2016年 口演トピックス
基礎部門
AO-01-1
Development of rehabilitation accelerating agent based on neural plasticity mechanism
1Department of Physiology, Yokohama City University Graduate School of Medicine, 2Department of Neurology and Stroke Medicine, Yokohama City University Graduate School of Medicine, 3TOKIYA CHEMICAL CO., LTD, 4Systems Neuroscience Group, National Institute of Advanced Industrial Science and Technology

[Hiroki Abe1,2, Susumu Jitsukawa1, Takashi Komori2, Waki Nakajima1, Yumi Murata1, Noriyuki Higo1, Tomohito Okuda1, Fumiki Takanaka1, Takaaki Takahashi1]

[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 recovery potential is limited because the mechanism underlying functional recovery after stroke is still largely unknown. The restoration of functional deficits is considered to be the result of comprehensive neural plasticity in the intact brain regions. Synaptic AMPA receptor delivery is a fundamental mechanism underlying beneficial 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 would 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 robust model revealed that T-817MA accelerates motor functional recovery in a training-dependent manner. Further analysis was conducted with naive monkeys, which have more complex manual dexterity. Using two reach-grasp-test 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. [Conclusion] These results indicated the great potential of a novel rehabilitation facilitator.

AO-01-2
Analysis of molecular mechanism and development of therapeutic method in spioncerebellarataxia type 1
1Department of Neuropathology, Medical Research Institute and Center for Brain Integration, Tokyo Medical and Dental University, 2Department of Neurology, Hiroshima University

[Hikaru Ito1,2, Kyoto Fujita1, Kigui Chen1, Hitoshi Okazawa1]

[Objective] We previously searched for nuclear proteins quantitatively affected by mutant Atx(A) in neurons and found a significant decrease in high-mobility group box group (HMGB) 1/2 proteins in the soluble nuclear fraction. HMGB supplementation actually ameliorated eye degeneration in an SCA1 fly model and restored impaired DNA damage repair (Q et al., 2007). We established that transgenic or virus-mediated complementation with HMGB1 ameliorates motor dysfunction and prolongs lifespan in mutant Atxn1 knock-in (Atxn1KI) mice. [Methods] We analyzed mitochondrial DNA damage repair by mitoH2AX focus formation in an exosome-dependent manner. Further, we found that HMGB1 is physiologically secreted from cells via exosomes, independent of the classical ER–Golgi secretion pathway, and taken up by surrounding cells. Addition of HMGB1 to virus non-infected neurons unexpectedly suppresses polyQ inclusions even in virus non-infected neurons. Here we propose that HMGB1 ameliorates polyQ disease caused by nuclear DNA damage repair and nuclear transcription. Moreover, we show that the rescue of Purkinje cell dendrites and dentritic spines by HMGB1 could be downstream factors of HMGB1 ameliorating polyQ-induced motor dysfunction. [Conclusion] These results indicate that HMGB1 augments functionally recovery even in virus non-infected neurons and suggest that HMGB1 exosomes may play a role in polyQ disease.

AO-01-3
Insight into the Pathophysiology of the Human Mutant TARDBP Knock-In Mice
1Keio University School of Medicine, Department of Neurology, 2Jikei University School of Medicine, Department of Regenerative Medicine, 3Tokyo Metropolitan Institute of Gerontology, 4Riken Brain Science Institute, 5Nagita University Brain Research Institute, 6Department of Cellular Neurobiology, Keio University School of Medicine, Department of Physiology

[Yugaku Date1, Chikako Haramiyauchii1, Junko Fujisaki1, Naoki Kogo1, Chie Sano1, Yuki Kobayashi1, Shigesato Ichihara1, Kenji Sakamura1, James Hirotaoka2, Hidetuji Okano3, Noruhiro Suzuki4]

[Objective] A human mutant TARDBP transgenic animal model could be a strong tool to comprehend the mechanism of TD-43 pathology, but the fact that elevated level of human wild type TARDBP also develops disease, makes it difficult to simply apply the role of mutant human TARDBP gene by the observation of promoter-mediated transgenic mice models. So the aim of our project is to comprehend the pathophysiology of TD-43 pathology utilizing human mutant TARDBP KI mouse models. [Methods] We designed, and produced two lines (G348C / A382T) of mutant TARDBP KI mice models. [Results] 1) We obtained two lines of G348C / A382T mice (G348C / A382T) which was expected to be like the human TARDBP KI mice. 2) Immunohistological analysis revealed that G348C / A382T mice showed SFPQ protein decrease and motor neuronal loss. [Conclusion] These results indicate that SFPQ may be a pathological mechanism of TD-43 pathology.

AO-01-4
Loss of PSF/SPFQ, an intra-nuclear counterpart of FUS causes FTLD-like phenotypes
1Department of Neurology, Nagoya University Graduate School of Medicine, 2Department of Brain Development and NeuroRegeneration, Tokyo Metropolitan Institute of Medical Science, 3Research Institute of Dementia and Neurodegenerative Disease, Nagoya University Graduate School of Medicine

[Yusuke Fujikawa1, Shinshuke Ishigaki1, Satoshi Yokoi1, Daiyu Honda1, Haruo Okado1, Hirohisa Watanabe2, Masahisa Katsuno2, Gen Sobue1]

[Objective] We identified splicing factor, pre-mRNA and glutaminic-rich (PSF) as a counterpartner of FUS in the nucleus. SFPQ regulates alternative splicing of the Mapt gene at exon 20 as FUS does. Because the balance of these two interactions between FUS and SFPQ is a key point that this 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 transferred AAV encoding shRNA against SFPQ (shSFPQ) and control to the bilateral hippocampus of C57BL/6 mice. Next, we performed co-injection of AAV encoding mRFP against Mapt exon 20 (isoform 4 repeat trunca
tion, 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 showed fitlD-like behavioral impairments as well as reduced adult neurogenesis as seen in shSFPQ mice. Long-term observation revealed phosphorylated tau accumulation and increased 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. [Conclusion] 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 of FUS silenced mice, suggesting that SFPQ is essential for the pathogenesis of FTD/ALS in which quality loss of FUS is associated.

AO-01-5
Non-cell autonomous therapeutic effects on polyQ disease models by exosomal chaperone transporation
1Institute for Chemical Research, Kyoto University, 2National Institute of Neuroscience, National Center of Neurology and Psychiatry, 3Laboratory for Molecular Membrane Neuroscience, RIKEN Brain Science Institute

[Toshitake Takayama1,2,3, Mari Suzuki1, Nobuhiro Fujikake2, Akiko Poppei2, Hasee Kikuchi2, Shiroh Futaki2, Keiji Wada2, Yoshitaka Nagai2]

[Objective] The polyglutamine (polyQ) diseases including Huntington’s disease (HD) are commonly caused by an expansion (>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 oral 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] Hsp70 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 Hsp70 or Hsp70-containing exosomes to the culture medium of the polyQ-expressing cells results in efficient suppression of polyQ inclusion. Moreover, expression of Hsp70 or Hsp40 in remote tissues such as muscle and fat body in Drosophila significantly suppresses polyQ-induced photoreceptor degeneration in an exosome-dependent manner. [Conclusion] We conclude that exosome-mediated intercellular transmission of molecular chaperones contributes to non-cell-autonomous therapeutic effects on polyQ disease models.

AO-01-6
GABAA deficiency accelerates alpha-synuclein priro-like conversion and promotes its neurotoxicity
1Department of Degenerative Neurological Diseases, National Institute of Neuroscience, NCPD, 2Laboratory for Molecular Membrane Neuroscience, RIKEN Brain Science Institute

[Mari Suzuki1, Nobuhiro Fujikake2, Toshitake Takayama1, Akiko Poppei2, Hasee Kikuchi2, Shiroh Futaki2, Keiji Wada2, Yoshitaka Nagai2]

[Objective] alpha-synuclein (αSyn) 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 (GBA) gene are strong risk factors for PD and DLB. The purpose of this study is to examine the mechanism link between the functional loss of GBA [αSyn(priro)] and the toxicity of the αSyn in vivo. [Methods] We employed Drosophila models to examine the effect of GBA gene deficiency on the neurotoxicity of αSyn and its molecular mechanism. [Results] Behavioral and histological analyses showed that knockdown of the Drosophila GBA exacerbates the locomotor dysfunction and loss of dopaminergic neuron in PD models. [Conclusion] We conclude that GBA deficiency accelerates the alpha-synuclein priro-like conversion and promotes its neurotoxicity. A specific intervention that counteracts the GBA deficiency may be a therapeutic approach for PD and DLB.
These results in new animal models suggest that T-817MA may have a remarkable effect, in addition to the mechanisms already associated with HMGB1 function, such as ameliorates eye degeneration in an SCA1 fly model and restores impaired DNA repair and nuclear transcription. Moreover, we show that the effect of TNF-α on HMGB1 levels can be increased through the use of viral vectors, which can be delivered in vivo.

**[Conclusions]**

Three lines of our KI mice show cognitive dysfunction. In A382T KI mice, Bunina bodies are identified (8 months old), and motor neuron decrease was observed. Each line of our KI mice shows a different level of cognitive dysfunction, indicating that the absence of TARDBP can have a significant impact on brain function. Additionally, we observed that the reduction of TARDBP expression results in changes in gene expression and protein levels, which could contribute to the development of neurological disorders.

**[Methods and Results]**

To verify this hypothesis, we used simple voluntary exercise. We found that voluntary exercise significantly improves motor function and reduces the severity of pathological changes in the TARDBP KI mice.

**[Conclusions]**

The results of this study indicate that TARDBP deficiency can lead to cognitive dysfunction and pathological changes in the brain. These findings suggest that TARDBP may be a potential target for the treatment of neurological disorders. Further research is needed to understand the mechanisms underlying these effects and to develop effective therapeutic strategies.
Cerebrospinal fluid -CRMP5 is a diagnostic biomarker of NMOSD with AQPD-igG

【背景】NMOSDは神経伝導を障害する疾患で、神経伝導に影響を与える抗体が関与されている。CRMP5は神経伝導を障害する抗体の一つとされている。特に神経伝導の障害が顕著であることを示す有用な指標であることが示唆されている。

【目的】CRMP5の臨床的重要性を明らかにすることを目的として、本研究ではCRMP5の臨床的意義を検討した。

【方法】CRMP5の臨床的意義を検討するために、病態が明らかでない場合の有効性を検討した。CRMP5の測定は、神経伝導を障害する抗体の一つとされている。

【結果】CRMP5の測定は、神経伝導を障害する抗体の一つとされている。特に神経伝導の障害が顕著であることを示す有用な指標であることが示唆されている。
2016年 ポスタートピックス
基礎部門
Neuropathological examination of familial Parkinson’s disease with LRRK2 G2019S mutation

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Objective: LRRK2 is the most common known cause of idiopathic Parkinson's disease (PD). Neuropathological examination of familial Parkinson's disease (FAD) is expected to be fairly heterogeneous. The neuropathological examination of familial Parkinson's disease (FAD) will show that the Lewy body is mainly characterized by pore signal degeneration without Lewy bodies. Also previous study has reported that it is accompanied by various tauopathies. 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, phosphatase tau and anti-β amyloid. [Results]: Majority of Sagamihara family presented pore signal degeneration. Two cases with a synaptopathy may need further discrimination from sporadic cases. This is the largest series of pathological report of Sagamihara family.

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

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Objectives: To establish NMO rat model closer to NMO [Method]: We investigated whether the formation of severe NMO-like lesions in Lewis female rats injected with pathogenic IgG (hIgG NMO and E5415A) without the presence of demyelination (DLB). Recent studies revealed that intracranial injection of α-syn fibrils into wild-type mouse brains induced prion-like propagation of hyperphosphorylated α-syn pathology. Gene knockdown of endogenous α-syn by antisense oligonucleotide (AOSO) could be a new strategy for these diseases [Method]: We first designed several sequences of AOSO to target the mRNA of α-syn and identified highly effective five sequences by transfection studies in vitro (n=4). To assess these AOSOs in vivo, we injected AOSO 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 cerebellum by qRT-PCR at 7, 14 and 28 days after injection. Subsequently, we injected a syn pbs with AOSO targeting α-syn with a syn pbs into striatum of WT mouse (n=4), and compared the distribution of phosphorylated α-syn pathologies at 14 and 28 days after injection. In addition, we performed Western blot analysis of intrastriatal injection of α-syn in mouse heart, but not in striatum. Protonic analysis of heart from 2-month-old male mutant mice suggests that the structure of α-syn is intact and the intrastriatal injection of α-syn was maximal on day 7, and it lasted for 4 weeks with no toxicity.

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

1Department of Regenerative Medicine and Tissue Engineering, National Cerebral and Cardiovascular Center Research Institute, 2Department of Diabetes Endocrinology and Nutrition, Graduate School of Medicine, Kyotou University, 3Division of Neurology, Graduate School of Kobe University, 4Center for iPS Cell Research and Application (CiRA), Kyoto University, 5Department of Degenerative Neurological Diseases, National Institute of Neurosciences, National Center of Neurology and Psychiatry, 6Department of Dementia Prevention and Therapeutics, Graduate School of Medicine, Meitou University, 7Department of Neurology, Kyotou Prefectural University Hospital, 8Department of Neurology, Kyotou University Graduate School of Medicine, 9Department of Stroke and Cerebrovascular Diseases, National Neurocenter and Cardiovascular Center Research Institute

Objectives: CADASIL is a rare autosomal dominant disease caused by NOTCH3 mutations. This study aimed to establish a severe experimental model of CADASIL in mice. We investigated whether the formation of severe NMO-like lesions in Lewis female rats injected with pathogenic IgG (hIgG NMO and E5415A) without the presence of demyelination (DLB). Recent studies revealed that intracranial injection of α-syn fibrils into wild-type mouse brains induced prion-like propagation of hyperphosphorylated α-syn pathology. Gene knockdown of endogenous α-syn by Antisense Oligonucleotide (ASO) could be a new strategy for these diseases [Method]: 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 ASO 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 cerebellum by qRT-PCR at 7, 14 and 28 days after injection. Subsequently, we injected a syn pbs with ASO targeting α-syn with a syn pbs into striatum of WT mouse (n=4), and compared the distribution of phosphorylated α-syn pathologies at 14 and 28 days after injection. In addition, we performed Western blot analysis of intrastriatal injection of α-syn in mouse heart, but not in striatum. Protonic analysis of heart from 2-month-old male mutant mice suggests that the structure of α-syn is intact and the intrastriatal injection of α-syn 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 pbs reduces LB/LN pathology. Conclusion: We conclude that α-syn targeting ASO could exert therapeutic effects in F/D/DLBD by knockdown of endogenous α-syn.

AP-01-1

AP-01-3

AP-01-4

AP-01-6

AP-04-4

AP-05-1

AP-06-1

AP-04-1
Medicine, 6Department of Neurology, Hakone National Hospital, 7Department of
and Development Center for New Medical Frontiers, Kitasato University School of

Michio Hirano 2

redistribution of TDP-43.

However, administration of rPGRN with delayed tPA treatment inhibited this phenomenon.

ischemic model of PGRN knock-out (KO) mice and wild-type (WT) mice to examine the
treatment. We also performed immunohistochemical analyses using a transient focal
activated caspase-3 using a rat autologous thromboembolic model with delayed tPA
performed Western blot analyses to determine the expression levels of TDP-43 and

demonstrated that the administration of the tissue plasminogen activator (tPA) with
[Purpose] Mutation of the progranulin (PGRN) gene causes frontotemporal lobar

Takayoshi Shimohata

Proteomic analysis of heart from 20 month-old double mutant female mice suggests that integrin
lower fractional shortening (wild: 31.1 ± 4.4%, mean ± SD; heterozygous: 22.7 ± 2.5%, P<

20 months, mutant female mice showed increased systolic diameter (wild: 2.74 ± 0.22 mm,

abnormalities in skeletal muscle at any age. Echocardiograms were normal at 10 months, but at

homozygous female mice. [Results] Exercise test showed transient mild muscle weakness (15%

[Objective] X-linked scapuloperoneal myopathy (X-SPM), one of the Four-and-a Half LIM 1

Kazuo Fujihara 2, 8, Takao Hamakubo 7, Masato Yasui 5, 6, Masashi Aoki 1

○Yumi Yamamoto 1, Katsutoshi Kojima 2, Daisuke Taura 2, Masakatsu Sone 2, Kazuo Washida 3,

○Jindong Song 1, Tetsuya Nagata 1, Wenying Piao 1, Kazutaka Nishina 1,

1Department of Neurology and Neurological Science, Tokyo Medical and Dental

mice

Inhibition of alpha-synuclein fibril assembly by Antisense Oligonucleotide in

AP-01-5

[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

[Objective] Leucine-Rich Repeat Kinase 2 (LRRK2, PARK8) gene is the most common known cause of autosomal

1Department of Neurology, Kitasato University School of Medicine, 2Department of

Science and Technology, The University of Tokyo, 8Department of Multiple Sclerosis

To establish NMO rat model closer to NMO.

[Objective]

2016年 ポスタートピックス
臨床部門
Early and extensive spinal white matter pathology in neuromyelitis optica

1Department of Neurology, Nagoya University Graduate School of Medicine. 2Department of Radiology, Kinki University Faculty of Medicine

**[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=6), amyotrophic lateral sclerosis (ALS) (n=25), and healthy controls (n=26). 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, as well as the protein and mRNA expression levels of creatine transporter in autopsied muscle specimens using immunohistochemistry, immunoblotting, and quantitative reverse transcription-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 non-displaceable binding potential (BPND) 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 impaired uptake of creatine via astrocyte endfoot transport protein.

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

1Department of Biomedical Imaging, Medical Photonics Research Center, Hamamatsu University School of Medicine. 2First Department of Medicine, Hamamatsu University School of Medicine

**[Objectives]** Microglia, the resident immune cells of the brain, play a key role in the pathogenesis and progression of various neurodegenerative diseases. Microglial activation is characterized by changes in the expression of surface markers (e.g., CD163, CD204) and the production of inflammatory cytokines. However, the role of microglia in the pathogenesis of dementia with Lewy bodies (DLB) remains unclear. DLB is a neurodegenerative disorder characterized by Lewy bodies, a hallmark feature of Parkinson's disease (PD), and cognitive impairment. In DLB, microglial activation has been observed in various brain regions, including the substantia nigra, hippocampus, and cerebral cortex.

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

1Department of Neurology and Geriatrics, Kagoshima University Graduate School of Medical and Dental Sciences. 2Department of Neurology, Inamurabara hospital, 3Center for Chronic Viral Diseases, Kagoshima University Graduate School of Medical and Dental Sciences

**[Objectives]** Microglia, the resident immune cells of the brain, play a key role in the pathogenesis and progression of various neurodegenerative diseases. Microglial activation is characterized by changes in the expression of surface markers (e.g., CD163, CD204) and the production of inflammatory cytokines. However, the role of microglia in the pathogenesis of dementia with Lewy bodies (DLB) remains unclear. DLB is a neurodegenerative disorder characterized by Lewy bodies, a hallmark feature of Parkinson's disease (PD), and cognitive impairment. In DLB, microglial activation has been observed in various brain regions, including the substantia nigra, hippocampus, and cerebral cortex.

First Archaela Infection in Human Brain: a new type of encephalomyelitis

1Department of Neurology and Geriatrics, Kagoshima University Graduate School of Medical and Dental Sciences. 2Department of Neurology, Inamurabara hospital, 3Center for Chronic Viral Diseases, Kagoshima University Graduate School of Medical and Dental Sciences

**[Objectives]** Encephalomyelitis is a rare and severe inflammatory disease of the central nervous system that can be caused by various pathogens. While bacterial and viral infections are among the most common etiologies, other pathogens such as fungi, parasites, and microorganisms have also been implicated in certain cases of encephalomyelitis. In recent years, there has been increasing evidence for the role of microorganisms in the etiology of encephalomyelitis, particularly in cases where the cause is not readily apparent. This has led to the development of new diagnostic tools and strategies for the identification of these pathogens.

**[Methods]** We conducted a retrospective review of brain biopsy specimens from patients with encephalomyelitis to identify microorganisms that might be causative agents. We analyzed the specimens using a combination of histological, molecular, and immunohistochemical techniques to detect a wide range of potential pathogens, including bacteria, viruses, fungi, and protozoa.

**[Results]** In total, we reviewed 100 brain biopsy specimens from patients with encephalomyelitis. We identified microorganisms in 15 cases (15%), including bacteria, viruses, fungi, and protozoa. The most common microorganisms identified were bacteria, followed by fungi, viruses, and protozoa.

**[Conclusions]** Our findings suggest that encephalomyelitis is a multifactorial disease and that the causative agent can be identified in a subset of cases. Further research is needed to better understand the role of microorganisms in the pathogenesis of encephalomyelitis and to develop effective diagnostic and therapeutic strategies for these cases.
Nominees for the Best Presentation Award for the International Participants
Clinical features of MELAS: an analysis of 190 cases

1Neurology Department of Peking University First Hospital, 2Neurology Department of Navy General Hospital of PLA

Objective: To summarize the clinical features of Chinese patients with mitochondrial encephalomyopathy, lactic 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 recorded. Results: Males accounted for 54.7% and the male-to-female ratio was 1.4:1. The median age of onset was 14 years (from 7 months to 45 years). The median onset of the first stroke-like episode was 16 years (from 1 to 53 years). Fatigable and upper respiratory tract infection were the most common predisposing factors of stroke-like episodes (32.88% 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 common neurological manifestations included seizure (89.42%), mental retardation or dementia (82.67%), headache (74.30%), hemiparesis or cortical blindness (67.72%), exercise intolerance (50.87%). The common manifestations of extra-nervous systems included hirsutism (65.58%), fever (65.58%), lever (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.

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

1Neurology Department of Peking University First Hospital, 2Neurology Department of Navy General Hospital of PLA

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 adults 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. The 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 348.18 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 0.33μmol/L in mitochondrial disease, higher than 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 0.33μmol/L in mitochondrial disease, higher than 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). Conclusion: 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.

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

1Laboratorio di Neurogenetica, CERR-RBCS Santa Lucia, Rome, Italy, 2Department of Medicine of the Santi, Università di Tor Vergata, Rome, Italy, 3Laboratorio di Neurologia Clinica e Comportamentale, IRCCS Santa Lucia, Rome, Italy, 4Movement Disorders Centre, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, 5Department of Neurology, Universidade Federal de São Paulo, São Paulo, Brazil, 6Department of Clinical Neuroscience, University of Yokohama, Yokohama

Objective: To characterize clinical characteristics and progression in patients with SPG4/SPAST genetic screening on HSP patients. Epidemiological and genetic screening was performed on 284 HSP patients. Methods: Fifty patients with mitochondrial disease, twenty patients with multiple acyl-CoA dehydrogenase deficiency (MADD) and twenty-two cases of healthy adults 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. The 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 348.18 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 0.33μmol/L in mitochondrial disease, higher than 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). Conclusion: 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.

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

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Objective: To characterize clinical characteristics and progression in patients with LRRK2 risk variants. Methods: A total of 352 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 (ECAGQ). 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<0.002) and PDQ-39 domain 1 (mobility) (P=0.023), domain 2 (activities of daily living) score (P = 0.01) 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=0.004) Conclusion: PD patients with Asian specific risk variants (G238R, R1628P and S647T) in LRRK2 may experience severe disease progression in the long-term follow up.

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Greater progression of Parkinson disease in patients carrying LRRK2 risk variants

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Objective: To characterize clinical characteristics and progression in patients with LRRK2 variants. G238R, R1628P and S647T, which are associated with increased risk for Parkinson disease (PD) in Asian population. Methods: A total of 352 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 (ECAGQ). 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<0.002) and PDQ-39 domain 1 (mobility) (P=0.023), domain 2 (activities of daily living) score (P = 0.01) 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=0.004) Conclusion: PD patients with Asian specific risk variants (G238R, R1628P and S647T) in LRRK2 may experience severe disease progression in the long-term follow up.
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, -208b 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 myomiRNAs 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-133a 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 (24 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 (> 6 years). Conclusion. Suggesting that circulating myomiRNAs might reflect the effects of cytokines and growth factors on degenerating and regenerating muscles.

Clinical Profile of Patients with Myotonic Dystrophy in Czech Republic

Background and objective. 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 2 seems to be more frequent than type 1. 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 includes (November 2015) 426 patients from 8 centres. Results. Only patients with completed files (n=23) were analyzed. 297 (69%) are suffering from myotonic dystrophy type 1 (DM1), 110 (26%) from myotonic dystrophy type 2 (DM2). Mean age at the time of the registry entering was 45 years, approximately 10 years after disease manifestation which was in patients with DM2 (25-54) years and in persons with DM1 (40-74) years. We did not find any difference in muscle force between both types, measured by MRC score. The presence of symptoms was similar in both groups. Patients suffering from DM1 have more severe myotonic and heart problems (e.g. arrhythmias), which have been manifesting since younger age (8 mo, 35 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. Conclusions. In Czech population (Middle Europe, 0-55 inhabitants), diaphragm is more frequent DM1 than DM2. Patients with DM1 are younger and more compromised than patients with DM2.