顕著であった．[考察] 本剤の投与により，6分間歩行距離は投与48週以降に変化率が緩やかになることが示された．これらの結果から，長期継続投与により本剤の疾患修飾効果が検出されると推測される．この傾向は，発症10年未満の発症早期例に顕著であり，本剤による早期治療介入の有用性を示唆するものと考えられる．

AO-2-3　最優秀候補演題

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

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Background: We aimed to describe the clinical features of Japanese patients with chronic inflammatory demyelinating polyneuropathy (CIDP) associated with autoantibodies to neurofascin 155 (NF155).

Methods: Enzyme-linked immuno-sorbent assay (ELISA) was used to identify antibodies to NF155. Clinical features was obtained retrospectively and compared with antibodies-negative CIDP patients.

Results: Sera from 38 of 533 (7%) CIDP patients contained anti-NF155 IgG4 antibodies by 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 antibodies-negative CIDP patients ($p = 0.048$). Twelve patients (32%) 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-NF155 IgG4 antibodies are associated with a subgroup of juvenile-onset CIDP patients with sensory ataxia and tremor. Autoantibodies to NF155 are thus potential biomarkers to differentiate typical CIDP, and characterized by a poor response to IVIG.

AO-2-4　最優秀候補演題

軸索スフェロイド形成を伴うびまん性白質脳症（HDLS）の診断基準案の策定

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【目的】軸索スフェロイド形成を伴う遺伝性びまん性白質脳症(Hereditary diffuse leukoencephalopathy with spheroids, HDLS)は，若年性認知症を呈する遺伝性の白質脳症であり，*CSF1R* (colony stimulating factor 1 receptor)が原因遺伝子である．本研究は，HDLSの臨床像を明らかにし，これに基づいた診断基準案を策定し，その妥当性を検討する．【方法】*CSF1R*変異を有するHDLS自験例と既報例を合わせた101例について，臨床像と頭部画像所見を抽出し，これに基づき診断基準案を策定した．診断基準調査シートを作成し，臨床情報を収集し得た*CSF1R*変異陽性55例，変異陰性であった白質脳症53例，*Notch3*変異を有するCADASIL32例について，診断基準案の感度・特異度を算出し妥当性を検討した．【結果】101例中，本邦例が28例（28%）と多い．発症年齢は43歳，死亡年齢は52歳，死亡までの罹病期間は5年だった（いずれも中央値）．38%は家族歴を認めない孤発例であった．初発症状は認知機能障害が最も多い（62%）．調査シートによると，臨床症状では認知機能障害（96%），性格変化・行動異常（75%），錐体路徴候（75%），前頭葉徴候（75%），パーキンソン症状（63%）を呈することが多く，頭部画像所見では両側性の大脳白質病変（100%）に加えて，脳梁の菲薄化（92%），錐体路の異常信号（58%），脳内石灰化病変（50%）を認めることが特徴であった．診断基準案を用いると，変異陽性例を95%以上の感度で検出できた．特異度は，変異陰性白質脳症例で42%，CADASIL例で88%であった．【結論】*CSF1R*変異陽性HDLS症例は，比較的均一な中核症状を呈し，それに付随する臨床像の多様性が認められた．HDLSは本邦に多い白質障害型の若年性認知症であり，HDLSの臨床診断に寄与する診断基準の策定は重要である．

2015年　ポスター部門トピックス

基礎部門

AP-01-1　最優秀候補演題

Passive transferred NMO rat model with high affinity mouse anti-AQP4+ antibody

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Background We previously reported the passive transferred model with anti-AQP4$^+$ Ab purified from NMO patients sera (hAQP4 model), but the problem in such model is that astrocytopathy was quite mild.
Purpose To elucidate the pathological feature of passive transferred NMO rat model with high affinity mouse anti-AQP4$^+$ antibody (mAQP4 model).
Method We immunized 11 Lewis rats (8weeks of age) with myelin basic protein. When the ascending paresis or weight loss (10g/day) developed, we injected intraperitonealy 40mg of hAQP4 to 5 rats and 1mg of mAQP4 to 6 rats. Finally, 2days later, we examined spinal cord lesions histopathologically - 84 slices in hAQP4 model, 98 slices in mAQP4 model.
Result AQP4 loss was found in 23/84 slices(27.4%) of hAQP4 model and in 94/98(95.9%) of mAQP4 model. AQP4 loss at white matter (WM), gray matter (GM), cortico-medurally junction (CMJ) was seen in 0/84, 14/84(16.7%), 12/84(14.3%) of hAQP4 model, 39/98 (39.8%), 55/98 (56.1%), 93/98 (94.9%) of mAQP4 model, respectively. In mAQP4 model, we observed AQP4/GFAP/EAAT2 loss particularly in Iba1$^+$perivascular area in GM and CMJ, but also in areas without inflammation. In WM, there were several lesions with subpial AQP4 loss facing CSF space, possibly suggesting the direct IgG penetration from the CSF. The demyelination was limited in both models, but the intensive large AQP4 loss with neutrophil infiltration and tissue vacuolation were easily found.
Conclusion In rat mAQP4 model, intensive large astrocytopathy was much productively found and the lesion was compatible with hAQP4 model and human NMO pathology.

AP-01-2　最優秀候補演題

Different effects of STN and GPi stimulation to primate striatal interneuron

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Objective: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or Globus pallidus interna (Gpi)is an established therapy for advanced motor symptoms in Parkinson's disease (PD), however, the therapeutic mechanisms of each therapy are still unclear. To investigate this issue, we recorded neuronal activity of interneurons of primate putamen during high-frequency stimulation of STN or GPi.
Method:Neuronal activity of the interneurons in the putamen (tonically active neurons: TANs) was recorded extracellularly during electrical stimulation of the STN or GPi in three normal monkey.Furthermore, to explore the effect of dopamine or GABA to TANs response, we injected sulpiride or gabazine locally to TANs during stimulation of STN and GPi.
Results:We examined 96 TANs activity during STN or GPi stimulation. Many TANs reduced their activity during STN or GPi stimulation. (88%of recorded neurons during STN stimulation, 76% $p<0.05$ Mann-Whitney U test). Inhibitory responses of TANs during STN stimulation were diminished after local injection of sulpiride. On the other hand, TANs during GPi stimulation were kept as a pause after local injection of sulpiride or gabazine.
Conclusion: This study showed that high frequency electrical stimulation of the STN or GPi induce reduction of cholinergic tone in the striatum, and dopamine and GABA may have different role in the response. These results indicate that modulating of TANs activity may be one possible therapeutic mechanism of the STN or GPi DBS.

AP-01-3　最優秀候補演題

Distinct patterns of neuronal and glial TDP-43 inclusions in motor cortex of ALS

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Objective: TDP-43 is the major disease protein in ALS. Two distinct distribution patterns of TDP-43-immunoreactive inclusions in brains of patients with ALS have been noted (Nishihira et al.). In type 1 brains the inclusions are mainly localized to the pyramidal motor system,whereas in type 2 brains widespread occurrence of the inclusions is evident. To clarify TDP-43 cellular pathology in the motor cortex of both types of ALS, we performed morphometric 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 1 and 2 patterns, respectively. We performed double labeling of *in situ* hybridization (ISH) with a RNA probe for neurofilaments and immunohistochemistry with an anti-phosphorylated TDP-43 antibody. The numbers of ISH-labeled neurons and immuno-labeled neuronal and glial cytoplasmic inclusions (NCI and GCI) were counted. Statistical significance on the differences between the numbers of both types was evaluated.
Results: On both types, there were no difference on the densities per unit area of both neurons ($p = 0.68$) and GCI ($p = 0.29$). In type 2, the density of NCI and the percentage of NCI to overall neuron number were significantly greater than those in type 1 ($p = 0.002$ and 0.004, respectively).
Conclusion: Neurons in type 2 are invloved much frequently in TDP-43 cellular pathology than those in type 1, even though glia in both types are involved evenly. This evidence appears noteworthy when considering the varidity of the protein propagation mechanism underlying ALS.

AP-01-4
取り下げ演題

AP-01-5　最優秀候補演題

Astrocyte-derived TGF-beta1 accelerates disease progression in ALS mice

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Objectives: This study is aimed to explore the roles of TGF-β1, the elevated levels of which has been observed in the peripheral blood and the cerebrospinal fluid of ALS patients, in non-cell autonomous cell death mediated by glial cells.
Methods: TGF-β1 levels were examined in mutant SOD1 mice and sporadic ALS patients. SOD1^{G93A} mice with astrocytic overproduction of TGF-β1 were generated using GFAP-TGF-β1 mice which overexpressed TGF-β1 in astrocytes, and disease phenotypes, glia/immune cells, and expression profiles of glia/immune-related molecules were analyzed. TGF-β1 levels were also examined in loxSOD1^{G37R} mice with astrocytic deletion of mutant SOD1. Blocking TGF-β signaling by SB-431542 was tested to slow disease progression of SOD1^{G93A} mice. **Results:** TGF-β1 levels were elevated in astrocytes of symptomatic mutant SOD1 mice and sporadic ALS patients, and astrocytic overproduction of TGF-β1 in SOD1^{G93A} mice accelerated disease progression with reduced IGF-I production in deactivated microglia and fewer infiltrated T cells with a dysregulated IFN-γ/IL-4 balance. Astrocytic deletion of mutant SOD1 in loxSOD1^{G37R} mice resulted in slowing disease progression with a decreased level of astrocytic TGF-β1. Blocking TGF-β signaling in SOD1^{G93A} mice tended to slow disease progression. **Conclusions:** We identify astrocytic TGF-β1 as a determinant of disease progression of ALS through inhibiting the neuroprotective inflammatory response by microglia and T cells. Blocking TGF-β signaling in these cells might be a therapeutic target for slowing disease progression of ALS.

AP-01-6　最優秀候補演題

Development of tau imaging probes using the mouse model of tauopathy

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【目的】PBB3(Pyridinyl-Butadienyl-Benzothiazole 3)は認知症患者脳内のタウ蓄積量を可視的に標識するリガンドとして開発され，現在[^{11}C]PBB3によるPET画像解析の臨床研究が進められている．しかし^{11}C誘導体では半減期が短く，臨床での実用性向上と放射薬剤の搬送のために半減期の長い^{18}F誘導体を開発することがPET標識として重要となる．本研究ではP301L変異型タウを大脳皮質・海馬特異的に発現するrTg4510マウスを用い，新規PBB3フッ素誘導体の開発を目的とした．さらに神経炎症の指標であるTSPO(translocator protein)のリガンド[^{11}C]Ac5216とPBB3を比較し，神経炎症とタウ病変の関連性を検証した．
【方法】[^{11}C]PBB3，[^{18}F]PBB3フッ素誘導体PET，[^{11}C]Ac5216-PETと形態MRIをrTg4510マウスでおこなった．検体数n(rTgマウス，野生型)，n29(14，16)．さらにマウス脳切片のPBB3リガンド蛍光組織染色と免疫組織染色をおこないPBB3リガンドとタウ病変との相関を調べた．
【結果】rTg4510マウスの[^{11}C]PBB3-PET評価ではMRIの萎縮部位に集積増加がみられた．[^{18}F]F-PBB3-PETでは[^{11}C]PBB3-PETと同様にrTg4510マウスの大脳皮質に優位な取り込みが認められた．PBB3の蛍光染色像とタウ抗体 免疫染色像が概ね一致した．[^{11}C]Ac5216の集積部位においてTSPO抗体の染色像の増大が認められ，大脳での[^{11}C]Ac5216と[^{18}F]F-PBB3集積量に正の相関関係が認められた．
【結論】今回の結果でタウ病変選択的にPBB3が結合する実証が得られた．また[^{18}F]F-PBB3-PETでもタウ病変への親和性を認め，今後タウリガンドPBB3のPET標識の普及が見込めると思われた．さらに[^{11}C]Ac5216と[^{18}F]F-PBB3の同部位での集積増加の相関がみられ，神経炎症とタウ病変の関連性が推測されたことから，新規タウイメージング薬剤の開発と共に，rTg4510マウスによる複合的なリガンドを用いたPETイメージング研究は，病態メカニズムの解明に貢献すると考えられる．

2015年　ポスター部門トピックス

臨床部門

AP-02-1　最優秀候補演題

筋萎縮性側索硬化症患者の発症・進展様式の検討

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【目的】筋萎縮性側索硬化症（ALS）患者の経過は様々である．ALSの発症・進展様式を自験例にて調査しその傾向を検討した．【方法】当院に受診したALS患者141例に対して下位運動ニューロン症状の初発症状，その後の進展形式を調査した．ALSの診断は神経学的所見，筋電図所見，超音波所見，臨床経過を総合しておこなった．発症・進展様式を評価する下位運動ニューロン症状としては自他覚的な筋力低下，筋萎縮の有無でおこなった．進展形式は初発症状から隣接した部位に症状が続発した場合は連続性，隣接していない部位に続発した場合は非連続性とした．連続性では，初発部位を起点に2部位目・3部位目に進展する場合を放射状，3部位目の進展が2部位目から連続する場合をリレー型と定義した．【結果】初発部位は球症状 28例(19.9%)，上肢60例(42.6%)，下肢53例(37.6%)であった．第2部位への進展は連続性が121例(85.8%)，非連続性20例(14.2%)であった．非連続性の方が速い経過の傾向にあった．初発部位別では球症状からは連続性22例(78.6%)，非連続性6例(21.4%)．上肢からは連続性57例(95.0%)，非連続性3例(5.0%)．下肢からは連続性42例(79.2%)，非連続性11例(20.8%)であった．初発部位別では第3部位目まで追跡できた90例については放射状が67例（74.4%），リレー型が23例（25.6%）であった．【結論】ALSでは連続性進展を示す方が多く，特に上肢発症の場合にその傾向が強い．連続性の場合は放射状に進展することが多い．非連続性に進展した場合は経過が速い傾向にある．

AP-02-2　最優秀候補演題

Clinical study of ASIA after HPV vaccination: 10 cases with neurological symptom

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Introduction: Recently, the appearance of severe adverse events after HPV vaccination, what is called autoimmune/inflammatory syndrome induced by adjuvants (ASIA), give rise to widespread public concern. The objective of this study is to demonstrate the neurological phenotypes and develop applicable treatment for the patients with ASIA after HPV vaccination.
Methods: Ten patients were hospitalized to our hospital from 2012 to 2014. We evaluated the clinical symptoms, serum antibodies, brain perfusion SPECT image, and therapeutic effect of these patients.
Results: All the patients were female, aged 14-19 years. Clinically, 9 cases had suffered with localized pain, and higher brain dysfunction was identified in 6 cases. Autonomic symptom was revealed in 6 cases, whereas 4 cases exhibited movement disorders. Serum autoantibody measurement was carried out in 9 patients, and anti-ganglioside antibody and anti-ganglionic acetylcholine receptor antibody were positive in 6 and 2 cases, respectively. In brain perfusion SPECT imaging, hypoperfusion of cerebral cortex was observed in 7 out of 8 cases. In 9 cases who received immunological treatment, 7 cases were treated with prednisolone, and slight improvement was found in 3 cases. Immunoadsorption plasmapheresis (IAPP) therapy was applied in 6 cases, and therapeutic effect was recognized in half.
Conclusion: The improvement of symptoms by means of immunological treatment supports hypothesis that these events are caused by autoimmune mechanism. Therefore, we recommend active immunological treatment for ASIA after HPV vaccination.

AP-02-3　最優秀候補演題

A novel familial prion disease with autonomic/sensory neuropathy

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(Backgroud) Sensory neuropathy is not common in prion diseases and autonomic failure has not been considered to be the main symptom of prion disease. However, the sensory/autonomic neuropathy as initial symptom due to the prion mutation has been reported recently. We report a novel familial prion disease causing panautonomic-sensory neuropathy. (Method) We have experienced 2 cases in 1 family. Case 1, a big sister, showed complex symptoms consist of polyneuropathy, memory disturbance, dysuria, alternate stool abnormality, and orthostatic hypotension started at age 26 years. She died at age 37 years old. Case 2, a little brother, also showed same symptoms at age 20 years. Their mother had same symptoms at age 49 years old and died 1 year after the onset. We performed several clinical examinations, the prion gene analysis, and sensory nerve biopsies with both 2 cases. (Result) In both of 2 cases, tendon reflexes showed areflexia and the severe orthostatic hypotension was present. Their cognitive functions were mildly affected. Their brain MRI showed neither cerebral atrophy nor abnormal signal intensities. The sural nerve biopsies revealed moderate loss of myelinated fibers with no deposits of amyloid material, but deposits of prion proteins. The prion gene analysis showed a 2 bp deletion in codon 178 that causes a premature stop codon and additional variable 25 amino acid at C-terminal from the mutation in both cases compared to the normal pattern in their father. (Conclusion) The novel prion gene mutation causes the familial autonomic/sensory neuropathy.

AP-02-4　最優秀候補演題

高齢者のてんかん重積状態：臨床的特徴と予後因子について

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【目的】これまで高齢者のてんかん重積状態に関するまとまった報告は乏しいため，その臨床的特徴と予後因子について明らかにする．【方法】2011年7月から2014年6月までの3年間に当科で入院加療を行った65歳以上のてんかん重積状態患者連続96名（男性38名，女性58名）の臨床的特徴を後方視的に調査し，その予後因子を検討した．【結果】年齢の中央値は79.5歳（範囲66-98歳）．病前のmodified Rankin Scale (mRS) の中央値は3で，入院日数の中央値は15.5日 (IQR 8-27日) であった．てんかんの既往は29名 (30.2%) に認めた．非けいれん性てんかん重積状態であったのは8名 (8.3%)，refractory status epilepticus (RSE) であったのは16名 (16.7%) だった．病因としては，acute symptomatic (AS) が20名 (20.8%)，remote symptomatic (RS) が58名 (60.4%)，cryptogenicが18名 (18.8%) であった．AS群では急性期脳血管障害が9名，薬物離脱が3名と多く，RS群では陳旧性脳血管障害が34名，認知症が12名と多かった．予後は，34名 (35.4%) が病前に比べ退院時のmRSが低下し，うち5名 (5.2%) が死亡した．単変量解析では，てんかんの既往がないこと (p = 0.004)，病因がASであること (p = 0.04)，RSEであること (p <0.001) が有意に退院時のmRS低下と関連していた．これらの因子に年齢（80歳以上もしくは未満）と病前のmRS（2以下もしくは3以上）を加えて多変量解析を行ったところ，RSEのみが有意にADLの低下と関連していた (p = 0.002, odds ratio = 8.31 [95%CI 2.13-32.4])．【結論】高齢者のてんかん重積状態は元々のADLが低下している人に生じることが多く，病因の約6割を陳旧性脳血管障害，認知症，急性期脳血管障害が占めていた．てんかん重積状態を契機にさらにADLが低下することも多く，発作のコントロールが不良であることのみが独立した予後不良因子であった．

AP-02-5　最優秀候補演題

Facilitating SMA using a NIRS-mediated neurofeedback improves postural stability

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Purpose:
There is much evidence that the supplementary motor area (SMA) is involved in various aspects of motor control. However, its essential role as therapeutic target in poststroke functional recovery remains controversial.
To investigate if SMA facilitation affects postural control and/or hand dexterity in a cause-and-effect manner, we used a NIRS-mediated neurofeedback (NF) system to modulate the voluntary control of brain activities with real-time presentation.
Method:
20 healthy subjects were recruited (7 men, age 28.1 ± 4.6). Brain activation was measured using oxyHb derived signals by 50ch NIRS system with 4 short distance channels to adjust the skin blood flow. Each subjects tried to increase the feedback signals without any specific task in 2 sessions of the REAL (feedback of their own SMA activation) and the SHAM (feedback of prerecorded other's brain activation), with intervals of more than 1 week. Before and after NF sessions, postural stability and hand dexterity were assessed using the center of pressure and 9-hole peg test. We investigate the proficiency effect of NF on brain activation using comparison between the latter and former task repetitions.
Results:
The SMA activation was facilitated only in REAL condition. The SMA facilitation kept postural stability with significant interaction by group and time ($F_{1,38}$=6.2, P<0.05), however, it did not affect hand dexterity.
Conclusion:
Our findings revealed the cause-and-effect relationship between SMA and postural control, and provided the rational for the SMA as therapeutic target for poststroke postural disability.

AP-02-6　最優秀候補演題

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

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[Purpose] MAPT N279K is most common mutation among the patients clinically defined as fronto temmporal lober degeneration (FTLD) stained by Tau. Herein, we screened this mutation for three pedigrees emerging from same region in northern area of Kanto distinction.
[Method] We screened MAPT N279K in exon 10 for the patients constructed from three pedigrees manifesting autosomal dominant heredity, and young-onset of cognitive decline.
[Results] All three patients accompanied with MAPT N279K mutation. We detected five patients more in three pedigree, who already died at our examination. Combined them, age at onset was 40.6 ± 2.08 (±SD). Age at death was 46.2 ± 6.14. The average life duration was about four years. Initial manifestations were anosodiaphoria, disinhibition, character change, and reducing persistent attention, thought to be typical symptoms as FTLD. Brain MRI demonstrated hemi-atrophic changes in temporal lobe. SPECT-IMP study showed severe hypoperfusion in unilateral fronto-temporal lobes. DAT-scan also indicated severe decreasing values of dopamine transporter in bilateral striatum. All three patients showed rapid progression after one or two years from onset.
[Conclusion] All three patients shared common symptoms and rapid progression of parkinsonism and cognitive decline. MAPT N279K is seemingly a critical gene of onset of FTLD, influencing more directly the each prognosis. Our radiological studies confirmed diffuse and multitude dysfunction in the cerebral hemisphere. Our next aim is to expand the MAPT screening adding more patients emerging from same region.

AP-02-7 最優秀候補演題

Introducing the Glucose Metabolism to Amyloid Deposition Ratio Image

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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 regionin 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 78.8% 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.