**MONOCEROS**

### AO-01-1

**Monodermization of TDP-43 is a key determinant for inducing TDP-43 pathology in ALS**

Kotaro Oiwa,1,2 Seiji Watanabe,2 Kazunori Omerdo,1,3 Yohei Iuchi,1 Yohei Okada,1 Masahisa Katsuno,1 Koji Yamakana1

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**Background**

Cytoplasmic aggregation of TDP-43, also known as TDP-43 pathology, is a pathological hallmark of amyotrophic lateral sclerosis (ALS). Recently, terminal dimerization of TDP-43 has been reported, but its role in ALS pathogenesis remains unknown. [Methods] We evaluated the dimer/monomer state of cytoplasmic TDP-43 from sporadic ALS cases using diacetylimidazolinyl glutarate (DSG)-crosslinking. Biochemical analyses in Neuronal cells or iPSC-derived motor neurons expressing the dimerization-deficient mutants of TDP-43 were performed. [Results] DSG-crosslinking with Hoechst (Ho) and Heterochromatin (Het) mutants significantly increased in iPSCs-mDA with Ho and Het mutations (p < 0.05). [Conclusion] Our results suggest a pathological association among PSAP, GM1, and Ho mutations.

### AO-01-2

**Dysregulated endocannabinoid metabolism is a therapeutic target for amyotrophic lateral sclerosis**

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**Objective**

This study aims to reveal progression factors of sporadic ALS by metabolomics and to develop therapy targeting dysregulated metabolites. [Methods] Subjects with sporadic ALS whose disease durations were less than 2 years and healthy controls (HC) were recruited. Disease severity was measured using the ALS Functional Rating Scale-Revised (ALSFRS-R) and the disease duration was measured using the progression rate defined by ALSFRS-R changes. Metabolomics demonstrated several metabolic changes including endocannabinoid metabolism. Several endocannabinoids were increased in rapid progressed ALS. A very similar pattern of dysregulation of effective chemical compounds including PF04157845, a fatty acid amide hydrolase which inhibits degradation of endocannabinoids. Oral administration of PF-04157845 extended survival and attenuated motor neuron loss in the mutant SOD1 knock out (SOD1-KO) mice. [Conclusion] Endocannabinoid metabolism is a progression factor of sporadic ALS. PF-04157845, an endocannabinoid activator, is a promising candidate for ALS treatment.

### AO-01-3

**CDP-ribitol prodig treatment ameliorates SPD-deficient muscular dystrophy**

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**Objective**

A group of muscular dystrophy, including Fukuyama-type congenital muscular dystrophy, is caused by defects in CDP-ribitol synthetase domain containing (ISPD) encoding an enzyme that synthesizes ribitol-phosphate modification, which is crucial for the functional maturation of α-dystroglycan (α-DG). Currently, no effective treatments are available for this disease group. A recent study revealed that fibroblasts from ISPD-deficient mice showed a significant decrease in the dimer/monomer ratio of TDP-43 compared to the controls. Expression of dimerization-deficient TDP-43 in cells recapitulated TDP-43 pathology. We also identified that the nuclear export of monomeric TDP-43 is mediated by Nxf1. Furthermore, TDP-43 mRNA levels were elevated, suggesting that transcription inhibition linked to aberrant RNA metabolism in ALS lead to spirocerebral defects and impairment of endogenous TDP-43 dimerization, which preceded the appearance of TDP-43 pathology. Conclusions: We discovered for the first time that TDP-43 monomerization is a critical determinant for the development of TDP-43 pathology. Monodermization of TDP-43, an early molecular event of TDP-43 pathology, might constitute a potential biomarker and an attractive therapeutic target for ALS.

### AO-01-4

**Intrinsic blood-brain barrier dysfunction contributes to multiple sclerosis pathogenesis**

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**Objective**

The mechanisms leading to blood-brain barrier (BBB) dysfunction in multiple sclerosis (MS) are incompletely understood and generally thought to be a consequence of neuroinflammation. Here, we have challenged this view and asked if intrinsic alterations in BBB of MS patients could contribute to MS pathogenesis. We made use of human induced pluripotent stem cells (iPSCs) derived from 6 donors from healthy controls (HC) and 7 donors from MS patients and differentiated them into brain microvascular endothelial cell (BMVEC) like cells as in vitro model of the BBB. [Results] MS-derived BMVEC-like cells showed impaired junctional integrity, barrier properties and reduced adhesion profile compared to HC-derived BMVEC-like cells. Also, MS-derived BMVEC-like cells displayed an inflammatory phenotype with increased adhesion molecule expression and impaired cell-cell interactions. Moreover, the presence of IL-6, a key inflammatory cytokine, was known to be involved in BBB maturation and maintenance, was increased in MS-derived BMVEC-like cells harboring barrier characteristics similar to HC-derived BMVEC-like cells. This study suggests that the BBB alteration in MS could be modeled with hiPSC-derived BMVEC-like cells in vitro. [Conclusions] MS-derived BMVEC-like cells are thus suitable tools to explore the molecular underpinnings of BBB dysfunction in MS and assist in the identification of potential novel therapeutic targets for BBB stabilization.

### AO-01-5

**Decrease of GM1 ganglioside and LAMP2 in PARK24-linked proapo gene mutation**

Yukata Oji,1 Taku Hatano,1 Kazutaka Ikeda,1 Risa Noraka,1 Kei-ichi Ishikawa1,2, Ryo Wakahama3,1, Kentaro Gejima,3,1 Shinichi Ueno1,2, Ayami Okuzumi,1 Wado Akamatsu,1 Nobutaka Hattori4,5

1Department of Neurology, Juntendo University School of Medicine, Japan; 2Laboratory of Biomolecule Analysis, Kazusa DNA Research Institute; 3Center for Genomic and Regenerative Medicine, Juntendo University School of Medicine.

**Objective**

Recently, we identified the proapo gene (PSAP) as a novel gene for familial Parkinson’s disease (PD). Four phosphoribokinase activator (saposin) derived from PSAP activate lysosomal glycosphingolipid degradation. However, it remains unclear whether PSAP mutations could affect lysosomal lipid degradation. [Method] We generated isogenic induced pluripotent stem cells (iPSCs) by introducing the PSAP c.497T>C heterozygous (Het) or homozygous (Ho) mutation using CRISPR-Cas9 gene editing system for three cell lines such as wild-type (WT), Ho, and Wt were differentiated into dopaminergic neurons (iPSC-mDA). [Results] Chemical compounds including PF-04157845, a fatty acid amide hydrolase which inhibits degradation of endocannabinoids. Oral administration of PF-04157845 extended survival and attenuated motor neuron loss in the mutant SOD1 knock out (SOD1-KO) mice. [Conclusion] Endocannabinoid metabolism is a progression factor of sporadic ALS. PF-04157845, an endocannabinoid activator, is a promising candidate for ALS treatment.

**IL-6 deposition in the dorsal root of the spinal nerve in Neuromyelitis Optica Spectrum Disorder**

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**Objective**

In neuromyelitis optica spectrum disorder (NMOSD), serious pain often persists as a sequelae of myelitis. IL-6 is a pro-inflammatory cytokine that has been clinically and experimentally implicated in neuropathic pain, and are elevated in the CSF during the acute phase of NMOSD. The purpose of this study is to clarify the pathological relationship between IL-6 deposition and tissue damage caused in the spinal nerve in patients with NMOSD. Methods: We investigated autopsied tissues of the spinal cord derived from 18 patients with NMOSD. We examined staining patterns of IL-6 at the dorsal root ganglia and chronic lesions using immunohistochemical techniques. Results: The cohort of NMOSD in the analysis comprised 13 women and 5 men. The median age at onset was 54.5 years (range 14-79). IL-6 deposition was observed in 18 patients (100%) with GM1 ganglioside and LAMP2 in the pathogenesis of PD, although further studies will be needed.
Objective Parkinson’s disease (PD) and multiple system atrophy (MSA) are synucleinopathies caused by abnormal alpha-synuclein (αS) aggregation. The pathogenic β-sheet sheet conformation of αS can be found in various tissues, but its potential as a serum biomarker is unclear. METHODS We developed a novel assay system using immunoprecipitation-based real-time quaking-induced conversion (IP-RT-QuIC) to detect αS in serum of patients with synucleinopathies. Diagnostic performance was assessed with receiver operating characteristic (ROC) analysis. The IP-RT-QuIC results were evaluated using transmission electron microscopy (TEM), and the seeding properties in cell and mouse models were evaluated. RESULTS We collected sera from 268 participants with synucleinopathies (92I with PD and 39 with MSA) and 128 controls. IP-RT-QuIC displayed high diagnostic performance for differentiation of the PD vs controls (area under the curve (AUC) 0.95 [95% CI 0.89-0.98]) and MSA vs controls (AUC 0.64 [50% CI 0.49-0.79]). TEM analysis revealed that the IP-RT-QuIC-derived fibrils had distinct fibrillar structures for PD and MSA. The propagative potential of the amplified αS fibrils was confirmed both in cells and in vivo. CONCLUSIONS IP-RT-QuIC enables detection of serum pathogenic αS fibrils and quite useful diagnostic biomarker for synucleinopathies.

AO-02-3 Dysbiosis in the Salivary Microbiome; Promising Biomarker for Early Detection of Multiple Sclerosis

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Objective: The aim of this study is to reveal the characteristics of salivary microbiome in patients with MS and evaluate its validity as a diagnostic biomarker. METHODS We prospectively analyzed the alpha and beta diversity of saliva from MS patients, healthy controls, and healthy participants. The secondary survey was performed from 604 facilities (49.8%) leading to an estimated number of 41.2 FOSMN cases in Japan. The secondary survey to confirm the prevalence of FOSMN in Japan and establish the characteristics of this disease.

AO-02-5 A nationwide epidemiological survey of Facial Onset Sensory Motor Neuropathy (FOMSN) in Japan

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Objective: FOMSN is a rare disease with only about 100 cases reported worldwide. Clinical features are atypical autonomic facial and/or sensory deficits followed by bulbar symptoms and spreading of sensory and motor deficits from the face to the scalp, neck, upper trunk, and upper extremities. Its epidemiology and etiology remain unknown. To investigate the prevalence of FOMSN in Japan and establish the characteristics of this disease, we performed a nationwide epidemiological survey of FOMSN in the world and we reviewed the clinical features of FOMSN leading to treatment response in Japan.

AO-02-6 Clinical features and mechanism of LG4-lg4-positive inflammatory demyelinating polyneuropathy

O Xia Zhang1, Jun-ichi Kira1,4,5, Hidenori Ogata1, Akayo Sakoda1,4, Masaki Kobayashi2, Kazuto Kitagawa1, Yukihiro Shinotoh3, Yusuke Ohya2, Tomohiro Imamura1, Guzalaiyli Maimaitijiang1, Ryo Yamasaki1, Noriko Isebo1, Yuri Nakanishi1
1Translational Neuroscience Center, Graduate School of Medicine, International University of Health and Welfare and Japan, 2Department of Neurology, Brain and Nerve Center, Fukuoka Central Hospital, International University of Health and Welfare, 3Department of Pharmacology, School of Pharmacy at Fukuoka, International University of Health and Welfare, 4Department of Neurology, Tokyo Women’s Medical University Hospital, 5Department of Functional Brain Imaging, Institute for Quantum Medical Science, National Institutes of Health, Japan, 6Department of Neurology, Department of Functional Brain Imaging, Institute for Quantum Medical Science, National Institutes of Health, Japan

Objective: We reported a novel LG4-like IgG antibodies to Leucine Rich Repeat Ig-like Family Member 1 (LRIG1) in chronic inflammatory demyelinating polyneuropathy (CIDP). We aimed to elucidate clinical features and mechanism of anti-LRIG4 antibodies-positive (LG4-lg4) CIDP. METHODS We reviewed 15 LG4-lg4 CIDP cases with known antibody to LRIG4 at the Department of Neurology, Kindai University Hospital. Results: 15 LG4-lg4 CIDP patients were included in this study. We examined clinical manifestations, clinical course and treatments. Additionally, we examined the expression of LRIG4 and Krox20 mRNA using qPCR. Treatment was optimized in 8. All patients were on prednisolone and immunosuppressants. A total of 63% had beneficial treatment response. In conclusion, we found that a significant proportion of LG4-lg4 CIDP patients had beneficial treatment response following immunosuppressive treatment.

AO-02-2 Exosomal microRNA profiles in peripheral blood are useful for early diagnosis of Alzheimer’s disease

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Objective: Blood biomarkers to diagnose Alzheimer’s disease (AD) are increasingly important. We aimed to identify novel blood longitudinal microRNA (miRNA) markers for AD using human β amyloid precursor protein (AβPP) 695 transgenic mouse. RESULTS A βPP transgenic mouse was used to establish a transgenic model of human AD. Blood was extracted using an ExoQuick Exosome Isolation and RNA Purification kit (SBI, CA, USA) from 6-month-old APP23 (AβPP)25-35 wild type mice and 10 human subjects (5 AD patients and 5 age-matched healthy controls). MR varied in h AβPP mice compared to wild type mice; brain ischemia sequence (Hillman, RI), and each candidate miRNA was validated by individual qPCR analyses using the TaqMan microRNA assays (Thermo Fisher Scientific). Each miR amount was normalized to total miR8-B. The relative expression values of miRNAs were calculated using the 2-ΔΔCT method. Results: AD mouse miR-20 and 5 downregulated miR were found at the emergence of memory impairment compared to wild type mice. The miR20 upregulated in AD mice was also >4-fold higher in AD than patients. miR-20 was upregulated in AD mice tended to decrease in AD patients compared to controls. CONCLUSION In conclusion, we identified 6 miR as potential biomarkers for early AD in mouse. An upregulation of miR-20 was also confirmed in AD patients, blood exosomal miR-20, a suppressor of cell proliferation and migration, may be useful for early diagnosis of AD in human. Validation using a large scale cohort of patients is now under way.
**AP-01-1**

**Atypical live-cell image analysis for spinal and bulbous muscular atrophy pathology**

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**Objective:** Spinal and bulbous muscular atrophy (SBMA) is a neuro muscular disease caused by CAG repeat expansions in the androgen receptor gene. We demonstrate an innovative approach of an A1 artificial intelligence-based cell-morphological analysis to determine pathological processes and to find novel therapeutics for SBMA. 

**Methods:** We used a muscular CK21 cell model of SBMA (90Q cells) and control (2Q cells). We administered the farnesyltransferase inhibitor, SCH66336 or the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, atorvastatin, to the cells. We performed a morphological analysis using the Sanger database (https://bioinf/morpho) by image analysis. In the control and SCH66336-treated 2Q cells, the cytoskeleton was formed into a network structure, while the atorvastatin-treated 2Q cells formed fibrils. The SCH66336-treated 90Q cells also developed a fibrous network structure, whereas the atorvastatin-treated 90Q cells showed a disorganized fibril. These results suggest that SCH66336 suppressed the typical pathological features of SBMA, whereas atorvastatin did not.

**Results:**

1. SCH66336 treatment suppressed the typical pathological features of SBMA, whereas atorvastatin did not.
2. The morphological changes were observed in the cytoskeleton and the intracellular structures of the cells.

**Conclusions:** The morphological analysis using the Sanger database and the image analysis revealed the changes in the cytoskeleton and intracellular structures of the cells. The results suggest that SCH66336 is a potential therapeutic agent for SBMA.

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**AP-01-2**

**Two novel variants in CHCHD2 associate with TDP-43 pathology among amyotrophic lateral sclerosis**


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**Objective:** The objective of the study was to analyze the function of phospholipid scramblase 2 (PLSCR2) and associated TDP-43 pathology among amyotrophic lateral sclerosis (ALS). We identified two novel variants in PLSCR2, including W101stop and R523X. We also detected the expression of TDP-43 in the spinal cord of ALS patients. The results suggest that PLSCR2 plays a critical role in ALS pathology and TDP-43 expression.

**Methods:** We performed immunohistochemistry and Western blot analysis to detect TDP-43 expression in the spinal cord of ALS patients. We also performed Sanger sequencing to identify novel variants in PLSCR2.

**Results:**

1. We identified two novel variants in PLSCR2, including W101stop and R523X.
2. We detected the expression of TDP-43 in the spinal cord of ALS patients.

**Conclusions:** The results suggest that PLSCR2 plays a critical role in ALS pathology and TDP-43 expression.
**AP-02-1** Toxic Aβ 42 conformer may accelerate the preclinical stage

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**ABSTRACT**

The aim of the study was to investigate the molecular epidemiology of degenerative ataxias in Japan based on J-CAT study.

**Molecular epidemiology of degenerative ataxias in Japan based on J-CAT study**

**Methods**

From December 2016 to November 2021, 2043 patients were registered in Japan Consortium of Ataxias (J-CAT) nation-wide, roughly proportional to prefectural population. Initial mutational analysis including sequencing method. 

**Results**

Ataxias in Japan based on J-CAT study

**Conclusions**

The J-CAT has elucidated the most updated epidemiology of degenerative ataxias in Japan. Further confirmation of AM2A variants is under way.

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**Objective**

Patients with ataxia have abnormal loading conditions in the brainstem, spinal cord and peripheral nerves, which may trigger tau accumulation leading to neuronal impairment in AD pathogenesis.

**Methods**

We compared 5 patients with preclinical AD, 11 patients with MCI due to AD, 21 patients with moderate cognitive impairment (MCI) due to AD using an enzyme-linked immunosorbent assay kit. The presence of tau protein was confirmed in patients with MCI due to AD.

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**Conclusions**

The presence of tau protein was confirmed in patients with MCI due to AD.
APe-01-1 Screening compounds library using seed-dependent cellular tau aggregation for Alzheimer’s disease.

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1Juntendo University, Japan, 1University of Maryland

Objective: While in previous studies, in vitro tau protein aggregation has been used for screening drug library to reposition a drug, in our study, Alzheimer’s Disease (AD) tau-seeded cellular model was used for screening. Methods: SH-SY5Y cells were transfected with Tau-T72F2 (243-414 aa), and seeded with a patient’s brain seed to induce intracellular tau aggregates. Drugs from an FDA approved drug library of 800 compounds were added at 10 µM concentration and Sarkosyln-insoluble tau levels were analyzed. Results: So far, 52 compounds have been observed to significantly decrease tau aggregation with low cytotoxicity. These compounds include NMDA receptor antagonists, microtubule stabilizing taxane drugs, dixidropyridine type Ca2+ channel blockers, α and κ opioid receptors modulators. Some Aβ aggregation inhibiting compounds were also observed to lower tau aggregation in this model as well. Additionally, these compounds were tested by using another case of AD seed and different tauopathy (Corticobasal Degeneration [CBD] and Progressive supranuclear palsy [PSP]) seeds. Conclusion: We found drugs with different target pathways as AD tau aggregation inhibitor candidates. Moreover, these drugs varied in the effectiveness against different non-AD tauopathy seeds. These candidates will be tested in vivo and molecular mechanism of inhibition will be studied in future.

APe-01-2 Different peripheral immune modulation between Pink1+/− and Parkin−/− mice during EAE

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Objective: although the pathogenesis of neurodegenerative diseases is still widely unclear, mitochondrial dysfunctions and inflammation are thought to have a key role. Recent evidence has shown that PINK1 and PARKIN, two enzymes involved in mitophagy, play also a pivotal role in adaptive immnity. Methods: To elucidate their functions during neuroinflammation, Pink1+/- and Parkin−/− mice of different age groups were immunized with myelin oligodendrocyte glycoprotein (MOG) 35-55 to develop experimental autoimmune encephalomyelitis (EAE). Results: compared with young wild type controls, Pink1 and Parkin mice showed earlier disease onset. Parkin mice displayed more severe acute symptoms, while Pink1+/− milder clinical score. Both middle-aged Pink1+/− and Parkin−/− mice showed an early onset and more severe acute phase than controls, with no EAE recovery in Parkin+ mice. Aged (more than 1 year old) Parkin−/− mice developed an earlier onset and most severe EAE compared to the other group. In addition, aged Pink1+/− and Parkin−/− mice showed persistent disease during the recovery phase. These different clinical courses of EAE in these genetically modified mice were associated with variation in the percentage of IAE/CD11c+ dendritic cells and CD11c+ Y66 myeloid cells in the spleen. Conclusions: PINK1 and PARKIN proteins play an age-related role in the modulating of peripheral inflammatory response during EAE. The mechanisms involved aging, neuroinflammation and neurodegeneration, will open many potential avenues for the development of new therapies.

APe-01-3 withdrawn

APe-01-4 Driver gene KRAS mutation contributes to cancer-associated stroke aggravation via repressing MEK/ERK

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Objective: although the pathogenesis of neurodegenerative diseases is still widely unclear, mitochondrial dysfunctions and inflammation are thought to have a key role. Recent evidence has shown that PINK1 and PARKIN, two enzymes involved in mitophagy, play also a pivotal role in adaptive immnity. Methods: To elucidate their functions during neuroinflammation, Pink1+/− and Parkin−/− mice of different age groups were immunized with myelin oligodendrocyte glycoprotein (MOG) 35-55 to develop experimental autoimmune encephalomyelitis (EAE). Results: compared with young wild type controls, Pink1 and Parkin mice showed earlier disease onset. Parkin mice displayed more severe acute symptoms, while Pink1+/− milder clinical score. Both middle-aged Pink1+/− and Parkin−/− mice showed an early onset and more severe acute phase than controls, with no EAE recovery in Parkin+ mice. Aged (more than 1 year old) Parkin−/− mice developed an earlier onset and most severe EAE compared to the other group. In addition, aged Pink1+/− and Parkin−/− mice showed persistent disease during the recovery phase. These different clinical courses of EAE in these genetically modified mice were associated with variation in the percentage of IAE/CD11c+ dendritic cells and CD11c+ Y66 myeloid cells in the spleen. Conclusions: PINK1 and PARKIN proteins play an age-related role in the modulating of peripheral inflammatory response during EAE. The mechanisms involved aging, neuroinflammation and neurodegeneration, will open many potential avenues for the development of new therapies.

APe-01-5 An Alteration of microRNAs and Cognitive Impairment in Exercised Mice

Mohammad Nasir Ud din1, Montasir Elahi1, Shotoro Shimonaka1, Koeichi Ishiguro1, Yumiko Moto1, Nobutaka Hattori1

1Juntendo University, Japan, 1University of Maryland

Objective: Currently, emerging research interest is on the ability of microRNAs (miRNAs) to modulate the central nervous system function and pathophysiology of Alzheimer’s Disease. Exercise can prevent and improve the pathophysiology of diseases and promote healthy aging. In the present study, we sought to investigate the alteration of miRNAs in voluntarily exercised mice. Methods: Ten C57BL/6 mice were separated to a “wheel runner” group with 5 months of exercise, and a “sedentary” group kept in the cage. Reference learning (acquisition) and memory (retention) were assessed by Morris water maze test and mice were sacrificed by cervical dislocation. The unilateral hippocampi was used for miRNA and cytokine array analysis. Results: Behavior studies exhibited improvement of learning and memory after exercise: miRNAs microarray data analyzed by transcriptome analysis revealed 9 miRNAs (miR-693, miR-714, miR-190, miR-218, miR-195, miR-704, miR-6931, miR-6909, miR-6982) were upregulated and 8 miRNAs were downregulated (miR-434, miR-532, miR-467, miR-431, miR-669, miR-6705, miR-8, miR-764) upon exercise. Cytokine microarray data showed the number of inflammatory mediators, such as IL-1β, CRP, IFN-γ, TNF-α were decreased after the exercise. Conclusion: Taken together, we speculated miRNAs could be regulated in the inflammatory related to cognitive impairment. The further functional genomic study will be needed to detect signaling molecules responsible for the regulation miRNAs and cytokines.

APe-01-6 Deviation of BP from autoregulation limits after intravascular treatment correlates with outcomes

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Objective: Blood pressure (BP) management at the early time after endovascular thrombectomy (EVT) lacks evidence. Determination of cerebral autoregulation (CA) limits might guide BP management. Our study aimed to evaluate the association between outcomes and the duration as well as the degree of deviation of BP out of CA limits. Methods We enrolled patients who received EVT for acute anterior circulation stroke in our Hospital. Lower and upper limits of CA were determined by the BP at time 0.81 P=0.008, aOR per 10 h·mmHg 0.96 P=0.003) . Time-BP area correlated with infarct volume growth (aOR per 10 h·mmHg 1.02 P=0.031) . No correlation was noticed between outcomes and the duration as well as the degree of deviation of BP out of CA limits. Approaching the CA-preserved BP range might guide BP management. Our study aimed to evaluate the association between outcomes and the duration as well as the degree of deviation of BP out of CA limits.