The 22nd “Takamatsu” International Symposium for PD & MD in TOKYO

Date

2023. 3. 24（Fri）～ 3. 26（Sun）

Venue

Tokyo International Exchange Center
Tokyo Academic Park, 2-2-1 Aomi, Koto-ku, Tokyo, Japan

Secretariat

Department of Neurology, Juntendo University School of Medicine

Venue：
Tokyo International Exchange Center
Tokyo Academic Park, 2-2-1 Aomi, Koto-ku, Tokyo 135-8630 Japan

会場：
東京国際交流館内　国際交流会議場
〒135-8630 東京都江東区青海2-2-1

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Welcome to The 22nd “Takamatsu” International Symposium for PD and MD in TOKYO

Welcome Message from Chairpersons

Dear Colleagues,

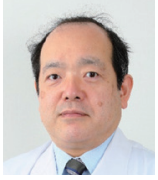
Hybrid Strategy for Movement Disorder Diseases for the Future by Integrating Basic and Clinical Research

The 22nd "Takamatsu" International Symposium for PD & MD in TOKYO will be held at the Tokyo International Exchange Center (Koto-ku, Tokyo) under the theme of "Hybrid Strategies for Movement Disorder Diseases for the Future by Integrating Basic and Clinical Research." We look forward to having the international speakers at the Tokyo International Exchange Center to share the latest information on Movement Disorder Diseases and deepen international exchanges.

As in the previous symposiums, to prevent the spread of COVID-19, the symposium will be held as a hybrid of an on-site symposium with advanced registration required and a web-based symposium (real-time streaming). We apologize for any inconvenience this may cause you. Still, we will take all possible measures to prevent the spread of infectious diseases during the conference. Still, please understand that we may have no choice but to change the conference to a web-based event (real-time streaming), depending on the future infection situation.

We are looking forward to seeing you at the conference.

Nobutaka Hattori, MD, PhD, FANA
Chair



Atsushi Takeda, MD, PhD
Co-Chair

The Organizing Committee

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Department of Neurology, Juntendo University School of Medicine, Tokyo, Japan

Co-Chair

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National Hospital Organization, Sendai Nishitaga Hospital, Miyagi, Japan

Advisor

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Taku Hatano, MD, PhD
Department of Neurology, Juntendo University School of Medicine, Tokyo, Japan

Genko Oyama, MD, PhD
Department of Neurology, Juntendo University School of Medicine, Tokyo, Japan

Program

1st Day：24 Mar 2023 (Friday)

10：00-10：15

Opening remarks

Nobutaka Hattori, Mitsutoshi Yamamoto

10：15-11：45

Symposium 1　Diagnosis and Management in Movement Disorders

Chair：Ryosuke Takahashi, Kenjiro Ono

1. Parkinson's disease
   Speaker：Eduardo Tolosa
2. Multiple System Atrophy - Clinical Challenges and Recent Advances
   Speaker：Werner Poewe
3. Common Pitfalls in Hyperkinetic Disorders : Case-Based Examples
   Speaker：Roongroj Bhidayasiri

11：45-12：10　**Short Break**

12：10-13：10

Lunch on Seminar

Chair：Kazushi Takahashi

1. Therapy for early stage of Parkinson’s Disease
   Speaker：Eng-King Tan
2. Therapy for advanced stage of Parkinson’s Disease
   Speaker：Loius Tan

13：10-13：30　**Coffee Break**

13：30-14：30

Symposium 2　Therapeutic Tagert in Movement Disorders

Chair：Atsushi Takeda

1. Blood biomarkers and Neurodegenerative disorders
   Speaker：Shinji Saiki
2. Where does Parkinson's disease begin?-Microbiota double hit hypothesis : gut-brain hypothesis in Parkinson's disease
   Speaker：Masaaki Hirayama

14：30-14：50　**Coffee Break**

14：50-15：50

Premium Seminar　Eisai Co., Ltd.

Chair：Genko Oyama

1. Neuropathology of α-synucleinopathies
   Speaker：Masaki Takao
2. Recent experiences of deep brain stimulation for Parkinson's disease
   Speaker：Hidemoto Saiki

15：50-16：10 **Coffee Break**

16：10-17：10

Evening Seminar

Chair：Yoshikazu Ugawa

1. Brain Networks in Parkinson’s disease
   Speaker：Wataru Sako
2. What roles of cerebellum in PD?
   Speaker：Hirohisa Watanabe

2nd Day：25 Mar 2023 (Saturday)

9：00-10：00

Symposium 3

Chair：Yasushi Shimo

1. Amantadine for the treatment of Parkinson disease and other movement disorder
   Speaker：Olivier Rascol
2. Pathomechanisms of Parkinson's disease due to prosaposin gene mutations
   Speaker：Yutaka Oji

10：00-11：30

Hot Topics

Chair：Tatsushi Toda, Yoshio Tsuboi

1. Molecular pathogenesis of Parkinson's disease illuminated by small fish models
   Speaker：Hideaki Matsui
2. Rehabilitation for Parkinson’s Disease
   Speaker：Tadashi Ichikawa
3. Exosomes contribute to the development of Parkinson’s disease
   Speaker：Taiji Tsunemi

11：30-12：00 **Coffee Break**

12：00-13：00

Lunch on seminar

Chair：Masahiko Tomiyama

1. Genomic background of Parkinson's disease and clinical application of genomics towards the development of percision
   Speaker：Wataru Satake
2. Treatment of autonomic dysfunction in movement disorders
   Speaker：Tomohiko Nakamura

13：00-13：10 **Short Break**

13：10-14：40

Symposium 4 How to establish the QOL of PD Takeda Pharmaceutical Co., Ltd.

Chair： Yasuyuki Okuma, Kazuko Hasegawa

1. Neuropsychiatric complications in Parkinson’s disease
   Speaker：Jinsoo Koh

2. Restless Legs Syndrome in patients with Parkinson disease
   Speaker：Yuichi Inoue
3. Multidisciplinary Care for PD
   Speaker：Morinobu Seki

14：40-15：10 **Coffee Break**

15：10-16：10

Educational Lecture Sumitomo Pharma Co., Ltd.

Chair：Satoshi Orimo

1. α-synuclein; Biomarker of Synucleinopathy
   Speaker：Taku Hatano
2. How does alpha-synuclein transfer from cell to cell: A cell biological perspective
   Speaker：Takafumi Hasegawa

16：10-16：40 **Coffee Break**

16：40-18：00

VTR Session

Chair：Mitsutoshi Yamamoto, Genjiro Hirose

TBA

18：00 **Closing Remark**

Speaker：Nobutaka Hattori

3rd Day：26 Mar 2023（Sunday） Japanese session

9：00- 9：40

認知機能障害を伴うレビー小体病のマネジメント 協和キリン株式会社

Chair：伊藤 和則 Speaker：平野 成樹

9：40-10：20

運動障害疾患と運動ニューロン病 エフピー株式会社

Chair：金井 数明 Speaker：狩野 修

10：20-11：00

運動障害疾患診療に役立つバイオマーカー アッヴィ合同会社

Chair：柏原 健一 Speaker：上野 真一

11：00-11：15 **Short Break**

11：15-11：55

運動障害疾患と加齢 小野薬品工業株式会社

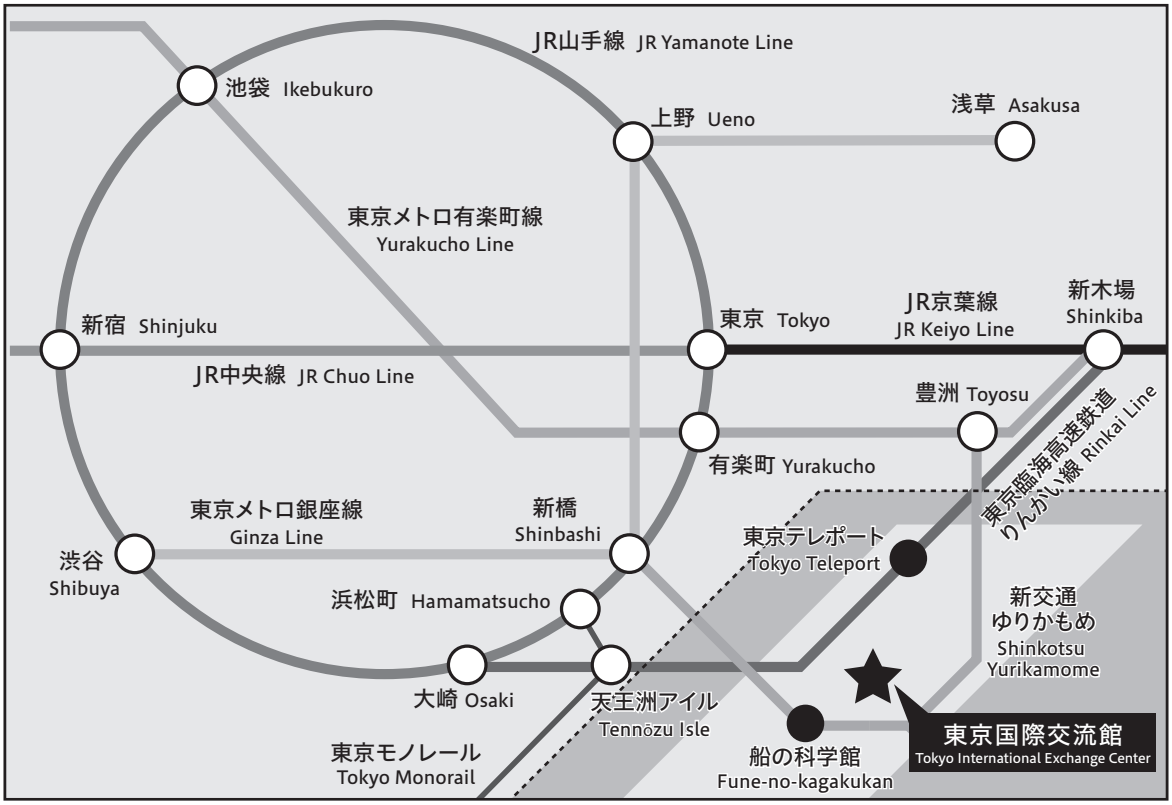
Chair：花島 律子 Speaker：荒若 繁樹

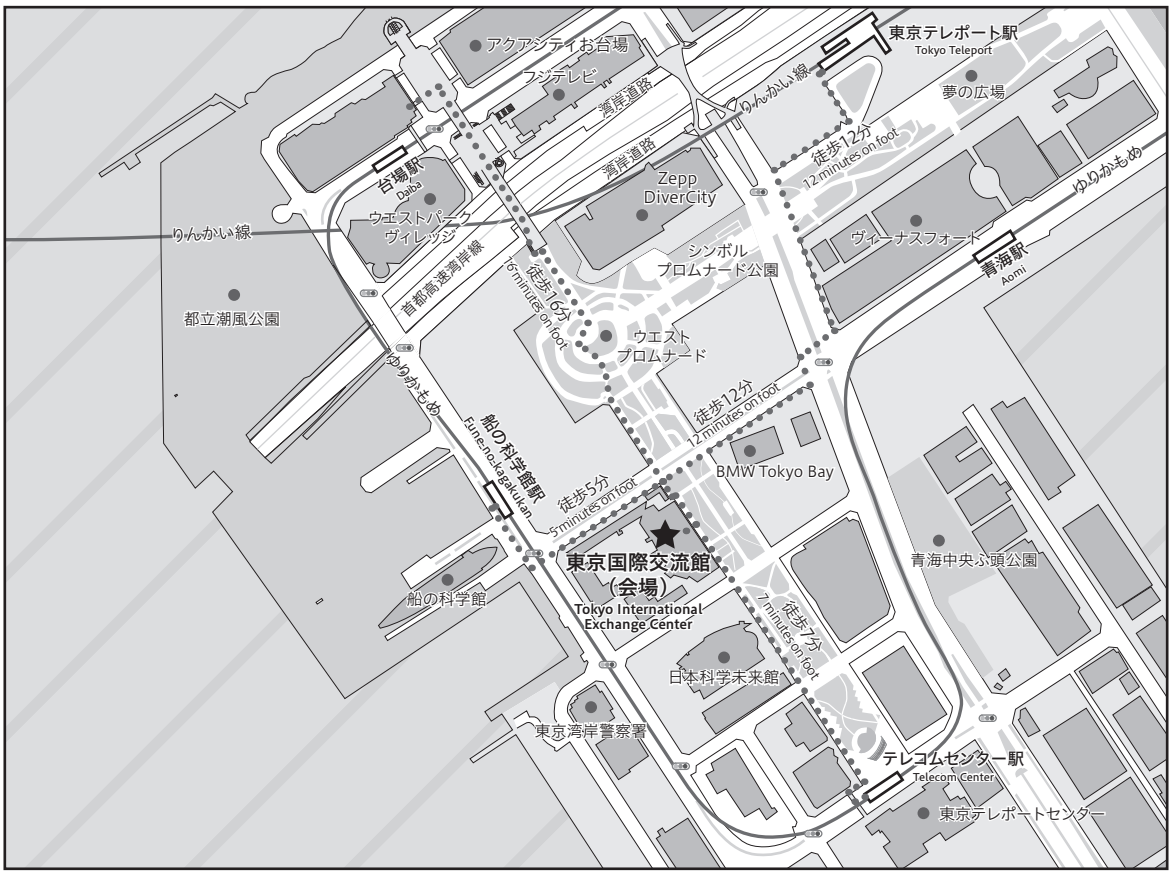
11：55-12：35

PDのうつ update 2023 大塚製薬株式会社

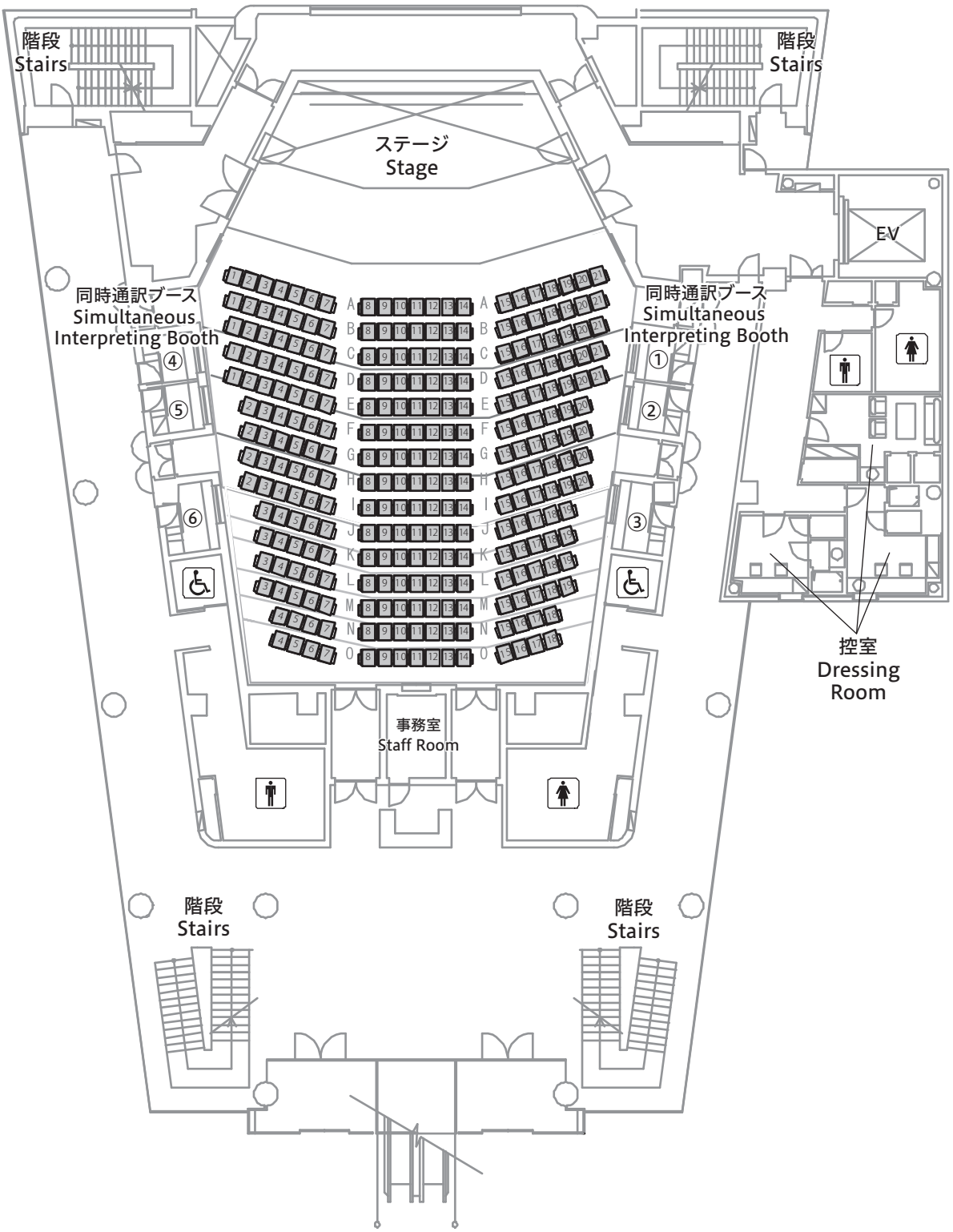
Chair：前田 哲也 Speaker：永山 寛

Access, Floor Map





1F　国際交流会議場（Room A）
International Conference Hall



Abstracts

1st Day
24 Mar 2023（Friday）

Symposium 1 Diagnosis and Management in Movement Disorders

Chair:

Ryosuke Takahashi
Department of Neurology, Kyoto University, Kyoto, Japan

Kenjiro Ono
Deparment of Neurology, Kanazawa University

1. Parkinson's disease

Speaker:

Eduardo Tolosa, MD, PhD
Hospital Clinic Universitari, University of Barcelona, Barcelona, Catalunya, Spain

Abstracts:

Parkinson disease (PD) is a progressive neurodegenerative disorder characerized by rest tremor , rigidity and slow movements as well as a variety of non motor symotoms (NMS) such as constipation, sleep problems and, in advanced stages, cognitive changes.The cause is unknown in about 95% of cases and “genetic” (linked to known PD genes) in 3 to 5 %.

Aggregates of synuclein (Lewy bodies and neurites) are present in both central and peripheral nervous system and currently synuclein is thought to play a role in cell death and disease progression but its exact role in PD is unclear. Dopaminergic nigral cell loss occurs consistently and results in striatal dopamine depletion, the cause of the classical motor symptoms.

Diagnosis is clinically based and may be difficult due to the great clinical heterogeneity of the disorder. Is based on history and examination.

History can include prodromal features (eg, rapid eyemovement sleep behavior disorder, hyposmia, constipation), characteristic movement difficulty (eg, tremor, stiffness, slowness), and psychological or cognitive problems (eg, cognitive decline, depression, anxiety). Examination typically demonstrates bradykinesia with tremor, rigidity, or both. Bradylinesia may be apparent as soon as a patient enters the consulting room but in other cases early diagnosis depends on scrupulous history taking and a detailed neurological examination.

No disease modifying drugs are available and treatment is symptomatic.

Treatment goals vary from person to person, emphazising the need for personalized management.

Medical treatment is centered in the dopamine precursor drug levodopa. Adjuvant drugs to levodopa (dopamine agonists, MAO-B and COMT inhibitors) are also frequently used. Device-aided therapies (deep brain stimulation, apomorphine and levodopa infusions) are succesfully used for the managment of treatment complications in advanced stages and medication-resistant tremor. Nonmotor symptoms require nondopaminergic approaches (eg, selective serotonin reuptake inhibitors for psychiatric symptoms, clonazepam for RBD, botulinum toxin for sialorrhea). Non pharmacological interventions such as physiotherapy, occupational and speech therapies are also important and specialized nurses play a crucial role in managment. Experimental therapies are focused in reducing synuclein burden by inmune therapy. More specific therapies are currently being tested in genetic forms of PD such as LRRK2 or GBA associated PD.

Biosketch:

Prof. Eduardo Tolosa obtained his MD degree from the University of Barcelona and received his neurological training at the University of Minnesota in the US. He is a founding member and past President of the Movement Disorder Society. He is the recipient of the American Academy of Neurology 2014 Movement Disorders Research Award. Prof. Tolosa is the past Chairman of the Department of Neurology at the University of Barcelona Hospital and is currently Emeritus Professor at the University of Barcelona and Neurology consultant Hospital Clinic University Hospital.

Professor Tolosa was involved in pioneering studies on motor fluctuations and the role of DAT SPECT in Parkinson disease and his team has been among the first in Europe to evaluate the efficacy of novel therapeutic strategies for Parkinson's disease. His research is currently focused on the search of biomarkers in the prodromal phase of Parkinson disease, both idiopathic and genetic forms.

Key articles (Up to 5):

1. Garrido A, Fairfoul G, Tolosa E et al. Brain and Cerebrospinal Fluid α-Synuclein Real-Time Quaking-Induced Conversion Identifies Lewy Body Pathology in LRRK2-PD. Movement Disorders 2022, DOI: 10.1002/mds.29284
2. Tolosa E, Garrido A, Scholz SW, Poewe W. Challenges in the diagnosis of Parkinson's disease. Lancet Neurol. 2021 May;20（5）:385-397. doi: 10.1016/S1474-4422（21）00030-2.
3. Stefani A, Iranzo A, Holzknecht E, Perra D, Bongianni M, Gaig C, Heim B, Serradell M, Sacchetto L, Garrido A, Capaldi S, Sánchez-Gómez A, Cecchini MP, Mariotto S, Ferrari S, Fiorini M, Schmutzhard J, Cocchiara P, Vilaseca I, Brozzetti L, Monaco S, Jose Marti M, Seppi K, Tolosa E, Santamaria J, Högl B, Poewe W, Zanusso G; SINBAR（Sleep Innsbruck Barcelona）group. Alpha-synuclein seeds in olfactory mucosa of patients with isolated REM sleep behaviour disorder. Brain. 2021 May 7;144（4）:1118-1126. doi: 10.1093/brain/awab005.
4. Tolosa E, Ebersbach G, Ferreira JJ, Rascol O, Antonini A, Foltynie T, Gibson R, Magalhaes D, Rocha JF, Lees A. The Parkinson's Real-World Impact Assessment（PRISM）Study: A European Survey of the Burden of Parkinson's Disease in Patients and their Carers. J Parkinsons Dis. 2021;11（3）:1309-1323. doi: 10.3233/JPD-212611. PMID: 34024784
5. Tolosa E, Vila M, Klein C, Rascol O. LRRK2 in Parkinson disease: challenges of clinical trials. Nat Rev Neurol. 2020 Feb;16（2）:97-107. doi: 10.1038/s41582-019-0301-2. Epub 2020 Jan 24.

2. Multiple System Atrophy – Clinical Challenges and Recent Advances

Speaker:
Werner Poewe
Past Chair and emeritus Professor, Dept of Neurology, Medical University Innsbruck, Austria

Abstracts:

Multiple System Atrophy (MSA) is a rare neurodegenerative disease that is characterized by neuronal loss and gliosis in multiple areas of the central nervous system including striatonigral, olivopontocerebellar and central autonomic structures. Oligodendroglial cytoplasmic inclusions containing misfolded and aggregated α-synuclein are the histopathological hallmark of MSA. A firm clinical diagnosis requires the presence of autonomic dysfunction in combination with poorly levodopa-responsive parkinsonism and/or cerebellar ataxia. Clinical diagnostic accuracy is suboptimal in early disease because of phenotypic overlaps with Parkinson disease or other types of degenerative parkinsonism as well as with other cerebellar disorders. A recent revison of MSA clinical diagnostic criteria aims at better discriminative performance and includes a suggestion for research criteria for prodromal disease stages. Neuroimaging using advanced MR techniques including automated volumetric analysis, diffusion tensor and multimodal imaging as well as microglial imaging with PET tracers can significantly enhance diagnostic accuracy. Biofluid and tissue biomarkers like α-synuclein histochemistry and seeding aggregation assays and CSF or plasma NfL levels will play an increasing role in early and differential diagnosis of MSA.

The symptomatic management of MSA requires a complex multimodal approach to compensate for autonomic failure, alleviate parkinsonism and cerebellar ataxia and associated disabilities. None of the available treatments significantly slows the aggressive course of MSA. Despite several failed trials in the past, a robust pipeline of putative disease modifying agents, along with progress towards early diagnosis and the development of sensitive diagnostic and progression biomarkers for MSA offer new hope for patients.

Biosketch:

Professor Werner Poewe is emeritus Professor of Neurology in the Department of Neurology at the Medical University of Innsbruck in Austria. He completed a residency in clinical neurology and psychiatry at the University of Innsbruck and then a British Council research fellowship at University College and Middlesex Hospital Medical School in London. He previously served as a senior lecturer in the Department of Neurology at the University of Innsbruck and as a professor of neurology and acting director of the Department of Neurology at the Virchow Hospital of the Free University of Berlin in Germany before becoming director of the Department of Neurology at the Medical University of Innsbruck in 1995 – a position he held until 2019.

Professor Poewe has served as president of the International Parkinson and Movement Disorder Society (MDS) , chair of the MDS European Section, president of the Austrian Society of Neurology, and president of the Austrian Parkinson's Disease Society. He is a corresponding member of the American Neurological Association and French Neurological Society and an honorary member of the German Neurological Society, Japanese Neurological Society, and MDS. He has received the Walther Birkmayer Prize from the Austrian Parkinson's Disease Society, the Dingebauer Prize from the German Neurological Society, and the Research Excellence Award from the Medical University and Leopold-Franzens University of Innsbruck.

Professor Poewe's main research interests are in the field of Parkinson's disease and movement disorders, with particular emphasis on the diagnosis, natural history and clinical trials in the fields of Parkinson's disease and atypical parkinsonism. He has authored or co-authored more than 800 original articles and reviews in the field of movement disorders with a total of more than 112.000 citations and an h-index of 159 (Google Scholar) . Professor Poewe is listed among top 1% of ‚highly cited researchers' in neuroscience (Clarivate Web of Science 2022).

Key articles (Up to 5):

1. **Poewe W**, Stankovic I, Halliday G, Meissner WG, Wenning GK, Pellecchia MT, Seppi K, Palma JA, Kaufmann H. Multiple system atrophy. Nat Rev Dis Primers. 2022 Aug 25;8 (1) :56. doi: 10.1038/s41572-022-00382-6. PMID: 36008429
2. Tolosa E, Garrido A, Scholz SW, **Poewe W**. Challenges in the diagnosis of Parkinson's disease. Lancet Neurol. 2021 May;20 (5) :385-397. doi: 10.1016/S1474-4422 (21) 00030-2. PMID: 33894193; PMCID: PMC8185633.
3. Stefani A, Iranzo A, Holzknecht E, Perra D, Bongianni M, Gaig C, Heim B, Serradell M, Sacchetto L, Garrido A, Capaldi S, Sánchez-Gómez A, Cecchini MP, Mariotto S, Ferrari S, Fiorini M, Schmutzhard J, Cocchiara P, Vilaseca I, Brozzetti L, Monaco S, Jose Marti M, Seppi K, Tolosa E, Santamaria J, Högl B, **Poewe W**, Zanusso G; SINBAR (Sleep Innsbruck Barcelona) group. Alpha-synuclein seeds in olfactory mucosa of patients with isolated REM sleep behaviour disorder. Brain. 2021 May 7;144 (4) :1118-1126. doi: 10.1093/brain/awab005. PMID: 33855335.
4. Mahlknecht P, Foltynie T, Limousin P, **Poewe W**. How Does Deep Brain Stimulation Change the Course of Parkinson's Disease? Movement Disorders. 2022 May 12. doi: 10.1002/mds.29052
5. Wenning GK, Stankovic I, Vignatelli L, Fanciulli A, Calandra-Buonaura G, Seppi K, Palma JA, Meissner WG, Krismer F, Berg D, Cortelli P, Freeman R, Halliday G, Höglinger G, Lang A, Ling H, Litvan I, Low P, Miki Y, Panicker J, Pellecchia MT, Quinn N, Sakakibara R, Stamelou M, Tolosa E, Tsuji S, Warner T, **Poewe W**, Kaufmann H. The Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy. Movement Disorders. 2022 Apr 21. doi: 10.1002/mds.29005.

3. Common Pitfalls in Hyperkinetic Disorders : Case-Based Examples

Speaker:
Roongroj Bhidayasiri, MD, FRCP
Chulalongkorn Centre of Excellence for Parkinson's Disease & Related Disorders
Chulalongkorn University Hospital and the Academy of Science, The Royal Society of Thailand, Bangkok, Thailand.

Abstracts:

Hyperkinetic disorders comprise various conditions of different phenomenologies that are heavily dependent on visual observation for recognition and are prone to many pitfalls. These pitfalls may occur as a result of examination oversights, diagnostic errors, and therapeutic disappointments. In this session, case examples will be presented to uncover diagnoses missed or wrongly attributed, difficult-to-characterise hyperkinetic disorders, tests that are inappropriately ordered or interpreted, and treatment incorrectly chosen or dosed. I am hopeful that these cases will provide enduring lessons that positively impact individual clinical practice.

Lunch on seminar

Chair:
Kazushi Takahashi
Department of Neurology, Institute for Medicine, University of Tsukuba

1. Therapy for early stage Parkinson's Disease

Speaker:
TAN Eng-King, MD, MRCP, FRCP
Deputy Chief Executive Officer (Academic Affairs) and Senior Consultant Neurologist, National Neuroscience Institute, Professor, Duke-NUS Medical School, Honorary Professor, Lee Kong Chian School of Medicine

Abstracts:

Parkinson's disease (PD) is a heterogenous neurodegenerative disorder, with several clinical and genetic subtypes. In addition to classic motor symptoms, non-motor manifestations such as rapid eye movement sleep disorder, anosmia, constipation and depression appear at early stages and cognitive impairment and dysautonomia may occur as the disease progresses. The involvement of dopaminergic as well as noradrenergic, glutamatergic, serotonergic and adenosine pathways provide insights into its variable clinical phenomenology and provides alternative therapeutic approaches in addition to dopamine replacement therapies.

The approach to early PD involves a multidisciplinary team involing the patient and caregivers. Communication to the patient on the diagnosis when and how to start treatment is equally important as the type of medications to be prescribed. The strategy in early PD is should aim to slow down clinical progression, control motor and non-motor symptoms, improve activities of daily living and forestall disabling motor complications and reduce long term drug related complications. Development of potential neuroprotective therapies has been a challenge due to the lack of reliable and sensitive biomarkers of progression, and proven efficacy. Emerging therapies, such as new symptomatic drugs, and immunotherapy, with innovative drug delivery systems may help to reduce the burden of disease in early PD.

Biosketch:

Professor Tan Eng King is the Deputy Chief Executive Officer (Academic Affairs), and Senior Consultant with the Department of Neurology, National Neuroscience Institute (NNI) of Singapore. He is also a Professor at the Duke-NUS Medical School and Lee Kong Chian School of Medicine.
Prof Tan has served as an editor in Parkinsonism related disorders, European Journal of Neurology and Journal of Parkinson's disease, among several others. He has received various national and international accolades including the David Marsden lectureship and Yoshi Mizuno lectureship awards.
He has broad research interest including epidemiology, neuroimaging, clinical and functional genomics and experimental therapeutics in Parkinson's disease, essential tremor and other movement disorders.

Key articles (Up to 5):

1. Ma D et al. Association of NOTCH2NLC Repeat Expansions With Parkinson Disease. JAMA Neurol. 2020 Dec 1; 77 (12) : 1559-1563.
2. Sun AX et al. Potassium channel dysfunction in human neuronal models of Angelman syndrome. Science. 2019 Dec 20; 366 (6472) : 1486-1492.
3. Jo J et al. Midbrain-like organoids from human pluripotent stem cells contain functional dopaminergic and neuromelanin-producing neurons. Cell Stem Cell. 2016 Aug 4; 19 (2) : 248-57.
4. Tan et al. Parkinson disease and the immune system - associations, mechanisms and therapeutics. Nat Rev Neurol. 2020 Jun; 16 (6) : 303-318.
5. Lim et al. Parkinson's disease in the Western Pacific Region. Lancet Neurol. 2019 Sep; 18 (9) : 865-879.

Lunch on seminar

2. Therapy for the advanced stage of Parkinson's Disease

Speaker:
Loius Tan
National Neuroscience Institute, Singapore

Abstracts:

Therapy for advanced stages of Parkinson's disease (PD) focuses on management of both motor and non-motor complications of PD. The motor complications of PD include the presence of motor fluctuations, various degree of dyskinesias, and disability with functional impact on activities of daily living and independence. Therapeutic management aims to extend levodopa benefit while minimizing motor complications. In milder forms of motor complications, these can often be controlled with manipulation of levodopa dose and the introduction of supplemental therapies such as catechol-O-methyl transferase inhibitors, monoamine oxidase B inhibitors, and dopamine agonists including apomorphine. When motor complications cannot be controlled by medications, patients should be assessed and considered for device-aided therapies. Device-added therapies include deep brain stimulation or brain lesioning with different techniques, with the latest technique being MRI-guided focused ultrasound surgery. Continuous delivery of medication subcutaneousy (apomorphine pump) or through percutaneous ileostomy (levodopa infusions) may also be considered. Management of non-motor complications in advanced PD is equally challenging especially when treatment-limiting complications such as postural hypotension, dementia and hallucination set in. An overview of the management strategies for motor and non-motor complications in advanced PD will be presented at this talk.

Biosketch:

Prof Louis Tan is a Senior Consultant Neurologist and Research Director at the National Neuroscience Institute, Singapore. He is also Co-Director of its Parkinson's Disease and Movement Disorders Centre (TTSH campus) and a Clinical Professor of Duke-NUS Graduate Medical School, Singapore.

He is the Co-Chair of the Publication Oversight Committee of the *International Parkinson and Movement Disorder Society* and previously served as Treasurer, Chair of the Education committee, Chair of the Asian-Oceanian Section of the Society, and a member of the International Executive Committee.

Upon graduating from the National University of Singapore and completing his neurology training at Tan Tock Seng Hospital, he underwent a movement disorders fellowship at the Parkinson's Institute in Sunnyvale, California.

His areas of specialty and research interests are Parkinson's disease and movement disorders. He is also interested in the interested in the epidemiology, clinical studies and clinical trials in Parkinson's disease and other movement disorders.

Symposium 2 herapeutic Tagert in Movement Disorders

Chair:
Atsushi Takeda
National Hospital Organization, Sendai Nishitaga Hospital, Miyagi, Japan

1. Blood biomarkers and Neurodegenerative disorders

Speaker:
Shinji Saiki, MD, PhD
Department of Neurology, Institute for Medicine, University of Tsukuba

Abstracts:

Parkinson's disease (PD) is the 2nd common neurodegenerative disease characterized by motor symptoms including akinesia, skeletal muscle rigidity, and tremor and non-motor symptoms like orthostatic hypotension, constipation, REM sleep behavior disorders and dysosmia. Although radiological examinations including ioflupane dopamine transporter imaging, neuromelanin imaging and cardiac iodine-meta-iodobenzylguanidine scintigraphy enable us to detect neurodegeneration in the disease status, clinically available tests with peripheral blood specimen have not been identified clinically. We have reported PD-specific metabolic changes in fatty acid β-oxidation, caffeine metabolism and polyamine metabolism using mass spectrometry analysis with the plasma/serum. In this presentation, I would like to summerize fatty acid β-oxidation and polyamine pathway in PD as a potential therapeutic target against PD.

Biosketch:

1999 Graduated from Kyoto Prefectural University of Medicine
2001 Instructor (Neurology) at Department of Neurology, Kanazawa Medical University
2005 Visiting Scientist at Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge
2008 Instructor at Department of Neurology, Juntendo University School of Medicine
2011 Associate Professor at Department of Neurology, Juntendo University School of Medicine
2023 Professor at Department of Neurology, Institute of Medicine, University of Tsukuba

Key articles (Up to 5):

Ann Neurol 93: 303, 2023; *EMBO J* 41: e111476, 2022; *Mov Disord* 35: 1438-1447, 2020; *Ann Neurol* 86:251-263, 2019; *Neurology* 90: e404-e411, 2018

2. Microbiota double hit hypothesis : gut-brain hypothesis in Parkinson's disease

Speaker:
Masaaki Hirayama, Associate Professor
Department of Pathophysiological Laboratory Sciences, Nagoya University Graduate School of Medicine, Nagoya, Japan

Abstracts:

In Parkinson's disease (PD), ascending propagation of α-synuclein, in which Lewy body pathology gradually progresses from the intestinal tract to the dorsal vagal nucleus to the locus coeruleus and substantia nigra, is now considered to be involved in the pathogenesis of the disease. We performed a metagenomic analysis of our own cases as well as a meta-analysis of RBD and PD patients from four previously reported countries to identify the intestinal microbiota that varies across borders in Lewy body disease (Mov Disord 2021). REM sleep behavior abnormalities, which are considered a preclinical disorder of Lewy body disease, were found to be characteristic of the prodoromal gut microbiota of PD (mSystems 2020). They also found that LPS-binding protein , which binds to lipopolysaccharide produced by intestinal bacteria, is decreased in the blood (PloS One 2015) and the permeability of the intestinal epithelium is increased. He performed a longitudinal analysis of PD patients with respect to gut bacteria and symptoms, and found that after 2 years, severity of disease can be predicted by SCAF-producing bacteria at 2 years by machine learning in patients with mild disease (NPJ 2022). We also reported that in Lewy body dementia, specific bacteria may inhibit the progression of the disease (NPJ 2022). Based on these results, we propose "Microbiota double hit hypothesis :gut-brain hypothesis in Parkinson's disease" as a mechanism of Lewy body disease pathogenesis by intestinal bacteria. Currently, we are not only analyzing the microbiota, but also analyzing the function of intestinal bacteria using shot gun analysis.In my presentation, I will discuss the evidence that intestinal bacteria are the cause of PD, and our latest research on the pathogenesis of PD.

Biosketch:

Graduate from Gifu University Graduate School of Medicine
Nagoya University clinical resident system at Minato genrral hospital 1984 Okazaki city hospital 1888
Clinical attending staff, NagoyaUniversity hospital 1989
Assistant professor, department of Clinical Laboratory, Nagoya university hospital 1996
Vice manager, department of Clinical Laboratory, Nagoya university hospital 2007
Associate professor, department of Pathophysiological Laboratory Sciences, Nagoya University Graduate School of Medicine 2010

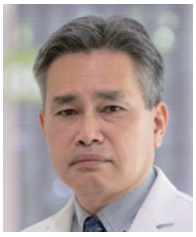
Key articles (Up to 5):

Microbiota, shot gun analysis, Parkinson’s disease, Dementia with Lewy body, REM sleep disorder

Premium Seminar (Eisai Co., Ltd.)

Chair:
Genko Oyama
Department of Neurology, Juntendo University School of Medicine, Tokyo, Japan

1. Neuropathology of α-synucleinopathies



Speaker:
Masaki Takao, MD, PhD
Department of Clinical Laboratory and Internal Medicine, National Center of Neurology and Psychiatry (NCNP), National Center Hospital

Abstracts:

In this mini-lecture, I would like to introduce basic aspects of neuropathologic changes seen in the α-synucleinopathies. There are three major diseases such as Parkinson's disease (PD), dementia Lewy body disease (DLB), and multiple system atrophy (MSA). In PD and DLB, the presence of Lewy bodies, accumulation of α-synuclein, is the essential pathology. Besides the central nervous systems, Lewy body related pathologies may be present in the peripheral nervous systems. In MSA, the accumulation of α-synuclein is known as glial cytoplasmic inclusions (GCIs) in the oligodendroglias. In addition, deposits of α-synuclein may be observed in the neurons in MSA cases. According to the analysis of electron cryo-microscopy, the filament structures of MSA and PD (DLB) are different. Lewy bodies are also reported in other neurological disorders such as neurodegeneration with brain iron accumulation, progressive supranuclear palsy, corticobasal degeneration, adult polyglucosan body disease, Gerstmann-Sträussler-Scheinker disease, Creutzfeldt-Jakob disease, subacute sclerosing panencephalitis. Alzheimer's disease, and spinocerebellar ataxia. I will also provide neuropathologic aspects of those diseases.

Biosketch:

School of Medicine, Keio University, Tokyo, Japan
Indiana University, Indiana Alzheimer Disease Center
Department of Neurology, Saitama Medical University, International Medical Center, Saitama
Department of Clinical Laboratory and Internal Medicine, National Center of Neurology and Psychiatry (NCNP), National Center Hospital

Key articles (Up to 5):

1. Mizutani M, Sano T, Ohira M, Takao M. Neuropathological studies of serotonergic and noradrenergic systems in Lewy body disease patients with delusion or depression. Psychiatry Clin Neurosci. 2022 Sep;76 (9) :459-467.
2. Yang Y, Shi Y, Schweighauser M, Zhang X, Kotecha A, Murzin AG, Garringer HJ, Cullinane PW, Saito Y, Foroud T, Warner TT, Hasegawa K, Vidal R, Murayama S, Revesz T, Ghetti B, Hasegawa M, Lashley T, Scheres SHW, Goedert M. Structures of α-synuclein filaments from human brains with Lewy pathology. Nature. 2022 Oct;610 (7933) :791-795.
3. Lionnet A, Leclair-Visonneau L, Neunlist M, Murayama S, Takao M, Adler CH, Derkinderen P, Beach TG.Does Parkinson's disease start in the gut? Acta Neuropathol. 2018 Jan;135 (1) :1-12.
4. Hatsuta H, Takao M, Nakano Y, Nogami A, Uchino A, Sumikura H, Kanemaru K, Arai T, Itoh Y, Murayama S. Reduction of Small Fibers of Thoracic Ventral Roots and Neurons of Intermediolateral Nucleus in Parkinson Disease and Dementia with Lewy Bodies. J Parkinsons Dis. 2016 Apr 2;6 (2) :325-34.
5. Sumikura H, Takao M, Hatsuta H, Ito S, Nakano Y, Uchino A, Nogami A, Saito Y, Mochizuki H, Murayama S. Distribution of α-synuclein in the spinal cord and dorsal root ganglia in an autopsy cohort of elderly persons. Acta Neuropathol Commun. 2015 Sep 15;3:57.

2. Recent experiences of deep brain stimulation for Parkinson's disease

Speaker:
Hidemoto Saiki, MD
Parkinson's Disease Advanced Therapy Center, Aichi Medical University Hospital, Aichi, Japan

Abstracts:

Deep brain stimulation (DBS) provides significant improvement of motor complications which cannot be adequately improved by medication therapy in advanced Parkinson's disease patients. To maximize the benefits of DBS, it is necessary to fully assess cognitive and mental function and symptomatic levodopa response, and to initiate DBS in appropriate patients at the appropriate time. Increased beta oscillations are observed in the subthalamic nucleus of Parkinson's disease patients. Recent neurostimulators feature sensing technology designed to capture local field potentials (LFP) using implanted DBS leads. Since beta oscillations are enhanced in the "off" state and attenuated in the "on" state, continuous recording of LFP provides an objective symptom diary. By adjusting the stimulation using this LFP trend as a guide, the amount of stimulation current can be adjusted appropriately. In addition, adaptive DBS, which automatically adjusts the amount of stimulation current within a set range in response to changes in LFP, can be used to reduce unnecessary stimulation and suppress dyskinesia. In order to implement DBS as part of the overall Parkinson's disease treatment and improve the patient's quality of life, it is important that a neurologist experienced in the treatment of Parkinson's disease works as a team with the patient and caregivers.

Biosketch:

Dr. Saiki, a Japanese neurologist, has been Professor of Parkinson's Disease Advanced Therapy Center of Aichi Medical University Hospital since 2020. He received his MD from the Faculty of Medicine, University of Tsukuba in 1989 and completed his neurology residency at Kyoto University and Utano National Hospital. He spent fifteen years as Deputy Director of the Department of Neurology, Kitano Hospital, Tazuke Kofukai Medical Research Institute in Osaka from 2005 to 2020. He is a clinician with special interest in Parkinson's disease, other related movement disorders, and stereotactic brain surgery for movement disorders such as deep brain stimulation. He has experienced more than 200 cases of stereotactic surgery for Parkinson's disease since 1993. In 2017, he was awarded as an excellent teacher by the Japanese Society of Neurology.

Evening Seminar

Chair:

Yoshikazu Ugawa
Department of Human Neurophysiology, Fukushima Medical University, Fukushima, Japan

1. Brain Networks in Parkinson's disease

Speaker:

Wataru Sako, MD, PhD
Department of Neurology, Juntendo University School of Medicine

Abstracts:

Brain network analysis is classified as functional or structural network analysis. Functional network analysis is based on glucose metabolism assessed by fluorodeoxyglucose positron emission tomography (FDG PET), blood oxygen level-dependent signal in resting state functional MRI (RSfMRI), and perfusion. In contrast, structural network analysis is based on diffusivity of water. The former analyses detect synchronizing regions as a network, which does not guarantee true connectivity, while the latter analysis detects connectivities close to the anatomical tract. These allow us to find two types of networks: normal and disease-associated networks. The talk will focus on Parkinson's disease (PD) -associated networks, which are PD-related pattern (PDRP) and PD-related cognitive pattern (PDCP). The PDRP is associated with the underlying disease, while the PDCP is associated with language and executive function. The functional abnormalities in PD always include hyperactivity of the cerebellum, suggesting the only cerebellar activity has the potential for differential diagnosis between PD and atypical parkinsonian disorders. In this line, simple cerebellar perfusion measured by iodoamphetamine single photon emission computed tomography help to differentiate multiple system atrophy with predominant parkinson feature from PD. Further network analysis in RSfMRI clarified cerebellar contribution to cognitive function and underlying disease.

Biosketch:

Professional Training

1997-2003	M.D., Tokushima University
2003-2006	Residency: Internal Medicine and Neurology, Kitano Hospital
2006-2011	Ph.D. and Fellowship: Molecular biology and Movement Disorders, Tokushima University (Prof. Ryuji Kaji)
2011-2014	Postdoctoral Research Trainee: Neuroimaging, Center for Neurosciences, The Feinstein Institutes for Medical Research (Prof. David Eidelberg)

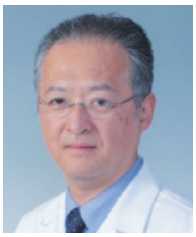
Academic Position

2014-2021	Assistant Professor, Tokushima University Graduate School of Biomedical Sciences
2021-present	Associate Professor, Juntendo University School of Medicine

Key articles (Up to 5):

Sako et al., 2014 In Movement Disorders, Second Edition: Genetics and Models. Elsevier; Sako et al., Brain 2014; Mattis, Niethammer, Sako et al., Neurology 2016; Vo, Sako et al., Hum Brain Mapp 2017; Murakami, Sako et al., J Neurol Sci 2019.

Evening Seminar



2. What roles of cerebellum in PD?

Speaker:

Hirohisa Watanabe, MD, PhD

Department of Neurology, Fujita Health University, School of Medicine

Abstracts:

It is well-established that damage to the cerebellum can result in both motor deficits and cognitive and affective symptoms, known as the cerebellar cognitive affective syndrome (CCAS). Damage to the anterior cerebellum is associated with motor deficits, while damage to the posterior cerebellum is associated with CCAS. Resting state functional MRI studies have shown that the posterior cerebellum is closely connected to core neurocognitive networks such as default mode networks, salience networks, and executive control networks. Recent studies showed that the cerebellum and the basal ganglia, which are involved in error-based learning and reward-based respectively, influence many of the same cortical areas and support various functions including motor, cognition, behavior and emotion in the cerebral cortex. In Parkinson's disease (PD), the cerebellum and other interconnected structures such as the primary motor cortex and basal ganglia, as well as abnormal sensorimotor processing, have been linked to the presence of symptoms such as bradykinesia, tremors, cognitive decline, and dyskinesia. Studies using FDG PET and fMRI have shown that the severity of impairment in PD is correlated with increased metabolism in certain areas of the cerebellum and that cerebellar and sensorimotor connector hubs are significantly involved in the disorder, with their connectivity dysfunction potentially driving the clinical manifestations. The cerebellum and its network play a crucial role in the pathogenesis of PD.

Biosketch:

Dr. Hirohisa Watanabe is currently a Professor and Chairperson of the Department of Neurology, Fujita Health University school of medicine. He graduated from Mie University School of Medicine in 1993, received his neurological training at Nagoya Daini Red Cross Hospital and Nagoya University Hospital, and was certified as a neurologist by the Japanese Society of Neurology. He intensively investigated the relationship between brain network changes and aging as well as neurodegenerative diseases in Brain and Mind Research Center, Nagoya University as a designated professor. He is currently a Delegate of the Japanese Society of Neurology, Movement Disorders Society Japan, Delegate of the Japan Society of Neurovegetative Research, Delegate of the Japanese Society for Dementia Research, and Delegate of the Japanese Society of Neurological Therapeutics. He is particularly interested in developing imaging and clinical biomarkers for early diagnosis and disease progression of Parkinson's disease, Parkinson syndromes, and neurodegenerative dementia.

Key articles (Up to 5):

1. Bagarinao E, Kawabata K, **Watanabe H**, et al. Connectivity impairment of cerebellar and sensorimotor connector hubs in Parkinson's disease. **Brain Commun** 2022, Published: 20 August 2022, fcac214, https://doi.org/10.1093/braincomms/fcac214
2. Kawabata K, Bagarinao E, **Watanabe H**, et al. Functional Connector Hubs in the Cerebellum. **Neuroimage**. 2022 Apr 29:119263. doi: 10.1016/j.neuroimage.2022.119263. Epub ahead of print. PMID: 35500805.
3. Kawabata K, **Watanabe H**, Bagarinao E, et al. Cerebello-basal ganglia connectivity fingerprints related to motor/cognitive performance in Parkinson's disease. **Parkinsonism Relat Disord**. 2020 Nov;80:21-27.
4. Bagarinao E, **Watanabe H**, Maesawa S, et al. Identifying the brain's connector hubs at the voxel level using functional connectivity overlap ratio. **Neuroimage** 2020;222:117241.
5. Kawabata K, **Watanabe H**, Hara K, et al. Distinct manifestation of cognitive deficits associate with different resting-state network disruptions in non-demented patients with Parkinson's disease. **J Neurol**. 2018;265:688–700.

Abstracts

2nd Day
25 Mar 2023 (Saturday)

Symposium 3

Chair:
Yasushi Shimo
Department of Neurology Juntendo University Nerima Hospital

1. Amantadine for the treatment of Parkinson disease and other movement disorders

Speaker:
RASCOL Olivier, MD, PhD
University of Toulouse 3, Toulouse, FRANCE

Abstracts:

The efficacy of amantadine in the symptomatic treatment of patients with Parkinson's disease (PD), discovered serendipitously more than 50 years ago, has stood the test of time and the drug is still commonly used in this indication. Its pharmacological actions are unique in combining dopaminergic and glutamatergic properties, which account for its dual effect on parkinsonian symptoms and levodopa-induced dyskinesias. Furthermore, amantadine has additional and less well-defined pharmacological effects, including on anticholinergic and serotonergic activity. Evidence from randomised controlled trials have demonstrated the efficacy of amantadine to treat levodopa-induced dyskinesias and motor fluctuations in advanced stages of PD. Recent data have re-assessed its potential role at an earlier stage of the disease. Other uses of amantadine, such as in the treatment of drug-induced parkinsonism, atypical parkinsonism, Huntington's disease, or tardive dyskinesia, lack a strong evidence base. Future trials should examine its role in the management of motor and non-motor symptoms of PD (including freezing of gait and fatigue) and those with other movement disorders.

Biosketch:

Doctor Olivier Rascol is a neurologist specialized in Movement Disorders, Professor of Clinical Pharmacology at the Toulouse University Hospital. He obtained his MD in Neurology (Toulouse, 1985) and his PhD in Neurosciences (Paris, 1992). Dr Rascol is running the Toulouse Clinical Investigation Centre (CIC14136) since 1994 and the Toulouse Space Clinic since 1998. He is the coordinator of the Toulouse Expert Center for Parkinson Disease (PD) and of the national French Reference Center for Multiple System Atrophy (MSA) . Dr Rascol is chairing the NS-Park/F-CRIN Neurosciences Network on clinical research in PD since 2010, and is coordinating the National French Clinical Research Infrastructure Network F-CRIN (PIA1 grant of > 20 M€).

As a clinical neuropharmacologist, Pr Rascol's main fields of interest are PD, MSA and other movement disorders, drug development for PD and atypical parkinsonian syndromes and neuroimaging. Pr Rascol has been actively involved in the development of most marketed antiparkinsonian medications within the last 30 years (ropinirole, rasagiline, entacapone, safinamide, pramipexole ER, opicapone, amantadine ER, istradefylline, novel extended-release formulations of L-DOPA, device-based delivery of L-DOPA and apomorphine…). He is currently running several trials for disease progression (neuroprotection) or symptomatic management of PD and MSA (motor signs, dyskinesias and on-off problems, non-motor signs such as pain and sleep problems) with new dopaminergic and non-dopaminergic (serotonergic, glutamatergic, …) drugs in collaboration with national and international academic and industry partners. Pr Rascol is a scientific advisor for French and European scientific organisations, patients' associations, drug agencies and international pharmaceutical companies. As the chair of the National F-CRIN Clinical Research infrastructure, Pr Rascol is deeply involved in the management and organisation of clinical research in France.

Pr Rascol has served as the Secretary of the International Parkinson & Movement Disorders Society (2006-2009), as the chair of IP-MDS European Section (2013-2015) and as the chair of the Movement Disorder Scientific Panel of the European Academy of Neurology (2013-2015). Pr Rascol is serving or has served as editor/associate-editor for Movement Disorders Journal, J Neural Transmission, Fundamental and Clinical Pharmacology. He is or has been at the editorial board of Lancet Neurology, Neurology, European J Neurology…

Pr Rascol has been invited worldwide to give more than 500 lectures in Europe, North America, South America and Asia. Pr Rascol's H factor is >80, with >550 publications in International Scientific journals (New England Journal of Medicine, Lancet, Lancet Neurology, Annals of Neurology, Neurology, Archives of Neurology, Brain, JAMA Neurology, Movement Disorders…)

Key articles (Up to 5):

1. **Rascol O** et al, A five-year study of the incidence of dyskinesia in patients with Parkinson disease who were treated with ropinirole or levodopa. N Engl J Med 2000.
2. **Rascol O** et al. Rasagiline as adjunct to levodopa in Parkinson disease patients with motor fluctuations: the LARGO Study. The Lancet 2005.
3. Olanow W*, **Rascol O*** et al. A double-blind, delayed start study of rasagiline in early Parkinson disease: the ADAGIO Study. N Engl J Med 2009 (*co-first authors).
4. Tolosa E, …, **Rascol O**. LRRK2 in Parkinson disease: challenges of clinical trials. Nat Rev Neurol. 2020.
5. **Rascol O**, Fabbri M, Poewe W. Amantadine in the treatment of Parkinson's disease and other movement disorders. The Lancet Neurol. 2021.

Symposium 3

2. Pathomechanisms of Parkinson's disease due to prosaposin gene mutations

Speaker:
Yutaka Oji, MD, PhD
Department of Neurology, Juntendo University Graduate School of Medicine

Abstracts:

Recently, the genetic variability in lysosomal storage disorders (LSDs) has been implicated in the pathogenesis of PD. Heterozygous mutations in the GBA1 gene, which is a causative gene for Gaucher disease, have been known to be the most common genetic risk factor for PD. Additionally, mutations in other genes linked to LSDs such as Krabbe disease, Niemann-Pick disease, and metachromatic leukodystrophy, have been associated with the development of PD, which suggests that LSD gene mutations and subsequent pathological processes could be involved in the pathomechanisms of PD. In 2020, we reported the PSAP gene (*PSAP*), which encodes prosaposin (PSAP) that is a precursor protein of four sphingolipid activator proteins that promote sphingolipid degradation metabolism in the lysosome, as a novel causative gene for familial PD (PARK24). We identified three *PSAP* mutations linked to autosomal dominant inherited PD which were found in the saposin D domain of PSAP that is required for the lysosomal transport of PSAP. We will demonstrate new our data of iPS cells-derived dopaminergic neurons and mice and discuss how pathogenic PSAP mutations are associated with neurodegeneration.

Biosketch:

Yutaka Oji obtained an MD degree from Juntendo University in 2007. After completing the medical training program at the Juntendo University Hospital and several hospitals, YO researched about lysosomal storage disorders such as Gaucher disease in the pathogenesis of PD at Juntendo Univestity Graduate School. YO currently is a clinician and researcher at Juntendo University Hospital (2016～present). The main research interests are in PD and other neurodegenerative disorders. The ongoing research is to analyze the function of the PSAP gene which is involved in lysosomal storage disorder and also a causative gene for familial Parkinson's disease.

Key articles (Up to 5):

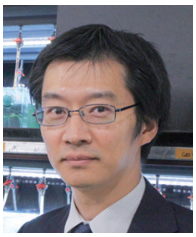
Oji Y, Hatano T, Ueno SI, Funayama M, Ishikawa KI, Okuzumi A, Noda S, Sato S, Satake W, Toda T, Li Y, Hino-Takai T, Kakuta S, Tsunemi T, Yoshino H, Nishioka K, Hattori T, Mizutani Y, Mutoh T, Yokochi F, Ichinose Y, Koh K, Shindo K, Takiyama Y, Hamaguchi T, Yamada M, Farrer MJ, Uchiyama Y, Akamatsu W, Wu YR, Matsuda J, Hattori N. Variants in saposin D domain of prosaposin gene linked to Parkinson's disease. Brain. 2020 Apr 1; 143 (4): 1190-1205. doi: 10.1093/brain/awaa064. PMID: 32201884.

Hot Topics

Chair:
Tatsushi Toda
Department of Neurology, University of Tokyo, Tokyo, Japan

Yoshio Tsuboi
Department of Neurology, School of Medicine, Fukuoka University

1. Molecular pathogenesis of Parkinson's disease illuminated by small fish models



Speaker:
Hideaki Matsui, MD, PhD
Brain Research Institute, Niigata University

Abstracts:

Parkinson's disease (PD) is one of the common neurodegenerative diseases that cause movement disorders and non-movmement symptoms, and its pathogenesis remains elusive. It has long been suggested that mitochondrial and lysosomal dysfunction are involved in the pathogenesis of PD, but the detailed mechanisms remain unknown. In the first half of this talk, I will introduce our research on PD using various fish species. In particular, I will report the phenotypes of African killifish (Nothobranchius furzeri). African killifish, the fastest aging vertebrate, exhibited PD-like phenotypes during aging. Genetic removal of α-synuclein suppressed PD-like neurodegeneration in this fish. We will also discuss why α-synuclein can be toxic in the African killifish.

In the latter half, I will discuss the pathogenesis of PD which we have discovered through observation of PD models and human brains. In cultured cells, the genetic manipulation associated with PD caused an increase of mitochondria-derived cytoplasmic DNA which induced a type I interferon response and cell death. These phenotypes were rescued by overexpression of DNase II, a DNA-degrading enzyme in lysosomes that degrades DNA, or suppression of IF I16, which we identified as a sensor of cytoplasmic DNA of mitochondrial origin. The motor deficits and dopaminergic neurodegeneration of gba mutant zebrafish, which is one of the zebrafish models of PD, was also ameliorated by overexpression of human DNaseII. The sensor protein IFI16 and cytoplasmic DNA of mitochondrial origin were accumulated in the disease lesions of the brains of human PD patients. These results suggest that leakage of mitochondrial DNA into the cytoplasm can be an important cause of neuro-degeneration in PD.

Biosketch:

2001.03	Graduated from Kyoto University School of Medicine, Faculty of Medicine
2001.05~	Kyoto University Hospital, Sumitomo Hospital, etc.
2006.04-2010.03	Completed Doctoral program in Dept. Neurology, Graduate School of Medicine, Kyoto University (Prof. Ryosuke Takahashi)
2011.01~2012.12	Postdoctoral Fellowship (Humboldt Foundation Fellowship), Dept. Cell-Physiology, Zoological Institute, TU Braunschweig (Prof. Reinhard Köster)
2013.01-2016.01	Postdoctoral fellow → Assistant Professor in Dept. Neuroscience, Faculty of Medicine, Miyazaki University
2016.01-2020.03	Associate Professor, Dept. Neuroscience of Disease, Interdisciplinary Academy, Niigata University
2016	The Japan Neuroscience Society Young Investigator Award
2020.04	Professor, Dept. Neuroscience of Disease, Brain Research Institute, Niigata University

Key articles（Up to 5）:

1. **Matsui, H**.*, Ito, J., Matsui, N., Uechi, T., Onodera, O., Kakita, A. Cytosolic dsDNA of mitochondrial origin induces cytotoxicity and neurodegeneration in cellular and zebrafish models of Parkinson's disease. *Nat. Commun*. 12（1）:3101, 2021.
2. **Matsui, H**.*, Kenmochi, N., Kazuhiko, N. Age- and α-Synuclein-Dependent Degeneration of Dopamine and Noradrenaline Neurons in the Annual Killifish Nothobranchius furzeri. *Cell Rep*. 26（7）:1727-1733, 2019.
3. **Matsui, H**.*, Namikawa, K., Babaryka, A. and Köster, R. Functional regionalization of the teleost cerebellum analyzed in vivo. *Proc. Natl. Acad. Sci. USA* 111（32）: 11846-11851, 2014.
4. **Matsui, H**., Sato, F., Sato, S., Koike, M., Taruno Y., Saiki, S., Funayama, M., Ito, H., Taniguchi, Y., Uemura N., Toyoda, A., Sakaki, Y., Takeda, S., Uchiyama, Y., Hattori, N. and Takahashi, R. ATP13A2 Deficiency Induces a Decrease in Cathepsin D Activity, Fingerprint-like Inclusion Body Formation and Selective Degeneration of Dopaminergic Neurons. *FEBS Lett*. 587（9）: 1316-1325, 2013.
5. **Matsui, H**.*, Gavinio, R., Asano T, Uemura N., Ito, H., Taniguchi, Y., Kobayashi Y., Maki, T., Shen J., Hattori, N., Takeda, S., Uemura K., Yamakado H. and Takahashi, R. PINK1 and Parkin complementarily protect dopaminergic neurons in vertebrates. *Hum. Mol. Genet*. 22（12）: 2423-2434, 2013.

Hot Topics

2. Rehabilitation for Parkinson's Disease

Speaker:
Tadashi Ichikawa MD, PhD
Saitama Prefectural Rehabilitation Center

Abstracts:

The definition of rehabilitation by WHO was renewed and became wider. Purpose of rehabilitation includes not only recovery from disease condition but also prevention of disease progression and keeping healthy condition. I will show short-term effect on motor and non-motor symptoms by exercise and physiotherapy. This functional improvement is interpreted as recovery firm disease and disuse condition.
Exercise and physiotherapy have other mechanisms those contribute to neuroprotection and prevention of Parkinson's disease (PD) progression. Etiological evidence from cohort studies those showed lower incidence rate of PD in higher physical activity groups were published.

The mechanisms of prevention of PD progression were clearly shown in animal experiments. Major factors of neuroprotective mechanism are thought including effects by Brain Derived Neurotrophic Factor (BDNF), improvement of mitochondrial survive, and suppression of α-synuclein aggregation and spreading. I will introduce you evidences showed in animal experiments. BDNF is well known neuroprotective substances and the neuroprotective mechanism via BDNF are researched by many scientists. In recent studies, BDNF is promoted by lactate whose serum and tissue level is elevated by exercise with loads. It is ambiguous that BDNF can pass blood brain barrier (BBB), but lactate can pass BBB to make BDNF increased in neurons. Thus, lactate is a candidate for neuroprotective mechanism in exercise and physiotherapy.

Conclusion: Rehabilitation has short-term and long-term effect on PD. From the point of prevention or suppression of PD progression, starting in early stage and continuing along PD course is important for people with PD. Exercise and physiotherapy are safe and people with PD can obtain benefits world widely.

Biosketch:

Graduated Faculty of Medicine, Tokyo Medical and Dental University in 1986.
Graduated Postgraduate School, Tokyo Medical and Dental University in 1994.
1994- Department of Neurology, Saitama Prefectural Rehabilitation Center (SRC)
2022- Director of SRC

Key articles (Up to 5):

1. Ichikawa T, Yokota T. F wave change by decreased motor excitability: sleep study Bull TMDU 1994 Mar 41
2. Kato H, et al. J Cereb Blood Flow Metab 2022 Jul 7; 271678X221113001.
3. Kaushik MK, et al. Proc Natl Acad Sci U S A.2018 Jun 5;115(23): 6046-6051

3. Exosomes contribute to the development of Parkinson's disease

Speaker:
Taiji Tsunemi, MD, PhD
Department of Neurology, Juntendo University School of Medicine

Abstracts:

Parkinson's disease (PD) is the most common movement disorder, affecting around 15 million people worldwide. The incidence increases with age, suggesting that PD is an imperative issue in an aging society. PD has been clinically characterized by four main motor symptoms, which are mainly caused by the loss of dopaminergic neurons in the substantia nigra. During the disease, patients also show a broad range of non-motor symptoms that reflect pathological changes spreading throughout the entire body. The pathological hallmark of PD is alpha-synuclein (a-syn) -containing insoluble aggregates named Lewy bodies and Lewy neurites in both the central nervous system (CNS) and the peripheral nervous system (PNS) , either of which can be an initial source of a-syn aggregates. Recent evidence indicates the involvement of exosomes, nano-sized extracellular vesicles, in the development of PD. Exosomes physiologically play important roles in transmitting information in the body, carrying various proteins, lipids, and RNAs depending on the original cells, and are involved in the development of several disorders, including PD.

In this talk, I will summarise the recent advances in the research of a-syn propagation in PD pathology. Then I will talk about exosomes, from their biogenesis to their physiological roles. Finally, I will talk about the usefulness of exosomes as biomarkers for PD, their significant roles in disseminating Lewy pathology, by carrying a-syn accumulated in the PNS into the CNS, and vice versa., and possible therapeutic targets for attenuating PD pathology.

Biosketch:

Taiji Tsunemi graduated from Tokyo Medical and Dental University in 1994 and joined the department of Neurology. After residency training, I have been working as an academic neurologist as well as a researcher who tries to understand the molecular mechanism of neurodegenerative disorders including synucleinopathies. Previous studies focused on the pathways of insoluble protein accumulation in neurons (2012 *Sci Transl Med*, 2016 *Nat Med*) . Recent discoveries include exosomes, small extracellular vesicles, which play an important role in releasing alpha-synuclein from neurons in a couple of monogenic forms of PD (2014 *J Neurosci*, 2016, *J Neurosci*) , and enhancing this pathway can attenuate alpha-synuclein accumulation in neurons (2020 *J Neurosci*).

Key articles (Up to 5):

1. **Tsunemi T***, Ishiguro Y, Yoroisaka A, Valdez C, Miyamoto K, Ishikawa K, Saiki S, Akamatsu W, Hattori N, Krainc D. (2020) Astrocytes protect human dopaminergic neurons from α-synuclein accumulation and propagation. **J Neurosci** 40:8618-8618.
2. **Tsunemi T**, Perez-Rosello T, Ishiguro Y, Yoroisaka A, Jeon S, Hamada K, Rammonhan M, Wong YC, Xie Z, Akamatsu W, Mazzulli JR, Surmeier DJ, Hattori N, Krainc D (2019) Increased Lysosomal Exocytosis Induced by Lysosomal Ca^{2+} Channel Agonists Protects Human Dopaminergic Neurons from α-Synuclein Toxicity. **J Neurosci** 39:5760-5772.
3. Mazzulli JR, Zunke F, **Tsunemi T**, Toker NJ, Jeon S, Burbulla LF, Patnaik S, Sidransky E, Marugan JJ, Sue CM, and Krainc D (2016) Activation of α-Glucocerebrosidase Reduces Pathological α-Synuclein and Restores Lysosomal Function in Parkinson's Patient Midbrain Neurons. **J Neurosci** 36: 7693-7706.
4. Song P, Trajkovic K, **Tsunemi T**, and Krainc D (2016) Parkin modulates endosomal organization and function of the endo-lysosomal pathway. **J Neurosci** 36: 2425-2437.
5. **Tsunemi T**, Hamada K, Krainc D. (2014) ATP13A2/PARK9 regulates secretion of exosomes and a-synuclein. **J Neurosci** 34:15281-15287.

Lunch on seminar

Chair:

Masahiko Tomiyama
Department of Neurology, Hirosaki University Graduate School of Medicine, Aomori, Japan

1. Genomic background of Parkinson's disease and clinical application of genomics towards the development of percision medicion.

Speaker:

Wataru SATAKE, MD, PhD
Dept Neurol, The Univ of Tokyo, Tokyo, Japan.

Abstracts:

The majority of patients with Parkinson's disease (PD) have a sporadic onset. And a certain degree of familial clustering (λ s 6.7) is observed in a few percent of patients. This indicates that PD is a polygenic disease involving many disease risk genes. We performed a genome-wide association analysis (GWAS) of Parkinson's disease using SNP arrays to find disease risk genes for PD and found four disease risk genes that passed the genome-wide significance level (*Nature Genet* 2009). Furthermore, in an attempt to utilise genomic information for drug discovery, drug repositioning drug discovery was conducted by in silico drug screening using GWAS findings. GWAS-identified PD disease risk genes and protein-protein interaction genes were searched in the database, and drugs targeting these genes were extracted from the drug database. To test whether these drugs actually have neuroprotective effects, we investigated them in vitro and in vivo and found that dabrafenib, an approved drug for malignant melanoma, is a potential disease modifier for PD (*Hum Mol Gent* 2018). In a pharmacogenomics study for PD, we found genomic markers that could predict the efficacy of zonisamide, a PD drug developed in Japan (*J Hum Genet* 2020). Furthermore, we performed whole transcriptome analysis and found the importance of glutamate-related synaptic modulation in the efficacy of zonisamide (*J Neurol Neurosurg Psychiatry* 2022). We hope that these studies will contribute to the realisation of precision medicine in PD.

Biosketch:

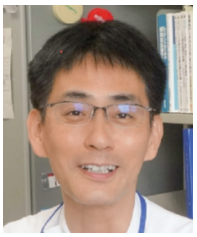
I have been involved in clinical practice as a clinical neurologist at Osaka University Hospital, Kobe University Hospital and the University of Tokyo Hospital. My research interests include the elucidation of the pathogenesis of neurological diseases, particularly Parkinson's disease, by genome analysis, and I am interested in the clinical application of genomics and Precision Medicine in the field of neurology.
Present Position: Associate Professor at Dept Neurol, the Univ of Tokyo.
Education: MD from Osaka University in 2000 and PhD from Osaka University in 2007.
Award: Japanese Society of Neurology Award in 2018 and Young Investigator's Award of Japanese Society of Human Genetics in 2011.

Key articles (Up to 5):

1. **Satake W**, Nakabayashi Y et al. Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease. *Nat Genet*. 41(12): 1303-7, 2009.
2. Uenaka T, **Satake W** et al. In silico drug screening by using genome-wide association study data repurposed dabrafenib, an anti-melanoma drug, for Parkinson's disease. *Hum Mol Genet*. 27(22): 3974-3985, 2018.
3. Cha PC, **Satake W** et al. Genome-wide association study identifies zonisamide responsive gene in Parkinson's disease patients. *J Hum Genet*. 65(8): 693-704, 2020.
4. Naito T, **Satake W** et al. Trans-Ethnic Fine-Mapping of the Major Histocompatibility Complex Region Linked to Parkinson's Disease. *Mov Disord*. 36(8): 1805-1814, 2021.
5. Naito T, **Satake W*** et al. Comparative whole transcriptome analysis of Parkinson's disease focusing on the efficacy of zonisamide. *J Neurol Neurosurg Psychiatry*. 93(5): 509-512, 2022.

Lunch on seminar

2. Treatment of autonomic dysfunction in movement disorders



Speaker:

Tomohiko Nakamura, MD, PhD

Department of Neurology, Hamamatsu University Hospital

Abstracts:

Autonomic dysfunction is one of the common manifestations in Parkinson's Disease and multiple system atrophy. The cardinal symptoms of autonomic dysfunction are orthostatic hypotension, gastrointestinal dysfunction, urinary dysfunction, sweat dysfunction, and sexual dysfunction. In other movement disorders, autonomic dysfunction rarely occurs, but urinary dysfunction is also observed in patients with progressive supranuclear palsy or corticobasal syndrome and constipation is also common symptom in supranuclear palsy and Huntington's disease.

The first step in the treatment of autonomic dysfunction is to suspect that the patient in front of you may have it, and to actively ask questions about it. Patients are unaware that autonomic dysfunction is a disease-related condition and therefore do not dare to consult their physician. Next step is to check whether any of the drugs the patient is taking is causing autonomic dysfunction. There are many drugs that cause autonomic dysfunction. If possible, such drugs should be reduced or discontinued. In the next step, non-pharmacological therapy with daily life guidance is performed. Drug therapy should be performed if these measures do not improve the condition.

Improvement of one autonomic dysfunction may exacerbate other autonomic dysfunction, and the purpose of treatment for autonomic dysfunction is not to eliminate symptoms, but to alleviate symptoms and improve quality of life. Overall balance is important.

Biosketch:

Tomohiko NAKAMURA graduated from Nagoya University in 1995. After completing the medical training program at several hospitals, TN researched about pathophysiology of cardiac sympathetic denervation in Parkinson's disease and gained PhD form Nagoya University Graduate School. After that, TN continued research at Nagoya University Hospital, focusing on cardiovascular autonomic dysfunction in movement disorders. TN is currently professor of neurology at Hamamatsu University Hospital (2021～present). The main research interests are in Parkinson's disease and other movement disorders. The ongoing research is further elucidating the pathophysiology of cardiovascular autonomic dysfunction in Parkinson's disease and other movement disorders.

Key articles (Up to 5):

1. **Nakamura T**, Suzuki M, Ueda M, Harada Y, Hirayama M, Katsuno M: Difference in cardiovascular response during orthostatic stress in Parkinson's disease and multiple system atrophy. J Neural Transm (Vienna) 127:1377-1386, 2020.
2. **Nakamura T**, Suzuki M, Okada A, Suzuki J, Hasegawa S, Koike H, Hirayama M, Katsuno M, Sobue G: Association of leptin with orthostatic blood pressure changes in Parkinson's disease. Mov Disord 31:1417-1421, 2016.
3. **Nakamura T**, Hirayama M, Hara T, Mizutani Y, Suzuki J, Watanabe H, Sobue G: Role of cardiac sympathetic nerves in preventing orthostatic hypotension in Parkinson's disease. Parkinsonism Relat Disord 20:409-414, 2014.
4. **Nakamura T**, Hirayama M, Hara T, Hama T, Watanabe H, Sobue G: Does cardiovascular autonomic dysfunction contribute to fatigue in Parkinson's disease? Mov Disord 26:1869-1874, 2011.
5. **Nakamura T**, Hirayama M, Yamashita F, Uchida K, Hama T, Watanabe H, Sobue G: Lowered cardiac sympathetic nerve performance in response to exercise in Parkinson's disease. Mov Disord 25:1183-1189, 2010.

Symposium 4 How to establish the QOL of PD

(Takeda Pharmaceutical Co., Ltd.)

Chair:

Yasuyuki Okuma
Juntendo University Shizuoka Hospital

Kazuko Hasegawa
NHO, Sagamihara National Hospital / clinical rearch center

1. Neuropsychiatric complications in Parkinson's disease

Speaker:

Jinsoo Koh, MD, PhD
Department of Neurology, Wakayama Medical University

Abstracts:

Parkinson's disease (PD) causes complex neuropsychiatric symptoms. Depression, anxiety, apathy, psychosis, and impulse control disorders are common neuropsychiatric symptoms (ICDs). Younger people are more likely to have ICDs and apathy, whereas older people are more likely to have depression and anxiety. Conversely, ICDs and depression are likely to coexist.

The prevalence of ICDs is estimated to be about 15%, with a 5-year incidence rate of about 50%. Because ICDs range in intensity and frequency of activity, patients with mild ICDs may be more latent. Furthermore, high impulsivity is a risk factor for developing ICDs and can lead to the development of severe ICDs. Although hyper-stimulation of the mesolimbic dopaminergic pathway is a key factor in ICDs, other factors, such as complex pathophysiology, genetics, and environmental factors, are also involved. One important factor is D2/3 receptor stimulation. ICD patients have high functional connectivity in the default-mode and salience networks, but low functional connectivity in the central executive network. In contrast, we found that high impulsivity in PD is associated with high functional connectivity between the right frontoparietal network and the medial visual network. ICD management in patients with PD is still in its early stages. Reduced dopamine replacement therapy can improve ICDs, but it can also worsen motor symptoms and occasionally cause dopamine agonist withdrawal syndrome. There have been a few pharmacological and nonpharmacological trials for ICD reported. The effects of naltrexone and amantadine are still debatable, and cognitive-behavioral therapy is supported by Class IV evidence. Mindfulness meditation is also a potential treatment for ICDs and impulsivity in PD.

Biosketch:

2022-present	Senior Lecturer, Department of Neurology, Wakayama Medical University
2015 - 2022	Assistant Professor, Department of Neurology, Wakayama Medical University
2011 - 2015	Clinical Fellow, Department of Neurology, Wakayama Medical University
2010 - 2011	Clinical Fellow, Department of Neurology, Wakayama-Rosai Hospital
2009 - 2010	Clinical Fellow, Department of Neurology, Wakayama Medical University

Key articles (Up to 5):

1. Weintraub D, et al. Lancet Neurol 2022; 21: 89-102.
2. Takahashi M, et al. Parkinsons Dis 2022; 2022: 1503167.
3. Koh J, et al. Sci Rep 2020; 10: 11418.
4. Koh J, et al. PLoS One 2022; 17: e0266354.
5. Kwok JYY, et al. JAMA Neurol 2019; 76: 755-763.

3. Restless Legs Syndrome in patients with Parkinson disease

Speaker:

Yuichi Inoue, MD, PhD

Department of Somnology, Tokyo Medical University Yoyogi Sleep Disorder Center

Abstracts:

Previous reports have shown that restless Legs Syndrome (RLS) is not a risk factor for Parkinson disease (PD) per se but rather that PD is a risk factor for a diagnosis of RLS, and a diagnosis of RLS may be an early manifestation of PD. The prevalence of RLS in recent PD cohorts ranges from 3% to 21.3% (compared to 0.5%). Reportedly, late-onset patients develop RLS sooner after PD diagnosis compared to those with young-onset. Although primary RLS is frequently associated with periodic limb movements during sleep (PLMS), the relationship between PLMS and RLS in PD is less well understood, with research yielding conflicting results.

The question of possible pathophysiological overlap between PD and RLS has been a subject of debate. A recent imaging study demonstrated evidence for different pathophysiological pathways between RLS and PD with finding that striatal dopamine transporter binding measured by SPECT was reduced in PD but not in primary RLS. In a genotyping study of patients with RLS the Rep1 allele 2, which is known to confer a risk of PD, showed a significantly decreased frequency compared with healthy controls, possibly suggesting that low alpha-synuclein function may contribute to the RLS pathogenesis. As for transcranial sonographic findings, while it is clear that PD is associated with substantia nigra (SN) hyperechogenicity, RLS is associated with SN hypoechogenicity.

While many of the dopaminergic agents used to treat PD have been independently demonstrated in randomized trials to be effective in treating RLS, there are no randomized trials examining the treatment of RLS in the PD population. In addition, the occurrence and management of augmentation of RLS symptoms in PD patients being treated with dopaminergic medications for their motor symptoms is poorly described. Several groups reported positive postoperative effects of subthalamic nucleus deep brain stimulation DBS on RLS. However, emergence of RLS subsequent to STN DBS may occur as well, emphasizing the need to screen for RLS postoperatively as the reduction in antiparkinsonian medications may lead to unmasking of RLS.

Biosketch:

Yuichi Inoue is currently Professor of Department of Somnology, Tokyo Medical University. He is also President of Yoyogi Sleep Disorder Center and Director of Japan Somnology Center, Institute of Neuropsychiatry.

He got a doctor of medicine degree in graduate school of Tottori University in 1986.

He became a Professor of the Department of Psychiatry at Tokyo Medical University in 2007. He also assumed the position of Director of Japan Somnology Center and Professor of Department of Somnology at Tokyo Medical University in 2008. He became President of Yoyogi Sleep Disorder Center in 2011.

He now is the Board Directors of The Japanese Society of Sleep Research, Japanese Society for Chronobiology, Secretary general of Asian Sleep Research Society and chair of World Sleep Society Nominating Committee. Main target of his research is clinical sleep medicine including researches on insomnia, RBD, movement disorders and hypersomnia.

Key articles (Up to 5):

restless legs syndrome, Parkinson disease, insomnia, dopaminergic drugs, augmentation

(Takeda Pharmaceutical Co., Ltd.)

3. Multidisciplinary Care for PD

Speaker:
Morinobu Seki, MD, PhD
Department of Neurology, Keio University School of Medicine

Abstracts:

Multidisciplinary care is important to support the health of PD patients. In recent years, the need for providing PD patients with multidisciplinary care has increased significantly. This is due to the need for comprehensive understanding and management of various symptoms, the increasing complexity of treatment including device-aided therapy, and the rapid increase of elderly PD patients who face many challenges. There are several types of care models with increasing integration, among which interdisciplinary and transdisciplinary models may be better than multidisciplinary model for PD. In addition to the "patient-centered approach", the "patient-as-partner approach", in which patients and caregivers participate as team members and are involved in decision-making, has been advocated. Interprofessional work with government, welfare and local communities is important, especially for elderly PD patients. It has been reported that multidisciplinary care for PD patients improves motor symptoms, non-motor symptoms including depression, self-efficacy of patients, and well-being of caregivers. Team members for PD involve physicians, nurses, rehabilitation staff, pharmacists, nutritionists, psychologists, and medical social workers, and so on. In some countries, PD specialist nurses are officially certificated, who have high-level and broad expertise in PD and play a central role in team care. In April 2022, MDS-Japan launched an educational program for healthcare professionals to train certificated PD educators.

Biosketch:

2022/10-Present	Associate Professor in Department of Neurology, Keio University School of Medicine, Tokyo
2018/10-2022/9	Assistant Professor in Department of Neurology, Keio University School of Medicine, Tokyo
2017/7-2018/9	Instructor in Department of Neurology, Keio University School of Medicine, Tokyo
2014/11-2017/6	Research Fellow in Department of Neurology, Innsbruck Medical University, Innsbruck
2007/4-2014/10	Instructor in Department of Neurology, Keio University School of Medicine,, Tokyo

Key articles (Up to 5):

1. **Seki M**, Takahashi K, Koto A, et al. Camptocormia in Japanese patients with Parkinson's disease: a multicenter study. *Mov Disord*. 26 (14) :2567-71, 2011.
2. **Seki M**, Takahashi K, Uematsu D, et al. Clinical features and varieties of non-motor fluctuations in Parkinson's disease: a Japanese multicenter study. *Parkinsonism Relat Disord*. 19 (1) :104-8, 2013.
3. Tuovinen N, Seppi K, **Seki M**, et al. The reorganization of functional architecture in the early-stages of Parkinson's disease. *Parkinsonism Relat Disord*. 50:61-8, 2018. (contributed as senior author)
4. **Seki M**, Seppi K, Mueller C, et al. Diagnostic Potential of Multimodal MRI Markers in Atypical Parkinsonian Disorders. *J Parkinsons Dis*. 9 (4) :681-91. 2019.
5. Tezuka T, Takahata K, **Seki M**, et al. Progressive Ataxia and Palatal Tremor Showing Characteristic Tau Depositions in [18 F]PM-PBB3 PET. *Mov Disord*. 37 (6) :1317-9. 2022. (corresponding author)

Educational Lecture

(Sumitomo Pharma Co., Ltd.)

Chair:

Satoshi Orimo

Kamiyoga Setagaya-Dori Avenue Clinic

1. α-synuclein; Biomarker of Synucleinopathy

Speaker:

Taku Hatano, MD, PhD

Department of Neurology, Juntendo University, Faculty of Medicine, Tokyo Japan

Abstracts:

α-synuclein (AS) is known as one of the main components of Lewy body and glial cytoplasmic inclusions. Furthermore, pathogenic mutations and multiplications of AS cause familial Parkinson's disease (PD). Therefore, AS is considered the key protein of synucleinopathy. Especially the oligomer of AS is the center of the pathogenesis in PD and disrupts its own binding abilities to membranes resulting in inducing the aggregation of membranous organelles, such as mitochondria, lysosomes, synaptic vesicles, and autophagosomes. Therefore, the AS-oligomers have been considered as seeds for developing the aggregation of AS, and detecting them may shed light on diagnosing PD and understanding the pathomechanisms of synucleinopathy.

Although previous studies indicated that AS might be useful as a diagnostic biomarker of synucleinopathy, there have been controversial. Several reports described that patients with PD are likely to show decreasing monomer AS and increasing oligomer AS in CSF. Moreover, several groups discovered oligomers of AS in PD patients' blood samples. We also revealed serum AS oligomers by using real-time quaking-induced conversion combined with immunoprecipitation (IP/RT-QuIC) assays. The technique takes advantage of the seeding properties to amplify small quantities of seeds. We found that the assay can detect serum AS-seeds in synucleinopathy, which is useful as a diagnostic biomarker of synucleinopathy. Furthermore, the aggregation and propagation propensity and microstructures of fibrils obtained from IP/RT-QuIC showed differences between synucleinopathy.

We will review AS as the diagnostic biomarker and introduce our study in this session.

Biosketch:

Dr. Hatano entered the Graduate School of Juntendo University in 2003. He graduated with his PhD in 2007 and was appointed Assistant Professor of Neurology at Juntendo University School of Medicine in the same year. Since 2011, Dr. Hatano has been Associate Professor of Neurology at Juntendo University School of Medicine.

His main research interests include the pathogenesis of Parkinson's disease. In 2010, he received a silver medal for a case presentation at a Video Olympic event at the 14th International Congress of PDMD in Buenos Aires. In 2016, he received the LEAP program from the international MDS. In 2020, he received a grant from the Setsuro Fujii Memorial Osaka Foundation for the Promotion of Fundamental Medical Research and the Juntendo Academic Encouragement Award. He is a member of the International Congress Scientific Program Committee of the International Congress of the International Parkinson's disease and Movement Society.

Key articles (Up to 5):

1. Ogawa T, Hatano T et. al. White matter and nigral alterations in multiple system atrophy-parkinsonian type. *NPJ Parkinson Dis*. 2021 DOI; 10.1038/s41531-021-00236-0
2. Oji Y, Hatano T et. al. Variants in saposin D domain of prosaposin gene linked to Parkinson's disease. *Brain* 2020 Apr 1; 143 (4) : 1190-1205. doi: 10.1093/brain/awaa064.
3. Mori A, Hatano T et. al. Parkinson's disease-associated iPLA2-VIA/PLA2G6 regulates neuronal functions and α-synuclein stability through membrane remodeling. *Proc Nat Acad Sci U.S.A.* 2019 Oct 8; 116 (41) : 20689-20699.
4. Hatano T, et. al. Identification of novel biomarkers for Parkinson's disease by metabolomics technologies. *J Neurol Neurosurg Psych*. 2016; 87: 295-301 Doi: 10.1136/bcr-2014-208272.
5. Hatano T, et. al. Leucine-rich repeat kinase 2 associates with lipid rafts. *Human Molecular Genetics.* 2007;16 (6) : 678-90.

2. How does alpha-synuclein transfer from cell to cell : A cell biological perspective

Speaker:
Takafumi Hasegawa, MD, PhD
Division of Neurology, Department of Neuroscience & Sensory Organs,
Tohoku University Graduate School of Medicine, Sendai, Japan

Abstracts:

A recent breakthrough in the field of neurodegenerative disease came with the discovery that disease-related protein aggregates can transfer from one cell to another, thereby converting normal proteins to toxic species in a prion-like manner. The precise mechanisms responsible for cellular transfer of α-synuclein (aS) remain to be fully understood; however, a myriad of evidence suggests that membrane trafficking machineries including endocytic pathway, exosomal secretion, nanotube tunneling, and autophagy-lysosome pathway cooperatively regulate cellular burden and intercellular transmission of aS. Furthermore, the cellular mechanisms responsible for the spreading of aS may differ based on the biochemical nature of protein aggregates and cell- autonomous/non-cell-autonomous circumstance, making a story more complicated. In this symposium, I will discuss the current knowledge of the molecular and cellular mechanisms of aS transmission and open up a future prospect of disease-modifying therapy.

Biosketch:

Dr. Hasegawa received M.D. in 1995 and Ph.D. in 2000 from Tohoku University School of Medicine, Sendai Japan. In 2006, he joined as Alexander von Humboldt fellow in Hertie-Institute, Tübingen, Germany (Prof. Dr. Philipp Kahle). In 2008, he went back to Japan and currently serves as an associate professor and PI of Parkinson's Disease (PD) Group in Department of Neurology, Tohoku University School of Medicine. In 2017, he was appointed Associate Professor, in Division of Neurology, Department of Neuroscience & Sensory Organs, Tohoku University Graduate School of Medicine. His research focuses on elucidating the molecular pathogenesis of PD and related disorders leading to the development of disease-modifying therapies. He has made many discoveries, particularly regarding the cell biological mechanisms of prion-like propagation of α-synuclein, and the involvement of vesicle trafficking machinery in sporadic and familial PD.

Key articles (Up to 5):

1. Yoshida S., **Hasegawa T**.*, *Front Neurosci* 2022
2. Yoshida S., **Hasegawa T**.*, *Neurochem Int* 2022
3. Kobayashi J., **Hasegawa T**.*, et al., *FASEB J* 2019
4. Yoshida S, **Hasegawa T**.*, et al., *Hum Mol Genet* 2018
5. Sugeno N, **Hasegawa T**.*, et al., *J Biol Chem* 2014
(*corresponding author)

VTR Session

Chair:

Mitsutoshi Yamamoto
Takamatsu Neurology Clinic, Kagawa, Japan

Genjiro Hirose
Neurological Center, Asanogawa General Hospital, Ishikawa, Japan

Abstracts

3rd Day
26 Mar 2023 (Sunday)

Japanese session

（協和キリン株式会社）

Chair:
伊藤 和則
いわみざわ神経内科・内科CLINIC

1. 認知機能障害を伴うレビー小体病のマネジメント

Speaker:
平野 成樹
千葉大学大学院医学研究院脳神経内科学

Abstracts:

レビー小体病による認知機能障害の特徴は、注意・遂行機能・視空間機能の障害である。レビー小体型認知症のコア特徴として、注意や明晰さの著明な変化を伴う認知機能の変動、構築され、具体的な内容の繰り返される幻視体験、レム睡眠行動異常症、パーキンソニズムなどがあり、その組み合わせによって、例えば幻視やレム睡眠行動異常症などの特徴的症状がかける場合、診断に苦慮することがある。認知症を伴うレビー小体病は転倒や誤嚥などが合併しやすいため、全身をみながら脳の治療も行える脳神経内科医の役割が大きい。一方ではせん妄、幻覚、妄想、抑うつなどの精神症状も高頻度に合併するため、精神科的なアプローチの習熟も必要となる。

レビー小体病の認知機能障害はアセチルコリン神経系障害と後方脳領域の機能低下が想定され、コリンエステラーゼ阻害剤が一定程度有効である。治療可能である点から見逃してはならない認知症性疾患として位置づけられると考えられるため、どんな些細な症状でも見逃さず各医学検査を駆使して診断に導くと良い。レビー小体病において、特にドパミン受容体遮断薬は忌避する必要があるが、それ以外にもヒスタミン受容体遮断薬やカルシウム受容体遮断薬も症状を悪化させる可能性があるため、これらの薬剤を早期から整理し、服薬アドヒアランスを高めるようにすることが肝要である。ヒスタミン神経系は視床下部を起源として脳全体に広く神経が投射され、覚醒や日内リズムなどと関係していると考えられ、レビー小体病の睡眠障害や覚醒の異常と関連しているものと考えられる。運動障害はレビー小体型認知症においてはその一部でL-dopa不応性であることもあり、非定型パーキンソニズムとの鑑別も必要である。その他、自律神経障害、睡眠障害、感覚障害、精神症状などを伴い、対症療法と非薬物療法とを組み合わせてマネジメントする。

略歴:

1998年3月　千葉大学医学部卒業
1998年4月　千葉大学医学部附属病院神経内科
1999年10月　ロンドン大学神経研究所（Queen square）学位
2003年4月　千葉大学大学院神経病態学（神経内科）
2006年10月　米国ニューヨーク州ファインスタイン医学研究所留学
2011年4月　千葉大学医学部附属病院神経内科 特任助教
2012年4月　千葉大学医学部附属病院神経内科　助教
　　千葉市認知症疾患医療センター開設
2014年2月　千葉大学医学部附属病院脳神経内科 講師
2021年9月　同 診療准教授

Japanese session

（エフピー株式会社）

Chair:
金井 数明
福島県立医科大学医学部脳神経内科学

2. 運動障害疾患と運動ニューロン病

Speaker:
狩野 修
東邦大学医学部 脳神経内科

Abstracts:

一般的に筋萎縮性側索硬化症（ALS）をはじめとした運動ニューロン病とパーキンソン病（PD）などの運動障害疾患は別の疾患と考えられている。しかし両者が合併したという報告は散見されており、その最初の報告が、1973年にNeurology誌に掲載されている。レボドパが有効であった孤発性PDにALSを合併した3症例のまとめで、以降この論文の著者の名前をとって、Brait-Fahn-Schwarz diseaseと呼ばれるようになった。

データベースを用いた後方視的な研究では、両者の合併は1％前後であるが、各々の罹患率を考えると高いといえる。またBrait-Fahn-Schwarz diseaseでは、約半数の症例でレボドパがパーキンソニズムに効果を示している。前方視的研究においてALS患者の約3割にパーキンソニズムがみられたという報告もあるが、これはパーキンソニズムのbradykinesiaとrigidityが、それぞれ上位運動ニューロン障害によるmotor slowingとspasticityと混同されている可能性もあり、注意が必要である。より詳細な臨床的検討では、運動ニューロン病はALSではなく原発性側索硬化症であったり、また運動障害疾患ではPDではなく、多系統萎縮症や進行性核上性麻痺であったりと多彩な組み合わせを呈している。いずれにせよ、運動ニューロン病と運動障害疾患においては何らかの共通の病因論的なプロセスが存在している可能性もあり、臨床、病理、遺伝などの側面をさらに観察することで、これらの病因解明や治療法開発に向けた新たな知見が得られると期待される。

略歴:

学歴：
1999年3月　東邦大学医学部卒業
2005年3月　東邦大学大学院医学研究科博士課程修了 博士（医学）

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2002年5月　順天堂大学 放射線科 研究員
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2002年11月　国立精神・神経医療研究センター 神経内科 研究員
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2007年10月　Methodist Neurological Institute, Weill Cornell Medical College ポスドクフェロー（Stanley Appel教授）
2011年4月　東邦大学医学部 内科学講座 神経内科学分野 助教
2013年3月　東邦大学医学部 内科学講座 神経内科学分野 講師
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Japanese session

（アッヴィ合同会社）

Chair:
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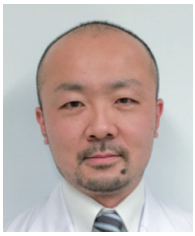

3. 運動障害疾患診療に役立つバイオマーカー

Speaker:
上野 真一
順天堂大学脳神経内科

Abstracts:

運動障害疾患には、パーキンソン病（PD）や、多系統萎縮症（MSA)、進行性核上性麻痺（PSP）といった種々の疾患が含まれており、症状の類似点が多い一方で、各疾患毎に治療法や経過、予後が異なることからも鑑別が重要である。多くは、臨床症状から鑑別が可能であるが、時に専門医であっても非常に難しい場合に直面する。無論、病初期には各種検査をもってしても診断に苦慮する症例に遭遇する場合もあるが、現在までに確立されている画像検査や、血液、髄液など各種診断バイオマーカーに基づいて診断を進めていくことが求められる。また病態の観点から、PDでは病理学的に中脳黒質ドパミン神経細胞の脱落と、α-シヌクレインの凝集から成るレビー小体の形成が特徴であり、治療の主軸はL-ドパを中心としたドパミン補充療法である。しかし、それ以外の変性疾患では対症療法ですら困難であるものも存在し、総じて現在までに神経変性を抑制するような疾患修飾療法は未だ開発されていない。この理由の一つとして、例えばPDでは運動症状発症時点で約50％の中脳黒質ドパミン神経細胞が脱落しており、前駆期（prodromal phase）を正確に診断し治療介入を行わないと、疾患修飾療法の意味を成さないことが挙げられる。よって、いかに早期に、特に運動症状発症前のprodromal phaseに診断する方法を確立できるかといった病態を反映するバイオマーカーの開発も喫緊の課題である。本講演では、現在までに確立されているものから、現在開発検討が進められている運動障害疾患に対するバイオマーカーの紹介と今後の展望を提示する。

略歴:

2011年3月　順天堂大学医学部医学科 卒業
2013年4月　順天堂大学医学部神経学講座 専攻医
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2020年4月　順天堂大学医学部神経学講座 非常勤助教
2021年4月　順天堂大学医学部神経学講座 特任助教
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現在に至る

Japanese session

（小野薬品工業株式会社）

Chair:
花島 律子
鳥取大学医学部脳神経医科学

4. 運動障害疾患と加齢

Speaker:
荒若 繁樹
大阪医科薬科大学内科学IV脳神経内科

Abstracts:

加齢の影響は認知症と変性性の運動障害疾患では異なると思われる。認知症は75歳を超えると指数関数的に罹患率が増加し、90歳を過ぎると半数以上が認知症になる。ヒトはデフォルトでは加齢とともにSD-NFTといった認知症への道を進んでいる。ApoEをはじめとするアミロイド蓄積の危険因子が作用すると、アルツハイマー病への道を辿ると考えられる。一方、パーキンソン病は認知症ほど加齢現象のデフォルトとして待ち受けられていない。その説明として、パーキンソン病の発症には生理的な加齢現象の寄与は小さく、レビー小体蓄積の危険因子による効果が大きいのかもしれない。また、加齢現象による変化の大きい群がパーキンソン病になり、元気な超高齢者はレビー小体蓄積を打ち消すほど細胞機能が保たれているのかもしれない。

神経細胞レベルで、レビー小体を構成するα-シヌクレイン凝集体形成の条件として、1）α-シヌクレインの産生増加、2）GBA変異で示されるα-シヌクレインの分解低下、3）酸化ストレスといった外的刺激によるα-シヌクレインの凝集活性の亢進がある。私たちは4番目の条件として、α-シヌクレイン細胞外分泌の抑制を見出した。この細胞外分泌は、secretory autophagyと呼ばれるオートファジーの作用を介し、神経細胞活性およびMAO-B阻害によって刺激された。また、α-シヌクレインの細胞外分泌はライソソーム分解の働きとクロストークしている可能性が示唆された。さらに、動物モデルにおいてMAO-B阻害は、α-シヌクレインの凝集体形成を遅延させた。オートファジーは、パーキンソン病の病態に関与していることが示唆される。

オートファジーは不要なタンパク質・細胞内小器官を分解する働きに加え、細胞外へ排出する働きを担っていることが明らかとなり、様々な疾患への関与が注目されている。今回、変性性の運動障害疾患と加齢の関係について、secretory autophagy during lysosome inhibition（SALI）といった新しい現象を含むオートファジーの新しい視点から考察する。

略歴:

1991年3月　山形大学医学部卒業
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2017年4月～ 大阪医科薬科大学内科学IV教室脳神経内科 教授

専門分野：
臨床神経学、パーキンソン病・認知症の病態解析

Japanese session

（大塚製薬株式会社）

Chair:
前田 哲也
岩手医科大学内科学講座（脳神経内科・老年科分野）

5. PDのうつ update 2023

Speaker:
永山　寛
日本医科大学 脳神経機能解析学講座

Abstracts:

ここでは、主に2021年から2023年までに発表されたParkinson病（PD）に関する論文であり、かつ主題がうつ、アパシー、アンヘドニアに関する文献を軸に、これまでの知見と合わせて最近の研究動向を解説する。

報告は内容、大きくは① 発症メカニズムに関する検討、② うつの存在が影響する事項の検討、③ COVID-19に関する報告、④ 治療に関する検討、⑤ その他へ分類される。
発症メカニズムに関する検討では、fMRIを用いた検討が多く、特に側座核に関連する検討が多い。また小脳を含む連絡機構に関する障害や、免疫系がPDのうつに与える影響も複数報告されている。

うつの存在が影響する事項の報告は、報告数は多くはないが主にquality of life に関連するものが目立った。これまでにPDのうつはquality of life（QoL）に最も影響することが知られていることもあり、新しい切り口として十分な医療体制が整った医療機関のcohortで、運動機能重症度とうつのどちらがQoLに影響するかの検討も行われている。

また、世界的なCOVID-19 pandemicの中、COVID-19に関するPDのうつに関する文献も目立った。しかし報告により背反する結果となっているものもあり、条件を鑑みて多くの検討を慎重に解釈することが必要であろう。

治療に関するものでは、非薬物療法の有用性を示したものが非常に多い。特に運動療法や認知行動療法などでの報告が突出していた。また経頭蓋磁気刺激に関するものも複数存在した。薬物療法ではMAOB阻害薬、pramipexole、抗うつ薬などを含む検討が多い。

その他、多くの報告があるが、アパシー発症のメカニズムに関するnoradrenaline系の関与に関する報告など、既存の報告より、明確な関連を示した文献が存在する。

略歴:

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1995年2月　東京都多摩老人医療センター神経内科
1999年7月　日本医科大学付属病院第二内科医員（神経内科）
2000年4月　日本医科大学 内科学第二 助手
2008年4月　日本医科大学付属病院 病院講師
2010年4月　日本医科大学 内科 神経・腎臓・膠原病リウマチ部門 講師
2015年10月　日本医科大学 脳神経内科 准教授
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2021年4月　日本医科大学 脳神経機能解析学講座 教授

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