Keynote Lecture

KL
Infantile spasms syndrome：past, present and future

Solomon L. Moshé
Charles Frost Chair in Neurosurgery and Neurology, Saul R. Korey Department of Neurology, Dominick P. Purpura Department of Neuroscience, and Department of Pediatrics, Laboratory of Developmental Epilepsy, Montefiore/Einstein Epilepsy Management Center, Albert Einstein College of Medicine and Montefiore Medical Center

The ILAE has introduced the term Infantile Spasms Syndrome（ISS）to encompass both West syndrome and also infants with epileptic spasms who do not fulfill the criteria for West syndrome（the triad of epileptic spasms, hypsarrhythmia and developmental stagnation or regression）. There is a need to develop tools to better understand the pathogenesis and develop better treatments for infantile spasms（IS）and this has led to an increasing number of animal models of infantile spasms. These models have been developed in mice or rats and are based on either known genetic or nongenetic etiologies or pathologies of infantile spasms, the expression of seizures resembling epileptic spasms or exhibit characteristic electrographic patterns seen in West syndrome, such as electrodecremental responses or hypsarrhythmia. The existing models have been classified in acute models of spasms, which manifest epileptic spasms during the immediate post-induction period, and the chronic models which demonstrate spasms, other seizures and in some cases behavioral or cognitive deficits for longer periods. Acute models of spasms include models induced by administration of N-methyl-D-aspartate（NMDA）in infantile rats which are either naïve or predisposed due to pre- or perinatal stressors or interventions that lead to brain malformations. Another acute model is induced by gamma-butyrolactone（prodrug of gamma-hydroxybutyrate）model of epileptic spasms in Down syndrome. Chronic models include the tetrodotoxin model of hypsarrhythmia, the *Arx* models that carry genetic defects in the aristaless X-linked homeobox protein gene associated with epileptic spasms and epileptic encephalopathies, adenomatous polyposis conditional knockout（*Apc* cKO）model, a tuberous sclerosis complex 1（$Tsc1^{-/+}$）model and the multiple-hit rat model due to structural lesions induced at postnatal day 3 following right intracerebral injections of doxorubicin and lipopolysaccharide followed by systemic p-chlorophenylalanine on postnatal day 5. In this model, the common behavioral manifestation of IS was clusters of sudden-onset, synchronous, high amplitude, flexion or extension or mixed flexion/extension spasms occurring in clusters. Such events were observed only during the first two weeks of life, but not in older rodents. Compared to normal neonatal jerks and startles, epileptic spasms seemed to have aggravated behavioral manifestations（higher frequency and amplitude, more synchronous events）and protracted developmental period of occurrence, appearing till the end of second postnatal week. Using surface EEGs, the ictal electrographic correlates included brief EDRs with fast, low amplitude oscillatory activities or bursts of epileptic discharges（polyspikes, polyspike and slow wave complexes, fast rhythmic activities）, focal or bilateral. As in humans, IS did not always have ictal EEG correlates within the same pup, suggesting involvement of deep source generators. IS were also different than sudden movements seen in controls, which lacked epileptic activity or electrodecremental responses. This model also shows evidence of interneuronopathy indicated by a preferential loss of parvalbumin immunoreactive（PRV-ir）interneurons contralateral to the induced lesion. Structural cortico-hippocampal/basal ganglia lesions, but not focal cortical inflammation alone, increase the risk for post-IS epilepsy, features of Lennox-Gastaut syndrome and sleep dysregulation. Focal cortical inflammation alone accentuates spike and wave discharges, suggesting long-lasting corticothalamic hypersynchrony. In this model, we have identified disease-modifying approaches that can be translated to therapeutic applications and possible cures in infants with ISS. Indeed, pulse rapamycin controls the spasms early in life, has antiepileptogenic effects later in life and reverses sleep dysregulation, despite the structural lesions. These promising developments suggest that, by forming effective multi-institutional collaborations among clinicians and scientists we will be able eradicate ISS in the near future.

Solomon L. Moshé, M. D., is the Charles Frost Chair in Neurosurgery and Neurology, and Professor of Neurology, Neuroscience and Pediatrics at the Albert Einstein College of Medicine/Montefiore Medical Center in the Bronx, New York. He is the Vice Chair of the Saul R. Korey Department of Neurology, Director of the Isabelle Rapin Child Neurology Division and Director of Clinical Neurophysiology. Dr Moshé received his MD degree from the National University of Athens, School of Medicine, in Athens Greece. He trained in Pediatrics at the University of Maryland and in Child Neurology at Albert Einstein College of Medicine.

Since 1979, his research has focused on understanding the mechanisms underlying age and sex-related differences in epilepsy in humans and animal models. Current research interests include studies on the role of subcortical circuitries involved in the control of seizures as a function of age and sex；the consequences of seizures on the developing brain and the development of models of catastrophic epilepsies. His laboratory has patented a model of infantile spasms that can be used to identify novel treatments. He is co principal investigator of a Center Without Walls grant on interdisciplinary research aimed at accelerating the development of disease modifying or prevention therapies for epilepsy following traumatic brain injuries. He is also involved in a large multicenter study examining the consequences of prolonged febrile seizures.

He has served as President of the International League Against Epilepsy（ILAE, 2009-2013）, the American Epilepsy Society（2000-2001）, the American Clinical Neurophysiology Society（1996-1997）and the Eastern Association of EEGers（1992-1994）. During his ILAE presidency, he collaborated closely with the World Health Organization（WHO）governmental and non-governmental agencies to increase the access of care for people with epilepsy.
He is the recipient of several honors and awards, including the Teacher-Investigator Development Award from NINDS；the 1995 Jacob Javits Neuroscience Investigator Award from NINDS；the 1984 Michael Prize for Achievements in Epilepsy Research；the 1990 American Epilepsy Society Research Award；the 1999 Ambassador for Epilepsy Award from the International League Against Epilepsy；the 2005 Gloor Award from the American Clinical Neurophysiology Society；the 2007 J. E. Purkyne Honorary Medal in Biomedical Research by the Czech Academy of Sciences；the 2008 Mentor of the Year Award from Albert Einstein College of Medicine；the 2010 Global and Awareness Award from CURE, Citizens United for Research in Epilepsy；the First 2012 Saul R. Korey Award in Translational Science and Medicine, Albert Einstein College of Medicine, the 2017 Bernard Sachs Award from the Child Neurology Society and Foreign member of the Russian Academy of Science.

Invited Lecture 1

IL1
Novel insights into epilepsy genetics

Ingrid E. Scheffer
Laureate Professor, AO MBBS PhD FRACP FAA PresAHMS FRS, University of Melbourne, Austin and Royal Children's Hospital, Florey Institute and Murdoch Children's Research Institute, Melbourne, Australia

New concepts and insights into genetic factors underlying the epilepsies are rapidly emerging, transforming our diagnostic strategies and paving the way to precision therapies. Novel hidden mechanisms such as repeat expansions, mosaicism and epigenetic factors are revealing why epilepsies occur, and enabling phenotype−genotype insights. Efforts to identify these genetic aetiologies via innovative strategies are also proving useful, such as CSF liquid biopsy and DNA extracted from SEEG electrodes. Somatic mosaicism limited to brain explains some malformations and may show a gradient that correlates with the most epileptogenic brain region. In some instances, in dominantly inherited focal epilepsy, an inherited pathogenic variant may be associated with a 'second hit' with a second pathogenic variant that explains a focal region of malformation.
For the common epilepsies, genetic insights are now emerging through the study of large cohorts, such as Epi25 and the International League Against Epilepsies Consortium on Complex Epilepsies. Exome sequencing is identifying ultrarare variants in a range of genes for generalized epilepsies, focal epilepsies and developmental and epileptic encephalopathies. This is complemented by genome wide association studies which enable calculation of polygenic risk scores, informing risk for epilepsy and comorbidities such as psychiatric features. These large scale international collaborative studies are finally shedding light on the genetic architecture of the epilepsies.

Professor Ingrid Scheffer AO MBBS PhD FRACP FAES FAA FRS PresFAHMS is a physician−scientist whose work as a paediatric neurologist and epileptologist has led epilepsy genetics research for >26 years. She identified the first epilepsy gene with Professor Berkovic and molecular geneticists, and many genes subsequently. She led the first new International League Against Epilepsy revision of epilepsy classification in 28 years and co−received the 2014 Australian Prime Minister's Prize for Science.

Invited Lecture 2

IL2
Leigh Syndrome Seventy Years on —A Reappraisal with a focus on *NDUFV1* mutation—

Asuri N. Prasad[1, 3, 4], Prashanth Rajasekar[2], Victoria M. Siu[3, 4, 6], C. Anthony Rupar[3,4,5,6], Chitra Prasad[3,4,5,6].
Division of Pediatric Neurology[1], Queens University School of Medicine, Kingston, ON, Canada[2], Division of Medical Genetics[3], Department of Pediatrics[4], Departments of Pathology and Laboratory Medicine and Biochemistry, Faculty of Medicine, Western University and London Health Sciences Centre, London, ON, Canada.[5], Children's Health Research Institute, London, ON, Canada[6]

Leigh syndrome（LS）（subacute necrotizing encephalomyelopathy）was first described in 1951 by Denis Leigh a neuropathologist who reported characteristic pathological findings in an infant with developmental regression. The findings included multiple symmetric foci of spongy degeneration with microvascular proliferation in the brainstem tegmentum, thalami, cerebellum, posterior columns of the spinal cord, and optic nerves. Diagnostic criteria for the condition were described in 1996 and progress in research has led to a better understanding. Seventy years on, LS is seen in association with disorders of energy metabolism related to PDHC deficiency, and disruption of electron transport chain. At a molecular level, the disorder displays genetic heterogeneity, and can be caused by a mtDNA or mitochondrial directed nDNA mutation. In this talk, I propose to review the clinical presentation, the typical imaging findings, biochemical perturbations, and molecular genetic basis for typical LS or LS like conditions with a focus on our experience with this disorder in five affected children with a p.E214K variant in nuclear DNA encoded *NDUFV1*, in mitochondrial respiratory chain complex 1. This mutation has been identified in 2 families of Low-German Speaking（LGS）Mennonite background. NADH Ubiquinone Flavoprotein I（*NDUFV1*）is coded for by a nuclear gene and is directly responsible for the oxidation of NADH through binding of the flavin cofactor which oxidizes NADH. Mutation at this highly conserved flavin mononucleotide（FMN）binding site hinders complex I function and contributes to the clinical presentation of LS.

BIO SKETCH
Dr. Asuri N Prasad is currently Professor in Pediatrics with a continuing appointment（Provost Stream）and is cross appointed to the Department of Clinical Neurological Sciences at the Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada. His clinical appointment includes duties as Staff Pediatric Neurologist to the Children's Hospital, London Health Sciences Centre.

He graduated with a bachelor's degree in Medicine and Surgery（MBBS）at the University of Delhi（1979）completed his residency training in Pediatrics at Post Graduate Institute of Medical Education and Research, Chandigarh, India（1981-1983）. His specialty and subspecialty training in Neurology（Memorial University）and Pediatric Neurology at Tufts-New England Medical Centre Hospitals（Tufts-NEMCH）, Boston, MA., USA（1993-1996）was followed by a fellowship in Pediatric Epilepsy and Clinical Electroencephalography at the Floating Hospital for Children @ New England Medical Centre Hospitals, Boston, MA, USA. He is certified as a specialist in Pediatrics（1992）and Neurology（1996）and is a Fellow of the Royal College of Physicians and Surgeons of Canada（FRCPC）in addition to board certification in Pediatrics with the American Board of Pediatrics（1992）and Neurology with special certification in Pediatric Neurology and American Board of Neurology and Psychiatry（1996）. He is an elected Fellow of the Royal College of Physicians of Edinburgh, UK（FRCPEdin）since 2003-2004. He is a nominated Fellow of the American Epilepsy Society（FAES）.
Dr. Prasad co-directs the Neurogenetic and Neurometabolic clinic in collaboration with Dr. C Prasad in Medical Genetics and Metabolism. He is a member of the multidisciplinary team running the Rett Syndrome Clinic in collaboration with Dr. V Siu in the Division of Genetics. Dr. Prasad has pursued an active academic and research career along with his clinical practice. His publishing record includes peer reviewed papers）in international medical journals, and research abstracts, book chapters and invited commentaries（～160）. He has been a member of both the departmental and faculty of Medicine promotions committee, and is currently a member of the Mentorship Committee at Schulich Medicine and Dentistry.
He has served as reviewer for research manuscripts for several journals including Neurology, Epilepsia, PLOS, Archives of Disease of Childhood, Developmental Medicine Child Neurology, and Journal of Pediatric Neurology, and is a Review Editor for Frontiers in Neurology. He has been an invited speaker at national and international scientific and has served on scientific committees of the American Epilepsy Society and the Canadian Association of Child Neurology and as a domain expert for grant reviews for the Israel Ministry of Science and Technology, and the European Science Foundation. He is a member of several academic societies including the American Academy of Neurology, Child Neurology Society, Canadian Neurosciences Federation, the Canadian Association of Child Neurology, American Epilepsy Society, Child Neurology Society and the Garrod Association of Canada. He is a nominated member of the Faculty of 1,000 by the International League Against Epilepsy. He is on the teaching faculty for the Advanced EEG course on the VIREPA Academy and facilitates the section on EEG maturation and neonatal EEG. His leadership experience includes positions of Secretary-Treasurer of the Canadian Association of Child Neurology, Vice President, and past President of the Canadian Association of Child Neurology（2012-2014）.

Invited Lecture 3

IL3
Developmental and epileptic encephalopathies —what we know and what we don't know—

Nicola Specchio
Bambino Gesu' Children's Hospital, IRCCS, Rome, Italy

Developmental encephalopathies, including intellectual disability and autistic spectrum disorder, are frequently associated with infant epilepsy. Epileptic encephalopathy is used to describe an assumed causal relationship between epilepsy and developmental delay. Developmental encephalopathies pathogenesis more independent from epilepsy is supported by the identification of several gene variants associated with both Developmental encephalopathies and epilepsy, the possibility for gene-associated Developmental encephalopathies without epilepsy, and the continued development of developmental encephalopathies even when seizures are controlled. Hence, 'developmental and epileptic encephalopathy' may be a more appropriate term than epileptic encephalopathy. This review considers the best studied 'developmental and epileptic encephalopathy' gene variants for illustrative support for 'developmental and epileptic encephalopathy' over epileptic encephalopathy. Moreover, the interaction between epilepsy and developmental encephalopathies is considered with respect to influence on treatment decisions. Continued research in genetic testing will increase access to clinical tests, earlier diagnosis, better application of current treatments, and potentially provide new molecular-investigated treatments.

Invited Lecture 4

IL4
Anti-NMDA receptor encephalitis —experience at the Philippine Children's Medical Center (2011-2021)—

Marilyn H. Ortiz, Madelyn P Pascual, Melady Imperial-Gilbuena, Rdayne Cansanay, Katrina Manibog, Lillian V Lee *
Child Neuroscience Division Philippine Children's Medical Center

INTRODUCTION
Since its identification by Dalmau in 2007, anti N-methyl D-aspartate Receptor (anti-NMDAR) Encephalitis had become increasingly recognized and diagnosed in countries where laboratory confirmation of the presence of neuronal anti-NMDAR antibody in the CSF could be done. At the Philippine Children's Medical Center, awareness of anti-NMDAR encephalitis as a probable etiology in children and adolescents presenting with acute or subacute onset of behavioral changes, cognitive/speech dysfunction, seizures, movement disorder and insomnia, diagnostic confirmation had been difficult at the beginning, when CSF specimens had to be sent to research laboratories of J Dalmau and A Vincent. Antibody testing in the CSF became available locally in 2018, and since then there was an increasing number of confirmed cases of anti-NMDAR encephalitis at our medical center.

OBJECTIVE
This report aims to describe the patients with confirmed anti-NMDAR encephalitis seen at the Philippine Children's Medical Center from 2011-2021：clinical presentation, paraclinical findings, treatment strategies, and outcome.

METHOD
Review of medical records of all patients with confirmed diagnosis of anti-NMDAR encephalitis was done by the authors. The study specifically looked at the age and gender, clinical presentation at the start of the illness, progression of symptoms during the course of the illness, duration of illness before diagnosis and initiation of treatment, type of treatment given, clinical outcome on discharge and follow-up. Assessment of outcome was made using the modified Rankin scale (mRS). Correlations between the various clinical parameters and outcomes were done.

RESULTS
There were 73 cases diagnosed with anti-NMDAR encephalitis from 2011-2021. Ages ranged from 2.4 years to 18.10 years. Majority (55%) were in the adolescent age group. There was a slight female preponderance. Screening for neoplasm did not yield any positive findings. Prodromal symptoms (fever, headache, GI/respiratory symptoms) were reported in 57% of cases. The earliest symptoms seen in the first week of illness were seizures and behavioral changes. In the succeeding week, movement disorder and speech dysfunction became more prominent. EEG was abnormal in 93% (64/69). CSF findings were abnormal in 68% (50/73). Cranial CT/MRI results were normal in 49% (22/45). Treatment consisted of immunomodulation using IV methylprednisolone as first line agent in 35% (24/68) of cases, and combination of IV methylprednisolone + IVIG in 25% (17/68) of cases. Eighteen patients (26%) underwent Therapeutic Plasma Exchange (TPE)；in one patient as initial therapy, in 17 patients, in combination with IV methyprednisolone (n = 9), with methylprednisolone + IVIG (n = 7), and with IVIG (n = 1). Using the mRS scoring, 87% were found to have good outcome (completely/almost completely to very substantially recovered). Three patients died. Causes of death were dysautonomia (n = 1), RDS secondary to Covid19 infection and dysautonomia (n = 1), and severe non-Covid pneumonia (n = 1). Early initiation of immunotherapy and use of combination IV methylprednisolone + IVIG were found to be significant predictors of good outcome.

CONCLUSION
Anti-NMDAR encephalitis has become increasingly recognized and diagnosed at the Philippine Children's Medical Center in the last decade. It should be clinically suspected in a child or adolescent who presents with seizures, behavioral changes, movement disorder and speech/cognitive dysfunction. Early initiation of immune therapy in this study population was a significant predictor of good outcome.

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Invited Lecture 5

IL5
Unravelling the spectrum of malformations of cortical development

Ahmad Rithauddin Mohamed
Paediatric Neurologist, Paediatric Institute & Hospital Tunku Azizah Kuala Lumpur, Malaysia

Malformation of cortical development（MCD）comprise a heterogenous group of disorders of abnormal formation of cerebral cortex, due to genetic, infectious, metabolic and vascular aetiologies. Each subtypes of MCDs share distinct imaging appearance and frequently cause epilepsy, learning disability and cerebral palsy. Traditionally, MCDs are classified into disorders of cellular proliferation, neuronal migration and post−migration organisation and differentiation, according to the different stages of cortical development. New genetic discoveries however suggest MCD−related genes affect processes at different stages of cortical development, and that a single gene defect may cause several different types of MCDs and vice versa. Aetiologic identification would allow for better counselling and prognostication, as well as the potential for more precise treatment, but except for a few subtypes such as lissencephaly, the causes of many MCDs are unknown. Accurate classification of the imaging abnormalities and knowledge of the associated clinical features may help clinicians to choose the most appropriate testing and increase the yield of aetiologic identification. In this talk, I will share our local data and outline an approach to investigating and understanding MCDs.

Feb 2012−present	Paediatric Neurologist, Paediatric Institute & Hospital Tunku Azizah Kuala Lumpur, Malaysia
Feb 2010−Jan 2012	Epilepsy Research Fellow, Royal Children's Hospital, Melbourne, Australia
Feb 2009−Jan 2010	Paediatric Neuromuscular Fellow, Royal Children's Hospital, Melbourne, Australia
Feb 2008−Jan 2009	Epilepsy Clinical Fellow, Royal Children's Hospital, Melbourne, Australia
Jan 2006−Jan 2008	Paediatric Neurology Fellow, Hospital Kuala Lumpur, Malaysia
May 2005−Dec 2005	General Paediatrician, Hospital Temerloh, Malaysia
Nov 2003−April 2005	Paediatric Clinical Specialist, Hospital Kuala Lumpur, Malaysia
Jan 2002−Oct 2003	Paediatric Medical Officer, Hospital Kuala Lumpur, Malaysia
Feb 1999−Dec 2001	Medical Officer（in Paediatrics, Surgery, Orthopaedics, Casualty）, Hospital Kajang, Malaysia
Sep 1997−Jan 1999	Houseman/Junior Medical Officer, Hospital Universiti, Petaling Jaya, Malaysia

Invited Lecture 6

IL6
Diagnostic challenges and genetic roles in children with neurodevelopmental disorders

Wang−Tso Lee
Department of Pediatric Neurology, National Taiwan University Children's Hospital, and Graduate Institute of Brain and Mind Sciences, National Taiwan University College of Medicine, Taipei, Taiwan

Neurodevelopmental disorders are common and important neurological disorders in children. Except for some common neurodevelopmental disorders, many neurodevelopmental disorders have genetic origin. Because the diversity of genetic bases for neurodevelopmental disorders, the diagnosis of different neurodevelopmental disorders becomes challenging. The clarification of genetic causes for these disorders may have therapeutic merits, and may be of some help to predict the neurological outcome of these children. Because developmental medicine becomes an emergent subspecialty for pediatric neurology, we have spent much time in the past to clarify the genetic role of these diseases. In my talk, I will focus on only some genes responsible for neurodevelopmental disorders, and stress the challenging issue in diagnosis and treatment of these children.

Major Education
M. D., School of Medicine, College of Medicine, National Taiwan University, Taiwan
Ph. D., Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taiwan

Professional Experience
1991−1996, Resident and chief resident, Department of Pediatrics, National Taiwan University Hospital, Taiwan
1996, attending physician, Department of Pediatrics, National Taiwan University Hospital, Taiwan
Neurology Research, Department of Neurology, Children's Hospital of Philadelphia, PA, USA
Visiting scholar, Laboratory of Neuroscience, NIA, NIH, Baltimore, USA
Visiting scholar, Division of Epilepsy, Department of Child Neurology, Hospital for Sick Children, Toronto, Canada
Visiting scholar, Department of Neurology, Rochester University Medical Center, USA

Research Interest
Epilepsy, movement disorders, neurodevelopmental disorders, neurotransmitter diseases

Invited Lecture 7

IL7
Improving the Quality of Life among children with epilepsy － the Malaysian experience －

Choong Yi Fong
Consultant Paediatric Neurologist University Malaya, Kuala Lumpur, Malaysia

Managing epilepsy is beyond just controlling seizures with the ultimate aim to improve the quality of life of the child. Evaluation and challenges of improving the quality of life of children with epilepsy will be broadly discussed. Examples of steps to improve awareness, knowledge and attitude among the child, family and community will be given using educational software programmes. Vigilance of managing associated comorbidities including optimising bone health and trying to improve seizure control will be highlighted. The importance of discussion about SUDEP among Malaysian children with epilepsy will be reiterated and tips on how to broach this topic will be shared.

Professor Dr Choong Yi Fong is a medical graduate from University of Nottingham, UK. He trained in Paediatrics and Paediatric Neurology in UK and have further subspecialty epilepsy fellowship training in Australia. His UK Paediatric Neurology training include working in tertiary Neurology units at Great Ormond Street Hospital London, Evelina Children's Hospital London and Bristol Royal Children's Hospital. He had subspecialty dual-fellowship training in Paediatric Epilepsy and Paediatric Electroencephalography at Brisbane and Melbourne, Australia.
He is currently Professor and Consultant Paediatric Neurologist at University Malaya, Kuala Lumpur, Malaysia. He is head of the Paediatric Neurology division from 2014. He is currently an executive council member of the Malaysian Society of Neurosciences, Malaysian Epilepsy Council and the Malaysian Chapter of Child Neurology and Developmental Paediatrics. In the Asian region, he is a member of the Asian Epilepsy Academy（ASEPA）and taskforce member of the International League against Epilepsy.

International Symposium 1：Cutting Edge —Treatment of Autoimmune Encephalitis—

座長

Kazuhiro Muramatsu[1)], Hiroshi Sakuma[2)]
1）Department of Pediatrics, Jichi Medical University, 2）Department of Brain & Neural Science, Tokyo Metropolitan Institute of Medical Science

企画・趣旨のねらい

Anti-NMDA receptor encephalitis（NMDARE）and myelin oligodendrocyte glycoprotein antibody-associated disease（MOGAD）are two major central nervous system（CNS）syndromes caused by autoantibodies against neuronal or glial antigens. Although observational studies have suggested the beneficial roles of high-dose corticosteroids and plasma exchange for the treatment of attacks, problems remain unsolved in the treatment strategy for refractory or frequently relapsing cases. In this symposium, we invite experts in both NMDARE and MOGAD to share their perspectives on the current trends in the treatment of autoantibody-mediated CNS diseases.

IS1-1
Overview：Immune therapy for autoimmune encephalitis

Hiroshi Sakuma
Department of Brain and Neural Science, Tokyo Metropolitan Institute of Medi cal Science

One of the notable features of autoimmune neurological diseases is their chronic and relapsing course. Thus, the goal for their treatment is not only to terminate attack but also to maintain remission（or delay disease progression）and prevent（or reduce）relapse. In the case of multiple sclerosis, acute attacks are mainly treated by conventional immunotherapies including corticosteroids, intravenous immunoglobulins, or plasmapheresis, while we use different strategy, which is called disease-modifying therapy（DMTs）, for long-term treatment. In particular, numerous DMTs have emerged over the past decade, leading to drastic improvement in the prognosis of multiple sclerosis. Although evidence-based treatment for autoimmune encephalitis is still limited, we are having increasing therapeutic options, some of which were developed based on the understanding of disease mechanisms. Rituximab, an anti-CD20 monoclonal antibody targeting B cells, proved effective for anti-NMDA receptor encephalitis, and several drugs that specifically act on plasma cells are under development. Interferon-beta, a standard DMT for multiple sclerosis, rather exacerbate neuromyelitis optica spectrum disorder（NMOSD）and thus is not recommended to be used for autoantibody-mediated diseases. Humanized anti-interleukin-6 receptor antibodies（tocilizumab, satralizumab）have been reported to reduce relapse of NMOSD and are potential treatment strategy for refractory autoimmune encephalitis.

IS1-2
How to improve treatment and prognosis of anti-NMDA receptor encephalitis?

Yoshitaka Mizobe, Kazuhiro Muramatsu, Takahiro Ikeda, Hitoshi Osaka, Takanori Yamagata
The Department of Pediatrics, Jichi Medical University, Tochigi, Japan

Anti-NMDA receptor encephalitis（NMDARE）is an autoimmune disease characterized by complex neuropsychiatric symptoms and the presence of antibodies against the GluN1 subunit of NMDAR in the central nervous system. The symptoms of approximately 80% patients improve after immunotherapy and, if needed, tumor removal, but recovery is slow. Corticosteroids, intravenous immunoglobulin（IVIg）, or plasma exchange（PE）therapies are administrated as first-line treatments, while rituximab and cyclophosphamide are considered after failure of first-line therapy. Currently, this field requires further study on several important issues, such as earlier and faster diagnosis by detecting antibodies and ascertaining the time for transition from first-line to second-line therapy. We summarize the treatment and outcome of NMDARE, in our hospital by retrospective. In the past 13 years, we have experienced seven cases of NMDARE in our hospital. Only one patient had ovarian teratoma. First-line treatment was started on average 13 days from onset. In all cases, methylprednisolone pulse therapy and IVIg were administered, and second line treatment with rituximab and cyclophosphamide was selected for patients with poor functional improvement over two weeks of first line treatment. Rituximab was administered to five patients and cyclophosphamide to three patients. PE was performed in three patients and discontinued because of worsening autonomic symptoms and hypovolemic shock. However, the patients received PE treatment within two weeks of onset tended to have a better neurological prognosis. Thus, PE might be effective to avoid neurological sequelae if no side effects occur. In this symposium, we show our cases and discuss to treat NMDARE for early intervention.

IS1-3
The clinical courses of three cases of MOG antibody-associated demyelinating diseases (MOGAD)

Naomi Hino-Fukuyo
Tohoku Medical and Pharmaceutical University, Sendai, Japan

In contrast to the clear evidence supporting acute treatment for myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), the benefit of relapse prevention for MOGAD has yet to be proven. Clinical reports and retrospective studies have suggested that long-term immunosuppression be considered in patients with a high frequency of relapse and/or high risk of neurological disability. However, at what point we should stop relapse prevention treatment is unclear. Furthermore, because of the better neurological prognosis of MOGAD compared with AQP4-IgG (+) neuromyelitis optica spectrum disorders, it is unclear whether to use acute therapy for asymptomatic MOGAD cases which show a new lesion on follow-up magnetic resonance imaging. To discuss these points, I will introduce three MOGAD cases. Case 1 had not received long-term relapse prevention, and a diagnosis of MOGAD at about 20 years after onset. The expanded disability status scale score is 0 at present, after several relapses. Case 2 improved due to high-dose methylprednisolone, immunoglobulin therapy, and plasma exchange at onset. The patient continued to receive monthly immunoglobulin therapy without recurrence. Case 3 underwent oral administration of low-dose corticosteroids for several years without recurrence and became MOG-IgG seronegative. However, the during tapering of prednisolone period, MOG-IgG became positive several times.

IS1-4
Treatment of Paediatric Anti-NMDAR Encephalitis

Margherita Nosadini
Paediatric Neurology and Neurophysiology Unit, Department of Women's and Children's Health, University Hospital of Padova, Padova, Italy., Neuroimmunology group, Paediatric Research Institute 'Città della Speranza', Padova, Italy.

N-methyl-D-aspartate receptor antibody encephalitis (NMDARE) is one of the most common autoimmune encephalitides. It may be very severe in the acute phase, and relapses can occur. The final outcome is generally favourable but neuropsychological and psychiatric sequelae are relatively common.
With the limitations imposed by the lack of randomized controlled trials, immunotherapy has been shown to improve outcomes, especially with early administration, and to reduce the risk of relapses.
Currently, corticosteroids are recommended in all children with NMDARE (pulsed intravenous preferred), with additional intravenous immunoglobulin or plasma exchange in severe patients. Prolonged first-line immunotherapy can be offered (oral corticosteroids or monthly intravenous corticosteroids/immunoglobulin), dependent on disease severity. Second-line treatments are recommended for cases refractory to first-line (rituximab preferred over cyclophosphamide) and should be considered about 2 weeks after first-line initiation. Further immunotherapies for refractory disease after second-line initiation include another second-line treatment (such as cyclophosphamide), and escalation to tocilizumab. Maintenance immune suppression beyond 6 months (such as rituximab re-dosing or mycophenolate) is generally not required, except for patients with a more severe course or prolonged impairments and hospitalisation. Oncologic searches are mandatory. For patients with relapsing disease, second-line and prolonged maintenance therapy should be considered. Total treatment duration (first-line, second-line and maintenance), should be dictated by the severity and clinical course (i.e. median 3, 9 and 18 months in the best, average and worst responders respectively).

IS1-5
Treatment of Peadiatric MOG-Ab-Associated Diseases

Yael Hacohen
(Department of Neuroinflammation, Queen Square MS Centre, UCL Institute of Neurology)

抄録掲載無し

International Symposium 2：Classification & Management of Epilepsy Syndromes in Neonate, Infancy and Childhood

座長

Hideo Yamanouchi[1)], Wang-Tso Lee[2)]
1）Saitama Medical University, 2）National Taiwan University

企画・趣旨のねらい

The ILAE classification of epilepsies was released in 2017 and has been used as a powerful tool for the diagnosis of epilepsy as well as clinical and basic research on epilepsy for all physicians involved in epilepsy. Now we child neurologists have a new guide to classify and define epilepsy syndromes in neonate, infancy, and childhood. In this symposium, three internationally known experts in pediatric epilepsy, who were intimately engaged with this newly released classification, will discuss the diagnosis, management, and future challenges of epilepsy based on the classification. The symposium will provide an opportunity to learn more about pediatric epilepsy syndromes through enthusiastic discussions between symposium speakers and members.

IS2-1
Basic Mechanisms of Epilepsies in Neonate, Infancy, and Childhood

Solomon L. Moshé, MD
Saul R. Korey Department of Neurology, Dominick P. Purpura Department Neuroscience and Department of Pediatrics, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York USA

The International League Against Epilepsy has developed new classifications of seizures, epilepsies and syndromes that can be used by researchers to develop models that have translational value for age- specific syndromes. The immature brain is not a miniature version of the adult brain. Revisiting the key features of epileptogenesis and epilepsy as a function of age has led to the recognition that some concepts accepted as 'truisms' may need to be challenged. There is increasing knowledge that the identification of new etiologies（genetic, inflammation-related, structural or a combination of）as well systemic factors may have a key role in epileptogenesis, on how a seizure may induce changes resulting in a permanent epilepsy and associated comorbidities as well as the role of sex-related factors in shaping the consequences. These are important steps that may open new avenues of translational research. Better understanding of the discrete windows of the developmental process influence seizure and epilepsy related questions will provide unique insights. The newly acquired data will form the basis for the identification of risk factors and possible biomarkers and thus create novel therapeutic approaches leading to individualized treatments and precision based medicine.

IS2-2
Classification and Management of Epilepsy Syndromes in Neonate and Infancy

Ingrid E. Scheffer
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In this time of enormous change in our understanding of the epilepsies, classification of epilepsy syndromes is of paramount importance. An epilepsy syndrome diagnosis coupled with aetiological diagnosis inform tailored therapy for children with epilepsy. Epilepsy syndromes have never, until now, been formally classified by the International League Against Epilepsy. Here we present the new 2022 formal classification of epilepsy syndromes within the ILAE epilepsy framework published in 2017. Epilepsy syndromes in the neonate and infant are of critical importance as they are complex concepts that integrate clinical features, EEG findings and often associated imaging abnormalities. An epilepsy syndrome diagnosis may carry specific implications regarding aetiology, prognosis, reproductive counselling and management. Correct syndromic diagnosis means that appropriate anti-seizure therapies can be instituted and contraindicated drugs avoided, with the potential to have profound effects on developmental outcome. The new classification of epilepsy syndromes with onset in neonates and infants will be presented with a focus on diagnosis and management.

IS2-3
Classification & Management of Epilepsy Syndromes in Childhood

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The 2017 ILAE classification has defined a three-tier system with epilepsy syndrome identification at the third level. While a syndrome cannot be determined in all children with epilepsy, identification of a specific syndrome provides guidance on management and prognosis. In this paper, we describe here the childhood-onset epilepsy syndromes. Most of these syndromes have both mandatory seizure type (s) and interictal EEG features. Based on the 2017 Classification of Seizures and Epilepsies, some syndrome names have been updated using terms directly describing the seizure semiology. Epilepsy syndromes beginning in childhood have been divided into three categories : 1. Self-limited focal epilepsies, comprising four syndromes : Self-Limited Epilepsy with Centrotemporal Spikes, Self-Limited Epilepsy with Autonomic Seizures, Childhood Occipital Visual Epilepsy and Photosensitive Occipital Lobe Epilepsy ; 2. Generalized Epilepsies comprising three syndromes : Childhood Absence Epilepsy, Epilepsy with Myoclonic Absence and Epilepsy with Eyelid Myoclonia ; 3. Developmental and epileptic encephalopathies, comprising five syndromes : Myoclonic-Atonic Epilepsy, Lennox-Gastaut syndrome, Developmental and epileptic encephalopathies with spike-wave activation in sleep, Epileptic encephalopathies with spike-wave activation in sleep, Hemiconvulsion-Hemiplegia-Epilepsy and Febrile Infection-Related Epilepsy Syndrome. We define each highlighting the mandatory seizure (s), EEG features, phenotypic variations and findings from key investigations.

International Symposium 3：Tourette syndrome in Asia

座長

Yoshiko Nomura[1)], Lillian V. Lee[2)]
1）Yoshiko Nomura Neurological Clinic for Children, 2）Philippine Children's Medical Center

企画・趣旨のねらい

Tourette syndrome（TS）is a frequently observed developmental neuropsychiatric disorder occurring in children. Tics are an involuntary movement, and consist of motor tics and phonic tics. TS is one of the tic disorders and defined as the multiple motor tics associated with phonic tics lasting more than one year. It is associated with other behavior disorders such as attention deficit hyperactivity disorder（ADHD）, obsessive compulsive disorder（OCD）, and others.
The onset of tics and behavioral symptoms show the characteristic age dependency. The natural course takes also age related changes, i.e. starting in the early childhood, waxing and waning through the mid to late childhood, and subsiding by the late teens. There are some cases whose symptoms continue to the adulthood, and a few cases even exacerbate in adulthood.
There is gender difference involving male more than female. The familial occurrences of tic disorders are well known. Tics also fluctuate under the various environments.
Thus, the pathophysiology of TS involves both genetic and environmental factors.
The effects of haloperidol reported by Seignot in 1961 suggested the role of nigrostriatal dopamine（NS-DA）system as an essential part of the pathophysiology.
The hypothesis of the pathophysiology include the followings.
The activity of tyrosine hydroxylase（TH）which convert tyrosine to dopa takes age dependent changes at striatum, the terminal of NS-DA system. The activity is high in the early childhood, decreases rapidly till around 10 years of age, moderately till mid-teens, and reaches to low adult level. The hypothesis based on the data from sleep components analysis suggested the age dependent decrease of DA activity at the striatum is accelerated, and causes the DA receptor super-sensitivity.
Associated behavior abnormalities such as OCD, anxiety and depressive mood imply the possible involvement of serotonergic system.
The roles of basal ganglia-thalamo-cortical pathway are also discussed for the motor tics, and the non-motor circuits are thought to be involved in other behavior disorders and complex tics. There are three non-motor circuits, which are dorsolateral prefrontal circuit, lateral orbitofrontal and anterior cingulate circuit. Among these, lateral orbitofrontal and anterior cingulate circuit are involved in the pathophysiology of TS.
This symposium, titled as "Tourette Syndrome in Asia", covers the following subjects, and aims to share and to discuss about TS and associated behavior problems in Asia.
1）'Clinical features and Treatments' is presented by Huei-Shyong Wang, Taiwan
2）'Tourette syndrome in different cultures and environments；
Tics and Tourette syndrome at the Philippine Children's Medical Center：
A Single Center Experience' is presented by Marilyn Ortiz and Lillian Lee, The Philippines.
3）'Tourette syndrome；The Histories and Neurosciences' is presented by Yoshiko Nomura, Japan.

IS3-1
Introduction：Clinical features and managements of Tourette syndrome

Huei-Shyong Wang
Division of Pediatric Neurology, Chang Gung Children's Hospital, Taoyuan, Taiwan

Tourette syndrome（TS）is a common neurodevelopmental disorder presenting with tics as the hallmark for more than a year since childhood as young as 1-2 years of age. TS is often comorbid with attention deficit hyperactivity disorder, obsessive compulsive disorder, self-injurious behavior, sleep disorder, learning disorder, developmental coordination disorder, etc. The exact mechanism of TS is not clear yet. No anti-tic pharmacological agent has achieved a cure efficiently. On the other hand, non-pharmacological managements including behavior therapy and deep brain stimulation have been suggested. Large amount of physical activities may play a role in ameliorating tics in these particular children. Any sports, including baseball, biking, dancing, jogging, skating, squashing, swimming, and unicycle riding may be helpful. Life styles of children with TS may be changed to deal it well according to different ages as the following suggestions from Taiwan Tourette Family association since 2002:
1. Preschool years: safe labor works such as mopping the floor with a rug instead of a mop.
2. School years: 2 hours of physical activity at least daily to achieve doubling of basic heart rate or one hour of unicycle-riding daily with gradual increase of duration and intensity.
3. Occupation in adulthood: to be an athlete, farmer, performer, or a busy medical professional.

IS3-2
Clinical Profile of Pediatric Patients with Tics and Tourette's Disorder Seen at the Philippine Children's Medical Center from 2011-2021（A Single Center Study）

Marilyn H. Ortiz, Madelyn P. Pascual, Jean Marie Ahorro, Erickson F. Torio, Melady I. Gilbuena, Lillian V. Lee.
Child Neuroscience Division, Philippine Children's Medical Center

TIC is defined as a sudden, rapid, recurrent, non-rhythmic motor movement or sudden vocalization. Tics are common in childhood but transient in most cases. TOURETTE'S DISORDER, the most severe form of Tic Disorder, is characterized by the presence of both motor and vocal tics that may wax and wane but have persisted for more than 1 year. The estimated prevalence of Tourette's Disorder ranges from 3 to 8 per 1,000 school-age children.（DSM-5, American Psychiatric Association, 2013）. At the Philippine Children's Medical Center, tics and Tourette's Disorder are among the various neurological disorders diagnosed and managed by the medical staff of the Child Neuroscience Division. In this presentation, we will describe the clinical profile of our patients, including the demographic profile, types of tic disorders, management of these patients and clinical outcome.

IS3-3
Tourette syndrome —The Histories and Neurosciences—

Yoshiko Nomura
Yoshiko Nomura Neurological Clinic for Children

In 1885, Gilles de la Tourette described 9 cases who suffered from a disorder characterized by involuntary movements, echolalia, echopraxia, coprolalia, and strange uncontrollable sounds, which now bear his name, Tourette syndrome（TS）.
In 1961, Seignot, and Caprini and Melotti reported the successful treatment by haloperidol. Since early 1970th, Shapiro et al. proposed TS as a type of tic syndrome, and became to be defined as multiple motor tics and at least one vocal（phonic）tic, and usually lasting more than one year.
TS is a frequently observed developmental neuropsychiatric disorder occurring in children.　TS is often associated with other behavior disorders such as attention deficit hyperactivity disorder（ADHD）, obsessive compulsive disorder（OCD）, and others.
The onset of tics and behavioral symptoms, and the natural course take age related changes.
The roles of basal ganglia-thalamo-cortical pathway are discussed for the motor tics, and the non-motor circuits for other behavior disorders. Among three non-motor circuits, i.e. dorsolateral prefrontal, lateral orbitofrontal and anterior cingulate circuit, lateral orbitofrontal and anterior cingulate circuits are thought to be involved in the behavioral symptoms associated with TS.
The effects of haloperidol suggest that nigrostriatal dopamine（NS-DA）system is primarily involved.
Age related clinical features suggest the developmental changes of the responsible neuronal systems.
We proposed TS as a developmental dopamine disorders.
Tics fluctuate under the various environments.
Thus, the pathophysiologies of TS involve both genetic and environmental factors.
As to the managements of TS both pharmacological and environmental approaches are necessary.

International Symposium 4：Medical Care and Support for Developmental Disorders in the 'With-/Post-COVID-19' Era —Approaches in Asia, USA, and Japan

座長

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企画・趣旨のねらい

Due to the COVID-19 pandemic that began in 2020, a state of emergency was declared, and schools were closed in Japan；severe restrictions on going out were imposed in various countries around the world.
The COVID-19 pandemic has had a significant impact on the medical care and support for children with developmental disorders, and each country has had its difficulties, responses, and innovations.
In this symposium, doctors who are clinically treating children with developmental disorders and neurological disorders in Japan, four countries in Southeast Asia, and the United States will talk about the confusion and difficulties in medical treatment and support caused by the COVID-19 pandemic, as well as their efforts and current status in responding to these difficulties. We would like to take this opportunity to learn from the situation in each country and think about how to treat and support children with developmental disorders in the 'with-/post-COVID-19-era, and how to prepare for emergencies such as the COVID-19 pandemic.

IS4-1
Outpatient care and intervention for children with developmental disorders under COVID-19 pandemic

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When Japanese government declared its first state of emergency due to COVID-19, schools and businesses were closed and people were asked to stay home. Anyone with fever and suspected COVID-19 exposure should isolate oneself and contact the local public health center to receive PCR testing and to have close contacts identified. Many of the hospitals and clinics did not accept patients with suspected COVID-19, and told them to call the health centers or referred them to designated urgent care centers, so that they could continue to provide their regular services. We continued to provide our regular care of the developmental clinic, although many patients feared visiting medical facilities and postponed or canceled their appointments. Ministry of Health, Labor, and Welfare approved telemedicine for known patients with stable conditions to ensure continued care. With all infection prevention procedures and stay-at-home requests, there had been almost no infectious conditions among children, and pediatric visits dropped dramatically. Many daycares and facilities for therapies for children with disabilities also suspended their services. For many families, it was devastating to manage their behavior with no outside help. Therefore, public welfare facilities were asked to restart their services gradually with infection prevention protocol in place. Within two months, schools reopened and people got back to work. However, most of Japanese people have kept on wearing masks and keeping social distance ever since. Hospitals and clinics have become better equipped to see patients with COVID-19. We have gone through several surges of infection without closing schools and shutting down cities with no major medical crises.

IS4-2
A Malaysian Perspective —Life Post-pandemic for Children with Developmental Disorders—

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The COVID-19 pandemic has heightened anxiety and stress in children, and especially so in children with developmental disorders. The needs of their siblings are just as important, but often overlooked. Challenging and repetitive behaviour can be part of the core features of autism. However, emotional dysregulation if present, can worsen the behaviour. Additionally, emotional dysregulation is possibly one of the consequences of stress in children with developmental disorders, and this can increase anxiety levels in their siblings. This has been the impetus for a study［The Malaysian Autism Research Study（MARS）］at the Child Development Centre, Department of Paediatrics, University of Malaya Medical Centre. This study explores contributory factors towards emotional dysregulation and challenging and repetitive behaviour in children with different levels of autism severity. It also explores contributory factors to anxiety in neurotypical siblings of these children.

IS4-3
Telemedicine in Thailand during the COVID-19 pandemics —benefits and limitations—

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Since the outbreak of the SARS-CoV-2（COVID-19）pandemic in Thailand. Telemedicine platform has been built not only to monitor COVID-19 patients with mild symptoms at home, hospitel and at community isolation centers, but also for all patients and families in Ramathibodi Hospital, Bangkok, Thailand. Ramathibodi Hospital, has successfully cut one-thirds of about 4,000 hospital visits by patients with chronic diseases per day at outpatient clinics. It was significant challenges for children and families with chronic diseases in order to encourage the stay-at home, and social distancing policies to limit spread of the SARSCoV-2 virus.

At the peak of the outbreak, during the last 6 months of 2021, the rate of telemedicine replaced between approximately 10% to 90% in neurological and child development clinics. Families increased interest and openness to digital media long-distance system. Many modalities have been used to maintain medical care standard i.e. application, Line, telephone call and video call. Developmental assessment for children was adapted via telemedicine. The questionnaires that help diagnosis for some neurodevelopmental disorders were sent by using "LINE" or emailing system. Speech therapy and early intervention were also performed in a long-distance manner. Medicines are also delivered to patients via postal system.

We found that telemedicine is useful for delivering healthcare to communities especially in the COVID-19 pandemic era. We can maintain regular follow-up visits during the lockdown period. It can decrease the risk to viral infection in some children and toddlers who resisted to wear masks. Families can save a great deal of money and time spent in travelling from the remote area around Thailand. However, common barriers are technically challenged for both staff and patients, lack of high-speed internet for families in the remote rural area, high cost of setting up telemedicine infrastructure and limited digital applicability in low income populations that result in loss treatment follow up.

Telemedicine in the current COVID-19 pandemic at Ramthibodi Hospital seems to be successful to some extent and remains ongoing process to promote a more efficient telehealth system.

IS4-4
Continuity of Care for Children with Neurodevelopmental Disabilities Amidst The COVID-19 Pandemic —The Philippine Experience—

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Abstract
It has been 2 years into the COVID-19 pandemic and the restrictions imposed by the lockdown have been widely encompassing and has greatly affected people's lives, even for children. The Philippines, unfortunately, is one of the most affected in Asia. With a higher rate of COVID-19 cases, limitations in the access of resources, shift of education from face-to-face to remote online learning and rising concerns on mental health impact on children's development and behavior. For children with neurodevelopmental disabilities and their families, the scenario is more challenging. Apart from the aforementioned issues, there has been a disruption in the accessibility of essential child development services, learning resources and the needed intervention programs. How then have we adapted to the situation in order to provide children with neurodevelopmental disabilities the care and interventions they need? We navigate these challenges with accommodations, adaptations and innovations in order to provide continuity of care.

IS4-5
Learning to Dance in the Rain: Overcoming Challenges in Pediatric Neurology and Neurodevelopmental Disorders during the COVID-19 Pandemic in Indonesia

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The COVID-19 pandemic has led to activity restrictions in Indonesia and has had a significant impact on people's lives. Various restrictions were also imposed in the medical care of children with neurological diseases and developmental disabilities. On the other hand, there are only small number of pediatric neurologists in Indonesia, and the accessibility of these children to specialized medical institutions has always been a problem. For this reason, we developed a remote diagnosis method of children with autism spectrum disorder using telemedicine, validated our methods, and published a paper in 2021（Telemed J E Health）. In this talk, we will outline the impact and current status of COVID-19 on the treatment of children with neurological problems as well as discuss the possibilities and problems of telemedicine in the context of restricted activities.

IS4-6
Pandemic and Care for the Children with Developmental Needs in Boston United States

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Fetal Neonatal Neurology, Neurogenetics Program, Pediatrics and Neurology, Pediatric Neurology, Department of Pediatrics, Tufts Children's Hospital, Boston, MA, USA, Principal Investigator, Mother Infant Research Institute, Tufts Medical Center, Boston, MA, USA

COVID-19 pandemic has been affecting health care for children and families, especially for children with developmental needs. During pandemic, children and families and health care providers face multiple aspects and layers of challenges, including limited access to medical care, developmental support, special education, family burdens including isolation, care providers' illness, or financial challenges. In early 2022, the United States is still amid pandemic but also in transition to the "With-/Post-COVID-19" era at the same time. This session will present the regional experience in child neurology care for the children with developmental needs during the pandemic in Boston, MA, USA, and the ongoing efforts to improve their care, foreseeing the "With-/Post-COVID-19" era.

EO-001 Neuromuscular junction abnormalities in patients with centronuclear myopathy

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【Background】Mutations in *DNM2*, *BIN1* and *MTM1* cause centronuclear myopathies（CNMs）. Recent studies with *Dnm2*-mutant zebrafish have identified anomalies in neuromuscular junction（NMJ）. However, there has been no report to provide pathological evidence of NMJ abnormalities in human patients with CNMs.【Objective】To characterize NMJ abnormalities on muscle pathology and to identify clinical evidence for NMJ abnormalities in patients with CNMs.【Methods and patients】We re-reviewed muscle pathology of the 39 patients（18 women, age 432.1［250.8］months（mean［SD］）with genetically-confirmed CNMs（34 *DNM2*, 1 *BIN1* and 4 *MTM1*）, focusing on the circumferential acetylcholinesterase（AChE）activities on the sarcolemma which should reflect abnormality in AChE's clustering at NMJ. We also reviewed the findings on repetitive nerve stimulation（RNS）and the effects of AChE inhibitors（AChE-I）.【Results】AChE activities were observed circumferentially on the sarcolemma in all CNM patients. The frequency of the fibers with circumferential AChE activities was 24［23］%（mean［SD］）in CNMs. Decremental CMAPs were observed in all three patients with CNM due to *DNM2* mutation（CNM_*DNM2*）who underwent RNS. One of two patients who received AChE-I showed improvement in muscle manual testing.【Conclusions】On muscle pathology, myofibers with circumferential AChE expression were observed in all CNM patients. AChE-I seems to be effective albeit RNS performed only in a limited number patients with CNM_*DNM2*.

EO-002 Sibling cases of Duchenne muscular dystrophy with improvement after six months of Viltolarsen

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【Background】Viltolarsen is a Morpholino antisense oligonucleotide for the treatment of Duchenne muscular dystrophy（DMD）in people who have a mutation that is amenable to exon 53 skipping. We report sibling cases of DMD with improvement after treatment of Viltolarsen.【Methods】Non-ambulatory adolescents aged 19（P1）and 17 years（P2）with DMD were evaluated for motor function and activities of daily living（ADL）before and 6 months after the treatment of Viltolarsen.【Results】Motor function was improved in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders（CHOP INTEND）（P1：pre 11, post 21；P2：pre 20, post 26）. Functional disability scales and upper extremity functional scales in DMD according to the Ministry of Health and Welfare Research Group were not changed before and after the treatment of Viltolarsen in both patients. ADL was improved in Barthel Index（BI）in P1（pre 20, post 25）but not in P2（pre 30, post 30）. Canadian Occupational Performance Measure（COPM）was improved in both patients.【Discussion】In this study, motor function and ADL were improved after the treatment of Viltolarsen. CHOP INTEND, BI and COPM were useful in evaluating the efficacy of Viltolarsen in non-ambulatory patients with DMD. Other scales were difficult to show improvement in these patients.【Conclusion】Viltolarsen seems effective in motor function and ADL. Scores appropriate to the patient's motor function should be used to assess the efficacy of treatment.

EO-003 Urine miRNA in patients with Duchenne muscular dystrophy

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【Background】Recent advances in innovative therapies for Duchenne muscular dystrophy（DMD）have highlighted the necessity of developing less invasive and more sensitive biomarkers. Urine is one of the least invasive body fluids that could be obtained. Further, circulating micro RNAs（miRNAs）have been rigorously investigated as biomarkers in various settings.【Aim】To identify urine miRNAs that can represent the disease state in patients with DMD, and to assess their function.【Methods】Urine from 8 patients with DMD and age matched 8 healthy male volunteers were obtained. Total RNA from cell-free urine was extracted, and miRNA expression profiles were evaluated using miRNA array. DMD specific miRNAs were assessed in relevance to their clinical information. In addition, the function of the miRNA was assessed using human myoblasts and fibroblasts. This study was approved by the ethical committee.【Results】There were miRNAs that were significantly upregulated in patients with DMD compared to the healthy individuals. When the expression values were aligned to the clinical conditions, one of them was significantly correlated to the body mass index（BMI）, indicating the relevance to obesity or underweight. Over-expression or inhibition of this miRNA in myoblasts and fibroblasts revealed its function in cell proliferation, apoptosis induction, and cell growth, however.【Conclusion】The identified miRNA could be a candidate biomarker that represents the disease state of DMD patients.

EO-004 An exon skipping therapy by Viltolarsen on a presymptomatic patient with Duchenne muscular dystrophy

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Viltolarsen is a morpholino antisense oligonucleotide, which targets exon 53 of the dystrophin gene to restore the amino acid reading frame by skipping exon 53, allowing the production of functional dystrophin proteins. Reports have shown the improvement or stabilization of motor function on symptomatic Duchenne muscular dystrophy（DMD）. Here, we report an experience of exon skipping therapy using viltolarsen on a presymptomatic patient with genetically confirmed DMD. Our experience may provide the possibility of prophylactic treatment with viltolarsen on presymptomatic DMD patients detected by the birth screening tests. This four-year-old boy was referred for incidentally detected hyperCKemia（41,018 IU/L）. Motor milestones were normal, and muscle tone and strength were well-matched for his age, except for mild stiffness of calf muscles. Dystrophin gene test presented the deletion of exon 45-52, which is applicable for the exon skipping therapy with viltolarsen. Motor functional tests are conducted and evaluated chronologically according to the research project Remudy-DMD, including time to stand test and time to run/walk 10 meters test as well as Brooke upper extremity scale. Other clinical data of blood and urine tests, cardiac and respiratory function tests and skeletal muscle MRI are also evaluated before and 6 months after the treatment. The safety and efficacy of treatment at 6 months after the initiation of treatment will be addressed at the time of the presentation.

EO-005 Restoration of cortical plate organization in a brainorganoid model of Fukuyama muscular dystrophy

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TourokFukuyama congenital muscular dystrophy（FCMD）is a severe, intractable genetic disease that affects the skeletal muscle, eyes, and brain and is attributed to a defect in alpha dystroglycan（αDG）*O*-mannosyl glycosylation. We previously established disease models of FCMD；however, they did not fully recapitulate the phenotypes observed in human patients. In this study, we generated induced pluripotent stem cells（iPSCs）from a human FCMD patient and differentiated these cells into three-dimensional brain organoids and skeletal muscle. The brain organoids successfully mimicked patient phenotypes not reliably reproduced by existing models, including decreased αDG glycosylation and abnormal radial glial（RG）fiber migration. The basic polycyclic compound Mannan-007 restored αDG glycosylation in the brain and muscle models tested and partially rescued the abnormal RG fiber migration observed in cortical organoids. Therefore, our study underscores the importance of αDG *O*-mannosyl glycans for normal RG fiber architecture and proper neuronal migration in corticogenesis.

EO-006 Could Nusinersen from the neonatal period prevent the development of spinal muscular atrophy?

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Nusinersen is a survival motor neuron-2（SMN2）-directed antisense oligonucleotide that modifies SMN2 RNA splicing, increasing protein production. Reports have shown that it was effective for improving motor function and survival in spinal muscular atrophy. This case report presents a normal motor development found in a 2-year-6-month old girl, who was genetically diagnosed with spinal muscular atrophy and started nusinersen at 8 days of age. Her sister had been diagnosed as SMA type 1 with SMN1 exon 7 and 8 deletions and died of respiratory failure at 9 months. A genetic test using the umbilical cord blood soon after birth presented that she had a deletion of exons 7 and 8 of SMN1 gene and two copies of SMN2 gene. Intrathecal administration of nusinersen was started at 8 days of age. Motor function evaluation by CHOP INTEND and electrophysiological examination including MCV, SCV, and F wave were performed over time to evaluate the therapeutic effect of nusinersen until the age of 2 years and 6 months. Electrophysiological examinations were within the reference values for age. K. Vill et al. reported that early treatment with nusinersen on presymptomatic babies genetically diagnosed with SMA found in a newborn screening test exhibited normal development. Our longitudinal evaluations are consistent with the results of their study. It is suggested that early nusinersen administration from the asymptomatic period might be possible to prevent the development of SMA.

EO-007 Treatment with OA after Nusinersen in a patient with prenatally diagnosed spinal muscular atrophy

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【Background】A significant therapeutic effect in the early or pre-symptomatic disease stage has been reported in patients with SMA. Onasemnogen Abeparvovec（OA）is the first gene therapy approved in Japan. Here we report a patient with SMA treated with OA after Nusinersen（NUS）within two weeks after birth.【Case】The patient underwent prenatal diagnosis of SMA（SMN1：0 copy, SMN2：2 copies）because his elder brother had been diagnosed with SMA type 0. The patient was delivered by C-section at 37 weeks without asphyxia. At birth, he showed normal muscle tone, without paradoxical breathing or tongue fasciculation, but had slight muscle weakness and PTR was only transiently detected on the right. We administered NUS on day 2, and OA was then administered on day 11. Transient mild elevation of liver enzyme was seen on 4 days after OA injection. CHOP INTEND showed 36 and over 40 points at the age of day 1 and 2 months, respectively. Electrophysiologically, the frequency of F waves was stable during follow-up, and CMAP on the median and posterior tibial nerve were slightly reduced before treatment but improved after administration of OA. The patient showed natural motor development, although deep tendon reflexes are still negative.【Conclusion】It was suggested that early administration of NUS and OA had a significant impact on the disease process, although careful follow-up is needed to evaluate the efficacy of treatment.

EO-008 Spinal muscular atrophy-like features in a child with heterozygous MYBPC1 mutations

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【Background】The *MYBPC1* gene encodes myosin-binding protein C in sarcomeres and is associated with several muscle diseases. One of them is a phenotype characterized by muscle weakness and tremors in infancy.【Case】The patient is a 5-year-old girl with mild muscle weakness and tremor of the tongue and upper limbs. At 5 months of age, she had hypotonia, delayed motor development, stridor, and tremor of the tongue and upper limbs. *SMN1* gene analysis revealed deletion of one allele and a point mutation in the other allele. The point mutation was noted in an intronic sequence, and it might affect splicing. She was diagnosed with spinal muscular atrophy（SMA）and treated with nusinersen from the age of 1 year and 8 months. Her motor development progressed very well and she could walk independently at the age of 1 year and 10 months. The whole-exome analysis identified heterozygous mutations in *MYBPC1*. Administration of nusinersen was discontinued at the age of 5 years.【Discussion】In this case, SMA was suspected based on the neurological symptoms in early infancy and genetic test results. Cases of *MYBPC1* gene abnormality have been reported to be clinically diagnosed as SMA. The symptoms in infancy were partially similar among these diseases. However, our patient's motor development was atypical for SMA, and careful examination led to the identification of the gene mutation. In cases of infantile-onset hypotonia with tremors, *MYBPC1* gene abnormalities should be considered.

EO-009 Congenital insensitivity to pain with anhidrosis：A case report

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【Background】Congenital insensitivity to pain with anhidrosis（CIPA）is a rare autosomal recessive disorder that is characterized by insensitivity to pain, anhidrosis and mental retardation. Mutations in the NTRK1 gene are responsible for the disorder.【Case】A 3.5-year-old male born to healthy consanguineous Iranian parents presented with such symptoms as insensitivity to pain, anhidrosis, self-mutilation and intellectual disability. At the time of presentation he had multiple scars, especially on his hands, feet and knees resulting from previous trauma. It was ascertained that the wounds, caused by trauma and the self-mutilating behaviors of the patient, did not heal easily. CIPA was diagnosed based on clinical findings and information obtained from the family. Wound care was performed and the patient was started on a support program for cognitive function. In the absence of a cure for the condition, the family was informed about the measures to be taken and provided with genetic counseling, and the patient was followed up.【Conclusion】The characteristics of the disorder should be well known to ensure its inclusion in differential diagnosis. As there is as yet no cure for this condition, the family of the patient should be informed about the disease and the measures to be taken, and provided with genetic counseling.

EO-010 Presentation and outcome of two paediatric patients with critical illness polyneuropathy

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【Introduction】Paediatric critical illness polyneuropathy possesses a wide spectrum of manifestations but has only occasionally been reported. We describe our experience managing two patients of different severity, both had a favourable outcome.【Case Report 1】A 4-year-old boy with T-cell acute lymphoblastic leukaemia contracted severe Influenza A pneumonia complicated with acute respiratory distress syndrome and multi-organ failure. At 2.5 weeks ICU admission, generalised muscular weakness was apparent as sedation and mechanical ventilation were weaned. Absent sensori-motor potentials combined with fibrillations and positive sharp waves indicated denervation from axonal loss. He was extubated and made a full recovery one month later.【Case Report 2】A 6-year-old boy with Japanese Encephalitis failed extubation twice in 2 weeks. Concomitantly, he had new onset of right sided muscular weakness, weak pharyngeal reflex and an elevated right hemidiaphragm on chest X-ray suggestive of diaphragmatic paralysis. Reduction in motor amplitudes, presence of fibrillations, positive sharp waves and broad polyphasic motor units were consistent with an axonal neuropathy. He needed tracheostomy to assist prolonged ventilation due to respiratory muscle fatigue. After 2 months of intensive rehabilitation, he walked and was weaned off daytime ventilation.【Conclusion】Severity of electrophysiological study does not correlate with respiratory involvement. Supportive management is still mainstay.

EO-011 Early immunologic responses to the mRNA SARS-CoV-2 vaccine in patients with neuromuscular disorders

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【Background】Intramuscular injection of the SARS-CoV-2 vaccine has raised concerns about its use in patients with neuromuscular disorders（NMDs）. We evaluate the safety and efficacy of the BNT162b2 vaccine in patients with NMDs.【Methods】This was a multi-center prospective observational cohort study. Healthy subjects, patients with spinal muscular atrophy（SMA）, and patients with Duchenne muscular dystrophy（DMD）were included. SARS-CoV-2 antibody titers was compared between those with NMDs and healthy controls. Numeric variables are expressed as mean（standard deviation）.【Results】Eleven patients with NMDs［9 with SMA and 2 with DMD；7 male；aged 32.7（19.3）years and 346 healthy subjects［60 male, aged 40.0（12.4）years］were included. Antibody titers（U/mL）were similar at all time points between the two groups（baseline：less than 0.40 vs less than 0.40, two weeks after first vaccination, 145（258）vs 103（1,192）, two weeks after second vaccination, 1,528（1,265）vs 1,429（944）；p＝1, 0.909, 0.736, respectively）. The frequency of adverse reactions was comparable between groups.【Conclusion】Although BNT162b2 is given by intramuscular injection, it appears to be safe and effective in patients with NMDs.

EO-012 Chronic inflammatory demyelinating polyneuropathy in Malaysian children, a single centre experience

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Childhood chronic inflammatory demyelinating polyneuropathy（CIDP）is a rare immune-mediated disorder of the peripheral nerves with predominant motor involvement. We herein report three children（age between 7-11 years old）who suffered from progressive lower limb weakness resulting in gait instability with varying duration of symptoms（ranging from 2-17 months）. They fulfilled the mandatory clinical criteria and at least 3 of the major electrophysiological criteria outlined by European Neuromuscular Center consortium for CIDP, primarily presence of conduction block involving more than one nerves. All children tested positive for anti-ganglioside antibodies. Patient 1 was tested positive for Sulfatide IgM, GM1 IgM and GM2 IgM antibodies, while Patient 2 and Patient 3 were found to have positive GM1 IgM and Sulfatide IgG antibody respectively. They received initial high dose intravenous immunoglobulin（IVIg）（2 g/kg）followed by monthly IVIg infusion（1 g/kg）for at least another 6 months. Patient 2 received additional 6 months course of oral steroids due to deterioration of symptoms despite treatment with IVIg. Significant improvement was seen in all children throughout the treatment course. Little is known regarding the relationship between presence of anti-ganglioside antibodies and the outcome of patients with childhood CIDP.

EO-013 Exome sequencing identify FKTN mutation in Indonesian patient with congenital muscular dystrophy

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【Purpose】Fukuyama congenital muscular dystrophy（FCMD）is an autosomal recessive disorder characterized by severe muscular dystrophy associated with brain malformation. FCMD is the second most common form of muscular dystrophy after Duchenne muscular dystrophy. The report of FCMD from other countries is scattered. Here we report clinical and genetic characteristic of FCMD seen in an Indonesian patient.【Methods】Whole exome sequencing was performed to find pathogenic variant causing clinically diagnosed congenital muscular dystrophy. Clinical data was gathered from medical record.【Result】a 4-year-old-old boy was brought to our clinic because he still cannot sit by himself. He was born from a consanguineous marriage. He has severe motor delay, weakness in both superior and inferior extremities, and contractures of the hips and knees. He also has myopathic facial appearance with tenting upper lips. His creatine kinase level was 4,199 U/L. Echocardiography showed tiny VSD. MRI showed widened Sylvian fissure, hyperintense lesion in white matter on T2-weighted image. EMG finding showed myopathic changes. Exome sequencing revealed homogenous mutation in FKTN gene NM_001079802.1：c.-1_2del（p.Met1del）, likely pathogenic for Fukuyama type muscular dystrophy.【Conclusions】we identify a likely pathogenic variant in FCMD, highlighting the usage of exome sequencing in clinical setting.

EO-014 Ketogenic diet introduction and modification in an adulthood patient with Glut1 deficiency syndrome

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【Introduction】The ketogenic diet（KD）is the principal treatment for glucose transporter 1 deficiency syndrome（Glut1DS）. There are limited reports of KD introduction to adult patients.【Patient description】The patient is 55 years of age. She was born without particular familial or perinatal history. She had a developmental delay from infancy, and refractory epilepsy from infancy to puberty. Since her 40s, she had repetitive transient consciousness loss or brief tonic seizure, especially in the early morning or fasting. At age 47, she was referred to us with suspicion of Glut1DS. She had a moderate intellectual disability, spasticity, ataxia, and paroxysmal exertion-induced dyskinesia（PED）. Her CSF glucose was 35 mg/dL. We found a pathogenic variant of the SLC2A1 gene（N34K）and diagnosed Glut1DS. We introduced KD with a ketogenic ratio of 1.5：1. The level of beta-hydroxybutyrate（BHB）ranged from 300 to 600 μmol/L. Then her ataxia and PED improved. Two years later, she wanted to eat the same meal with her roommate. In response, we modified her diet；adjusting overall calories, adding MCT oil on the regular diet, and taking ketone-formula twice a day. Afterward, she did not show any aggravation, although the level of BHB was 100 to 400 μmol/L.【Discussion】We successfully introduced KD for a middle-aged patient with Glut1DS, and changed it to a regular diet-based one. This experience will contribute to other adult patients who are unable to cook on their own.

EO-015 Childhood-onset glucose transporter 1 deficiency syndrome 2 in three generations in a family

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Glucose transporter 1（GLUT1）deficiency syndrome 2 is primarily characterized by childhood-onset paroxysmal exercise-induced dyskinesia. Epilepsy and mild mental retardation may accompany. Clinical improvement can be observed with the ketogenic diet. A 7.5-year-old male patient who presented with episodes of dyskinesia and was diagnosed with GLUT1 deficiency syndrome 2 in whole-exome sequencing is presented. The father and the mother of the father also carried the same mutation. The patient was admitted at the age of 5 years with the complaint of abnormal movements in the arms and legs twice a month. The attacks mostly occurred when he was tired and lasted 20-30 minutes. His unrelated parents had epilepsy and intellectual disability. The patient had dysarthria and mild spasticity in the lower extremities. In whole-exome sequencing, c.277C T p.R93W mutation in the SLC2A1 gene was found to be heterozygous, consistent with the diagnosis of GLUT1 deficiency syndrome type 2. After the genetic result, they said that the father, the father's mother, and the father's grandfather had similar complaints. The same mutation was detected in the father and the mother of the father. After the ketogenic diet treatment, the attacks decreased significantly. Early diagnosis is important because GLUT1 deficiency syndrome 2 can be treated with ketogenic diet therapy. Avoidance of fatigue, hunger, and insomnia that may trigger dyskinesia attacks is also recommended in terms of reducing the attacks.

EO-016 A novel bronchoscopic finding of cluster cholesteatoma in a case with end-stage I-cell disease

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We herein consider the basic pathogenesis in a patient with I-cell disease. Death usually occurs by 5 years of age. Our patient was a 10-year-old boy, diagnosed with I-cell disease at age 1 month, based on a compound heterozygous mutation of GNPTAB. He suffered from obstructive lung disease, necessitating SIMV. Chest XP and CT revealed asymmetric right lung hyyperlucency and multifocal bronchial stenosis, with calcifications. Bronchoscopy revealed multiple cluster cholesteatoma, resembling a pearl brooch, in the bronchi and bronchioles, which were difficult to excise surgically. No lysosomal and/or mucolipid storage was detected in biopsied bronchial epithelium adjacent to the cholesteatoma. Subepithelial fibrosis and mild lymphocytes infiltration were identified histologically. These findings are consistent with the "ominous pearl brooch sign" characteristic in the end-stage I-cell disease. No prior bronchoscopic examination have been reported for patients with I cell disease. Dysostosis multiplex and rickets-like lesions in the newborn period had been attributed to hyperparathyroidism. However, this patient showed no phosphorus, calcium or parathyroid hormone abnormalities. Impaired lysosomal enzyme trafficking may also adversely impact metabolism in bronchial epithelium, thereby possibly leading to insidious multifocal formation of cluster cholesteatoma in bronchi and bronchioles of relatively long-surviving patients with I-cell disease.

EO-017 Establishment of a flow cytometry screening method for Glucose transporter 1 deficiency syndrome

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【Introduction】Glucose transporter 1 deficiency syndrome（Glut1DS）is caused by haplo-insufficiency of *SLC2A1*. The principal diagnostic method for Glut1DS requires lumbar puncture to show hypoglycorrhachia, followed by genetic analysis. In preparing for gene therapy for Glut1DS, we need a screening method for early-stage Glut1DS, which lacks irreversible neurologic damage. Here, we assessed the use of flow cytometry to measure GLUT1 levels on the surface of red blood cells（RBCs）from Glut1DS patients.【Methods】We recruited genetically and clinically confirmed cases of Glut1DS from Apr. 2019 to Nov. 2021. We stained RBCs（1 microL）collected from Glut1DS patients with Glut1.RBD containing HTLV-1/2 receptor-binding domains fused to enhanced GFP. These domains recognize GLUT1 extracellular loop 6 with high affinity. Acquisition was measured with a flow cytometer. This study was approved by Jichi Medical University Clinical Research Ethics Committee.【Results】Fourteen patients（8 missense, 2 nonsense, 1 frameshift, 2 deletion, and 1 Glut1DS-like syndrome without *SLC2A1* mutation）were recruited. GLUT1 fluorescence intensity on RBCs of patients with a missense mutation reflected clinical severity. GLUT1 fluorescence intensity of nonsense, frameshift, and deletion patients was lower than that of those with a missense mutation and consistent with severe symptoms.【Conclusions】This method appears to be a suitable screening assay to evaluate GLUT1 expression levels and structural changes.

EO-018 Sleep-state-dependent functional connectivity networks in preterm infants at term

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【Purpose】To determine whether resting-state functional connectivity（FC）networks differed between active and quiet sleep（AS, QS）in preterm infants at term, we evaluated FC networks via simultaneous EEG and functional near-infrared spectroscopy（NIRS）.【Methods】We recruited 24 preterm infants（with Ethics Committee approval）. Written informed consent was obtained from all parents. EEGs were recorded polygraphically（at least eight electrodes）during both AS and QS. An eight-channel NIRS device was placed around each head to detect changes in oxy- and deoxy-hemoglobin（Hb）concentrations. We calculated the average FCs and phase synchronization indices of each pair of channels under slow（＜0.1 Hz）oxy- and deoxy-Hb fluctuations. We sought associations between FC network parameters and clinical variables.【Results】The median（range）ages at birth and recording were 32.4（24.6-34.9）and 38.1（37.0-39.6）weeks respectively. The oxy- and deoxy-Hb FC network parameters were significantly higher during AS than QS（all $p<0.01$）. The increased intra-hemispheric FC was largely attributable to the higher average FC during AS. No significant association was found between any FC network parameter and any clinical variable including sex.【Conclusions】Compared to QS, all（but especially the intra-hemispheric）FC network parameters increased during AS of preterm infants at term. Further study is needed to identify factors contributing to network development of the preterm brain.

EO-019 Gait performance and dual-task cost in school-aged children with Down syndrome

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【Objective】The aim of this cross-sectional study was to assess the gait performance, its correlation with physical functions, and dual-task cost for gait performance in school-aged children with Down syndrome（DS）in order to clarify the gait adaptation in daily life.【Methods】Gait performance with and without movie watching task using portable tablet were evaluated in 17 children with DS ranged from 6 to 12 years（median age, 8 years）and 51 age- and sex-matched controls. We compared patients' demographics, physical functions, gait speed, step length, and gait quality without task between two groups, and correlations between physical functions, intelligence quotient, and gait variables in DS group were assessed. Furthermore, we compared dual-task cost for gait variables between two groups.【Results】Children with DS had poor balance function and muscle strength. DS group showed a decreased gait quality than controls. In DS group, gait speed was correlated with balance function and step length was correlated with intelligence quotient. Dual-task costs for gait speed and step length in DS group were greater than that in controls, although there was no significant difference in dual-task cost for gait quality between two groups.【Conclusion】We demonstrated the gait performance and dual-task cost in school-aged children with DS. It is indicated that children with DS adopt the strategy of decreasing gait speed and step length to accomplish the additional task during gait safely.

EO-020 Effects of COVID-19-related refraining from going out on physical function in preadolescent children

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【Objective】In Japan, a state of emergency related to COVID-19 pandemic was declared in March 2020, and children's activities have been restricted since then. The purpose of this study was to examine the changes in physical functions and lifestyle habits among preadolescent children before and after the COVID-19 emergency.【Methods】Healthy children aged 10-12 years were enrolled from June 2018 to January 2020（pre-COVID-19 emergency group：102 children）and from January 2021 to August 2021（post-COVID-19 emergency group：22 children）. Questionnaires about lifestyle habits, body fat percentage, grip strength, single-leg standing time, two-step test, and the gait quality were compared between two groups.【Results】The post-COVID-19 emergency group had worse performance of the two-step test（$p = 0.015$）, higher body fat percentage（$p = 0.005$）, shorter physical activity（$p = 0.002$）and sleep time（$p = 0.032$）, longer screen time（$p = 0.028$）. The two-step test was positively correlated with physical activity（$p = 0.018$；$r = 0.212$）, and body fat percentage was positively correlated with screen time（$p = 0.030$；$r = 0.195$）.【Conclusion】The COVID-19 emergency have deprived preadolescent children of exercise opportunities, worsened their dynamic balance and increased their body fat percentage. Increasing physical activity time and decreasing sedentary behaviors during children's leisure time is necessary to prevent the adverse effects of refraining from going out on children's physical functions.

Platform Session

EO-021 The correlation between general movements and developmental quotient at 3 years of age

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【Background】General movements assessment（GMA）is useful for predicting cerebral palsy, but its predictive value for other developmental problems remains limited, especially in neonatal period. We examined the correlation between the detailed scoring of GMA and the Kyoto Scale of Psychological Development（KSPD）at 3 years corrected age in very low birth weight infants（VLBWI）.【Method】Prospective cohort study. General movements（GMs）were scored according to the semiquantitative scoring system：the GMs optimality score（GMOS）at 28-32 w, 33-36 w and 37-46 w of gestational age（GA）and the motor optimality score（MOS）at 9-22 w post term age. The developmental quotient（DQ）was assessed by KSPD at 3 years corrected ages.【Subjects】51 VLBWI cared for at Oita University from August 2012 to June 2018 who enrolled in the GMs clinical research and underwent KSPD. Their median birth GA and weight were 29w1d and 1,030 g, respectively.【Results】The MOS were strongly correlated with total DQ, postual-motor（P-M）, cognitive-adaptive（C-A）and language-social（L-S）domain DQ（$p < 0.01$）. The GMOS at 33-36wGA was correlated with total DQ and C-A domain DQ（$p < 0.05$）.【Conclusion】MOS is useful not only for predicting motor aspects but also for predicting cognitive and language development. GMOS at 33-36 weeks GA was correlated with cognitive development rather than motor development. To predict neurological development, 33 to 36 weeks GA was a suitable age for evaluating GMs in neonatal intensive care unit.

EO-022 Clinical characteristics and sleep disturbances in FOXG1 syndrome

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FOXG1 syndrome is a rare neurodevelopmental disorder characterized by early-onset hyperkinetic movement disorders, severe cognitive dysfunction and cerebral malformation. Sleep disturbances are common in these patients, however there was no study focusing on the sleep problems in FOXG1 syndrome to date. In this study, we explored the clinical manifestation as well as sleep disturbances in an international cohort of FOXG1 syndrome. Total 258 FOXG1 patients with mean age of 6 years（range 1-27 years）were enrolled. Those harboring genotypes of deletions, frameshift & nonsense variants over N-terminal and forkhead binding domain had more severe phenotypes. All patients with deletion and the majority of patients with frameshift & nonsense, FBD frameshift & nonsense variants were unable to sit or walk unassisted. The majority（70.93％）of the patients did not have verbal speech, with no significant difference among different genotypes. Total 51.16％ had sleep disturbances. Sleep disturbances occur across different ages, genders and genotypes in FOXG1 syndrome. Using multivariable binary regression analysis, we found that hyperkinetic movements and feeding difficulties significantly increased the possibility of sleep disturbance. In conclusion, sleep disturbances are common in FOXG1 syndrome and may in part related to clinical morbidities. Further study and management strategy are warranted.

EO-023 Objective Diagnosis of ADHD Children by Using Pixel Subtraction

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【Background】Various assessment tools to diagnose ADHD can be used, including the SNAP questionnaire. However, each of these scales provides a subjective perspective. Therefore, we employed an objective assessment method by pixel subtraction of patients' videos to assist diagnosis of ADHD.【Methods】20 ADHD patients and 20 controls were enrolled. The videos were recorded in the consulting room when participants visit a doctor in each group. Pixel subtraction techniques were used to analyze the movements from videos for providing a more measurable and objective approach in patients with ADHD and controls. The pixel subtraction is a technique in which pixels of one image were subtracted from another image to detect changes between two images, that is movement. We compared the average movement values between two groups. The movement value was defined as the result of calculation from the pixel subtraction technique used in video analysis. The movement value data set of 40 participants was used to classify ADHD and control groups using the Decision tree algorithm.【Results】The mean movement values of the ADHD and control groups were 718.01 + −362.91 and 187.05 + −83.92 respectively which are significantly different with p value less than 0.05. The trained model of the decision tree algorithm yields averages of 87.5％ accuracy with 89.4％ specificity, 85.7％ sensitivity.【Conclusions】In conclusion, the use of the pixel subtraction method is potentially an objective and reliable tool to diagnose ADHD.

EO-024 Lister hooded rats as a suitable animal model of attention-deficit hyperactivity disorder

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【Introduction】Attention-deficit hyperactivity disorder（ADHD）is a common developmental disorder. The main symptoms are hyperactivity, impulsivity, and inattention. We explored whether Lister hooded rats（LHRs）could serve as a suitable ADHD animal model.【Materials and methods】Male Wistar rats, spontaneously hypertensive rats（SHRs）, and LHRs were used for behavioral tests. We evaluated the effects of food restriction on behaviors of Wistar rats, and the behavioral effects of atomoxetine（ATX）and guanfacine（GAF）on LHRs. Immunofluorescence histochemistry, immunoblotting, measurements of monoamines, and quantitative real-time PCR（qPCR）were performed on the rat prefrontal cortex（PFC）.【Results】LHRs showed the most hyperactivity, impulsivity, inattention and did not show behaviors characteristic of autism and intellectual disability. ATX and GAF improved ADHD-like behavior of LHRs. Increased neuronal activity was observed in the medial PFC of LHRs. Eight genes associated with human ADHD cases had lower mRNA and TH protein expression levels in the PFC of LHRs, compared to Wistar rats and SHRs.【Discussion】SHRs showed impulsivity and inattention, but they were not hyperactive. No significant differences were observed in the DA and 5-HT contents in PFC tissues, although we did observe increased NA content in SHRs. These findings suggest that SHRs are not a suitable ADHD animal model.【Conclusion】LHRs may be served as a more suitable ADHD animal model than SHRs.

EO-025 演題取り下げ

EO-026 Therapeutic effects of bumetanide on neurological dysfunction in a mouse model of Angelman syndrome

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【Introduction】Angelman syndrome is a neurodevelopmental disorder caused by the loss of function of *UBE3A* gene. Clinical symptoms overlap with those of autism spectrum disorders, including speech impairment and repetitive behavior. Recently, bumetanide has been proposed as an effective compound for treating autism spectrum disorders by inhibiting the neuronal Na + −K + −Cl− cotransporter 1（NKCC1）, which facilitates Cl− influx.【Aim and Methods】To investigate the therapeutic potential of bumetanide in Angelman syndrome, we analyzed Cl− hemostasis and the effects of bumetanide on a mouse model of Angelman syndrome（AS mice）.【Results】We found increased NKCC1 expression at the protein level in the hippocampus of AS mice. The intracellular Cl− concentration（［Cl−］i）of CA1 pyramidal neurons was not significantly different on average, but it demonstrated more variance in AS mice. As its possible mechanism, we demonstrated that tonic $GABA_A$ receptor−mediated Cl− influx was significantly reduced in AS mice. Chronic administration of bumetanide restored cognitive dysfunction in AS mice. Seizure susceptibility was also reduced by bumetanide in both AS and WT mice.【Conclusion】［Cl−］i homeostasis is altered by multiple mechanisms, and aberrantly activated NKCC1 have a pathophysiological impact leading to cognitive dysfunction in AS mice. Bumetanide might be effective for improving cognitive function and epilepsy in patients with Angelman syndrome.

EO-027 Parent training effects on emotion recognition in mothers rearing ADHD children : an fMRI study

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【Objectives】To examine neurological changes in socioemotional processing skills through parent training（PT）in caregivers of children with attention−deficit/hyperactivity disorder（ADHD）.【Methods】Thirty mothers of children with ADHD were stratified into the PT and non−PT groups. Functional magnetic resonance imaging was performed during the "Reading the Mind in the Eyes" test, and parenting difficulties were evaluated using the Parenting Stress Index（PSI）and Parenting Scale（PS）twice : before and after PT.【Results】PSI and PS scores significantly decreased after PT（（PSI : child domain, $p = 0.003$, 95% confidence interval（CI）: −14.376, −3.470 ; parent domain, $p = 0.042$, 95% CI : −12.683, −0.240）;（PS : overreactivity, $p = 0.009$, 95% CI : −11.415, −1.816））. For the brain, activity in the left occipital fusiform gyrus increased during the task to estimate emotions from facial pictures, with decreased response time only after PT.【Conclusions】The study results suggest that PT promotes the mothers' understanding of problematic behaviour in children with ADHD, and that it could help build a more nurturing environment, reduce parenting stress and maladaptive parenting style, and improve mother−child relationship.

Platform Session

EO-028 Biallelic variants in PNPLA8 disrupt cortical gyrification through aberrant mitochondrial dynamics

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PNPLA8, encoding Ca-independent phospholipase A2gamma, plays an important role in mitochondrial membrane remodeling. Mitochondrial membrane-bound proteins can divide and fuse mitochondria, thereby maintaining its shape, distribution and function to regulate various biological processes including brain development. Here, we demonstrate that loss of PNPLA8 function disrupts neurogenesis and cortical gyrification through aberrant mitochondrial dynamics. We recently reported two patients with biallelic loss-of-function PNPLA8 variants with unknown mechanisms. Patients showed extreme microcephaly, early-onset epilepsy and severe developmental delay. The characteristic feature of brain MRI was simplified gyral pattern. Enlarged mitochondria and impaired mitochondrial respiration was observed in skin fibroblasts, suggestive of mitochondrial dynamics-related etiology. To investigate pathomechanisms during neurogenesis, we generated PNPLA8 knockout (KO) iPS cells (iPSCs). PNPLA8 KO iPSC-derived neural progenitor cells also showed mitochondrial hyperfusion. Using PNPLA8 KO brain organoids, we demonstrated that the amount of neural stem cells and differentiated neuron was decreased, consistent with the neurodevelopmental pattern of microcephaly and simplified gyrus. Thus, membrane quality control by PNPLA8 plays an essential role to regulate mitochondrial shape and function in neural stem cells, leading to canonical cortical gyrification in humans.

EO-029 Biallelic variants in LIG3 cause a novel mitochondrial neurogastrointestinal encephalomyopathy

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Seven patients, from three independent families, showed the common occurrence of gut dysmotility and neurological manifestations reminiscent of mitochondrial neurogastrointestinal encephalomyopathies. Whole exome sequencing revealed compound heterozygous variants in a new disease gene, called LIG3 in these patients. The LIG3 gene encodes the only mitochondrial DNA (mtDNA) ligase and therefore plays a pivotal role in mtDNA repair and replication. In vitro assays in patient-derived cells revealed a decrease of LIG3 protein levels and ligase activity. We demonstrated that LIG3 gene defects affected mtDNA maintenance, leading to mtDNA depletion without accumulation of multiple deletions as often observed in other mitochondrial disorders. The most prominent and consistent clinical signs were severe gut dysmotility and neurologic abnormalities including leukoencephalopathy, epilepsy, migraine, stroke-like episodes, and neurogenic bladder. A decrease in myenteric neurons, increased fibrosis and elastin were the most important changes in the gut. We also observed muscle pathology with decreased COX staining. Disruption of lig3 in zebrafish reproduced consistently brain alterations and impaired gut transit in vivo. In conclusion, we identified variants in the LIG3 gene that result in a mitochondrial phenotype characterized by predominant gut dysmotility, leukoencephalopathy and neuromuscular abnormalities.

EO-030 Leigh syndrome-like MRI lesions in a case with biallelic HPDL variants treated with ketogenic diet

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【Background】Biallelic 4-hydroxyphenylpyruvate dioxygenase-like protein (HPDL) variants were recently reported as a cause of progressive and incurable neurodegenerative diseases ranging from neonatal-onset leukoencephalopathy with severe developmental delay to spastic paraplegia. Although the physiological function of HPDL remains unknown, its subcellular localization in the mitochondria has been reported. 【Case report】A five-weeks-old girl who was born to non-consanguineous parents developed intractable cyanotic apnea. MRI revealed a diffuse abnormal intensity in the white matter predominantly in the frontal lobes. At 6 months of age, she again developed apnea. MRI revealed new signal hyperintensities in the bilateral putamen and brainstem resembling Leigh syndrome. The serum lactate level was high. She showed spastic quadriplegia, poor head control, strabismus, loss of ocular pursuit, and social smile. She started ketogenic dietary treatment at the age of 10 months. After 3 months, she recovered the abilities to support the head, to socially smile, and to follow objects with her eyes. The serum lactate level normalized. On MRI, the putamen and brainstem lesions were disappeared. Whole exome sequencing identified compound heterozygous mutations in the HPDL gene. 【Conclusion】We report a case of HPDL-related neurological disease that was clinically and neuroimaging compatible with Leigh syndrome, previously unreported, and was successfully treated with a ketogenic diet.

EO-031 Apomorphine as a new therapeutic drug for Leigh syndrome

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【Introduction】We discovered that apomorphine（Apo）has cell-protective effects on reactive-oxygen-species-induced cell death and improves mitochondrial respiratory activity in fibroblasts from patients with Leigh syndrome（LS）and MELAS（Miyauchi et al., 2018）. However, the DA effect of Apo results in emesis. We aim to identify an Apo-related chemical that shows similar potency with a lower DA effect.【Methods】The DA activity of 40 chemicals, including 26 structurally similar chemicals and 14 synthesized derivatives, was evaluated. The DA2 receptor affinity of the 40 was analyzed using florescence resonance energy transfer（FRET）. The 50％ inhibitory concentration（EC_{50}）of L-buthionine sulfoximine（BSO）-induced cell death of LS fibroblasts was also examined. LS fibroblasts were treated with the tracked chemicals and the mitochondrial function was measured using a flux analyzer. We analyzed oxygen consumption rates（OCR）of LS fibroblasts treated with the candidate chemicals.【Results】We selected 37 chemicals that showed low DA affinity of larger than 200 nM on FRET. Among them, 9 showed an anti-BSO-induced cell death effect with an EC_{50} of less than 200 nM. One chemical increased the OCR of LS fibroblasts at concentration of 10 and 100 nM.【Conclusion】We found one Apo-related chemical showing with similar efficacy to Apo, which would be associated with less vomiting.

EO-032 Atypical presentation of Primary HLH : Unlocking diagnosis through the brain, eye and genetics

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Central Nervous System Hemophagocytic Lymphohistiocytosis（HLH）is a rare presentation of primary and secondary HLH. We report a case of an infant who initially presented as post infectious bone marrow suppression with severe sepsis. Her cytopenia and inflammatory markers recovered with antibiotics. However, she developed multiple cranial neuropathies, left hemiparesis, choreo-athetosis, focal seizures and bilateral eye frosted angiitis with persistent hepatosplenomegaly. Her MRI brain showed multifocal asymmetric ill-defined supra and infratentorial, deep grey and white matter hyperintensities with associated enhancement with a normal MRA. She was extensively investigated for inborn errors of immunity, malignancy and systemic vasculitis. She was empirically treated with Methylprednisolone and Immunoglobulins. However, she deteriorated rapidly both clinically and radiologically, hence, perforin levels were done which showed marked depressed activity. She was immediately treated for familial HLH and disease progress was halted. Genetic results subsequently confirmed the diagnosis with homozygous PRF1 gene mutation. She is making gradual neurological improvements but with significant visual and motor delay. She underwent bone marrow transplant 11 months from initial presentation. Early molecular diagnosis in atypical cases can lead to earlier aggressive treatment which is essential to limit long term neurological sequelae.

EO-033 Acampomelic campomelic dysplasia due to a translocation involving chromosome 17q upstream of SOX9

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【Objective】We report the clinical features of a 34-year-old Japanese female patient with acampomelic campomelic dysplasia（ACMPD）and disorders of sex developments（DSD）. Cytogenetic and molecular genetic analyses are intended to reveal the genetic causes of this patient.【Case report】The patient underwent cleft palate surgery and gonadectomy in infancy, and has been treated for epilepsy since her teens and for diabetes mellitus since her twenties. The patient has consulted with our hospital since she was 32 years old. The patient presented with profound intellectual disability, marked deformation of the cervical spine and severe thoracic kyphoscoliosis. The long bones of the upper limbs and the femur were not bowed. Her menarche started at 33 years and 4 months after hormone therapy.【Methods】Chromosome analyses, Array CGH, WGS, and Sanger sequencing were performed.【Results】The female patient with a reciprocal translocation of t（11;17）（p15.4;q24.3）had Y chromosome and SRY gene. She was diagnosed with ACMPD and DSD. We determined the precise breakpoint positions of the reciprocal translocation, one of which was located 203 kb upstream of the SOX9 gene.【Conclusion】Considering the phenotypic variations previously reported among the campomelic dysplasia or ACMPD patients with a chromosomal translocation in the vicinity of SOX9, the identified translocation was concluded to be responsible for all major phenotypes observed in the patient.

Platform Session

EO-034 Novel mutations in two cases of complicated hereditary spastic paraplegia(HSP)in children

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HSP is a heterogenous group of neurological disorders affecting primarily the lower limbs which can be classified as either：1）pure HSP which has prominent lower limb spasticity without other significant findings, or 2）complicated HSP which is associated with other neurological or non-neurological features. The advancement of next-generation sequencing has led to the discovery of 80 different genetic types of HSP with distinctive clinical and radiological features. We herein report two novel mutations found in two unrelated children with complicated HSP. Case 1 was a 3-year-old Chinese boy who had non-progressive bilateral lower limb weakness, hypotonia and hyperreflexia since the age of 18 months without cognitive decline. His MRI brain and neurophysiological studies were normal. Whole exome sequencing（WES）revealed a novel mutation in the Kinesin Family Member 1 A（KIF1A）gene which is associated with HSP type 30. Case 2 was a 13-year-old Chinese boy who had upper motor neuron and cerebellar signs in his left upper and lower limbs since the age of 18 months. His MRI brain showed bilateral non-specific non-enhancing periaqueductal hyperintensities. Neurophysiological studies' findings were suggestive of sensory-motor neuropathy. A novel mutation was identified in the GBA2 gene by WES which is associated with HSP type 46. These findings add further insight into the clinical and genetic spectrum of HSP types 30 and 46.

EO-035 A boy of Cornelia de Lange syndrome 2 originally suspected to have MOPD

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Cornelia de Lange syndrome（CDLS）is a clinically heterogeneous developmental disorder characterized by malformations affecting multiple systems. Here we report a boy who was originally suspected to have microcephalic osteodysplastic primordial dwarfism（MOPD）, finally diagnosed to be CDLS2 with SMC1A hemizygous variant. A male baby came to our hospital at 11 days of age due to feeding difficulty and poor weight gain. He had multiple anomalies including cutis marmorata, microcephaly, peculiar facial features, simian crease, lumbo-sacral dimple, patent foramen ovale, stomach volvulus, astigmatism and right hypacusia. MOPD was suspected, but we found no abnormality in RNU4ATAC gene. At the age of 5 years, he showed profound developmental delay and was suffering from left-sided atonic seizure. This patient attended IRUD（Initiative on Rare and Undiagnosed Diseases）research. Whole-exome sequencing showed hemizygous c.C3130T：p.R1044C mutation in SMC1A on X chromosome, previously reported to become a cause of CDLS2. Both of his mother and maternal grandmother were heterozygotes. The transmission pattern of CDLS2 was consistent with X-linked recessive inheritance, and his carrier relatives had mild features. We carefully follow all the family members especially his mother. The usefulness of IRUD for undiagnosed and hereditary suspected patients is very high. Accumulation of such molecularly defined patients will help clarify the underlying mechanisms leading to CDLS.

EO-036 Early infantile stroke as a manifestation of Deficiency of Adenosine Deaminase 2（DADA2）

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【Introduction】DADA2 is the first molecularly described monogenic vasculitis. We present an infant with acute stroke at 10 weeks of age, to our knowledge, the youngest reported DADA2 to present this way.【Case Report】A pre-morbidly well, female infant of non-consanguineous union presented with acute bilateral up-gaze palsy at 10 weeks of age with no other neurological, cutaneous, or systemic signs. CSF and blood investigations for infective（including TB）, autoimmune, immunodeficiency and thrombophilic aetiologies were negative. There was mildly elevated CSF protein and high C-reactive protein（CRP）. On follow-up（4 months）, she showed persistently high CRP levels, had occasional fever, and developed new eye signs - the initially normal fundoscopy progressed into bilateral retinal vessel vasculitis（occlusive vasculitis of the right eye）, resulting in poor vision. Echocardiography showed dilated left main coronary artery. Repeat lumbar puncture showed increased CSF cytokines. Whole exome sequencing finally revealed compound heterozygous mutation for DADA2 gene（deletion of exon 7 and point mutation at exon 2）. She was pulsed high dose steroids and cyclophosphamide followed by infliximab. She responded well（left eye vision improved with resolution of coronary dilatation）with no new evidence of vasculitis and normalised inflammatory markers.【Conclusion】DADA2 needs to be considered in young infants presenting with unexplained vasculitis and raised systemic inflammatory markers.

EO-037 Long-term follow-up of primary neurotransmitter disorders- single centre experience (2004-2021)

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【Purpose】Pediatric neurotransmitter disorders include genetic defects of neurotransmitter metabolism. These disorders mimic common neurological conditions. The objective of this case series was to evaluate the clinical experience, diagnostic tests employed, natural history, progression, and outcomes.【Methods】Five pediatric patients with primary neurotransmitter defects were identified in the genetics database（London, ON, CA）between 2004-2021. Data on investigations, diagnosis, management and long-term outcomes was extracted.【Results】Three of five patients［6 PTPS deficiency（2）, Pyridoxine dependent epilepsy（1）］presented to the clinic in the neonatal period. Two children have normal development trajectories, while one is developmentally delayed. Two of five patients were born outside Canada,［Succinic Semialdehyde Dehydrogenase（SSADH）deficiency（1）and Amino Acid Decarboxylase（AADC）deficiency（1）］. Both were diagnosed late, one was subsequently diagnosed with SSADH deficiency at age 13. The other presented at age 7 with gross developmental and motor delays, AADC deficiency was confirmed via genetic testing.【Conclusions】Early detection and diagnosis of neurotransmitter deficiencies can carry a significant impact on long term outcomes such as motor function and cognitive ability in selected situations. Molecular genetics and biochemical investigations（blood, urine, CSF）are critical for early diagnosis and potential treatment.

EO-038 Severe developmental and epileptic encephalopathy due to SCN8A A1491V variant with citrin deficiency

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【Introduction】SCN8A variants show a wide phenotypic spectrum. A correlation between electrophysiological and clinical phenotypes has been revealed. We evaluated the effect of variants from the 3D structure model by AlphaFold2 published in 2021.【Case】A 1-year-old boy；from days 2, he was suffered from tonic-clonic seizures. Phenytoin（PHT）was effective at 1 month；however, it was discontinued due to cholestasis. We diagnosed him with citrine deficiency and SCN8A Developmental and Epileptic Encephalopathies（DEE）based on a homozygous SLC25A13 variant（p.M285P＊2）and a de novo heterozygous SCN8A variant（p.A1491V）respectively. Seizures were intractable despite various antiepileptic drugs. From 8 months of age, cardiac arrests during seizures occurred and improved by restarted PHT. Although he has been treated with multi-drug therapy, the seizures remain intractable.【Discussion】According to AlphaFold2, A1491 was situated in the inactivation gate, especially adjacent to the IFM residues, which were crucial for channel activity. In vitro electrophysiological studies of A1491V had also been reported showing a robust impairment of inactivation. Moreover, 2 of 4 A1491V variants reported previously died of sudden unexpected death（SUDEP）. PHT was reportedly effective for SCN8A variants with only minimal effects for the A1491V variant. Our case also showed multi-drug resistance for seizures and was considered high-risk for SUDEP by cardiac arrests during seizures.

EO-039 A homozygous novel variant in SCN1A gene associated with genetic epilepsy with febrile seizures plus

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Pathogenic variants in SCN1A result in a broad spectrum of disorders, from simple febrile seizures and genetic epilepsy with febrile seizures plus（GEFS＋）to Dravet syndrome. Almost all SCN1A variants reported were heterozygous. So recently, homozygous variants have been associated with GEFS＋ in four families from two studies. A 17 month-old boy with recurrent prolonged febrile seizures having a novel homozygous variant in SCN1A is presented. The patient had his first febrile seizure at 6 month-old after a vaccine-shot. He had eight prolonged febrile seizures until this age with intesive care unit hospitalization twice because of status epilepticus. At 17 months, he walks independently, takes one step simple commands and use a few single words with normal neurological examination. The parents are healthy and declare they have no consanguinity. He had two siblings, a boy with autism and epilepsy, and a healthy sister. His initial diagnosis was Dravet syndrome. Epileptic encephalopathy panel showed a novel homozygous c.5455delG p.Ala1819GlnfsTer39 variant in SCN1A. Parents and siblings are being tested for the variant. Our 17 month-old patient seems to show normal neurodevelopment in the absence of other seizure types at this early age. Other reported phenotypes associated with homozygous variants in SCN1A are milder than Dravet syndrome without severe cognitive impairment. The variant in heterozygous state presumed to be in healthy parents is not enough to cause epilepsy.

EO-040 Extent of leptomeningeal capillary malformation causes severity of epilepsy in Sturge-Weber syndrome

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【Backgroud】Sturge-Weber syndrome（SWS）patients have risks of intractable epilepsy and cognitive decline. We hypothesized that the extent of the leptomeningeal capillary malformation（LCM）correlate with the severity of neurological impairment due to SWS. We validate the hypothesis in a cross-sectional study of seizure severity and electroencephalography（EEG）findings and a retrospective cohort study for surgical indications related to extent of the LCM.【Methods】We enrolled 112 patients and classified them according to LCM distribution：bilateral（B）, hemispheric（H）, multilobar（M）, and single lobe. Age at seizure onset, semiology and frequency, and EEG findings were compared. Surgical indications were evaluated for each group by Fisher exact test, and predictors for surgery were evaluated by univariate and multivariate analyses. Therapeutic efficacy was evaluated by the SWS-Neurological Score（SWS-NS）.【Results】The B and H groups had early seizure onset, frequent seizures, focal-to-bilateral tonic-clonic seizures, and status epilepticus. There is no significant change in EEG findings among the groups. Surgical indications were present in 88.9% of the B, 87.1% of the H, and 46.8% of the M groups. Seizure subscores improved significantly postoperatively in the H and M groups.【Conclusion】Our study demonstrated a strong association between extensive LCM and epilepsy severity. Surgical intervention improved seizure outcome in patients with SWS with large LCMs.

EO-041 Developmental rate is highly accelerated within the first year after epilepsy surgery in children

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Symptoms of epilepsy are seizures and brain dysfunction. In the developmental stage, progressive brain dysfunction due to the epileptic encephalopathic effect is larger than the adult stage. Primary purpose of surgical treatments is controlling seizures, but is it effective for this encephalopathic effect on the brain functions? We have already reported that the postoperative developmental rate（DR, the value obtained by dividing the difference in developmental age before and after surgery by the follow-up period）in addition to the developmental quotient. We analyzed 64 children who underwent resective surgery before the age of 6, and total, and DR and its subscales were calculated in each patient. Total DR of the first year after surgery（1st year）was significantly higher than that of the second-to-final years（2nd-final years）. Verbal DR of the 1st year was also significantly higher than that of 2nd-final years. However, there was no difference in motor DR between the two periods. Results of this study suggest that recovery of the brain function by epilepsy surgery appears as early as less than 1 year after surgery, especially language functions in pediatric patients with drug-resistant epilepsy. On the other hand, the developmental rate decreased after the second year. It was also considered that the pathological condition probably due to the etiology was large in addition to the encephalopathic effect of epilepsy itself（developmental and epileptic encephalopathy）.

EO-042 Utility of Oxcarbazepine for Neonatal Seizures

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【Purpose】Effectiveness of sodium channel blockers like ox carbamazepine in non-structural nonmetabolic neonatal seizures【Methods】3 subsets of neonatal seizures were identified. The first subset was for perinatal insults Subset 2 was secondary to inborn errors of metabolism. Subset 3 was small- 7 patientsThere was no evident perinatal cause, normal metabolic profile, and normal neuroimaging. Seizure onset was in the second week of life, there were usually focal but frequent and EEG was epileptiform in all. They were loaded with levetiracetam and oxcarbazepine was started as oral dose and they were seizure-free, They were followed up for the next 2 years and they exhibited normal neurodevelopment except one of STXBP1 mutation. They were analyzed by exome sequencing.【Results】All neonatal seizures with suspected channelopathies were SCN2A. KCNQ and STXBP1 mutation. KCNQ1 and scn2a mutations were relatively benign. Later on we realized that sodium channel mutation in the neonatal period shows GoF. KCNQ 1 mutation showed LoF.. So we realized that for any neonatal seizures which have nonstructural and nonmetabolic ones, sodium channel blockers like phenytoin, oxcarbazepine, or lacosamide are to be used as first-line treatment.【Conclusion】Sodium channel blocker like ox carbamazepine is to be used as the first line of treatment for all neonatal seizures which are non-structural, nonmetabolic, and suspected to be channelopathies like KCNQ2/KCNQ3 and SCN2A, SCN1A, and SCN8A mutations.

EO-043 The predicting factors in infantile-onset epilepsies : a single center study

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Epilepsy has a high incidence in the first year of life and its course is highly variable. There are limited study on infantile onset epilepsy, excluding infantile spasms, in terms of prognostic factors in outcome measures. Therefore, we aimed to describe the seizure control, developmental outcome and prognostic factor in a single center study.【Methods】Data of patients with seizure onset before the age of 12 months and followed up more than 2 years, were retrieved from electronic patient records of Hospital Raja Perempuan Zainab II. The patients' records were retrospectively reviewed and clinical outcomes were assessed based on the last follow-up.【Results】Of the 89 patients, 61（68.5％）have seizure free period or entered remission. Twenty-five（28.1％）were found to have developmental delay at the last follow-up and seventeen（19.1％）have abnormal neuro-radiological findings. Onset of seizures before 4 months old, present of delay development at presentation and abnormal radiological findings were significantly associated with intractable epilepsies（p less than 0.05）.【Conclusions】This study demonstrated that most patient with infantile epilepsy can achieve seizure remission. There are factors that contributed to intractable epilepsies and associated with developmental delay. Intractable epilepsies might require extensive resources and precision intervention for better outcome.

EO-044 Adrenal function during long-term ACTH therapy for developmental and epileptic encephalopathy

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【Introduction】Some patients with developmental and epileptic encephalopathy（DEE）respond to adrenocorticotropic hormone（ACTH）therapy but relapse soon after. While long-term ACTH therapy（LT-ACTH）has been attempted for these patients, no previous studies have carefully assessed adrenal function during LT-ACTH.【Methods】We evaluated the effectiveness of LT-ACTH, as well as adverse effects（AE）, including their adrenal function in three DEE patients. Patients underwent a corticotropin releasing hormone（CRH）stimulation test during LT-ACTH, and those with peak serum cortisol below our cut-off level were considered to be at high risk of adrenal insufficiency（AI）.【Results】Two of three responded, and their life-threating seizures with post-generalized electroencephalogram（EEG）suppression decreased. Although no individuals had serious AE, CRH stimulation test revealed relatively weak responses, without reaching normal cortisol peak level. Hydrocortisone replacement during stress was prepared in a case with lower cortisol peak than our cut-off level.【Discussion】LT-ACTH could be a promising treatment option for cases of DEE that relapse soon after effective ACTH treatment. The longer duration and larger cumulative dosage in LT-ACTH than conventional ACTH could increase the relative risk of AI. Careful evaluation with pediatric endocrinologists, including hormonal stimulation tests, might be useful for continuing this treatment safely.

EO-045 Effects of perampanel on mental health in pediatric patients with focal-onset seizures in study 311

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【OBJECTIVE】We assessed mental health in a post hoc analysis of Japanese pediatric patients for long-term（1 year）treatment with perampanel（PER）.【METHODS】Study 311 was an open-label study of adjunctive PER in pediatric patients（4 to＜12 years）with focal-onset seizures（FOS）or generalized tonic-clonic seizures. In Japan, patients with FOS enrolled and received doses of 2-12 mg/day. Patients who completed the Core Study（4-week［w］Pretreatment；23-w Treatment）could enter Extension A（29-w Maintenance；4-w Follow-up）. The incidence of psychiatric treatment-emergent adverse events（TEAEs）and suicidal ideation/behavior were reported. Suicidality was assessed via the Columbia-Suicide Severity Rating Scale（C-SSRS）.【RESULTS】Overall, 53/65 Core Study patients entered Ext A. Twenty（30.8％）patients reported psychiatric TEAEs during the Core Study/Ext A, and psychiatric TEAE onset mostly occurred in the first 24 weeks of treatment. Most common psychiatric TEAEs：irritability（n＝12）, agitation（n＝4）, and aggression（n＝2）. Two patients discontinued PER from treatment-related psychiatric TEAEs；no serious psychiatric TEAEs were reported. No patients scored positive on the C-SSRS.【CONCLUSIONS】Long-term use of PER in Japanese pediatric patients with epilepsy did not increase the frequency of psychiatric TEAEs, and no on-treatment suicidality was reported. Like other anti-seizure medications, patients receiving PER should be monitored for psychiatric TEAEs.

EO-046 Late-stage pontosubicular neuron necrosis in a term infant operated for refractory epilepsy

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【Introduction】Pontosubicular neuron necrosis is classically observed in premature infants but may be associated with other perinatal brain injuries. We report the clinicopathological findings of suspected subicular neuron necrosis in a term infant following temporo-parieto-occipital（TPO）disconnection for refractory epilepsy.【Case report】A term infant of a diabetic mother, ventilated at birth for respiratory distress, developed massive left parieto-occipital and intraventricular haemorrhage on day 3. He required external ventricular drainage and later ventriculoperitoneal shunt for post-haemorrhagic hydrocephalus. Drop attacks started at age 13 months and were refractory to anti-epileptic medication. MRI showed left parieto-occipital encephalomalacia with haemosiderin rim. Left TPO disconnection using modified Schramm technique was performed at age 23 months. He became seizure-free despite an incomplete TPO disconnection. Histopathological examination of the resected anterior temporal lobe revealed profound subicular neuron loss and fibrillary astrogliosis, without a typical feature of hippocampal sclerosis. A retrospective review of imaging revealed a relatively small pontine diameter for age.【Discussion】The histopathology and imaging feature of this case is suggestive of late-stage pontosubicular neuron necrosis. Seizure cessation despite incomplete TPO disconnection suggests a possible role of the subiculum pathology in the epileptogenesis of this case.

EO-047 Genetic testing and epilepsy Management：An int'l study of clinical practice and patient outcomes

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【Objective】Epilepsy is a common condition for 50 million worldwide. Seizure management has implications for QOL and healthcare costs. Genetic testing has demonstrated a molecular etiology in up to 40 percent of cases and ～half of positive findings are associated with precision medicine implications. Studies on how genetic information is used to guide patient management and its impact on patient outcomes is limited. We investigated these changes after a genetic finding.【Methods】Between May-Nov 2020, a survey was sent to 1,567 clinicians representing 3,572 patients with diagnostic, likely pathogenic or pathogenic variants in an epilepsy gene. Genetic diagnosis, changes in clinical management, and impact on patient outcomes were analyzed.【Results】The final cohort included 429 patients. In half, the genetic finding led to changes in clinical management and often within 3 months after the molecular diagnosis. The most common change involved adding, starting, stopping an anti seizure medication. Positive outcomes were reported in 129 of 172 of patients, including reduced or no seizures, other improvements such as behavior, development, academics, movement disorders, and decreased medication side effects.【Conclusion】Molecular diagnostic findings can inform changes in clinical management of epilepsy. These may result in positive outcomes including improved seizure control. Our findings support the growing evidence that genetic testing for epilepsy can improve health outcomes and costs.

EO-048 Association Between Kawasaki Disease and Childhood Epilepsy：A Nationwide Cohort Study in Taiwan

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【Background】Kawasaki disease is a common vasculitis of childhood in East Asia；Non-cardiac complications have been reported but less studied. This study investigated potential epilepsy following Kawasaki disease（KD）in Taiwanese children.【Objectives】Through NHIRD, we retrospectively analyzed the data of children aged less than 18 years with clinically diagnosed Kawasaki disease from January 1, 2000 to December 31, 2012 in Taiwan. These patients were followed up to estimate the incidence of epilepsy in the Kawasaki cohort in comparison with that in the non-Kawasaki cohort in Taiwan.【Results】A total of 8,463 and 33,872 patients in the KD and non-KD cohorts were included in the study, respectively. Of the total eligible study subjects, most patients with newly diagnosed Kawasaki disease were aged less than 5 years［88.1％］. Patients with KD showed a higher incidence rate［47.98 vs. 27.45 every 100,000 person years］and significantly higher risk［adjusted hazard ratio＝1.66, 95％ confidence interval＝1.13-2.44］of epilepsy than those without the disease. Additionally, female sex［adjusted hazard ratio＝2.30, 95％ confidence interval＝1.31-4.04］and age less than 5 years［adjusted hazard ratio＝1.82, 95％ confidence interval＝1.22-2.72］showed a significantly higher risk of epilepsy in the KD cohort.【Conclusion】Results revealed a higher incidence rate and significant risk of epilepsy in Taiwanese children with KD than in those without the disease.

EO-049 A whole-brain quantitative susceptibility mapping analysis for children with febrile seizures

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【Objective】Febrile seizures（FS）are one of the most common neurologic disorders of infants and young children. The pathophysiology of FS has been suggested a link with iron deficiency anemia, that is clinically proven as lower serum ferritin levels, but remains to be elucidated. This study investigated the whole-brain pattern of iron distribution in patients with FS.【Methods】We enrolled 23 patients with FS and 23 age-matched healthy controls（HC）in this single-center observational cohort study. All participants underwent clinical assessments and brain MRI, including 3D-T1WI（MPRAGE：volumetric measure）and quantitative susceptibility mapping（QSM：iron deposition measure）. We compared clinical and imaging data between the groups and analyzed the correlations between the brain iron level and clinical data. This study was approved by the institutional review board at Toyokawa City Hospital.【Results】Among 23 patients with FS（median, 21 months；range 7 to 106 months）, 7 were simple-type and 16 complex-type FS. There were no gray matter volumetric differences between the groups. In contrast, the voxel-based QSM analysis showed that the patients with FS had the unique brain iron distribution compared with HC.【Conclusions】The findings of this study implicate the potential of QSM as an auxiliary biomarker for patients with FS.

EO-050 Developmental changes in brain activity of heterozygous Scn1a knockout rats

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【Objective】To characterize age-dependent changes in regional brain activity of *Scn1a* knockout rats.【Methods】We established an *Scn1a* knockout rat model and examined brain activity at each developmental stage from postnatal days 15 to 38 using a manganese-enhanced magnetic resonance imaging technique（MEMRI）.【Results】*Scn1a* knockout rats showed reduced expression of $Na_V1.1$ protein in the brain and heat-induced seizures as previously reported in a mouse model of Dravet syndrome（DS）. Neural activity was significantly higher in widespread brain regions of *Scn1a* knockout rats than in those of wild-type rats from postnatal days 19 to 22, but the difference did not persist thereafter. Bumetanide, a Na^+-K^+-$2Cl^-$ cotransporter 1 inhibitor, mitigated the hyperactivity to the wild-type level, although no change occurred in the fourth postnatal week. Bumetanide also increased the heat-induced seizure thresholds of the *Scn1a* knockout rats at postnatal day 21.【Conclusion】In *Scn1a* knockout rats, neural activity in widespread brain regions increased during the third postnatal week, corresponding to approximately 6 months of age in humans, when seizures most commonly develop in DS. The effects of bumetanide suggest a possible contribution of immature $GABA_A$ receptor signaling on the transient hyperactivity, seizure susceptibility, and DS development. We believe that MEMRI is a potential technique to visualize changes in developmental and epileptic encephalopathies.

EO-051 Regional Difference in Myelination in Monocarboxylate Transporter 8 Deficiency

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【Background】Monocarboxylate transporter 8（MCT8）is a thyroid hormone transmembrane transporter protein. MCT8 deficiency induces severe X linked psychomotor retardation. Delayed myelination in the central white matter（WM）have been reported in these patients；however, the regional pattern of myelination has not been fully elucidated.【Methods】We identified 36 patients with MCT8 deficiency from 25 families reported from Japan, including our four cases. The MRI images were obtained at age 2 years or younger in 13 patients, between 2 and 4 years in six patients, between 4 and 6 years in three patients, and at 6 years or older in eight patients. Signal intensity in the WM at T1WI and T2WI were classified into four grades. The myelinated appearance was defined as WM showing high intensity on T1WI and low intensity on T2WI.【Results】The median age of patients at the time of reporting was 6.5 years. Cerebellar WM, posterior limb of internal capsule, and optic radiation showed MRI signal of myelination by the age of 2 years, followed by centrum semiovale and corpus callosum by the age of 4 years. Most regions except for deep anterior WM showed MRI signal of myelination at the age of 6 years. Four of the eight patients older than 6 years（50％）did not show myelination on T2WI.【Conclusion】The sequential pattern of myelination in patients with MCT8 deficiency was largely similar to that in normal children；however, delayed myelination of the deep anterior WM was a remarkable finding.

EO-052 Iron deposition in the brain of Rett syndrome patients

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The natural course of the Rett syndrome can be briefly delineated into four stages by clinical symptoms and signs. The neuroimage of Rett syndrome is non-specific except for small brain volume and seems not changing as clinical deterioration. Most Rett syndrome patients exhibit deteriorated extrapyramidal movement disorders with age since childhood. The extrapyramidal symptoms are also prominent features of some neurodegenerative disorders. Some demonstrate significantly increased iron accumulation in basal ganglia compared to normal aging. We conducted a prospective study to see if iron accumulation in Rett syndrome patients can go with the clinical deterioration. 【RESULTS】 A total of twenty-five participants were included in this study. Fourteen patients with MeCP2 mutation and 11 healthy controls. The results showed a significant increase of QSM level in substantia nigra in the MeCP2-mutations Rett syndrome patients older than the age of 20. Besides, the increase of QSM in substantia nigra is highly correlated to age. But lower QSM level is noted in the caudate nucleus of Rett syndrome patients. The clinical severity seems correlated to the QSM level changes；however, the correlation is largely from the confounding effect of age. 【CONCLUSION】 There are uneven iron deposits in Rett syndrome patients, especially the substantia nigra and caudate nucleus. The clinical dystonia seems correlated to the substantia nigra QSM values but age may be the main contributor in this study.

EO-053 Molecular imaging（PET and SPECT）for children with HIE and cerebral palsy —a review—

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Glucose metabolism has been focus on to clarify pathology of cerebral ischemic disease such as neonatal hypoxic-ischemic-encephalopathy（HIE）, cerebral palsy（CP）, cerebral infarction. 【Objective】 To identify molecular imaging（PET and SPECT）as a biomarker of HIE and CP and propose future perspectives. 【Methods】 PubMed searchers were conducted for PET or SPECT studies examining HIE and CP（HIE, Encephalopathy, and Cerebral palsy）in humans. We identified 18 PET and 17 SPECT studies that have been performed in cases under age of 19 over the past three decades.（1991-2020）【Results】 Six articles on PET consist of one by human umbilical cord derived mesenchymal stromal cells, one mobilized peripheral blood mononuclear cells, three autologous bone marrow mononuclear cells, one allogeneic umbilical cord blood. Four of six paper reported that PET-CT scan showed much increase of glucose metabolism and one of six no significant change of glucose metabolism after cell therapy. One article on SPECT reported that two from five cases showed improvement of cerebral perfusion in the thalamus by SPECT after treatment. 【Discussion】 This improvement might be caused by improvement of GAP junction-mediated cell-cell interaction. 【Conclusion】 PET could be useful tool to estimate effectiveness of stem cell therapy.

EO-054 Iron Metabolism in SENDA/BPAN, an Autophagy Disease Due to WDR45 Variants

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【Introduction】 Autophagy is a major intracellular degradation process in which cytoplasmic materials are engulfed by autophagosome and subsequently, fuse with lysosomes for degradation. Static encephalopathy of childhood with neurodegeneration in adulthood（SENDA）/beta-propeller protein associated neurodegeneration（BPAN）is a subtype of neurodegeneration with brain iron accumulation and characterized by intellectual disability in childhood. MRI shows iron deposition in the globus pallidus and substantia nigra. The causative gene *WDR45* is essential for autophagy. How *WDR45* influences iron metabolism is unclear and the association of autophagy with iron metabolism is still unknown. 【Methods】 We examined autophagic flux and intracellular molecules involved in iron metabolism using fibroblasts derived from four patients and healthy participants. 【Results】 Patients' cells showed low levels of WIPI4, a protein coded by *WDR45*, and decreased autophagic flux. Ferritin and DMT1 were high, while FPN was low in patients' cells. Notably, autophagy-related factor-X was deficient in patients' cells. These changes were restored by *WDR45* gene transfer with adeno-associated virus vector. 【Discussion】 This study revealed for the first time that reduced factor-X expression impairs ferritinophagy and results in the accumulation of ferric iron stored in ferritin. These results indicate that impaired autophagic degradation of ferritin is a potential pathogenic mechanism of SENDA/BPAN.

EO-055 Neuronal cell pathology from induced pluripotent stem cells of Fabry disease and Niemann Pick C

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【Background】Fabry disease and Niemann Pick C（NPC）are lysosomal storage diseases, caused by deficiencies of alfa-galactosidase and NPC protein, respectively. Fabry disease clinically shows neuropsychiatric features such as depression and psychiatric problems, whereas Niemann Pick C patients exhibits gait disturbances, intellectual problems and seizure. To investigate neuropsychiatric problems in these disorders, we generated the neurons derived from Fabry and NPC induced pluripotent stem cells and studied the pathological and molecular mechanisms of neuronal involvement in these disorders.【Methods】Induced pluripotent stem cells from Fabry disease were generated from RNA reprograming method and Nieman Pick C were from Sendai virus. Neuro-progenitor and neural cell inductions were carried out by neural induction kit and neural stem cells were generated from neuronal differentiation medium.【Results and Discussions】Fabry disease neuronal cells derived from induced pluripotent stem cells demonstrated no distinct accumulation of glycolipids by electron microscopy and lipid staining. These data indicate that depression and psychiatric problems in Fabry disease are not caused by neuronal accumulation, but by cerebrovascular involvement. On the other hand, NPC neuronal cells showed abnormal massive accumulation of lipids in mature neurons. These data indicate the impairment of neuronal network formation associated with neurodegeneration in NPC neurons.

EO-056 Long-term efficacy of gene therapy for AADC deficiency using AAV2-AADC vector

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Aromatic L-amino acid decarboxylase（AADC）deficiency is an autosomal recessive neurotransmitter disorder caused by defects in DDC gene. AADC catalyzes from L-DOPA and 5-hydroxytryptophan to dopamine and serotonin. The main symptom is movement disorder, including loss of voluntary movements, oculogyric crisis（OGC）and dystonia. Since 2015, we performed gene therapy for AADC deficiency as a clinical study using AAV2 vector carrying DDC gene（AAV2-AADC）. Eight patients（7 severe type and 1moderate type）were subjected to gene therapy via the injection of AAV2-AADC into bilateral putamen by stereotactic neurosurgery. Before treatment, 7 severe-type patients had no head control and dystonia attacks. However, all of them can control their heads, and six can use walkers. Dystonia disappeared in all patients. The moderate-type patient was able to walk with assistance before gene therapy but could walk independently after gene therapy. She also showed intellectual development. PET using FMT, an AADC tracer, showed that FMT accumulation in the putamen after five years was at the same level as at six months after treatment. At the resting functional MRI activity, the functional connectivity of basal ganglia centered on putamen was improved after treatment. Although there was a difference in efficacy depending on the severity of gene mutation site and the age at time of treatment, gene therapy improved clinical symptoms in all cases.

EO-057 The effect of valproate for carnitine serum concentration in epilepsy patients

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【Introduction】Carnitine is a molecule that plays an important role in the mitochondrial oxidation of fatty acids. Carnitine deficiency may be caused by long-term tube feeding, or several drugs such as valproic acid（VPA）. We measured carnitine serum concentration in a patient who has VPA.【Methods】The case was an 8-year-old boy with focal epilepsy. He was diagnosed at 8 years of age, and VPA was started at 9 years of age due to status epilepticus. We measured serum carnitine concentration before and after VPA medication. We also evaluated serum carnitine concentration of tube feeding patients during years 2017-2019.【Results】Serum total carnitine concentration was 56.8 and 89.7 micromol/L for before VPA administration and the average of 3 times measurement after VPA administration. There was no remarkable abnormal laboratory data. Upon 77 carnitine measurements, no obvious correlation between carnitine concentration and nutritional agents.【Conclusions】Oral carnitine treatment is effective for epilepsy patients who have VPA, or tube feeding patients.

EO-058 Vertigo in childhood : how to evaluate vertiginous children?

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【Objective】 Vertigo is a complaint consisting of wide spectrum of diagnoses. The aim of this study was to evaluate clinical characteristics and differential diagnosis of pediatric patients with vertigo.【Material and Methods】 In this retrospective study, the medical records of a hundred patients were evaluated for age, gender, duration of symptoms, frequency of attacks, provoking factors, accompanying symptoms, physical examination, laboratory findings and final diagnosis.【Results】 There were different causes of vertigo, but the most common two were infection and psychogenic vertigo. The other frequent reasons were orthostatic hypotension and vitamin B12 deficiency. Most of the patients had symptom duration for less than one month, and the attacks were primarily seen every day. The most common accompanying symptoms were fatigue and headache. Laboratory data revealed vitamin B12 deficiency in nine patients ; all other tests were in the normal range. Thirty-nine patients had cranial MRI, only 2 of them revealed abnormal findings, one of them was responsible for vertigo.【Conclusion】 Vertigo in children creates a profound sense of anxiety both in parents and physicians leading to excessive number of functional testing and imaging examinations. Evaluation should begin with detailed history and physical evaluation to avoid superfluous testing and diagnostics. Serious cases are fortunately rare and can be detected by careful clinical examination.

EO-059 SARS-CoV-2 neurotropism in a 12-year-old Filipino boy with focal encephalitis

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Several neurological manifestations have been reported in pediatric patients with COVID-19. Few reports provide evidence to support the potential neurotropism and direct central nervous system invasion of COVID-19 through the detection of SARS-CoV-2 ribonucleic acid (RNA) in cerebrospinal fluid (CSF). This study describes a previously well 12-year-old male with a mild respiratory illness who presented with altered sensorium and his first focal seizure. Reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 were negative in nasopharyngeal swabs, but positive in CSF. Neuroimaging findings were compatible with focal meningo-encephalitis. To our knowledge, this is the first local report of focal encephalitis with the presence of SARS-CoV-2 RNA in CSF.

EO-060 Relationship between brain MRI findings and long-term outcomes in patients with AESD

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【Objective】 To evaluate early MRI findings of acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) as a predictor of the long-term outcome.【Methods】 We recruited 42 children (22 boys, 20 girls) with AESD (median age at onset 16 months) who underwent intensive rehabilitation at our hospital. Inclusion criteria were free of underlying diseases, followed up 1 to 11 years after the onset, and with brain MRI during acute (within 14 days after onset) and subacute (1 to 3 months after onset) phase. We evaluated the relationship between MRI findings and long-term outcomes of motor and eating function, intellectual ability, and epilepsy.【Results】 Acute phase MRI showed bilateral involvement in 38 children including 21 with central sparing. Central sparing related to better attainment of independent walk (57% vs 18%, $p<0.01$) and eating (43% vs 18%, $p<0.05$). Brain atrophy was mild in 12 children, moderate in 9, and severe in 17 on subacute phase MRI. The rate of severe intellectual disability and epilepsy were significantly lower in the mild atrophy group (17%, 8%, $p<0.01$) and significantly higher in the severe atrophy group (100%, 82%, $p<0.01$). All the four children with unilateral involvement were able to walk and eat by themselves, and without severe intellectual disability or epilepsy.【Conclusion】 Central sparing, unilateral involvement, and mild atrophy on brain MRI related to better outcomes. Early brain MRI is valuable for planning adequate rehabilitation.

EO-061 Geniospasm：Like grandfather, like father, like son

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Hereditary geniospasm, a.k.a. hereditary chin trembling, is a very rare movement disorder, characterised by involuntary, vertical, low-amplitude movement of the chin muscles, particularly the mentalis muscles. It is inherited via autosomal dominant pattern with genetic heterogeneity. Due to its rarity, there are only less than 50 families reported to have geniospasm in the literature over the past century. Hereby, we reported a family, involving four members of three generations with hereditary geniospasm. All presented with chin trembling of neonatal onset and clear emotional triggers. All improved with increasing age without any treatment but persisted even into late adulthood.

EP-001 Investigating CASK gene knockout on neuronal differentiation and survival

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The CASK gene encodes calcium/calmodulin-dependent serine protein kinase. The mutation in CASK gene can present with microcephaly with pontocerebellar hypoplasia, and X-linked intellectual disability with or without nystagmus. However, the pathogenic mechanism leading to different manifestations remains unclarified. Whether different phenotypes simply related to loss-of- function effect of CASK protein remains uncertain. CASK knockout cell model was successfully edited in IMR32 cells using CRISPR/Cas9 technology. We found that. in vitro CASK knockout can lead to increased neuronal death during differentiation. There were also increased reactive oxygen species（ROS）production and depolarization of mitochondrial membrane potential. Furthermore, there was also changes in expression of tyrosine hydroxylase（TH）and dopamine release. Treatment with Coenzyme Q10（CoQ10）decreased the ROS production and lead to less mitochondrial depolarization. This indicated that treatment targeting at mitochondria may have protective effect on CASK knockout neurons. We also found out loss-of- function effect of CASK protein may affect dopamine function which may contribute to some phenotype of CASK -related disorder.