2016年　口演トピックス

基礎部門

AO-01-1　最優秀候補演題

Development of rehabilitation accelerating agent based on neural plasticity mechanism

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[Objective] Acute damage to central nervous system such as stroke is a leading cause of serious functional disability. Although various interventions to accelerate rehabilitation have been established, the degree of functional recovery after stroke is still limited. Restoration of functional disability is considered to be the result of comprehensive neural plasticity in the intact brain regions. Synaptic AMPA receptor delivery is a fundamental mechanism underlying behavioral changes that require neural plasticity. Previously, we revealed that novel small molecular compound, T-817MA, facilitated the synaptic AMPA delivery in an experience-dependent manner. Accordingly, we hypothesized that pharmacological intervention to rehabilitation with T-817MA could be a promising strategy to augment functional recovery. **[Methods and Results]** To verify this hypothesis, simple voluntary movements of mice treated with T-817MA were evaluated by reaching task after cryogenic injury to motor cortex. This rodent model revealed that T-817MA accelerates motor functional recovery in a training-dependent manner. Further analysis was conducted with macaque monkeys, which have more complex manual dexterity. Using two reach-grasp-retrieval tasks, we evaluated manual dexterity after internal capsule hemorrhage induced by focal collagenase injection. This nonhuman primate model showed that T-817MA also augments complex motor functional recovery of primates. **[Conclusions]** These results in new animal models suggest that T-817MA may have a remarkable potential as a novel rehabilitation facilitator.

AO-01-2　最優秀候補演題

Analysis of molecular mechanism and development of therapeutic method in spinocerebellarataxia type1

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[Objective] We previously searched for nuclear proteins quantitatively affected by mutant Atxn1 in neurons and found a significant decrease in high-mobility group box (HMGB) 1/2 proteins in the soluble nuclear fraction. HMGB supplementation actually ameliorates eye degeneration in an SCA1 fly model and restores impaired DNA damage repair (Qi et al., 2007). We established that transgenic or virus vector-mediated complementation with HMGB1 ameliorates motor dysfunction and prolongs lifespan in mutant Atxn1 knock-in (Atxn1-KI) mice. [Methods] We analyzed mitochondrial DNA damage repair by a mitochondrial DNA amplification assay using PCR and a southern blot. Virus vector of injections into the cerebellar surface were performed on 5-week-old mice. We analyzed by rotarod test. [Results] We identified mitochondrial DNA damage repair by HMGB1 as a novel molecular basis for this effect, in addition to the mechanisms already associated with HMGB1 function, such as nuclear DNA damage repair and nuclear transcription. Moreover, we show that the rescue of Purkinje cell dendrites and dendritic spines by HMGB1 could be downstream effects. In addition, we have tested another AAV (AAV9/3) vector expressing "gene X" and found the recovery of motor dysfunctions of Atxn1-KI mice in rotarod test (at 9, 13, 40 weeks. The results suggested another strategy to treat SCA1. [Conclusion] Viral deliveries of HMGB1 and "gene X" are candidates approach by which to modify the disease progression of SCA1 even after the onset.

AO-01-3　最優秀候補演題

Insight into the Pathophysiology of the Human Mutant TARDBP Knock-In Mice

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[Objective] A human mutant *TARDBP* transgenic animal model could be a strong tool to comprehend the mechanism of TDP-43 proteinopathy, but the fact that elevated level of human wild type TDP-43 also develops the pathogenesis of ALS, makes it difficult to simply evaluate the role of mutations in *TARDBP* gene by the observation of promotor-mediated transgenic mice models. So the aim of our project, is to comprehend the pathophysiology of TDP-43 proteinopathy utilizing human mutant *TARDBP* KI mice models.[Methods] We designed, and produced two lines (G348C / A382T) of mutant *TARDBP* KI mice models and evaluated their motor functions, cognitive functions and pathological changes. [Results] From the comparison of 9 G348C KI mice, 9 A382 KI mice, and 16 wild type littermates, it was shown that both two lines (G348C / A382T) of mutant *TARDBP* KI mice show physiological upper and lower motor neuron dysfunction. In A382T KI mice Bunina bodies are identified (8months old) and motor neuron decrease was documented (22months old). From the assessment utilizing 132 wild type, and 106 KI mice, it was shown that G348C KI mice lack sense of alarm, and develop memory disorder. [Conclusion] Each line of our KI mice show both phenotypes of ALS and of FTLD-like dementia in a manner that varies in degree, which in turn, again assures the continuity of these two clinically isolated diseases. Our totally new set of mice models will help us further comprehend the undelying mechanism in which motor neuron / cortex dominancy of TDP-43 pathology is modulated.

AO-01-4　最優秀候補演題

Loss of PSF/SFPQ, an intra-nuclear counterpart of FUS causes FTLD-like phenotypes

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[Objective]We identified splicing factor, proline- and glutamine rich (SFPQ) as a counterpart of FUS in the nucleus. SFPQ regulates alternative splicing of the Mapt gene at Exon 10 as FUS does. Because the disease mutations in FUS affect the interaction between FUS and SFPQ, we speculated that the interaction is critical for the function of FUS, especially for maintaining the balance of Mapt isoforms. Therefore, we investigate the phenotypes of SFPQ-silenced animals.[Methods] We injected AAV encoding shRNA against SFPQ (shSFPQ) and control to the bilateral hippocampus of C57/BL6J. Next, we performed co-injection of AAV encoding shRNA against Mapt Exon10+ isoform (4-repeat tau:4R-T). These mice were subjected to various behavioral analysis. Sequentially, MRI and immunohistological analysis were performed.[Results]Silencing of SFPQ resulted in an increased ratio of 4R-T/3R-T and exhibited FTLD-like behavioral impairments as well as reduced adult neurogenesis as seen in shFUS mice. Long-term observation revealed phosphorylated tau accumulation and drastic neuronal loss in shSFPQ mice. Co-silencing of 4R-T ameliorated the behavioral phenotypes and reduced neurogenesis; however, it could not rescue neuronal loss in shSFPQ mice.[Conclusions]Loss of SFPQ caused FTLD-like phenotypes, including aberrant behaviors, reduced adult neurogenesis, and phosphorylated tau accumulation mediated by alteration of tau isoforms. These findings are similar with those in FUS-silenced mice, suggesting that SFPQ is essential for the pathogenesis of FTLD/ALS in which quality loss of FUS is associated.

AO-01-5　最優秀候補演題

Non-cell autonomous therapeutic effects on polyQ disease models by exosomal chaperone transmission

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[Objective] The polyglutamine (polyQ) diseases including Huntington's disease (HD) are commonly caused by an expansion mutation (>40) of the polyQ stretch within various disease-causing proteins, which trigger their misfolding/aggregation, and eventually lead to neurodegeneration. Molecular chaperones such as Hsp70 and Hsp40 have been shown to prevent polyQ protein misfolding and to exert therapeutic effects on various polyQ disease models. We previously found that viral vector-mediated gene therapy of Hsp40 for HD model mice unexpectedly suppresses polyQ inclusions even in virus non-infected neurons. Here we examined the mechanistic basis of this non-cell autonomous therapeutic effect of Hsp40. **[Methods]** We analyzed cell culture models and *Drosophila* models of polyQ diseases in which molecular chaperones were expressed in a tissue-specific manner. **[Results]** Hsp40 as well as Hsp70 and Hsp90 is physiologically secreted from cells via exosomes, independent of the classical ER-Golgi secretion pathway, and taken up by surrounding cells. Addition of Hsp40/Hsp70-containing exosomes to the culture medium of the polyQ-expressing cells results in efficient suppression of polyQ inclusions. Furthermore, expression of Hsp40 or Hsp70 in remote tissues such as muscle and fat body in *Drosophila* significantly suppresses polyQ-induced photoreceptor degeneration in an exosome-dependent manner. **[Conclusions]** We conclude that exosome-mediated intercellular transmission of molecular chaperones contributes to their non-cell autonomous therapeutic effects on polyQ disease models.

AO-01-6　最優秀候補演題

GBA deficiency accelerates alpha-synuclein prion-like conversion and promotes its neurotoxicity

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[Objective] Alpha-synuclein (α Syn) plays a central role in the pathogenesis of Parkinson´s disease (PD) and dementia with Lewy bodies (DLB). Recent genetic studies have revealed that mutations in the *glucocerebrosidase 1* (*GBA1*) gene are strong risk factors for PD and DLB. The purpose of this study is to examine the mechanistic link between the functional loss of glucocerebrosidase (GCase) and the toxicity of α Syn *in vivo*. [Methods] We employed *Drosophila* models to examine the effect of GCase deficiency on the neurotoxicity of α Syn and its molecular mechanism. [Results] Behavioral and histological analyses showed that knockdown of the *Drosophila* GBA1 exacerbates the locomotor dysfunction and loss of dopaminergic neurons of α Syn-expressing flies. This aggravation was associated with the accumulation of proteinase K (PK)-resistant α Syn, raising the possibility that glucosylceramide (GlcCer), a substrate of GCase, accelerates the misfolding of α Syn. Indeed, *in vitro* experiments revealed that GlcCer directly promotes the conversion of α Syn into the PK-resistant form, representing a prion-like conformational change. Similarly, knockdown of the *Drosophila* β-galactosidase (β-Gal) also aggravated locomotor dysfunction of the α Syn flies, and its substrate GM1 ganglioside accelerated the formation of PK-resistant α Syn. [Conclusion] Our results suggest that the functional loss of GCase or β-Gal promotes the toxic conversion of α Syn via aberrant interactions between α Syn and their substrate glycolipids, leading to the aggravation of α Syn-mediated neurodegeneration

2016年　口演トピックス

臨床部門

AO-02-1　最優秀候補演題

Cerebrospinal fluid -CRMP5 as a diagnostic biomarker of NMOSD with AQP4-IgG

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[Background] NMOSD is a neuroinflammatory autoimmune disease characterized by severe optic neuritis and transverse myelitis, and caused by AQP4-IgG selectively attack membranous AQP4 in foot process of astrocyte. Collapsin response mediator protein 5（CRMP5）is a membranous protein located on the filopodia in the foot process of astrocyte. It is reported anti-CRMP5 antibody-positive patient showed NMOSD-like symptoms, but the clinical significance of CRMP5 in the cerebrospinal fluid（CSF-CRMP5）of NMOSD with AQP4-IgG patient are still unknown.**[Methods]** We conducted cross-sectional study in Japan from January 1999 to November 2015 including 52 patients（20 NMOSD with AQP4-IgG, 3 NMOSD with MOG-IgG, 23 MS, 2 Neuro-Behcet's disease, and 4 Neurosarcoidosis）who were diagnosed as neurological inflammatory demyelinating diseases and 7 non-inflammatory neurological disease control cases（NIDC）. CSF-CRMP5, CSF-GFAP, and CSF-MBP were measured by sandwich ELISA kit. The corrected data was analyzed by Graphpad Prism 5.**[Results]** CSF-CRMP5 in the NMOSD with AQP4-IgG group was signinficantly elevated（0.0975 ± 0.1552 pg/mL, p=0.0298）than MS（0.00435 ± 0.0209）. CSF-CRMP5 was not detected in NMOSD with MOG-IgG, Neuro-Behcet's disease, Neurosarcoidosis, and NIDC patients. CSF-CRMP5 is weakly correlated with CSF-GFAP, but no correlation with CSF-MBP.**[Conclusion]** Elevated CSF-CRMP5 levels in NMOSD with AQP4-IgG reflect astrocytic foot process and growth corn damages by AQP-IgG. CSF-CRMP5 is also a beneficial biomarker of diagnosis and disease activity in NMOSD with AQP4-IgG.

AO-02-2　最優秀候補演題

Mitochondrial targeting sequence variants of the CHCHD2 gene are a risk for Parkinson's disease

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Objective: The *CHCHD2* gene, a gene associated with mitochondria, was reported as a causative gene for autosomal dominant Parkinson's disease（PD）and a susceptibility gene for sporadic PD in Japanese population in 2015. This multicenter study is aimed to assess the role of *CHCHD2* variants in patients with PD and Lewy body disease（LBD）in Caucasian populations.**Methods:** All exons of the *CHCHD2* gene were sequenced in a US Caucasian patient-control series（878 PD, 610 LBD, and 717 controls）. Subsequently, exons 1 and 2 were sequenced in an Irish series（355 PD and 365 controls）and a Polish series（394 PD and 350 controls）. Immunohistochemistry and immunofluorescence studies were performed on pathologic LBD cases with rare *CHCHD2* variants.**Results:** We identified 9 rare exonic variants of unknown significance. These variants were more frequent in the combined group of PD and LBD patients compared to controls; 13（0.6%）vs 1（0.1%）, odds ratio 8.36（95%CI: 1.25-355.19）, P value 0.013. Eight of these 9 variants were located within the gene's mitochondrial targeting sequence. Immunofluorescence staining suggested the expression level of CHCHD2 was decreased in patients with LBD with variants compared to age-matched controls.**Conclusions:** Although the role of variants of the *CHCHD2* gene in PD and LBD remains to be further elucidated, the rare variants in the mitochondrial targeting sequence may be a risk factor for Lewy body disorders, which may link CHCHD2 to other genetic forms of parkinsonism with mitochondrial dysfunction.

AO-02-3　最優秀候補演題

Cognitive dysfunction and rCBF changes in Japanese females following HPV vaccination

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【目的】ヒトパピローマウィルス（HPV）ワクチン接種後に難治性疼痛，全身倦怠感，認知機能障害などの多彩な症状を呈する一群の存在が報告されている．今回，HPVワクチンの副反応が疑われる症例の認知機能障害と脳血流変化について検討を行った．【方法】HPVワクチン接種後に認知機能障害を訴える女性17人（平均17.7歳）を対象とした（HPV群）．1）認知機能障害の特徴と脳血流を検討：脳血流評価は正常群（女性10名，平均19歳）とともにIMP-SPECTを行い，3D-SSPのSEE解析で比較した．有意な脳血流低下はZ-score＞2かつextent ratio＞15%となる部位と定義した．2）WAIS-IIIと脳血流低下に相関性のある脳部位を検討した．【結果】1）認知機能障害の特徴：認知機能障害は初回接種から平均14.5ヵ月後に認め，認知機能障害以外の症状は平均4.9ヵ月後に認めた．記憶障害17例，計算障害4例，相貌失認様症状・地誌失認・半側空間無視をそれぞれ（？）2例に認めた．有意な脳血流低下は，右内側前頭回・眼窩回・直回・紡錘状回・海馬傍回・梁下野・前方帯状回，左角回・上後頭回，両側視床で認めた．2）知能指数（IQ）と脳血流低下との相関性：全検査IQは右内側前頭回・直回（r = -0.56, p ＜ 0.020; r = -0.64, p ＜ 0.014），言語性IQは右梁下野・直回，左視床（r = -0.49, p ＜ 0.046; r = -0.54, p ＜ 0.027; r = -0.54, p ＜ 0.025），動作性IQは右内側前頭回（r = -0.56, p ＜ 0.019）で有意な負の相関を認めた．【結論】HPV群の認知機能障害は他症状と比べ遅発性であった．HPV群の脳血流低下は辺縁系と個々の症状に関連する部位で認め，WAIS-IIIのIQと辺縁系の脳血流低下には有意な負の相関を認めた．HPV群の認知機能障害は主に辺縁系の障害によって生じている可能性がある．

AO-02-4　最優秀候補演題

FMT-PET analysis in gene therapy for AADC deficiency

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[Objective] Aromatic $_{L}$-amino acid decarboxylase（AADC）deficiency is a rare metabolic disease that leads to combined catecholamine and serotonin deficiency. Few treatment options are available, and most patients remain bed-ridden. We have developed a gene therapy using an adeno-associated virus（AAV）vector to deliver the *AADC* gene into the putamen. To evaluate the expression of the *AADC* gene in the brain, we applied positron emission tomography（PET）with 6-[^{18}F]fluoro-$_{L}$-*m*-tyrosine（FMT）, a specific tracer of AADC. **[Methods]** Three children with AADC deficiency received the AAV vectors harboring the human *AADC* gene via intra-putaminal infusions. A total dose of 2×10^{11} vector genomes was administered bilaterally into two tracts per side and five deposits per tract, separated by approximately 1 mm. The *AADC* expression in the putamen was assessed by FMT-PET before surgery and 1 month after gene transfer. **[Results]** Before gene therapy, FMT uptake in the striatum was profoundly reduced and was almost the same as that in the other brain regions in two patients. Only weak FMT uptake was detected in the caudate and ventral part of the putamen in the 5-year-old girl. One month after gene therapy, a remarkable increase in FMT uptake was observed in the broad areas of the putamen in the two patients who completed the PET study. All three patients showed improved motor functions. **[Conclusions]** The level of *AADC* expression was directly monitored by FMT-PET in a clinical trial of AADC gene therapy. Efficient transduction of the putamen was confirmed *in vivo*.

AO-02-5　最優秀候補演題

Distinct clinical features associated with anti-SRP and and-HMGCR autoantibodies

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＜背景＞免疫介在性壊死性ミオパチー（immune-mediated necrotizing myopathy, IMNM）は筋線維の壊死・再生が中心で炎症細胞浸潤を欠く炎症性筋疾患（inflammatory myopathies, IM）の病型であり，signal recognition particle（SRP）と3-hydroxy-3-methylglutary-coenzyme A reductase（HMGCR）に対する自己抗体が高頻度で検出される．＜目的＞抗SRP抗体と抗HMGCR抗体が陽性となるIMの臨床像の相違点を明らかにする．＜方法＞2010年から2014年に筋炎の統合的診断プロジェクトに登録された症例の中で臨床像と筋病理からIM（封入体筋炎を除く）と診断した386例を対象とした．抗SRP抗体はRNA免疫沈降法，抗HMGCR抗体はELISA法で測定した．＜結果＞IM 386例の中で抗SRP抗体は68例（18%），抗HMGCR抗体は46例（12%）で陽性であり，1例は両者とも検出された．この症例を除いたSRP群（n = 67）とHMGCR群（n = 45）の2群で臨床像を比較した．女性の頻度はSRP群で57%，HMGCR群で67%，発症年齢はSRP群で55歳，HMGCR群で57歳，1年以上進行した慢性型の頻度はSRP群で25%，HMGCR群で24%であった．またHMGCR群の18%でスタチンが誘因であった．MMT3以下の四肢筋力低下の頻度はSRP群で63%，HMGCR群で24%（p ＜ 0.001），頚部筋力低下の頻度はSRP群で69%，HMGCR群で44%（p = 0.01），嚥下障害の頻度はSRP群で48%，HMGCR群で11%（p ＜ 0.001），筋萎縮の頻度はSRP群で67%，HMGCR群で44%（p = 0.02）であった．筋外症状と悪性腫瘍や膠原病の合併頻度は両群とも低頻度であった．血清CKの平均値はSRP群で6581 IU/L，HMGCR群で6436 IU/Lと高値であった．筋病理ではSRP群の90%が典型的なIMNMであったが，HMGCR群ではIMNMの頻度は56%であり（p ＜ 0.001），非特異的な炎症細胞浸潤を認める症例が含まれていた．＜結語＞抗SRP抗体と抗HMGCR抗体はそれぞれ独立したIMNMの疾患標識マーカーであり，抗SRP抗体の方がより重篤な筋症状を呈し，IMNMに特異的であった．

AO-02-6　最優秀候補演題

Hematopoietic stem cell transplantation for adolescent and adult onset cerebral adrenoleukodystrophy

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Purpose: There have been accumulating evidences supporting the efficacy of hematopoietic stem cell transplantation（HSCT）for childhood onset cerebral adrenoleukodystrophy（ALD）when performed at an early stage of the disease. To date, there have been only two reported cases of adult onset cerebral ALD（ACALD）treated with HSCT and the clinical efficacy remains to be established. The purpose of this study is to evaluate the clinical efficacy of HSCT for adolescent/adult onset cerebral ALD. **Methods:** To determine the optimum timing for HSCT, we have been following 31 ALD patients [1 adolescent cerebral ALD, 1 ACALD, 12 Adrenomyeloneuropathy（AMN）, 9 AMN with later development of cerebral ALD（AMN-Cer）, 3 cerebello-brainstem ALD（OPC）, 2 OPC-Cer, 2 Addison only and 1 presymptomatic male] in a prospective manner. The average observation period was 5.6 years. Indications for HSCT include an early stage of the disease and the presence of enlarging white matter lesions. **Result:** We performed HSCT for 5 patients who developed cerebral form at an early stage. Observation periods after HSCT for each patient are 7, 3, 1.5 and 1 years with stable clinical course. The other is a month after HSCT with stable clinical course. Enhancement on brain MRI remains disappeared after HSCT with no enlargement of white matter lesions. White matter lesions reduced after HSCT in 3 patients. **Conclusion:** The present study suggests the efficacy of HSCT for adolescent/adult onset cerebral ALD. It is important to determine the optimum timing of HSCT for cerebral ALD to accomplish a good outcome from HSCT.

2016年　ポスタートピックス

基礎部門

AP-01-1　最優秀候補演題

Neuropathological examination of familial Parkinson's disease with LRRK2 I2020T mutation

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[Objective] *Leucine-Rich Repeat Kinase 2* (*LRRK2*, PARK8) gene is the most common known cause of autosomal dominant Parkinson's disease (PD). Neuropathology of PARK8 is reported to be fairly heterogeneous. The neuropathological findings of Sagamihara district with *LRRK2 I2020T* mutation (Sagamihara family) are mainly characterized by pure nigral degeneration without Lewy bodies. Also, previous study has reported that it is accompanied by various tau pathologies. The purpose of this study is to report detailed neuropathological examination of Sagamihara family. [Materials and Methods] We immunohistochemically examined eleven cases in our institute with phosphorylated α-synuclein, phosphorylated tau and amyloid β. [Results] Nine cases from Sagamihara family showed pure nigral degeneration. One of those was accompanied by Alzheimer type pathology including 3 and 4 repeat tau pathology (Braak stage IV). Other cases had minimal tau pathology in the brainstem. One case showed Lewy body pathology in the brainstem and limbic area. Another case showed many synuclein positive glial cytoplasmic inclusions (GCIs) consistent with multiple system atrophy (MSA). [Conclusions] Majority of Sagamihara family presented pure nigral degeneration. Two cases with α-synucleinopathy may need further differentiation from sporadic cases. This is the largest series of pathological report of Sagamihara family.

AP-01-2　最優秀候補演題

Fhl1 W122S mutant female mice develop late-onset cardiomyopathy

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[Objective] X-linked scapuloperoneal myopathy (X-SPM), one of the Four-and-a Half LIM 1 (FHL1) related diseases, is an adult-onset slowly progressive myopathy, sometimes associated with cardiomyopathy. We generated a knock-in mouse model that has the same mutation (c.365 G>C, p.W122S) as human patients with X-SPM. Mutant male mice developed late-onset slowly progressive myopathy, but not cardiomyopathy. [Methods] We analyzed heterozygous and homozygous female mice. [Results] Exercise test showed transient mild muscle weakness (15% reduction) in both heterozygous and homozygous female mice at 10 months, but no pathological abnormalities in skeletal muscle at any age. Echocardiograms were normal at 10 months, but at 20 months, mutant female mice showed increased systolic diameter (wild: 2.74 ± 0.22 mm, mean ± SD; heterozygous: 3.13 ± 0.11 mm, $P<0.01$; homozygous: 3.08 ± 0.37 mm, $P<0.05$) and lower fractional shortening (wild: 31.1 ± 4.4%, mean ± SD; heterozygous: 22.7 ± 2.5%, $P<0.01$; homozygous: 22.4 ± 6.9%, $P<0.01$). Histological analysis of heart revealed frequent extraordinarily large box-shaped nuclei in mutant female mice. Western blot demonstrated decreased Fhl1 protein levels in double mutant female mice in heart, but not in skeletal muscle. Proteomic analysis of heart from 20 month-old double mutant female mice suggests that integrin signaling pathway is involved in cardiac dysfunction in this mouse model. [Conclusions] Fhl1 W122S female mice manifest late-onset cardiac dysfunction. This is the first mouse model of FHL1-related cardiomyopathy.

AP-01-3　最優秀候補演題

Progranulin might protect neuronal cells against ischemic injury by inhibiting proteolysis of TDP-43

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[Purpose] Mutation of the progranulin (PGRN) gene causes frontotemporal lobar degeneration with TAR DNA-binding protein-43 (TDP-43) inclusions. We previously demonstrated that the administration of the tissue plasminogen activator (tPA) with recombinant PGRN (rPGRN) may be a novel therapeutic strategy that enables neuroprotection in part by inhibiting cytoplasmic redistribution of TDP-43, although the mechanism remains poorly understood. The purpose of this study is to determine the mechanism of the neuroprotection by PGRN against ischemic injury. [Methods] We performed Western blot analyses to determine the expression levels of TDP-43 and activated caspase-3 using a rat autologous thromboembolic model with delayed tPA treatment. We also performed immunohistochemical analyses using a transient focal ischemic model of PGRN knock-out (KO) mice and wild-type (WT) mice to examine the subcellular localization of TDP-43 after ischemia. [Results] In the rat autologous thromboembolic model with delayed tPA treatment, the full-length of TDP-43 decreased, and the C-terminal 25 kDa fragment of TDP-43 and the activated caspase-3 increased. However, administration of rPGRN with delayed tPA treatment inhibited this phenomenon. The neuronal cells showing cytoplasmic redistribution of TDP-43 were more frequently observed in PGRN KO mice than in WT mice at 24 hours after reperfusion ($P<0.01$). [Conclusion] This study demonstrated that PGRN might protect neuronal cells against ischemic injury by inhibiting caspase-3 as well as the proteolysis and abnormal cytoplasmic redistribution of TDP-43.

AP-01-4　最優秀候補演題

Severely exacerbated neuromyelitis optica rat model with extensive astrocytopathy in the acute phase

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[Objective] To establish NMO rat model closer to NMO. **[Methods]** We investigated whether the formation of severe NMO-like lesions occurs in 45 female EAE-Lewis rats, intraperitoneally injecting incremental doses of purified human immunoglobulin-G from a NMO patient ($hIgG_{NMO}$) or a high affinity anti-AQP4 monoclonal antibody (E5415A), recognizing extracellular domain of AQP4 made by baculovirus display method. **[Results]** NMO-like lesions were observed in the spinal cord, brainstem, brain and optic chiasm of EAE-rats with injection of pathogenic IgG ($hIgG_{NMO}$ and E5415A), but not in control EAE. Only in higher dose E5415A rats, there were acute and significantly severer clinical exacerbations compared with controls, within half day after the injection of pathogenic IgG. Loss of AQP4 was observed both in EAE rats receiving $hIgG_{NMO}$ and E5415A in a dose dependent manner, but the ratio of AQP4 loss in spinal sections became significantly larger in those receiving high dose E5415A up to about 50 % than those receiving low-dose E5415A or $hIgG_{NMO}$ less than 3 %. These lesions were also characterized by extensive loss of GFAP but relatively preserved myelin sheaths with perivascular deposition of IgG and C5b-9. Only in high dose E5415A rats, massive neutrophil infiltration was observed especially at the lesion edge, and such lesions were highly vacuolated with partial demyelination and axonal damage. **[Conclusions]** We established a severe experimental NMO rat model with highly clinical exacerbation and extensive tissue destructive lesions typically observed in NMO patients.

AP-01-5　最優秀候補演題

Inhibition of alpha-synuclein fibril assembly by Antisense Oligonucleotide in mice

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[Backgrounds]Accumulation of misfolded alpha-synuclein (α-syn) into Lewy bodies (LBs) and Lewy neurites (LNs) is a major hallmark of Parkinson's disease (PD) and dementia with LBs (DLB). Recent studies revealed that intracerebral injection of α-syn fibrils into wild-type mouse brains induced prion-like propagation of hyper-phosphorylated α-syn pathology. Gene knockdown of endogenous α-syn by antisense oligonucleotide (ASO) could be a new strategy for these diseases.**[Methods]** We first designed several sequences of ASO to target the mRNA of α-syn and identified highly effective five sequences by transfection studies *in vitro* (n=4). To assess these ASOs *in vivo*, we injected ASOs to female C57BL/6 mice at 7 weeks old (n=4) by intrastriatal administration, and then evaluated the α-syn expression of striatum, cortex, hippocampus and cerebllum by qRT-PCR at 7, 14 and 28 days after injection. Subsequently, we injected α-syn pffs with PBS and ASO targeting α-syn with α-syn pffs into striatum of WT mouse (n=4), and compared the distribution of phosphorylated α-syn pathologies at 14 and 28 days after intrastriatal injections.**[Results]** After injection, the reduction of mRNA in striatum was maximal on day 7, and it lasted for 4 weeks with no toxicity. To the most important, intrastriatal administration of ASO with α-syn pffs reduces LB/LN pathology.**[Conclusion]** We conclude that α-syn-targeting ASO could exert therapeutic effects in PD/DLB by knockdown of endogenous α-syn.

AP-01-6　最優秀候補演題

An iPS cell model of CADASIL: insights into the pathogenesis of a hereditary small vessel disease

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Objective: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is one of the most common forms of hereditary small vessel disease. Although *NOTCH3* has been identified as the causative gene, the molecular pathogenesis of how it leads to altered vascular tone and the degeneration of vascular smooth muscle degeneration is still unclear. **Methods:** We generated induced pluripotent stem cells (iPSCs) from three patients with CADASIL (C106R, R141C and R182C) and differentiated them into mural cells (MCs) to evaluate various cellular functions that may be affected by the mutation. Four iPSCs from healthy donors were used as controls. **Results:** The iPSCs were successfully differentiated into mural cells expressing vascular smooth muscle markers. They also showed ability to shift phenotype from synthetic to contractile and vice versa, depending on the culture condition. We further examined the functional differences between control and CADASIL MCs and found altered migration, adhesion and hypoxic responses in CADASIL. The phenotypes were also confirmed in primary cerebrovascular smooth muscle cells from transgenic mice expressing wild-type or mutant (C455R) human *NOTCH3*. **Conclusion:** Patient-derived MCs can reproduce CADASIL pathology, and therefore is useful for elucidating its pathogenesis and developing potential treatment strategies.

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臨床部門

AP-02-1　最優秀候補演題

Early and extensive spinal white matter pathology in neuromyelitis optica

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Backgrounds: Longitudinally extensive spinal cord lesions (LESCLs), a characteristic feature of neuromyelitis optica (NMO), were reported to mainly involve the central gray matter. However, the axial distributions of LESCLs have not been extensively studied. **Objective:** To clarify the distribution patterns and the pathological characteristics of LESCLs in NMO. **Methods:** We analyzed the distribution of 50 spinal cord lesions from 11 autopsied NMO/NMOSD cases. **Results:** Anterior horns, central portions and posterior horns were involved in 14/44 (31.8%), 16/44 (36.4%), and 17/44 (38.6%), respectively, in 7 cases showing AQP4 loss pattern, and 4/6 (66.7%), 4/6 (66.7%), and 4/6 (66.7%), respectively, in 4 cases showing predominantly demyelinating pattern. Anterior (AC), lateral (LC) and posterior columns (PC) were affected in 15/44 (34.1%), 28/44 (63.6%), and 26/44 (59.1%), respectively, in the AQP4 loss cases, and 3/6 (50.0%), 4/6 (66.7%), and 5/6 (83.3%), respectively, in the predominantly demyelinating cases. Only in white matter of AQP4 loss cases, we found 24 isolated perivascular lesions with selective AQP4 and connexin 43 loss without GFAP and myelin loss, affecting more frequently PC and LC than AC (1/44 (2.3%), 13/44 (29.5%), and 10/44 (22.7%), respectively). In the nearby meninges, lymphocyte infiltrates were found in none of isolated perivascular lesions. **Conclusion:** Our findings suggest that NMO preferentially affects not only gray matter but also white matter, especially PC and LC, where isolated perivascular lesions with astrocyte endfoot protein loss emerge.

AP-02-2　最優秀候補演題

Disrupted muscle uptake of creatine in spinal and bulbar muscular atrophy

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[Objective] Spinal and bulbar muscular atrophy (SBMA) is a hereditary disorder resulting from the degeneration of motor neurons and skeletal muscles. Here we explore the pathomechanism underlying the reduction of serum creatinine (Cr) concentrations in SBMA. **[Methods]** We included patients with SBMA (n=65), amyotrophic lateral sclerosis (ALS) (n=27), and healthy controls (n=25). We used dual-energy X-ray absorptiometry (DXA) to measure appendicular lean soft tissue (ALST) mass as an index of skeletal muscle mass. We also examined the intramuscular concentrations of creatine, a precursor of Cr, as well as the protein and mRNA expression levels of creatine transporter in autopsied muscle specimens using immunohistochemistry, immunoblotting, and quantitative reverse transcriptase-polymerase chain reaction. **[Results]** In subjects with SBMA, serum Cr concentrations correlated well with ALST mass ($r = 0.424$, $p < 0.001$). Both serum Cr and muscle creatine concentrations were lower in SBMA than in ALS ($p < 0.001$ and 0.018, respectively), although ALST mass was similar between these two groups. Moreover, the protein and mRNA expression levels of muscle creatine transporter were suppressed in SBMA compared with ALS. **[Conclusion]** These results suggest that low serum Cr concentrations in SBMA are caused by not only neurogenic muscular atrophy but also the disrupted muscle uptake of creatine, which may lead to a therapeutic approach for SBMA.

AP-02-3　最優秀候補演題

Abnormal splicing of tau transcripts influences neuropathology of myotonic dystrophy

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Objective: Since splicing abnormality of the tau transcripts in myotonic dystrophy (MyD) was suggested, we investigated the tau variation of N- terminals in the brains of patients with MyD. *Material and methods:* We analyzed 28 MyD autopsy brains (18 men and 10 women). Serial sections from the medulla oblongata, pons, midbrain, and hippocampus were examined. Sections were stained with hematoxylin and eosin, Klver- Barrera, and immunostained with phosphorylated tau and each N-terminals of phosphorylated tau (0N, 1N, 2N). Neurofibrillary tangles (NFTs) and astrocytic glial tangles were semi-quantified. For two patients, western blot analysis was performed on frozen brain tissues derived from the transentorhinal cortex and hippocampal regions. Clinical information was retrospectively collected from medical charts. *Result:* The death age of the patients ranged from 39 to 74 years and the duration of the disorder was 2 to 45 years. Brain weight was 950- 1430g and Braak NFT stage was I - IV (mean stage 2.3). Furthermore, in the immunostaining with the N- terminals of phosphorylated tau, 0N isoform was the most abundant in the hippocampus. The astrocytic glial tangles were observed especially in the lower midbrain and 0N isoform was also the most abundant. Western blot analysis showed that 3R0N and 4R0N were the main isoforms of tau protein. *Discussion and conclusion:* In this study, 0N isoform of the N- terminals of phosphorylated tau was the most abundant in MyD neuropathologically and biochemically. The splicing abnormality of the tau transcripts was suggested in MyD.

AP-02-4　最優秀候補演題

Impact of MAR Image on Prediction of Conversion to Alzheimer's Disease

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PURPOSE: Our previous studies proposed the voxel-wise metabolism to amyloid deposits ratio (MAR) image as a novel marker for Alzheimer's disease (AD). The current study evaluated the predictive value of MAR image for future conversion to AD in subjects with mild cognitive impairment (MCI).METHODS: Consecutive 493 subjects with MCI were included from the ADNI database. Receiver operating characteristic analyses for predicting future conversion to AD at 2 and 3-year visit were examined in MAR, 18F-FDG-PET and 18F-florbetapir (AV-45) PET images at baseline.RESULTS: The area under the curve (AUC) for MAR image, AV45 and FDG-PET was 0.83, 0.78 and 0.75 at 2-year visit and 0.85, 0.80 and 0.77 at 3-year visit. The AUC for MAR image was significantly larger than that for AV-45 PET (p= 0.0013) and FDG-PET (p=0.0090) at 2-year visit, and larger than AV-45 PET (p= 0.0003) and FDG-PET (p=0.0045) at 3-year visit.CONCLUSION: MAR image more accurately predicted future conversion to AD in MCI than AV-45 and FDG-PET.

AP-02-5　最優秀候補演題

In vivo microglial activation and tau deposition in dementia with Lewy bodies

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＜Objective＞ The presence of misfolded proteins such as tau and alpha-synuclein, key players in the pathogenesis of dementia with Lewy bodies (DLB), can lead to activation of microglia in the brain. Indeed, microglia activation or neuroinflammation is reported to relate to the neuronal degeneration in DLB. Activated microglia develop an increased number of receptor known as a translocator protein (TSPO), which can be depicted in vivo by a 2nd-generation TSPO tracer [11C]-DPA713. In addition, a recently developed tracer [11C]-PBB3 has succeeded in imaging of tau deposition in humans. No study has been reported about in vivo relationship between tau deposition and neuroinflammation in the DLB brain so far. Here, we investigated this issue using positron emission tomography (PET) with [11C] -DPA713 and [11C] -PBB3. ＜Methods＞ Five probable DLB patients (mean age 74.2 ± 3.9 yrs) and age-matched healthy adults underwent [11C]-DPA713 and [11C]-PBB3 PET measurements. The non-displaceable binding potential (BP_{ND}) was estimated on the simplified reference tissue model (SRTM). Statistical Parametric Mapping (SPM) was used to compare BP_{ND} level between the DLB and control group. In addition, regional BP_{ND} was also evaluated using region of interest (ROI) analysis. ＜Results＞ The average levels of [11C]-DPA713 BP_{ND} and [11C]-PBB3 BP_{ND} from all ROIs in patients of DLB were significantly higher than those in healthy adults. Regional differences were also found in the temporal and parietal cortices. ＜Conclusions＞ Microglial activation and tau deposition are pathophysiologically important in DLB.

AP-02-6　最優秀候補演題

First Archaeal Infection in Human Brain: a new type of chronic encephalomyelitis

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[Background] The domain Archaea is one of the three domains of living organisms together with eukarya and bacteria, usually inhabiting extreme environments. No evidence of central nervous system disorders due to archaeal infection has been reported. [Objective] To determine the causative pathogen of a new type of encephalomyelitis. [Methods] We treated four patients with geographic clustering and comparable clinical features. Brain biopsy was conducted in all patients to analyze neuropathological changes. Genomic DNA was obtained from the affected brain tissues, and a next generation sequencing (NGS) was used to screen for specific genomic sequences indicative of the pathogen origin. [Results] All patients exhibited progressive dementia with involuntary tongue movements. Cytological examination of cerebrospinal fluid revealed elevated mononuclear cells. Abnormal MRI signals were observed in temporal lobes, subcortical white matter, and spinal cord. Biopsied brain tissue exhibited aggregated periodic acid-Schiff-positive macrophages and 2-7 μm diameter round/oval bodies without nuclei or cell walls scattered around the vessels. NGS identified more than 100 archaea-specific DNA fragments. All patients were responsive to trimethoprim-sulfamethoxazole plus corticosteroid therapy. [Conclusions] We propose a new disease entity resulting from a causative pathogen having archaeal features. Further elucidation of this unique pathogen causing the encephalomyelitis may provide insights into resolving undiagnosed cases of chronic inflammatory diseases.

Nominees for the Best Presentation Award for the International Participants

APe-01-1　海外最優秀候補演題

Clinical features of MELAS: an analysis of 190 cases

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Objective To summarize the clinical features of Chinese patients with mitochondrial encephalomyopathy, lactate acidosis, stroke-like episodes(MELAS). **Methods** A total of 190 MELAS patients who presented to Peking University First Hospital between 1997 and 2015 were studied. The clinical features, including predisposing factors of stroke-like episodes, the onset symptoms and frequencies of various manifestations were analyzed and reported. **Results** In our cohort, the male-to-female ratio was 1.44:1. The median age of onset was 14 years (from 7 months to 45 years). The median onset age of the first stroke-like episode was 16 years (from 1 to 53 years). Fatigue and upper respiratory tract infection were the most common predisposing factors of stroke-like episodes(37.88% and 34.85%, respectively). Stroke-like episodes appeared in 70.53% patients as an onset symptom and developed in all patients with disease progression. The relatively commom neurological manifestations included seizure (89.42%), mental retardation or dementia (82.87%), headache (74.30%), hemianopia or cortical blindness (67.72%), exercise intolerance (50.87%). The common manifestations of extra-nervous systems included hirsutism (67.57%), vomiting (65.58%), fever (62.07%). **Conclusion** The majority of the patients in this study had the disease onset during childhood. There were more male MELAS patients than females. Most common clinical manifestations were seizure, mental retardation or dementia, headache, cortical blindness, hirsutism, vomiting and fever in this patient cohort.

APe-01-2　海外最優秀候補演題

Blood amino acids and acylcarnitines spectrums in Chinese patients with mitochondrial disease

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Objective To report the characteristics of blood amino acids and acylcarnitines spectrums of patients with mitochondrial disease. **Methods** Fifty patients with mitochondrial disease, twenty patients with multiple acyl-CoA dehydrogenase deficiency (MADD) and twenty-two cases of healthy adult controls underwent analysis of amino acid and acylcarnitines by tandem mass spectrometry. Non-parametric analyses were used to compare the level of amino acids and acylcarnitines between each of mitochondrial disease, MADD and healthy control groups and one another among three groups. **Results** The median level of glutamate and ornithine in patients with mitochondrial disease was 89.80 μmol/L and 27.70 μmol/L, respectively, lower than 113.46 μmol/L(P=0.002) and 33.52 μmol/L(P=0.010) in MADD, respectively, 107.33 μmol/L(P＜0.001) and 34.08 μmol/L(P＜0.001) in healthy control, respectively. The median level of alanine/glutamate ratio was 2.72 in mitochondrial disease, which was higher than 1.86 in MADD (P＜0.001) and 1.55 in healthy control (P＜0.001). The median level of C5OH was 0.33 μmol/L in mitochondrial disease, higher than 0.19 μmol/L (P=0.011) in MADD and 0.20 μmol/L in healthy control(P＜0.001). The diagnostic sensitivity and specificity of alanine/glutamate ratio＞2.17 for mitochondrial disease was 76.00% and 85.71%, respectively. Conclusions mitochondrial disease have a specific pattern of blood amino acids and acylcarnitines spectrums. Blood amino acids and acylcarnitines spectrums may serve as a potential biomarker for mitochondrial disease.

APe-01-3　海外最優秀候補演題

EPIDEMIOLOGICAL, CLINICAL, AND GENETIC STUDY IN A LARGE COHORT OF PATIENTS WITH SPASTIC PARAPLEGIA

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Purpose: This study includes the evaluation of a comprehensive spectrum of clinical features and the mutational screening of the SPG4/*SPAST* gene in patients with hereditary spastic paraplegia (HSP). **Method:** A large cohort of patients were recruited from Italian, Brazilian, and Japanese populations in a period from 2008 to 2015. Clinical and instrumental functional analyses consist of neurological assessment and neuroimaging. Mutational screening was carried out by Sanger sequencing and MLPA analysis. Haplotype studies were also performed. **Results:** Our study highlights clinical and epidemiological differences among populations, showing unique genotype-phenotype correlations. Genetic analysis revealed a total of 52 different pathogenic nucleotide changes in 284 HSP patients: 21 sporadic cases and 263 cases from 96 families. Among them, six nucleotide changes were novel and pathogenic. The analysis revealed a great portion of private mutations worldwide and confirmed the founder effect for one recurrent variant in the Italian population. Interestingly, mutations were detected in 21% of sporadic cases and in a range from 16% to 100% of families, depending on the number of affected in the family. **Conclusion:** This study represents the first worldwide SPG4/*SPAST* genetic screening on HSP patients. Epidemiological and clinical results broaden the spectrum of the clinical presentations of HSP associated with mutations in SPG4/*SPAST*. Finally, our findings provide evidence that the chance to detect SPG4/*SPAST* mutations varies proportionally to the number of affected in the family.

APe-01-4

Withdrawn

APe-01-5　海外最優秀候補演題

Greater progression of Parkinson disease in patients carrying LRRK2 risk variants

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Objectives: To characterize clinical characteristics and progression in patients with LRRK2 variants, G2385R, R1628P and S1647T, which are associated with increased risk for Parkinson Disease (PD) in Asian population.**Methods:** A total of 202 patients with PD, including 133 patients with risk variants and 69 patients without these variants, were followed up and evaluated using Modified Hoehn and Yahr (H&Y) staging scale, Unified Parkinson's Disease Rating Scale (UPDRS) part III, Non-Motor Symptom Scale (NMSS), Parkinson's disease Questionnaire-39 item version (PDQ-39) and Elderly Cognitive Assessment Questionnaire (ECAQ). Means of generalized estimating equation (GEE) model was performed to compare the differences from baseline between LRRK2 risk variant carriers and non-carriers.**Results:** At baseline, patients with risk variants exhibited significantly worse ECAQ score (P=0.0202) and PDQ-39 domain 1 (mobility) (P=0.0253), domain 2 (activities of daily living) score (P = 0.0154) than control patients. Our longitudinal analysis revealed greater progression from 3 year of PD onwards by using Modified Hoehn and Yahr (H&Y) staging scale(P=0.041).**Conclusions:** PD patients with Asian specific risk variants (G2385R, R1628P and S1647T) in LRRK2 may experience severe disease progression in the long-term follow up.

APe-01-6　海外最優秀候補演題

Characterization of CADASIL among the Han Chinese in Taiwan: Distinct Genotypic and Phenotypes

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Objective Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is originally featured with a strong clustering of mutations in *NOTCH3* exons 3-6 and leukoencephalopathy with frequent anterior temporal pole involvement.**Methods** Mutation analyses of exons 2 to 24 of *NOTCH3* were performed by Sanger sequencing. Haplotype analysis was done by genotyping 6 polymorphic microsatellite markers flanking *NOTCH3* and covering a region of 7.54 kcM.**Results** A total of 112 CADASIL patients from 95 families were included. Twenty different mutations in *NOTCH3* were uncovered, including 3 novel ones, and R544C in exon 11 was the most common mutation, accounting for 70.5% of the pedigrees. Haplotype analyses were conducted in 14 families harboring *NOTCH3* R544C mutation and demonstrated a common haplotype linked to *NOTCH3* R544C at loci D19S929 and D19S411. Comparing with CADASIL in most Caucasian populations, CADASIL in Taiwan has several distinct features, including less frequent anterior temporal involvement, older age at symptom onset, higher incidence of intracerebral hemorrhage, and rarer occurrence of migraine. Subgroup analyses revealed that the R544C mutation is associated with lower frequency of anterior temporal involvement, later age at onset and higher frequency of cognitive dysfunction.**Conclusions** The present study broadens the spectrum of *NOTCH3* mutations and provides additional insights for the clinical and molecular characteristics of CADASIL patients of Han-Chinese descents.

APe-01-7 **海外最優秀候補演題**

Circulating Muscle-specific miRNAs in Duchenne Muscular Dystrophy Patients at Different Ages

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Objective Serum CK has been utilized as a diagnostic marker for DMD, but it correlates less well with the DMD pathological progression. In this study, we hypothesized that the serum levels of six muscle-specific miRNAs (miR-1,-206,-33,-499,-208a and -208b) may be useful for monitoring the DMD muscle pathological progression. **Method** We determined the levels of these miRNAs in serum samples from healthy (n=23),Duchenne (n=52) and Becker (n=15) children, aged from 1 to 14 years old. We examined serum levels of myomiRs in DMD and BMD patients (by using real-time quantitative reverse transcription-polymerase chain reaction) and compared the serum levels of miRNAs with clinical assessment including age, CK value, and muscle fiber composition. **Result** The serum levels of six muscle-specific miRNAs were all elevated in DMD patients ($P<0.01$). The receiver operating characteristic curves of circulating miR-206, miR-499, miR-208b, and miR-133 levels reflected strong separation between BMD and DMD patients ($P < 0.05$). miR-206, miR-499, and miR-208b levels were positively correlated with both age and type 2c muscle fiber content in DMD patients (2-6 years), indicating that they might represent the stage of disease as well as the process of regeneration. miR-499 and miR-208b levels were correlated with slow and fast fiber content and might reflect the ratio of slow to fast fibers in DMD patient (>6years). **Conclusion** suggesting that circulating myomiRs might reflect the effects of cytokines and growth factors on degenerating and regenerating muscles.

APe-01-8 **海外最優秀候補演題**

Clinical Profile of Patients with Myotonic Dystrophy in Czech Republic

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Background and objectives. Myotonic dystrophy is the most common form of muscular dystrophy in adulthood. The prevalence of the two types varies among different geographic and ethnic populations. In Middle Europe type II seems to be more frequent than type I. Patient registry is one of the key instruments of the epidemiological assessment in rare diseases.**Patients and Methods.** The Czech National Registry of Myotonic Disorders include (November 2015) 426 patients from 8 centres.**Results.** Only patients with completed files (n=348) were analysed: 207 (59%) are suffering from myotonic dystrophy type 2 (DM2) and 141 (41%) from myotonic dystrophy type 1 (DM1). Mean age at the time of the registry entering was 45 years, approximately 10 years after disease manifestation which was in patient with DM1 25 (10-54) years and in persons with DM2 40 (17-62) years. We did not find any difference in muscle force between both types (assessed by MRC score). The presence of cataracts was also similar in both groups. Patients suffering from DM1 have more severe myotonia and heart problems (esp. arrhythmias), which have been manifesting since younger age (40 vs. 55 years). Also dysphagia and fatigue are much more frequent in patients with DM1. Patients with DM1 have also lower forced vital capacity than people with DM2. ($p<0.001$, Fisher exact test for categorical and Mann-Whitney U test for continuous variables.)**Conclusion.** In Czech population (Middle Europe, 10,5 mil. inhabitants) is more frequent DM2 than DM1. Patients with DM1 are younger and more compromised than patients with DM2.