The 21st Annual Meeting of the Infantile Seizure Society (ISS)

International Symposium on the Pathophysiology of Developmental and Epileptic Encephalopathy (ISDEE2020)

Program & Abstracts

June 19(Friday)–June 21(Sunday), 2020

Venue: **Virtual Meeting**

President: **Katsuhiro Kobayashi**
Professor, Department of Child Neurology,
Okayama University Graduate School of Medicine,
Dentistry and Pharmaceutical Sciences, Okayama, Japan

Vice President: **Isao Date**
Professor, Department of Neurological Surgery,
Okayama University Graduate School of Medicine,
Dentistry and Pharmaceutical Sciences, Okayama, Japan

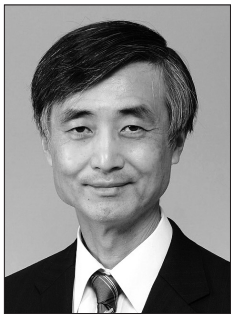
Artwork by Noriyoshi Yamashita (epilepsy patient since early childhood)

https://www.isdee2020.org/

CONTENTS

Message from the Presidents of ISDEE2020

Katsuhiro Kobayashi, President, ISDEE2020
Professor, Department of Child Neurology,
Okayama University Graduate School of Medicine,
Dentistry and Pharmaceutical Sciences, Okayama,
Japan



Isao Date, Vice President, ISDEE2020
Professor, Department of Neurological Surgery,
Okayama University Graduate School of Medicine,
Dentistry and Pharmaceutical Sciences, Okayama, Japan

Dear Friends and Colleagues,

On behalf of the organizing committee, it is our great pleasure to welcome you to the International Symposium on the Pathophysiology of Developmental and Epileptic Encephalopathy (ISDEE2020), which is being held as the 21st Annual Meeting of the Infantile Seizure Society (ISS).

At this symposium, we intend to discuss and investigate the issues of developmental and epileptic encephalopathy in infancy and childhood that involve clinical neurophysiology. Through neurophysiology, clinical epileptology can be understood as electrical dysfunctions of the brain, and basic neuroscience, including genetics, metabolism, brain ontogenesis, and other fields, reveals how electrical disturbances occur in the neuronal system, leading to the generation of seizures. Neurophysiology may be regarded as a link between clinical epileptology and basic neuroscience, and it is therefore the cornerstone of ISDEE2020.

The founder of the Department of Child Neurology at Okayama University was Professor Ohtahara, who discovered Ohtahara syndrome. We are proud of the history of this department, which has been dedicated to the development of pediatric neurology and epileptology and to the care of children suffering from neurological and seizure disorders.

We were initially preparing a real meeting of ISDEE2020. However, because of the Covid-19 pandemic, it is now held totally online. It is a great pity that we cannot see each other in person, but we hope to realize an exciting meeting within the limitations of teleconference.

We appreciate your contribution to the ISS, and sincerely wish for your health.

Katsuhiro Kobayashi, President, ISDEE2020
Professor, Department of Child Neurology, Okayama University Graduate School of Medicine,
Dentistry and Pharmaceutical Sciences, Okayama, Japan

Isao Date, Vice President, ISDEE2020
Professor, Department of Neurological Surgery, Okayama University Graduate School of Medicine,
Dentistry and Pharmaceutical Sciences, Okayama, Japan

Message from the Chairperson of Infantile Seizure Society

Hideo Yamanouchi, MD
Chairperson, ISS

Dear My Friends and Colleagues

From the early this year, all we have encountered a fearful pandemic of novel coronavirus, SARS-CoV-2, which human being have never experienced for over a decade. Through his time of the global scale disaster, we have been forced to reconsider the fundamental obligations, which Infantile Seizure Society has to do for our own patients and their families as well as our community in this moment and the future. we reflected the original mission of ISS; “To promote the highest quality patient-centered neurologic care and enhance member career satisfaction”. This is also a spiritual legacy from the late Prof Fukuyama, the founder of ISS. Finally, we have decided that no matter what happens, we will execute this mission in our own way.

Here I am very happy to address my greeting to welcome all of you who will get together virtually on the website from all over the world and all over the country to attend the 21st Annual Meeting of Infantile Seizure Society, which shall take place from June 19 (Fri) to 21 (Sun), 2020.

This is an international symposium highlighted on the Pathophysiology of Developmental and Epileptic Encephalopathy hosted by Professor Katsuhiro Kobayashi. He is one of the most crucial successors to the late professor Ohtahara, who found and established early infantile epileptic encephalopathy (Ohtahara syndrome), one of the most important epileptic syndromes in infancy. In this regard, it is really gratifying for us to create and prepare this global event on this topic.

We will surely bring you exciting and fruitful moments to discuss the basic and clinical neuroscience in the field of developmental and epileptic encephalopathy.

Let’s join this incredible and invaluable global event by using unconventional novel tactics, and promote international friendship each other.

Hideo Yamanouchi, MD
Chairperson, Infantile Seizure Society
Professor of Pediatrics, Comprehensive Epilepsy Center, Saitama Medical University

ORGANIZATION of ISDEE2020

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Host Organizer

Infantile Seizure Society (ISS)

Endorsement

International League Against Epilepsy (ILAE)
Japan Medical Association (JMA)
Asian & Oceanian Child Neurology Association (AOCNA)
Japan Epilepsy Society (JES)
Japanese Society of Child Neurology (JSCN)

ACKNOWLEDGEMENT

The ILAE Education council endorses this online symposium with condition that post-course evaluation will be performed by the ILAE using an online Survey Monkey tool.

ISDEE is also endorsed by the Asian and Oceanian Child Neurology Association (AOCNA), the Japan Epilepsy Society (JES), the Japanese Society of Child Neurology (JSCN), and the Japan Medical Association(JMA).

The organizing committee of ISDEE2020 would like to express sincrere thanks to the associations, companies, hospitals and persons to support ISDEE2020.
The details financial supports are shown in Page 129.

OVERVIEW of DAILY PROGRAM

*All dates and time are in Japan Standard Time.

Time	Day 1: June 19 (Friday)	Day 2: June 20 (Saturday)	Day 3: June 21 (Sunday)	Time
9:00	9:00-9:10 Opening Ceremony 9:10-9:30 **Presidential Lecture** *Introduction to ISDEE2020*/ Katsuhiro Kobayashi	9:00-10:00 **Special Lecture 2** *Neuronal maturational factors can change excitatory/inhibitory synaptic ratios in infantile epilepsies*/ Harvey B. Sarnat	9:00-9:30 **Lecture Session 8** **Treatment of DEE (surgical aspects)** *Surgical treatment*/Hiroshi Otsubo	9:00
10:00	9:30-10:30 **Keynote Lecture** *Overview of Developmental Epileptic Encephalopathies*/ Raman Sankar	10:00-10:10 Break 10:10-10:40 **Lecture Session 5** **Metabolic mechanisms in DEE** *Metabolic pathomechanisms*/ Tomoyuki Akiyama	9:30-10:30 **Talking Poster Session 3** 10:30-10:40 Break	10:00
11:00	10:40-11:10 **Lecture Session 1** **Electrophyiology in DEE (part 1)** *EEG analysis including HFOs*/ Hiroki Nariai	10:40-11:10 **Lecture Session 6** **Inflammatory mechanisms in DEE** *Inflammation in epilepsy*/Derrick Chan	10:40-11:10 **Lecture Session 9** **Neuroimaging studies in DEE** *Neuroimaging studies*/Jun Natsume	11:00
12:00	11:10-12:10 **Lecture Session 2** **Basic neuroscience of DEE** *Animal Model*/Atsuo Fukuda *iPS cells*/Shinichi Hirose	11:10-11:20 Break 11:20-12:20 **Joint Seminar 1** *Optimal management of epilepsy associated with TSC*/ Eiji Nakagawa (sponsored by Novartis Pharma K.K.)	11:10-11:20 Break 11:20-12:20 **Joint Seminar 2** *Network and molecular mechanisms of generalized spike-waves in developmental and epileptic encephalopathies*/Norimichi Higurashi *Beyond genetic basis of monogenic developmental epileptic encephalopathy*/Atsushi Ishii (sponsored by Eisai Japan Eisai Co., Ltd.)	12:00
13:00	12:10-13:10 Break (lunch on one's own) * The following videos will be played. P-01 to P-07 from Talking Poster Session 1 G-01 to G-05 from Platform Session 1	12:20-13:20 Break (lunch on one's own) * The following videos will be played. P-08 to P-11 from Talking Poster Session 1 P-12 to P-21 from Talking Poster Session 2 P-22 to P-25 from Talking Poster Session 3	12:20-13:20 Break (lunch on one's own) * The following videos will be played. P-26 to P-32 from Talking Poster Session 3 P-33 to P-43 from Talking Poster Session 4	13:00
14:00	13:10-14:10 **Talking Poster Session 1** 14:10-14:20 Break	13:20-14:20 **Talking Poster Session 2** 14:20-14:30 Break	13:20-14:20 **Special Lecture 4** *Genetics and precision medicine in the developmental and epileptic encephalopathies*/Ingrid Scheffer 14:20-14:30 Break	14:00
15:00	14:20-15:20 **Lecture Session 3** **Neonatal-/early-onset DEE** *Genetics in EOEE*/Mitsuhiro Kato *Neonatal onset DEE*/ Natrujee Wiwattanadittakul 15:20-15:30 Break	14:30-15:10 **Platform Session 2** 15:10-15:40 Break * The following videos will be played. G-06 to G-09 from Platform Session 2	14:30-15:40 **Lecture Session 10** **Neurocognitive/QOL issues in DEE** *Neurodevelopmental disorders*/ Yushiro Yamashita *Neurocognitive disturbances*/ Hideaki Kanemura *Burden of DEE*/Susumu Ito 15:40-15:50 Break	15:00
16:00	15:30-16:30 **Platform Session 1** 16:30-16:40 Break	15:40-16:40 **Lecture Session 7** **Genetic aspects of DEE** *Genetic studies of DEE*/Wang-Tso Lee *Genetic studies in DEE*/ Chaiyos Khongkhatithum 16:40-16:50 Break	15:50-16:50 **Talking Poster Session 4**	16:00
17:00	16:40-17:10 **Lecture Session 4** **Electrophyiology in DEE (part 2)** *Electrophysiology*/Nicola Specchio 17:10-18:10 **Special Lecture 1** *Phenotype-genotype correlations in DEE*/ Federico Vigevano	16:50-17:50 **Special Lecture 3** *A bridge between genetics and electrophysiology*/Renzo Guerrini	16:50-17:50 **Lecture Session 11** **Treatment of DEE (medical and dietary aspects)** *Medical and dietary treatment*/ Ki Joong Kim *UKISS and ICISS*/Andrew Lux 17:50-18:00 Closing Ceremony	17:00
18:00				18:00

*The extra viewing time of Platform Sessions and Talking Poster Sessions are available during the break. (Viewing only)

PROGRAM

PROGRAM

***The extra viewing time of Platform Sessions and Talking Poster Sessions are available during the break. (Viewing only) See the schedule below.**

DAY 1, FRIDAY, JUNE 19

9:00-9:10 **Opening Ceremony**

Presidential Lecture: Introduction to ISDEE2020

9:10-9:30 **L-01**
INTRODUCTION TO THE SYMPOSIUM ON DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY
Katsuhiro KOBAYASHI
Department of Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan

Keynote Lecture: Overview of DEE
Chairperson: Hideo YAMANOUCHI
(Pediatrics, Saitama Medical University, Saitama, Japan)

9:30-10:30 **L-02**
OVERVIEW OF DEVELOPMENTAL EPILEPTIC ENCEPHALOPATHIES
Raman SANKAR
Neurology and Pediatrics, Geffen School of Medicine UCLA, CA, USA

10:30-10:40 **Break**

Lecture Session 1: Electrophysiology in DEE (part 1)
Chairperson: Mitsugu UEMATSU
(Pediatrics, Tohoku University Hospital, Sendai, Japan)

10:40-11:10 **L-03**
COMPUTATIONAL EEG ANALYSIS IN EPILEPTIC ENCEPHALOPATHY
Hiroki NARIAI
Pediatric Neurology / Pediatrics, University of California, Los Angeles, USA

Lecture Session 2: Basic neuroscience of DEE
Chairperson: Shinji SAITOH
(Pediatrics and Neonatology, Graduate School of Medical Sciences, Nagoya City University, Nagoya, Japan)

11:10-11:40 **L-04**
PIVOTAL ROLES OF NEURONAL EXCITATION-INHIBITION DYNAMICS IN EPILEPTOGENESIS OF HUMAN AND ANIMAL MODELS
Atsuo FUKUDA
Department of Neurophysiology, Hamamatsu University School of Medicine, Japan

11:40-12:10 **L-05**

STUDIES ON THE PATHOMECHANISMS OF DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY USING INDUCED PLURIPOTENT STEM CELLS

Shinichi HIROSE
Department of Pediatrics, School of Medicine, Fukuoka University, Japan
Research Institute for the Molecular Pathomechanisms of Epilepsy, Fukuoka University, Japan

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12:10-13:10 **Break (lunch on one's own)**
The following videos will be played.
P-01 to P-07 fromTalking Poster Session 1
G-01 to G-05 from Platform Session 1

Talking Poster Session 1
Chairpersons: Yasuhiro SUZUKI
(Division of Pediatric Neurology, Osaka Women's and Children's Hospital, Japan)
Mitsuko ITOH
(Pediatrics, The University of Tokyo Hospital, Japan
Department of Public Health/Health Policy, The University of Tokyo, Graduate School of Medicine, Japan
Akasaka Family Clinic, Japan)

13:10-14:10 **P-01~P-11**
List of Presentations is available on page 18-19

14:10-14:20 **Break**

Lecture Session 3: Neonatal-/early-onset DEE
Chairperson: Akihisa OKUMURA
(Pediatrics, Aichi Medical University, Aichi, Nagoya, Japan)

14:20-14:50 **L-06**

GENETICS OF NEONATAL-ONSET EPILEPTIC ENCEPHALOPATHIES: A TRIBUTE TO PROF. OHTAHARA

Mitsuhiro KATO
Department of Pediatrics, Showa University School of Medicine, Japan
Epilepsy Medical Center, Showa University Hospital, Japan

14:50-15:20 **L-07**

NEONATAL AND INFANTILE ONSET DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY

Natrujee WIWATTANADITTAKUL
Division of Child Neurology, Chiang Mai University, Thailand

15:20-15:30 **Break**

Platform Session 1
Chairperson: Jun NATSUME
(Developmental Disability Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan)

15:30-16:30

G-01
PATHOLOGICAL GAIT IN PATIENTS WITH DRAVET SYNDROME: QUANTITATIVE EVALUATION USING THREE-DIMENSIONAL GAIT ANALYSIS
Takeshi SUZUKI
Department of Pediatrics, Nagoya University Graduate School of Medicine, Japan

G-02
CHOICE AND EFFICACY OF INTRAVENOUS ANTIEPILEPTIC DRUGS FOR STATUS EPILEPTICUS IN DRAVET SYNDROME
Kenjiro KIKUCHI
Division of Neurology, Saitama Children's Medical Center, Japan

G-03
LONGITUDINAL CORRESPONDENCE OF EPILEPSY AND SCALP EEG FAST (40 - 200HZ) OSCILLATIONS IN PEDIATRIC PATIENTS WITH TUBEROUS SCLEROSIS COMPLEX
Hiroki TSUCHIYA
Department of Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital, Japan

G-04
EVALUATION OF EPILEPTIC BRAIN ACTIVITY AT THE ONSET OF WEST SYNDROME USING SIMULTANEOUS EEG-fMRI
Yuki MAKI
Department of Pediatrics, Nagoya University Graduate School of Medicine, Japan
Brain and Mind Research Center, Nagoya University, Japan

G-05
FACTORS ASSOCIATED WITH TREATMENT LAG AND OUTCOMES OF INFANTILE SPASMS IN MALAYSIA - A MULTICENTRE PROSPECTIVE STUDY
Sumitha MURUGESU
Paediatric Neurology Unit, Kuala Lumpur Woman and Children Hospital, Malaysia

16:30-16:40 **Break**

Lecture Session 4: Electrophysiology in DEE (part 2)
Chairperson: Hideaki SHIRAISHI
(Pediatrics, Hokkaido University Graduate School of Medicine, Hokkaido, Japan)

16:40-17:10

L-08
ELECTROPHYSIOLOGY IN DEE
Nicola SPECCHIO
Department of Neuroscience, Bambino Gesù Children's Hospital, IRCCS, Italy

Special Lecture 1: Phenotype-genotype correlations in DEE
Chairperson: Hitoshi YAMAMOTO
(Pediatrics, St Marianna University School of Medicine, Kawasaki, Japan)

17:10-18:10 **L-9**

PHENOTYPE-GENOTYPE CORRELATIONS IN DEE

Federico VIGEVANO
Neuroscience Department, Bambino Gesù Paediatric Hospital, Rome, Italy

DAY 2, SATURDAY, JUNE 20

Special Lecture 2: Pathogenesis of elipsy
Chairperson: Takao TAKAHASHI
(Pediatrics, Keio University School of Medicine, Tokyo, Japan)

9:00-10:00 **L-10**

NEURONAL MATURATIONAL FACTORS CAN CHANGE EXCITATORY/ INHIBITORYSYNAPTIC RATIOS IN INFANTILE EPILEPSIES

Harvey B. SARNAT
University of Calgary and Alberta Children's Hospital Research Institute, Canada

10:00-10:10 **Break**

Lecture Session 5: Metabolic mechanisms in DEE
Chairperson: Hitoshi OSAKA
(Pediatrics, Jichi Medical School, Tochigi, Japan)

10:10-10:40 **L-11**

INHERITED METABOLIC DISEASES IN DEVELOPMENTAL/EPILEPTIC ENCEPHALOPATHY

Tomoyuki AKIYAMA
Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan

Lecture Session 6: Inflammatory mechanisms in DEE
Chairperson: Hiroshi SAKUMA
(Developmental Neuroimmunology Project, Department of Brain Development and Neural Regeneration, Tokyo Metropolitan Institute of Medical Science, Japan)

10:40-11:10 **L-12**

INFLAMMATION IN EPILEPSY

Derrick CHAN
Paediatric Neurology, KK Women's and Children's Hospital, Singapore

11:10-11:20 **Break**

Joint Seminar 1 **(sponsored by Novartis Pharma K.K.)**
Chairperson: Masashi MIZUGUCHI
(Department of Developmental Medical Sciences, School of International Health, Graduate School of Medicine, The University of Tokyo, Japan)

11:20-12:20 **L-13**

OPTIMAL MANAGEMENT OF EPILEPSY ASSOCIATED WITH TSC

Eiji NAKAGAWA
Department of Child Neurology, National Center Hospital, National Center of Neurology and Psychiatry, Japan

12:20-13:20 **Break (lunch on one's own)**
The following videos will be played.
P-08 to P-11 from Talking Poster Session 1
P-12 to P-21 from Talking Poster Session 2
P-22 to P-25 from Talking Poster Session 3

Talking Poster Session 2
Chairpersons: Gaku YAMANAKA
(Department of Pediatrics, Tokyo Medical University, Japan)
Masako SAKAUCHI
(Sakauchi Children's Clinic, Japan)

13:20-14:20 **P-12~P-21**
List of Presentations is available on page 19-20

14:20-14:30 **Break**

Platform Session 2
Chairperson: Kazuhiro MURAMATSU
(Department of Pediatrics, Jichi Medical University, Japan)

14:30-15:10 **G-06**
AN EFFECTIVENESS OF TRICLOFOS SODIUM ON TWO PATIENTS WITH OHTAHARA SYNDROME
Kaori SASSA
Department of Pediatrics, Saitama Medical University Hospital, Japan
Comprehensive Epilepsy Center, Saitama Medical University Hospital, Japan

G-07
TWO CASES OF DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY CAUSED BY *CYFIP2* GENE MUTATION
Atsuko ARISAKA
Department of Neuropediatrics, Tokyo Metropolitan Neurological Hospital, Japan
Department of Pediatrics, Tokyo Metropolitan Bokuto Hospital, Japan

G-08
COMBINATION THERAPY WITH TOPIRAMATE AND GABAPENTIN IN A CHILD WITH *CACNA1E*-ENCEPHALOPATHY
Hirofumi KASHII
Department of Neuropediatrics, Tokyo Metropolitan Neurological Hospital, Japan

G-09
SEIZURE OUTCOME AND COMPLICATIONS IN SURGICAL TREATMENT OF INFANTILE EPILEPSY
Masaki IWASAKI
Neurosurgery, National Center Hospital, National Center of Neurology and Psychiatry, Japan

15:10-15:40 **Break**
The following videos will be played.
G-06 to G-09 from Platform Session 2

Lecture Session 7: Genetic aspects of DEE
Chairperson: Norimichi HIGURASHI
(Pediatrics, Jikei University School of Medicine, Japan)

15:40-16:10 **L-14**

GENETIC ASPECTS OF DEE WITH MOVEMENT DISORDERS

Wang-Tso LEE

Pediatric Neurology, National Taiwan University Children's Hospital, Taiwan

16:10-16:40 **L-15**

GENETIC STUDIES IN DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY

Chaiyos KHONGKHATITHUM

Division of Pediatric Neurology, Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand

16:40-16:50 **Break**

Special Lecture 3: A bridge between genetics and electrophysiology
Chairperson: Mitsuhiro KATO
(Pediatrics, Showa University School of Medicine, Tokyo, Japan)

16:50-17:50 **L-16**

A BRIDGE BETWEEN GENETICS AND ELECTROPHYSIOLOGY

Renzo GUERRINI

Neuroscience Department, Children's Hospital A. Meyer-University of Florence, Italy

DAY 3, SUNDAY, JUNE 21

Lecture Session 8: Treatment of DEE (surgical aspects)
Chairperson: Tomoyuki AKIYAMA
(Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan)

9:00-9:30 **L-17**

EPILEPTOGENIC MODULATION AND SYNCHRONIZATION IN HYPSARRYTHMIA SECONDARY TO PERINATAL MIDDLE CEREBRAL ARTERY STROKE

Hiroshi OTSUBO
Neurology, The Hospital for Sick Children, Canada

Talking Poster Session 3
Chairperson: Kensuke KAWAI
(Department of Neurosurgery, Jichi Medical University, Japan)
Kazuhiro HAGINOYA
(Takuto Rehabilitation Center for Children, Miyagi Children's Hospital, Japan)

9:30-10:30 **P-22~P-32**

List of Presentations is available on page 20-21

10:30-10:40 **Break**

Lecture Session 9: Neuroimaging studies in DEE
Chairperson: Masaharu HAYASHI
(Department of Nursing, Faculty of Nursing and Nutrition, Shukutoku University, Chiba, Japan)

10:40-11:10 **L-18**

NEUROIMAGING OF DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES

Jun NATSUME
Department of Developmental Disability Medicine, Nagoya University Graduate School of Medicine, Japan

11:10-11:20 **Break**

Joint Seminar 2 **(sponsored by Eisai Japan Eisai Co., Ltd.)**
Chairperson: Kenji SUGAI
(Clinical Department, Soleil Kawasaki Medical Center for the Handicapped, Kawasaki, Japan)

11:20-12:20 **L-19**

NETWORK AND MOLECULAR MECHANISMS OF GENERALIZED SPIKE-WAVES IN DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES

Norimichi HIGURASHI
Department of Pediatrics, Jikei University school of Medicine, Japan
Central Research Institute for the Molecular Pathomechanisms of Epilepsy, Fukuoka University, Japan

L-20

BEYOND GENETIC BASIS OF MONOGENIC DEVELOPMENTAL EPILEPTIC ENCEPHALOPATHY

Atsushi ISHII
Department of Pediatrics, School of Medicine, Fukuoka University, Japan

12:20-13:20 **Break (lunch on one's own)**
The following videos will be played.
P-26 to P-32 from Talking Poster Session 3
P-33 to P-43 from Talking Poster Session 4

Special Lecture 4: Precision medicine for DEE
Chairperson: Shinichi HIROSE
(Pediatrics, School of Medicine, Fukuoka University, Fukuoka, Japan)

13:20-14:20 **L-21**

GENETICS AND PRECISION MEDICINE IN THE DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES

Ingrid SCHEFFER
Department of Medicine, Austin Health, The University of Melbourne, Australia
President, Australian Academy of Health and Medical Sciences, Australia
Department of Paediatrics, Austin Health, Australia
Department of Paediatrics, Royal Children's Hospital, Australia
The Florey Institute of Neuroscience and Mental Health, Australia
Murdoch Children's Research Institute, Australia

14:20-14:30 **Break**

Lecture Session 10: Neurocognitive/QOL issues in DEE
Chairperson: Eiji NAKAGAWA
(Department of Child Neurology, National Center Hospital, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan)

14:30-15:00 **L-22**

DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES AND NEURODEVELOPMENTAL DISORDERS

Yushiro YAMASHITA
Department of Pediatrics and Child Health, Kurume University School of Medicine, Japan

15:00-15:20 **L-23**

COGNITIVE AND BEHAVIORAL CONSEQUENCES IN ECSWS: THE RELATIONSHIP BETWEEN SEIZURES/PAROXYSMAL EEG ABNORMALITIES AND COGNITIVE/BEHAVIORAL DISTURBANCES

Hideaki KANEMURA
Department of Pediatrics, Toho University Medical Center Sakura Hospital, Japan

15:20-15:40 **L-24**

BURDEN OF DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY-AFFECTED CHILDREN ON FAMILIES, NURSERY SCHOOLING, AND EMPLOYMENT IN JAPAN

Susumu ITO
Department of Pediatrics, Tokyo Women's Medical University, Japan
Dravet Syndrome JP, Japan

15:40-15:50 **Break**

Talking Poster Session 4
Chairpersons: Jun TOHYAMA
(Department of Pediatrics, Nishi-Niigata Chuo National Hospital, Japan)
Kenjiro KIKUCHI
(Division of Neurology, Saitama Children's Medical Center, Japan)

15:50-16:50 **P-33~P-43**
List of Presentations is available on page 21-22

Lecture Session 11: Treatment of DEE (medical and dietary aspects)
Chairperson: Tohru OKANISHI
(Division of Child Neurology, Institute of Neurological Science,Tottori University, Japan)

16:50-17:20 **L-25**
TREATMENT OF DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY
Ki Joong KIM
Pediatrics, Seoul National University Hospital, Korea

17:20-17:50 **L-26**
HOW DO INFANTILE SPASMS AND WEST SYNDROME RELATE TO THE CONCEPTS OF DEVELOPMENTAL & EPILEPTIC ENCEPHALOPATHIES?
Andrew LUX
Women's and Children's Health / Department of Paediatric Neurology, University of Bristol, UK

17:50-18:00 **Closing Ceremony**

Talking Poster Session

P-01

THE ROLE OF INFLAMMATION ON EPILEPTOGENESIS AFTER NEONATAL HYPOXIC-ISCHEMIC BRAIN INJURY

YiFang TU Department of Pediatrics, National Cheng Kung University Hospital, Taiwan College of Medicine, National Cheng Kung University, Taiwan

P-02

POLYMICROGYRIA WITH CALCIFICATION IN PALLISTER-KILLIAN SYNDROME DETECTED BY MICROARRAY ANALYSIS

Akiko HIRAIWA Department of Child Neurology, NHO Nishiniigata Chuo Hospital, Japan

P-03

AGE-RELATED CHANGES IN GLUTAMATE AND GLUTAMINE CONCENTRATIONS OBSERVED ON MR SPECTROSCOPY

Nanako TAKASE Pediatrics, Tokyo Women's Medical University Yachiyo Medical Center, Japan

P-04

AN INFANT WITH PERSISTENT PERIVENTRICULAR HYPER-ECHOGENICITY WITH NO OTHER SYMPTOMS AND RADIOGRAPHIC ABNORMALITIES

Akihito TAKEUCHI Division of Neonatology, National Hospital Organization Okayama Medical Center, Japan
Division of Neuropediatrics, National Hospital Organization Okayama Medical Center, Japan

P-05

USEFULNESS OF VIDEO ELECTROENCEPHALOGRAPHY RECORDING FOR THE DIAGNOSIS OF DEXMEDETOMIDINE WITHDRAWAL IN TWO PATIENTS WITH INTRACTABLE EPILEPSY

Moe YOSHIMURA Department of Pediatrics, Saitama Medical University Hospital, Japan

P-06

EVOLUTIONAL PROCESS OF EPILEPSY ASSOCIATED WITH TUBEROUS SCLEROSIS COMPLEX (TSC) DURING INFANCY

Harumi YOSHINAGA Department of Child Neurology, National Hospital Organization Minami-Okayama Medical Center, Japan
Department of Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan

P-07

FIVE-DIMENSIONAL MAPPING OF AUDITORY LANGUAGE FUNCTION

Yasuo NAKAI Department of Neurological Surgery, Wakayama Medical University, Japan

P-08

EVOLUTION OF SEIZURES AND EEGS AMONG CHILDREN WITH BILATERAL BASAL GANGLIA AND THALAMIC LESION

Shizuka NISHIMOTO Neuropediatrics, Bobath memorial hospital, Japan

P-09

EXPRESSION OF INTRACELLULAR CYTOKINES IN TWINS WITH INTRACTABLE EPILEPSY ASSOCIATED WITH LISSENCEPHALY

Gaku YAMANAKA Department of Pediatrics and Adolescent Medicine, Tokyo Medical University, Japan

P-10

A BOY WITH SEVERE EARLY-ONSET DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY ASSOCIATED WITH A CASK VARIANT INHERITED FROM HIS MOTHER WITH MILD INTELLECTUAL DISABILITY

Ikumi HORI Pediatrics and Neonatology, Nagoya City University Graduate School of Medical Sciences, Japan

P-11

***ST3GAL5* MUTATION IN TWO CHINESE SISTERS WITH EPILEPSY, DEVELOPMENTAL DELAY, AND INVOLUNTARY MOVEMENTS**

Shiena WATANABE Department of Child Neurology, National Center Hospital, National Center of Neurology and Psychiatry, Japan

P-12

RETROSPECTIVE STUDY OF SEIZURE CONTROL IN WOLF-HIRSCHHORN SYNDROME: A SINGLE CENTER EXPERIENCE FROM JAPAN

Ayumi HORIGUCHI Division of Neurology, Saimata Children's Medical Center, Japan

P-13

EXAMINATION OF CAKUTHED DIAGNOSED BASED ON INTELLECTUAL DISABILITY IN WHICH A NEW PATHOGENIC VARIANT WAS IDENTIFIED

Shinichiro MORICHI Department of Pediatrics and Adolescent medicine, Tokyo Medical University, Japan

P-14

ALTERED PTERIDINE AND SEROTONIN METABOLISM IN *GNAO1*-RELATED CHILDHOOD-ONSET HYPERKINETIC MOVEMENT DISORDER: A CASE REPORT

Itaru HAYAKAWA Division of Neurology, National Center for Child Health and Development, Japan

P-15

A CASE OF DEVELOPMENTAL EPILEPTIC ENCEPHALOPATHY WITH *PPP3CA* MUTATION

Hirokazu KURAHASHI Department of Pediatrics, Aichi Medical University, Japan

P-16

LONG-TERM FOLLOW-UP STUDY OF MALAN SYNDROME WITH WEST SYNDROME : A CASE REPORT

Naomi HINO-FUKUYO Department of Pediatrics, Tohoku University Hospital, Japan

P-17

CAPABILITY OF DIFFERENT PREDICTION ALGORITHMS TO CLASSIFY PHENOTYPE AS BENIGN NEONATAL EPILEPSY OR DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY

Ayako GOTO Pediatrics, Fukuoka University, Japan

P-18

A PATIENT WITH WEST SYNDROME AND AUTISTIC SPECTRUM DISORDER WITH *SCN2A* GENE DELETION WITHOUT *SCN1A* INVOLVEMENT

Pin Fee CHONG Department of Pediatric Neurology, Fukuoka Children's Hospital, Japan
Deparment of General Pediatrics & Interdisciplinary Medicine, Fukuoka Children's Hospital, Japan

P-19

A CASE OF DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY WITH INVOLUNTARY MOVEMENTS DUE TO MUTATION OF THE *SCN2A* GENE

Ken NAKAJIMA Pediatric Neurology, Osaka Women's and Children's Hospital, Japan

P-20

COMPARATIVE CHARACTERIZATION OF *PCDH19* MISSENSE AND TRUNCATING VARIANTS IN *PCDH19*-RELATED EPILEPSY

Mami SHIBATA Research Institute for the Molecular Pathomechanisms of Epilepsy, Fukuoka University, Japan

P-21

ASSESSMENT OF ACUTE ENCEPHALOPATHY WITH BIPHASIC SEIZURES AND LATE REDUCED DIFFUSION FROM FEBRILE STATUS EPILEPTICS AND FEBRILE SEIZURE USING EEG SPECTRUM ANALYSIS

Masayoshi OGURI Division of Clinical Physiology, Department of Medical Technology, Kagawa Prefectural University of Health Sciences, Japan

P-22

A CASE OF INFANTILE SPASMS SUSPECTED OF METABOLIC BRAIN ABNORMALITY IN RESPONSE TO VIGABATRIN

Yurika NUMATA-UEMATSU Pediatrics, Tohoku University School of Medicine, Japan

P-23

INCIDENCE AND RISK FACTORS OF ACUTE ENCEPHALOPATHY WITH BIPHASIC SEIZURES AND LATE REDUCED DIFFUSION IN CHILDREN WITH PROLONGED FEBRILE SEIZURE

Fumio ICHINOSE Department of Pediatrics, Saga University, Japan

P-24

A COMPARISON OF CLINICAL FEATURES OF ACUTE ENCEPHALOPATHY WITH BIPHASIC SEIZURES AND LATE REDUCED DIFFUSION BETWEEN SHORT AND PROLONGED FIRST SEIZURE DURATION

Hiroshi YAMAGUCHI Department of Pediatrics, Kobe University Graduate School of Medicine, Japan

P-25

FIVE YEARS FOLLOW UP OF SCN8A DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY

Koyuru KURANE Pediatrics, Jichi Medical University, Japan

P-26

MOVEMENT DISORDERS IN CHILDREN WITH GENETIC EARLY INFANTILE EPILEPTIC ENCEPHALOPATHIES

Dianah ABD HADI Paediatric Neurology, Women and Children Hospital Kuala Lumpur, Malaysia

P-27

ATYPICAL EVOLUTION OF SELF-LIMITED IDIOPATHIC FOCAL EPILEPSIES

Akira NISHIMURA Department of Neonatology, Japanese Red Cross Society Kyoto Daiichi Hospital, Japan
Department of Pediatrics, Japanese Red Cross Society Kyoto Daiichi Hospital, Japan

P-28

PANAYIOTOPOULOS SYNDROME-LIKE EPILEPSY IN PEDIATRIC PATIENTS WITH HYPOPLASTIC LEFT HEART SYNDROME

Takashi SHIBATA Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital, Japan

P-29

EPILEPSY CHARACTERISTICS AND EFFICACY OF TREATMENT IN JAPANESE PATIENTS WITH DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY DUE TO *CDKL5* MUTATIONS

Yu KOBAYASHI Child Neurology, NHO Nishiniigata Chuo Hospital, Japan

P-30

SUSPECTED AUTONOMIC DYSFUNCTION IN INFANTS WITH APNEIC SEIZURES RELATED INSULA

Shinsuke MARUYAMA Division of Neurology, The Hospital for Sick Children, Toronto, Ontario, Canada

P-31

LATERALIZATION OF THE EPILEPTOGENIC HEMISPHERE GENERATING HYPSARRHYTHMIA SECONDARY TO PERINATAL ISCHEMIC STROKE; PHASE AMPLITUDE COUPLING AND FUNCTIONAL CONNECTIVITY

Hiroharu SUZUKI Neurology, The Hospital for Sick Children, Canada
Neurosurgery, Juntendo University, Japan

P-32

RAPID IMPROVEMENT OF ENCEPHALOPATHY IN CHILDREN WITH LENNOX-GASTAUT SYNDROME AND GENERALIZED EPILEPSY AFTER FOCAL RESECTION

Masanori TAKEOKA Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, USA
Neurology, Harvard Medical School, USA

P-33

THE ROLE OF FOCAL EPILEPSY FEATURES IN DEFINING SCN1A POSITIVE DRAVET SYNDROME AS GENERALIZED AND FOCAL EPILEPSY

Young Jun KO Pediatrics, Seoul National University Children's Hospital, Korea

P-34

INFANTILE EPILEPTIC ENCEPHALOPATHY ASSOCIATED WITH A KCNA2 GENE MUTATION

Masahiro ISHII Pediatrics, University of Occupational and Environmental Health, Japan

P-35

GENETICS AND CLINICAL CORRELATION OF DRAVET SYNDROME AND ITS MIMICS

Yun-Ju CHEN Division of Pediatric Neurology, Chang Gung Children's Hospital and Chang Gung Memorial Hospital, Taiwan

P-36

DRAVET-LIKE EPILEPTIC PATIENTS WITH PCDH19 MUTATIONS IN TAIWAN AND MALAYSIA

Yi-Hsuan LIU Division of Pediatric Neurology, Chang Gung Children's Hospital and Chang Gung Memorial Hospital, Taiwan

P-37

EVALUATION OF HYPOTHALOMO-PITUITARY-ADRENOCORTICAL FUNCTION AFTER SYNTHETIC ACTH THERAPY FOR INFANTILE SPASMS (WEST SYNDROME)

Yuri SAKAGUCHI Department of Neurology, Tokyo Metropolitan Children's Medical Center, Japan

P-38

A CASE REPORT OF CEREBRAL CAVERNOUS HEMANGIOMA-ASSOCIATED HEMORRHAGE DURING THE TREATMENT OF FOCAL EPILEPSY

Aya GOJI Pediatrics, The University of Tokushima, Japan

P-39

SUCCESSFUL TREATMENT OF KETOGENIC DIET IN A CASE WITH EPILEPTIC ENCEPHALOPATHY AND ALTERNATING HEMIPLEGIA WITH NOVEL *CACNA1A* MUTATION

Mitsugu UEMATSU Pediatrics, Tohoku University School of Medicine, Japan

P-40

SPASTICITY: A SIDE EFFECT OF ADRENOCORTICOTROPIC HORMONE THERAPY ?

Atsuro DAIDA Division of Neurology, Saitama Children's Medical Center, Japan
Division of Pediatrics and Adolescent Medicine, Tokyo Medical University, Japan

P-41

A CASE OF LEVETIRACETAM-RESPONSIVE POSTTRAUMATIC WEST SYNDROME

Takushi INOUE Pediatrics, NHO Okayama Medical Center, Japan

P-42

A CASE OF COMBINED GENERALIZED AND FOCAL EPILEPSY WITH IMPAIRED HIGHER CORTICAL FUNCTION

Kantaro KOBAYASHI Pediatrics, Shizuoka City Shimizu Hospital, Japan

P-43

AIMS AND OUTCOMES OF CORPUS CALLOSOTOMY IN CHILDREN WITH INTRACTABLE EPILEPSY: A SINGLE-CENTER RECENT EXPERIENCE IN JAPAN

Yuichi TATEISHI Pediatrics, Hiroshima University Hospital, Japan

CURRICULUM VITAE

Invited Lecturers

Katsuhiro KOBAYASHI

1983: Graduated from Okayama University Medical School (Japan)
1987: Received a degree of Doctor of Medical Science from Okayama University Graduate School (Japan)
1997: Assistant Professor, Department of Child Neurology, Okayama University Hospital (Japan)
July, 1997-June, 1998: A visiting researcher at the Montreal Neurological Institute (Montreal, Canada)
December, 2015-: Professor, Department of Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (Japan)

▪ Present Position

Professor, Department of Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (Japan)

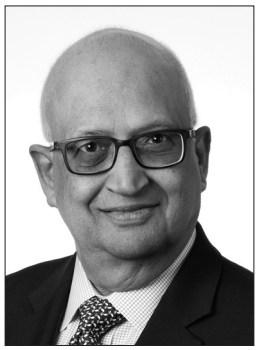
▪ Awards

1992: J. A. Wada Prize of the Japan Epilepsy Society
2003: Prize from the Japan Epilepsy Research Foundation

▪ Board

2001-: Board member of the Japanese Society for Brain Electromagnetic Topography
2004-: Board Director member of the Japanese Society of Child Neurology
2005-: Board Director member of the Japan Epilepsy Society
2005-: Board member of the Japanese Society of Clinical Neurophysiology
2018-: Vice Chairperson of the Board of Councilors of the Infantile Seizure Society

Raman SANKAR



MD, PhD, FAAN, FAES
Distinguished Professor of Neurology and Pediatrics
Rubin Brown Endowed Chair & Chief of Pediatric Neurology
David Geffen School of Medicine at UCLA
Children's Discovery and Innovation Institute
UCLA Mattel Children's Hospital
Los Angeles, California

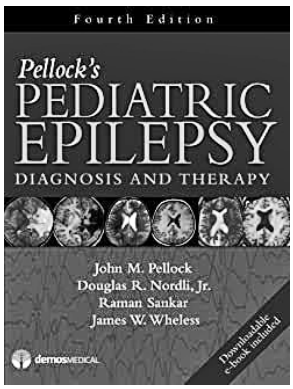
Raman Sankar, MD, PhD, is Distinguished Professor of Neurology and Pediatrics and Chief of Pediatric Neurology at the David Geffen School of Medicine at the University of California, Los Angeles. He holds the Rubin Brown Endowed Chair in Pediatric Neurology.

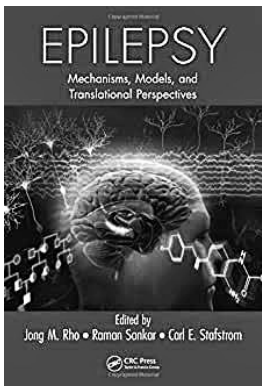
Dr. Sankar is a graduate of the University of Bombay, India. He obtained his PhD from the University of Washington in Medicinal Chemistry (1974) and was involved in teaching and research for several years prior to entering Tulane Medical School, where he obtained his MD in 1986. He trained in pediatrics at the Children's Hospital of Los Angeles. He completed his training in neurology and pediatric neurology at UCLA.

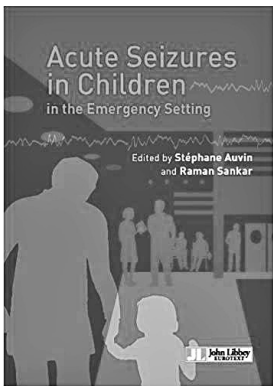
His laboratory research has addressed the mechanisms of seizure-induced injury and epileptogenicity in the developing brain. He has also undertaken studies to improve the throughput for screening compounds for antiepileptogenic action on the developing brain. Recent studies have demonstrated connections between the epileptic state, physiologic stress, inflammation and how these factors modify the serotonergic tone in the brain stem-hippocampal pathways resulting in depression. Ongoing studies are exploring the mechanistic connections between epilepsy and autism. He is a member of an active pediatric epilepsy program at UCLA that is well known internationally for many advances in pediatric epilepsy surgery.

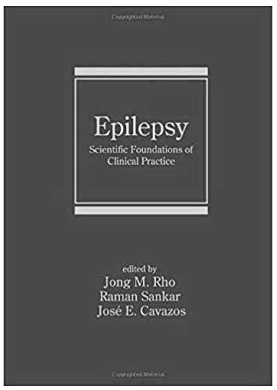
Dr. Sankar has authored more than 250 research articles, reviews and book chapters. He has also co-edited text books on pediatric epilepsy as well as the applications of basic science in epilepsy research. He is a member of the editorial board of *Epilepsy & Behavior* and has served on the editorial boards of *Epilepsia* and *Epilepsy Currents*. He is an elected Fellow of the American Academy of Neurology, the American Epilepsy Society, and the American Pediatric society. Dr. Sankar is a member of the Professional Advisory Board of the Epilepsy Foundation. He has been a member of the Commission on Neurobiology of the International League Against Epilepsy and presently serves on the Commission's Task Force for the Workshop on the Neurobiology of Epilepsy (WONOEP). **He received the highest recognition of the American Epilepsy Society, the Founders Award, in December of 2018.**

(Previous books edited/authored)









Hiroki NARIAI

Assistant Professor of Pediatrics, Division of Pediatric Neurology, David Geffen School of Medicine at UCLA

▪ Education

Medical School: Keio University School of Medicine, Tokyo, Japan
2005: Doctor of Medicine (M.D.)
2019: Doctor of Philosophy in Medicine (Ph.D.) by Dissertation

▪ Postgraduate Training

Rotating Residency and Pediatrics
2005-2009: Aso Iizuka Hospital, Fukuoka, Japan / Keio University Hospital, Tokyo, Japan

Research/Clinical Neurophysiology/Pediatric Epilepsy
2009-2011: Children's Hospital of Michigan / Wayne State University School of Medicine, Detroit, Michigan

Pediatric and Pediatric Neurology Residency
2011-2016: Albert Einstein College of Medicine, Bronx, New York

Clinical Neurophysiology and Epilepsy Fellowship
2016-2018: David Geffen School of Medicine at UCLA, Los Angeles, California

▪ Honors/Awards

2016: The Isabelle Rapin MD Scholarly Activity Award, Albert Einstein College of Medicine
2018: The Susan S. Spencer M.D. Clinical Research Training Scholarship in Epilepsy

▪ Reseaech Interst

- Pediatric epilepsy
- Epilepsy surgery
- EEG computational analysis
- Clinical research / Biostatistics

Atsuo FUKUDA

▪ Education

1989 Ph.D in Medical Sciences, Department of Physiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

1983 M.D. Faculty of Medicine, Kyushu University, Fukuoka, Japan

▪ Awards, Honors, Fellowships

2011 External Reviewer for the Chairman, University of Pittsburgh School of Medicine, USA

2010 Programme of European Neuroscience Schools, Lecturer, Obergurgl, Austria

2009 Advisor, Ewha Womans University, Korea

2006 Opponent in the Academic Dissertation, University of Helsinki, Finland

2001, 2006 External Reviewer of the Faculty, University of Wisconsin-Madison, USA

1989 Pimley Postdoctoral Fellowship, Stanford University, USA

1988 Outstanding Research Award, Alumni Society of the Department of Gynecology and Obstetrics, Kyushu University, Japan

▪ Research and Administrative Experiences

2016- Special Adviser to the President (Globalization Promotion)
Hamamatsu University School of Medicine, Hamamatsu, Shizuoka 431-3192, Japan

1998- Professor and Chairman
Department of Neurophysiology, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka 431-3192, Japan

1995 Associate Professor
Department of Physiology, Nagoya City University Medical School, Nagoya, Japan

1993 Assistant Professor
Department of Physiology, Nagoya City University Medical School, Nagoya, Japan

1989-1992 Postdoctoral Fellow with Dr. D.A. Prince, Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA, USA

1985-1989 Ph.D. Research, Graduate Student with Dr. Y. Oomura, Department of Physiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

▪ Publications

1 Watanabe *et al.* Developmentally regulated KCC2 phosphorylation is essential for dynamic GABA-mediated inhibition and survival. ***Science Signal*** 2019, 12: eaaw9315.

2 Murakami *et al.* MHC class I in dopaminergic neurons suppresses relapse to reward seeking. ***Science Advances***. 2018, 4, eaap7388.

3 Mutoh *et al.* Biallelic variants in *CNPY3*, encoding an endoplasmic reticulum chaperone, cause early-onset epileptic encephalopathy, ***Am J Hum Genet***. 2018 102: 321–329.

Shinichi HIROSE

Shinichi HIROSE MD, PhD is Professor and Chairman of Department of Pediatrics and Director of Research Institute for the Molecular Pathomechanisms of Epilepsy, Fukuoka University. He was an ex-executive committee member of the International Pediatric Association. His interests include the molecular pathomechanism of epilepsies and novel treatments for developmental and epileptic encephalopathies. He has worked extensively in the area of causative mutations and their molecular consequences in the neurophysiological mechanisms underlying epilepsies and has published extensively on molecular pathomechanisms of epilepsies. He is the principal investigator of numerous clinical studies and has directed various research projects, including studies on disease-specific induced pluripotent stem cells established for epilepsy, resulting in a prolific record of publication.

▪ Education

1980	M.D. Fukuoka University, School of Medicine
1984-1988	Graduate research in Biochemistry, Fukuoka University School of Medicine
1988	Ph.D. Fukuoka University, School of Medicine (Biochemistry)

▪ Postdoctoral Training

1980-1982	Resident, Fukuoka University Hospital
1982-1984	Clinical Fellow in Pediatrics, Fukuoka University Hospital
1988-1992	Research associate, Institute of Pathology, Case Western Reserve University, Cleveland Ohio

▪ Academic appointments

1992-1992	Associate Physician in Pediatrics, Fukuoka University Hospital
1992-1994	Instructor in Pediatrics, Fukuoka University Hospital
1994-1997	Assistant Professor, Department of Pediatrics, School of Medicine Fukuoka University
1997-2005	Associate Professor, Department of Pediatrics, School of Medicine, Fukuoka University
2006	Professor and Chairman, Department of Pediatrics, School of Medicine, Fukuoka University
2006-2010	Director, The Research Center for the Molecular Pathomechanisms of Epilepsy, Fukuoka University
2011-	Director, Central Research Institute for the Molecular Pathomechanisms of Epilepsy, Fukuoka University

Mitsuhiro KATO

Dr. Mitsuhiro Kato graduated Yamagata University in 1988 and underwent training in Pediatric Neurology at Tottori University (1991-1992) and worked at University of Chicago (2001-2003) to advance his research interest in brain malformations. In 2002, he initiated a research project to reveal the molecular mechanisms underlying age-dependent epileptic encephalopathies, now called developmental and epileptic encephalopathies, and found several responsible genes particularly for Ohtahara syndrome, such as *ARX, STXBP1, SPTAN1, KCNQ2, GNAO1*, etc. He served as one of editorial board members of Epilepsia (2011-2017) and also one of genetic commission members of ILAE (2013-2017). He organized a group of pediatric neurologists and neuroradiologists to discuss the undiagnosed cases in Japan, so called Zao seminar or the Annual Zao Conference on Pediatric Neurology, in 1996, which is now successfully making progress in communication and collaboration in the field of pediatric neurology with more than 1,200 members. He is serving as Chairman of Internationalization Promotion Committee of the Japanese Society of Child Neurology since 2014 and an executive board member of International Child Neurology Association since 2018. He is Board Certified in Pediatrics, Pediatric Neurology, Clinical Genetics, and Epileptology.

His research interests involve 1) the development of integrated system for the patients with brain malformation, 2) molecular mechanisms of developmental and epileptic encephalopathies (DEE), 3) precision medicine for the patients with DEE, 4) the establishment of the concept of 'interneuronopathy', 5) revealing etiology and gene therapy for pediatric neurotransmitter diseases, and 6) molecularly-targeted therapy for mTOR-related disorders.

▪ **Publication List** (198 papers)

1. Takata A, ... Kato M, Matsumoto N: Comprehensive analysis of coding variants highlights genetic complexity in developmental and epileptic encephalopathy. *Nat Commun* 2019;10:2506
2. Nakashima M, Kato M, Aoto K, et al.: *De novo* hotspot variants in *CYFIP2* cause early-onset epileptic encephalopathy. *Ann Neurol* 2018;83:794-806
3. Mutoh H*, Kato M*, Akita T*, et al.: Biallelic Variants in *CNPY3*, Encoding an Endoplasmic Reticulum Chaperone, Cause Early-Onset Epileptic Encephalopathy. *Am J Hum Genet* 2018;102:321-329 (*co-first author)
4. Miyatake S*, Kato M*, Sawaishi Y, et al.: Recurrent *SCN3A* p.Ile875Thr variant in patients with polymicrogyria. *Ann Neurol* 2018;84:159-161 (*co-first author)
5. Fassio A, Esposito A, Kato M, et al.: De novo mutations of the *ATP6V1A* gene cause developmental encephalopathy with epilepsy. *Brain* 2018;141:1703-1718
6. Akita T*, Aoto K*, Kato M*, et al.: *De novo* variants in *CAMK2A* and *CAMK2B* cause neurodevelopmental disorders. *Ann Clin Transl Neurol* 2018;5:280-296 (*co-first author)

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Natrujee WIWATTANADITTAKUL

Assistant Professor, Division of Child Neurology, Faculty of Medicine, Chiang Mai University, Thailand

▪ **Education:**
- 2000-2006 Doctor of Medicine, Chiang Mai University, Chiang Mai, Thailand
- 2008-2011 Residency in Pediatrics, Chiang Mai University, Chiang Mai, Thailand
- 2011-2013 Clinical fellowship in Pediatric Neurology, Mahidol University, Bangkok,Thailand
- 2014-2016 Research fellowship in Pediatric Epilepsy, Children's National Medical Center, Washington DC, USA

▪ **Publications:**

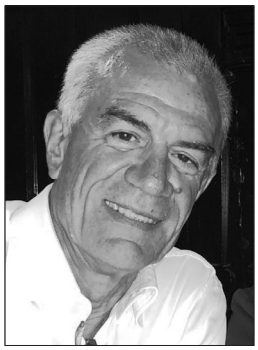
1. Wiwattanadittakul N, Katanyuwong K, Jetjumnong C, Sittiwangkul R, Makonkawkeyoon K. Pericardial effusion and cardiac tamponade after ventriculoperitoneal shunt placement: a case report. Acta Neurochir (Wien). 2016 Oct; 158(10): 2019-21.
2. Pearl PL, Wiwattanadittakul N, Roullet JB, Gibson KM. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Ledbetter N, Mefford HC, Smith RJH, Stephens K, editors. Succinic Semialdehyde Dehydrogenase Deficiency. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017.2004 May 5 [updated 2016 Apr 28].
3. Khongkhatithum C, Thampratankul L, Wiwattanadittakul N, Visudtibhan A. Intravenous levetiracetam in Thai children and adolescents with status epilepticus and acute repetitive seizures.Eur J Paediatr Neurol. 2015 Jul; 19(4): 429-34.
4. Attri SV, Singhi P, Wiwattanadittakul N, Goswami JN, Sankhyan N, Salomons GS, Roullett JB, Hodgeman R, Parviz M, Gibson KM, Pearl PL. Incidence and Geographic Distribution of Succinic Semialdehyde Dehydrogenase (SSADH) Deficiency. JIMD Rep. 2017; 34: 111-115.
5. Shellhaas RA, Wusthoff CJ, Tsuchida TN, Glass HC, Chu CJ, Massey SL, Soul JS, Wiwattanadittakun N, Abend NS, Cilio MR; Neonatal Seizure Registry. Profile of neonatal epilepsies: Characteristics of a prospective US cohort. Neurology. 2017 Aug 29; 89(9): 893-899.
6. Natrujee Wiwattanadittakul, Morgan Prust, William Davis Gaillard, An Massaro, Gilbert Vezina, Tammy N. Tsuchida, Andrea L. Gropman. The utility of EEG monitoring in neonates with hyperammonemia due to T inborn errors of metabolism. Molecular Genetics and Metabolism.125 (2018) 235-240.

Nicola SPECCHIO

Current position
Head of Epilepsy Unit at Department of Neuroscience, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

In 1999 I graduated in Medicine at the University of Bari, Bari, Italy. Between 1999 and 2004 I trained as a Neurologist at the Neurological Institute of the University of Bari, attending the general neurological ward, the Centre for the Study and Treatment of Epilepsy and the laboratory of neurophysiology. In 2000 I attended the King's College Hospital, London as research fellow where I participated to outclinic patients and epilepsy surgery meetings. In 2001 I attended the "Neuroscience Unit, Institute of Child Health and Great Ormond Street Hospital for Children, University College London" as research fellow. In 2004 I enrolled for a PhD course in Neuroscience at the "Department of Neurological and Psychiatric Science, University of Bari, Italy. In the same year I started my collaboration with Bambino Gesù Children's Hospital, IRCCS in Rome as Research Fellow under the supervision of Professor Federico Vigevano. During the years spent in Rome the research has been focused on classification and definition of epileptic syndromes, on genetics of epilepsy and epileptic encephalopathies. In 2007 I completed the PhD course in Neuroscience with the maximum scores. From 2008 to 2013 I had a Full position as a Consultant at Division of Neurology, Bambino Gesù Children Hospital, Roma. From the 2011 I am tutor for the Virtual Epilepsy Academy (VIREPA) of the International League Against Epilepsy. From 2014 I am Head of Rare and Complex Epilepsy Unit at Department of Neuroscience, Bambino Gesù Children's Hospital. During the year 2014 I received the National Scientific Award in Neurology (Associate Professor in the field 06/D6) and in Child Neuropsychiatry (Associate Professor in the field 06/G1). During the year 2018 I received the National Scientific Award in Child Neuropsychiatry (Full Professor in the field 06/G1). For the period 2011-2014, 2014-2017, 2017-2020 I was elected to the Board of Directors of the Italian League Against Epilepsy. I actively participated to national and international research projects. I am Author/coauthor of 130 articles published in International scientific journals, 8 book chapters. Current h-index: 31. I am habitual reviewer for the following journals: Epilepsia, Epilepsy Research, Brain Development, European Journal of Paediatric Neurology, Epileptic Disorders. In September 2016 I received the Young Investigator Award from the ILAE Europe. From April 2017 I am member of the ILAE Task force on Nosology and Classification. I was elected as Member of the ILAE Europe for the term 2017-2021.

Federico VIGEVANO



Federico was born in 1950 in Genoa, Italy. He completed his graduate education in medicine at the University of Rome La Sapienza Medical School in 1974 and his residency in Neurology in 1977. He continued his training in Marseille under the mentorship of such eminent epileptologists as Henri Gastaut and Carlo Alberto Tassinari. It was there that he developed a keen interest in the field of childhood epilepsy.

Since 1978 he joined the Children's Hospital Bambino Gesù as Pediatric neurologist, where he now holds the position of head of Neuroscience DPT. Here he dedicated his interest to the rigorous study of pediatric epilepsies, promoting prolonged video EEG and polygraphic seizure recordings. His endeavors enabled him to clearly define the semiology of seizures in early life and to better characterize some of the epilepsy syndromes, both focal such as Panayiotopoulos Syndrome and generalized as Reflex Benign Myoclonic Epilepsy. He identified a clinical entity that is currently recognized as a new syndrome called *Benign Infantile Familial Seizures*, of which now we know the genetic cause. His scientific work also was dedicated to a range of conditions associated with recurrent paroxysmal events that may imitate and/or be misdiagnosed as epilepsy. In 1989 he described a maneuver that can stop the attacks of sustained stiffening with prolonged apnea in genetic hyperekplexia. This "Vigevano maneuver" significantly reduced the risk of sudden death in children with this condition.

He has published as first author or co-author more than 200 papers in the most important international journals dedicated prevalently to epilepsy and paediatric neurology.
He has been President of the LICE (Italian League Against Epilepsy) from 1999 to 2002 and chair of the European Advisory Council of the ILAE from 2001 to 2005. In 2001 he received the Ambassador of Epilepsy title by ILAE and in 2016 the European Epileptology Award by the European ILAE Commission. He has been in the Scientific and/or Organizing Committee of the European Congress: Florence, Madrid, Vienna, Stockholm. Has been the Chair of the Scientific Committee of the International Congress on Epilepsy (Rome 2011).
He was the President of the 19th Annual Meeting of Infantile Seizure Society (ISS) that took place in Rome, September 2018. He is the organizer of the "International Course on Resistant Epilepsy" (Tagliacozzo – Italy). He participated as invited speaker at the most important international epilepsy and paediatric neurology congress.

Harvey B. SARNAT

▪ PERSONAL DATA

PRESENT POSITION
Professor of Pediatrics, Pathology (Neuropathology) and Clinical Neuroscience
University of Calgary Cumming School of Medicine (officially "retired" 1 July 2013; continue to work full-time without salary, mainly in research)
Paediatric Neurologist and Neuropathologist, Alberta Children's Hospital
Alberta Children's Hospital Research Institute, Owerko Centre, Calgary, Alberta, Canada

▪ CLINICAL INTERESTS

Fetal and neonatal neurology
Neuroembryology, developmental (fetal) neuroanatomy and neuropathology
Malformations of the nervous system of genetic and epigenetic origin

▪ RESEARCH INTERESTS

Neuroembryology and developmental neuropathology, with special reference to
a) immunocytochemical markers of neuronal and glial maturation in the normal human fetal and neonatal nervous system and in malformations;
b) neurodevelopmental basis of epileptogenic cortical dysplasias;
c) brain malformations due to genetic mutations, teratogenic toxins, congenital infections and fetal exposure to other adverse influences.

▪ BOARD CERTIFICATIONS AND ACCREDITATIONS

National Board of Medical Examiners, certified July 1, 1967
American Board of Pediatrics, certified March 25, 1973
American Board of Psychiatry and Neurology, certified "with special competence in child neurology" October 2, 1974
Royal College of Physicians and Surgeons of Canada, In Neurology, Fellowship December 6, 1982; recertified 2003, 2010

▪ EDUCATION:

DEGREES

Bachelor of Science (Zoology), June 15, 1963, University of Illinois, Urbana, Illinois
Master of Science (Neuroanatomy), June 11, 1965, University of Illinois College of Medicine, Chicago, Illinois
Doctor of Medicine, June 10, 1966, University of Illinois College of Medicine, Chicago, Illinois

POSTGRADUATE

Internship and Residency in Pediatrics, July 1, 1966 to June 30, 1968, University of Illinois Research and Educational Hospital, Chicago, Illinois
Residency in Neurology (Pediatric Neurology), September 1, 1970 to August 31, 1973, University of Virginia Hospital, Charlottesville, Virginia
Fellowship in Neuropathology, July 1, 1971 to June 30, 1972, University of Virginia Hospital, Charlottesville, Virginia (Dr. M.G. Netsky)

Tomoyuki AKIYAMA

▪ Education

1995-1999 Okayama University Graduate School of Medicine, Okayama, Japan
1989-1995 Okayama University School of Medicine, Okayama, Japan

▪ Postgraduate Training

1996-2001 Department of Child Neurology, Okayama University Hospital
1995-1996 Department of Paediatrics, Matsuyama Red Cross Hospital

▪ Fellowships

2007-2011 Division of Neurology, Hospital for Sick Children, Toronto, Canada (Clinical Fellow)
2004-2005 Division of Neurology, Hospital for Sick Children, Toronto, Canada (Research Fellow)
2003-2004 Department of Child Neurology, Okayama University Hospital (Clinical Fellow)
2002-2003 Department of Neonatology, Okayama Medical Center (Clinical Fellow)
2001-2002 Department of Child Neurology, Okayama University Hospital (Clinical Fellow)

▪ Professional Experience

2017-Present Department of Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (Associate Professor)
2017-Present Epilepsy Center, Okayama University Hospital (Vice Director)
2012-2017 Department of Child Neurology, Okayama University Hospital (Senior Assistant Professor)
2011-2012 Department of Pediatrics, Shizuoka Institute of Epilepsy and Neurological Disorders (Staff Pediatric Epileptologist)
2006-2007 Department of Child Neurology, Okayama University Hospital (Senior Assistant Professor)
2004-2006 Department of Child Neurology, Okayama University Hospital (Assistant Professor)

Derrick CHAN Wei Shih

Derrick Chan Wei Shih is a Senior Consultant and Head of Paediatric Neurology at KK Women's and Children's Hospital. He graduated from Nottingham University with Bachelor's in Medical Science (1996) and Bachelor of Medicine and Surgery (1998), passed his Membership exams for the Royal College of Paediatrics and Child Health in 2002 and obtained Specialist Accreditation in Paediatric Medicine in 2007. He trained in Paediatric EEG at Great Ormond Children's Hospital in London, UK and the Royal Children's Hospital in Melbourne, followed by Clinical Fellowship in Paediatric Epilepsy at the Hospital for Sick Children in Toronto. He obtained certification in Clinical Neurophysiology from the Canadian Society of Clinical Neurophysiology in 2008 and received my Master's Degree in Clinical Investigation in 2011. He set up the comprehensive epilepsy programme at KKH, including the epilepsy monitoring unit, ketogenic diet and complicated epilepsy clinics, vagus nerve stimulator implantation programme and epilepsy surgery programme. He is driving the paediatric epilepsy research programme and have established collaborations in Paediatric Epilepsy with Duke Durham. He has led the Paediatric Neurology team to clinical, research and educational excellence, expanding the team and establishing expertise in vital areas of paediatric neurology. He is an instructor and examiner for the ASEAN Epilepsy Academy (ASEPA) Electro-encephalography exam.

He has research interests in video analytics for seizure detection and HLA-B*1502 alleles in children with carbamazepine hypersensitivity. He is currently PI of NMRC HSRG grant "HSRG-OC17Jun: Cost containment in pharmacogenomic testing, identifying obstacles to implementation of pharmacogenomics and impact on anticonvulsant prescription patterns". He set up the Paediatric Autoimmune Epilepsy, Demyelination & Encephalitis Study (PAEDES) under the KKH NMRC Centre grant and has conducted translational research in close collaboration with Prof Salvatore Albani and the Singhealth/Duke-NUS Translational Immunology Institute. He is developing the Clinician Innovator track in Singhealth with A/Prof Henry Ho. As Vice-Chair (Research) for the Paediatrics ACP.

Wang-Tso LEE

Dr. Wang-Tso Lee is now professor and chief of Department of Pediatric Neurology, National Taiwan University Children's Hospital and professor of Department of Pediatrics and Graduate Institute of Brain and Mind Sciences, College of Medicine, National Taiwan University, Taipei, Taiwan. He finished University medical education in College of Medicine, National Taiwan University, Taiwan, and got the PhD degree from Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University. Dr. Lee did neurology research in Department of Neurology, Children's Hospital of Philadelphia, USA in 1999. He also went to several institutes in USA and Canada as visiting scholar in the past. He is interested in epilepsy, movement disorders, and neurotransmitter diseases. His Lab is focused on movement disorders and neurotransmitter research.

Chaiyos KHONGKHATITHUM

▪ Education

1997 The Degree of Doctor of Medicine (First Class Honors)
Mahidol University, Bangkok, Thailand
2003 The Diploma of Thai Board of Pediatrics, Medical Council of Thailand
2005 Certificate of Pediatric Neurology
The Royal College of Pediatricians of Thailand

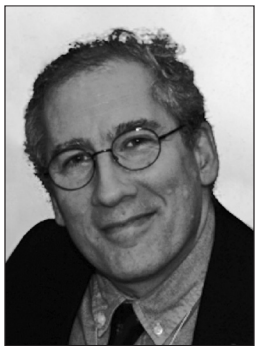
▪ Working Experiences

2000-2003 Resident in Pediatrics, Department of Pediatrics, Ramathibodi Hospital, Bangkok 10400, Thailand
2003-2005 Fellow in Pediatric Neurology, Division of Neurology, Department of Pediatrics, Ramathibodi Hospital, Bangkok 10400, Thailand
2005-2006 Lecturer in Pediatric & Pediatric Neurology
Division of Neurology, Department of Pediatrics, Ramathibodi Hospital, Bangkok 10400, Thailand
2006-2008 Pediatric Clinical Neurophysiology & Epilepsy Fellow
Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland, Ohio USA
2008-2009 Pediatric Neuromuscular Fellow
Children's Medical Center, UTSouthwestern Medical Centers, Dallas, Texas USA
2009-present Assistant Professor in Pediatric Neurology
Division of Neurology, Department of Pediatrics, Ramathibodi Hospital, Bangkok 10400, Thailand

▪ Researches and Publication

1. **Khongkhatithum C**, Khowsatit P. Outcome of myocarditis in children and effects of intravenous immunoglobulin therapy. (A thesis submitted in partial fulfillment of the requirements for the diploma of Thai board of Pediatrics 2003)
2. Visudhiphan P, Visudtibhan A, Chiemchanya S, **Khongkhatithum C**. Severe neonatal seizures in familial hypomagnesemia: Long-term outcomes of two siblings after 12 and 23 years of treatment. Pediatr Neurol. 2005 Sep; 33(3): 202-5.
3. **Khongkhatithum C**, Visudtibhan A, Chiemchanya S, Visudhiphan P, Sanvivad P, Larbcharoensub N, Phudhicharoenrat S. An unusual presentation of multicentric anaplastic astrocytoma in a child. J Clin Neurosci. 2007 Feb; 14(2): 176-9
4. **Khongkhatithum C**, Visudtibhan A, Thampratankul L, Chiemchanya S, Visudhiphan P Neurological and developmental outcomes following neonatal seizures. Poster Presentation in the International Symposium on Status Epilepticus in Infants and Young Children, Osaka, Japan, April, 2006
5. Visudtibhan A, Siripornpanich V, **Khongkhatithum C**, Chiemchanya S, Sirijunpen S, Raungkanchanasetr S, Visudhiphan P. Migraine in Thai Children: prevalence in junior high school students. J Child Neurol. 2007 Sep; 22(9): 1117-20.
6. **Khongkhatithum C**, Monisha G. Use of intravenous Levetiracetam in a pediatric tertiary care hospital. Poster presentation in the American Epilepsy Society 61st Annual Meeting, Philadelphia, PA, November 30-December 4, 2007
7. Koubeissi MZ, **Khongkhatithum C**, Janus AI, Lüders H. Scotosensitive myoclonic seizures in MERRF. Neurology. 2009 Mar 3; 72: 858
8. Thampratankul L, **Khongkhatithum C**, Visudtibhan A. Efficacy and safety of zonisamide in Thai children and adolescents with intractable seizures. J Child Neurol. 2015; 30(4): 527-31
9. **Khongkhatithum C**, Thampratankul L, Wiwattanadittakul N, Visudtibhan A. Intravenous levetiracetam in Thai children and adolescents with status epilepticus and acute repetitive seizures. Eur J Paediatr Neurol. 2015; 19: 429-34
10. Waisayarat J, Suriyonplengsaeng C, **Khongkhatithum C**, Rochanawutanon M. Severe congenital nemaline myopathy with primary pulmonary lymphangiectasia: unusual clinical presentation and review of the literature. Diagn Pathol. 2015 Apr 16; 10:27
11. Suriyonplengsaeng C, Dejthevaporn C, **Khongkhatithum C**, Sanpapant S, Tubthong N, Pinpradap K, Srinark N, Waisayarat J. Immunohistochemistry of sarcolemmal membrane-associated proteins in formalin-fixed and paraffin embedded skeletal muscle tissue: a promising tool for the diagnostic evaluation of common muscular dystrophies. Diagn Pathol. 2017 Feb 20; 12(1): 19.
12. Sudnawa KK, Chirdkiatgumchai V, Ruangdaraganon N, **Khongkhatithum C**, Udomsubpayakul U, Jirayucharoensak S, Israsena P. Effectiveness of Neurofeedback Versus Medication in Treatment of ADHD. Pediatr Int. 2018 Jun 22. doi: 10.1111/ped.13641. [Epub ahead of print]

Renzo GUERRINI



Prof. Renzo Guerrini is Head and Director of the Paediatric Neurology and Neurogenetics Unit and Laboratories, and of the Neuroscience Department at the Children's Hospital A. Meyer-University of Florence, Italy. His research focuses on the neurophysiology, neuroimaging, neurogenetics and the treatment of pediatric epilepsies, brain development and intellectual disability. He has been Associate Editor of Epilepsia (2006-2014) and Member of the Editorial Board of various scientific journals, including Neurology, Neuropediatrics, Journal of Child Neurology, Seizure, Epileptic Disorders. He has participated to, or coordinated, task forces, committees and commissions of international bodies and initiatives and has been the principal investigator of numerous research project, including DESIRE (Development and Epilepsy - Strategies for Innovative Research to improve diagnosis, prevention and treatment in children with difficult to treat Epilepsy), a major EU Research project of the 7th framework programme. He received the Ambassador for Epilepsy ILAE Award, 2003, the American Epilepsy Society's Clinical Research Recognition Award, 2012 and the Elisa Frauenfelder Prize on Research and Innovation, 2019. He has co-authored over 500 papers in Peer-reviewed journals and 12 books. His Official H-Index is 96.

Hiroshi OTSUBO

▪ CV

1983	Graduate Shinshu University, School of Medicine
1988-1989	Research fellow, Division of Neurosurgery, The Hospital for Sick Children
1989-1994	EEG Fellow, EEG & Clinical Neurophysiology, Laboratory, The Hospital for Sick Children
1994-2008	Assistant Professor, Department of Pediatrics, University of Toronto
1997-present	Director of Operations EEG & Clinical Neurophysiology and Epilepsy Monitoring Unit (EMU)
2008-2017	Associate professor, Department of Pediatrics, University of Toronto
2017-present	Professor, Department of Pediatrics (Neurology), University of Toronto

▪ Professional practice

Electroencephalography (EEG)
Magnetoencephalography (MEG)
Epilepsy surgery

▪ Committee

Japanese society of brain electromagnetic topography (JSBET)
Japan child neurology society
Japan epilepsy society
International society of active clinical MEG (ISACM)

PEER REVIEWED ARTICLES, 184
NON-PEER REVIEWED PUBLICATIONS
Journal Articles, 23
Book chapters, 16
Other publications, 14

Jun NATSUME

▪ Education

1990 M.D., Nagoya University School of Medicine, Nagoya
1998 Ph.D., Nagoya University Graduate School of Medicine, Nagoya

▪ Occupation

1990-1993 Residency, Department of Pediatrics, Anjo Kosei Hospital
1993-1994 Department of Pediatrics, Nagoya University Hospital
1998-1999 Department of Pediatrics, Gifu Social Insurance Hospital
1999-2002 Research Fellow, Department of Neurology and Neurosurgery, McGill University, Montreal, Canada
2002-2005 Department of Pediatrics, Japanese Red Cross Nagoya First Hospital
2005 Department of Pediatrics, Nagoya University Hospital
2006 Assistant Professor, Department of Pediatrics, Nagoya University Graduate School of Medicine
2007-2008 Lecture, Department of Pediatrics, Nagoya University Graduate School of Medicine
2009-2014 Associate Professor, Department of Pediatrics, Nagoya University Graduate School of Medicine
2015- Professor, Department of Developmental Disability Medicine, Nagoya University Graduate School of Medicine, Japan

▪ Selected Publications

1) Yokoi S, Natsume J, et al. Hippocampal diffusion abnormality after febrile status epilepticus is related to subsequent epilepsy. Epilepsia. 2019 Jul; 60(7): 1306-1316.
2) Ogawa C, Natsume J, et al. Cytotoxic edema at onset in West syndrome of unknown etiology: A longitudinal diffusion tensor imaging study. Epilepsia. 2018 Feb; 59(2): 440-448.
3) Natsume J, Ogawa C, Fukasawa T, et al. White matter abnormality correlates with developmental and seizure outcomes in West syndrome of unknown etiology. AJNR Am J Neuroradiol. 2015 Nov 19.
4) Natsume J, Bernasconi N, Andermann F, Bernasconi A. MRI volumetry of the thalamus in temporal, extratemporal and idiopathic generalized epilepsy. Neurology 2003; 60(8): 1296-1300.
5) Natsume J, Kumakura Y, Bernasconi N, et al. Alpha-[^{11}C] methyl-L-tryptophan and glucose metabolism in patients with temporal lobe epilepsy. Neurology 2003; 60(5): 756-761.
6) Natsume J, Watanabe K, Maeda N, et al. Cortical hypometabolism and delayed myelination in West syndrome. Epilepsia 1996; 37(12): 1180-1184.

Ingrid SCHEFFER

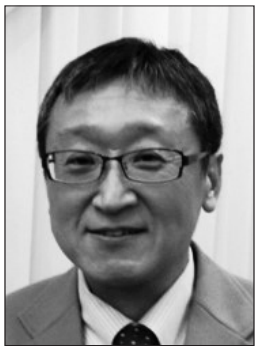
Laureate Professor Ingrid Scheffer AO MB BS PhD FRACP FAES FAA FRS PresAHMS

Laureate Professor Ingrid Scheffer AO is a physician-scientist whose work as a paediatric neurologist and epileptologist at the University of Melbourne and Austin Health has led the field of epilepsy genetics over more than 25 years, in collaboration with Professor Samuel Berkovic and molecular geneticists. This resulted in identification of the first epilepsy gene and many more genes subsequently. Professor Scheffer has described many novel epilepsy syndromes and refined genotype–phenotype correlation of many genetic diseases. Her major interests are in the genetics of the epilepsies, epilepsy syndromology and classification, and translational research. She collaborates on research focused on the genetics of speech and language disorders, autism spectrum disorders, cortical malformations and intellectual disability. She led the first major reclassification of the epilepsies in three decades for the International League Against Epilepsy in 2017. She has received many awards, including the 2007 American Epilepsy Society Clinical Research Recognition Award, the L'Oréal-UNESCO Women in Science Laureate for the Asia-Pacific region for 2012 and the ILAE Ambassador for Epilepsy Award. In 2014, she was elected as a Fellow of the Australian Academy of Science, and also as Vice-President and Foundation Fellow of the Australian Academy of Health and Medical Sciences. She was a co-recipient of the 2014 Australian Prime Minister's Prize for Science and she was awarded the Order of Australia in 2014. In 2018, she was elected as a Fellow of the Royal Society. In 2020, she became the second President of the Australian Academy of Health and Medical Sciences.

Yushiro YAMASHITA

Professor Yushiro Yamashita graduated from Kurume University School of Medicine, Kurume, Japan in 1983.
He worked as an expert on Pediatric Neurology for 2 months in Islamabad Children's Hospital, Pakistan sent by JICA in 1989.
From 1990 to 93, he worked as a Research Fellow at the Departments of Pediatrics (Section of Pediatric Neurology), in Baylor College of Medicine, Houston, Texas.
He learnt Summer Treatment Program for children with ADHD in State University of NY at Stony Brook, Buffalo in 2003, then he has been running STP in his hometown, Kurume for 15 years.
His major interest is neurodevelopmental disorders; ADHD, Rett syndrome, LD, and Autism Spectrum Disorder.
In 2013, he became Professor, Division of Developmental Disorders, Department of Pediatrics & Child Health, Kurume University School of Medicine and from 2015, he serves as a Professor and Chairman.

Hideaki KANEMURA



Dr Kanemura has received his PhD in University of Yamanashi during the period of 2003. Currently, he is working as professor in Department of Pediatrics, Toho University Medical Center Sakura Hospital. His research has included pediatric neurology, epilepsy, and developmental disorders. He is serving as an editorial member of several reputed journals like Brain & Development. He has authored epilepsy and pediatric neurological clinical research articles/books. He is a councilor of Japanese Society of Child Neurology, Japanese Epilepsy Society, Japanese Society of Clinical Neurophysiology, and Japanese Society of Cognitive Neuroscience.

Susumu ITO

Assistant Professor, Department of Pediatrics, Tokyo Women's Medical University
Member, Dravet Syndrome JP

▪ Education

2002 M.D. Shinshu University, School of Medicine
2010 Ph.D. Tokyo Women's Medical University, Graduate School of Medicine

▪ Postgraduate Training

2002 - 2003 Resident, Department of Pediatrics, Tokyo Women's Medical University
2003 - 2011 Fellow, Department of Pediatrics, Tokyo Women's Medical University
2011 - Present Assistant Professor, Department of Pediatrics, Tokyo Women's Medical University
2011 - 2013 Research Fellow, Epilepsy center, Cleveland Clinic
2015 - 2016 Fellow, Division of Critical Care Medicine, National Center for Child Health and Development

▪ Award

2010 The 43rd Japan Epilepsy Society Congress Excellent Poster Award
2013 The 30th International Epilepsy Congress Gold Star Poster Award

Ki Joong KIM

Department of Pediatrics, Seoul National University Children's Hospital, Seoul, Korea

Dr. Kim graduated and obtained MD, MS, and PhD degrees from the Seoul National University College of Medicine, Seoul, Korea. He completed his residency and fellowship training in the Department of Pediatrics at the Seoul National University Hospital.
He is a pediatric neurologist with a special interest in pediatric epilepsy.
His current status is a Professor and Chief of Department of Pediatrics at Seoul National University College of Medicine, and Seoul National University Children's Hospital.
He is interested in the diagnosis and management of pediatric patients with epilepsy, particularly video-EEG analysis of various epileptic encephalopathies and surgical treatment of intractable pediatric epilepsies.
His research interests are mainly focused on the genetic analysis of children and their families with neurogenetic disorders including developmental and epileptic encephalopathies.

Andrew Laurence LUX

Dr Andrew Laurence Lux, BMedSci BMBS MBA MSc PhD FRCPCH
Consultant Paediatric Neurologist

Andrew Lux a Consultant Paediatric Neurologist at Bristol Royal Hospital for Children, Bristol, UK. He has special responsibilities within his department for the management of epilepsy, seizures in the neonatal period and infancy, and fetal neurological abnormalities. He also runs regular clinics in at University Hospitals Plymouth NHS Trust. He graduated from Nottingham University Medical School and trained in General Practice in Kingston-upon-Hull before undertaking paediatric training there and in Cardiff, Wales. He worked as a General Paediatrician in St Lucia, West Indies for 3 years before returning to the UK to train in Paediatric Neurology in Bristol. He spent a year as a Fellow in Pediatric Epilepsy and Clinical Neurophysiology at St Louis Children's Hospital and Washington University in St Louis. He completed an MSc in Medical Statistics at the London School of Hygiene & Tropical Medicine, and a PhD at the University of Bath, where he presented a thesis on The Epidemiology and Treatment of Infantile Spasms. That work included research findings from the West Delphi Consensus on Case Definitions and Outcome Measures for Infantile Spasms (Epilepsia, 2004) and the initial trial findings from the United Kingdom Infantile Spasms Study (Lancet, 2004). He later completed an MBA at The Open University, where he did a case study on Improving Systems and Processes on the Paediatric Epilepsy Services Programme. He has been an editorial board member of the journals *Developmental Medicine and Child Neurology, Epileptic Disorders,* and the *European Journal of Paediatric Neurology*. He has been a member of the Trial Steering Committee of the International Collaborative Infantile Spasms Study (ICISS) and he retains a strong interest in research on infantile spasms.

ABSTRACTS

Invited Lecturers

L-01 INTRODUCTION TO THE SYMPOSIUM ON DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY

Katsuhiro KOBAYASHI

Department of Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan

Developmental and epileptic encephalopathy (DEE) is a grave clinical issue in infancy and childhood that requires multi-disciplinary approaches. It is very important to elucidate its pathogenesis and pathophysiology and to develop a rational treatment strategy. I intend to organize the 21st Annual Meeting of the Infantile Seizure Society (ISS) around investigating the issues of DEE involving clinical neurophysiology as the cornerstone of the meeting. Through neurophysiology, clinical epileptology can be understood as electrical dysfunctions of the brain, and basic neuroscience, including genetics, metabolism, brain ontogenesis, and other fields, reveals how electrical disturbances occur in the neuronal system, leading to the generation of seizures. Neurophysiology may be regarded as a link between clinical epileptology and basic neuroscience.

Epileptic encephalopathy embodies the notion that the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone, and that these can worsen over time. Abundant EEG epileptic discharges are considered to interfere with development, resulting in cognitive slowing and regression, sometimes with psychiatric and behavioral consequences. In DEE, such an epileptic encephalopathy process may be combined with developmental problems that are directly or indirectly brought about by etiologies, particularly genetic mutations. Therefore, intense neurophysiological abnormalities should play a crucial role in the pathogenesis of DEE. I hope that Okayama, where the late Professor Ohtahara discovered Ohtahara syndrome, would be an appropriate place to discuss DEE as it relates to neurophysiology.

OVERVIEW OF DEVELOPMENTAL EPILEPTIC ENCEPHALOPATHIES

L-02

Raman SANKAR
Neurology and Pediatrics, Geffen School of Medicine UCLA, CA, USA

The concept of epileptic encephalopathies draws from syndromic approaches to classifying epilepsies and the term dates back to its use by Henri Gastaut. It has evolved through versions of the classification of the epilepsies by the International League Against Epilepsy. These syndromes pose unique challenges to unraveling the mechanisms that drive the remarkably distinctive constellation of seizure types and electroencephalographic features, even in an era of explosion in the knowledge of genetic variants that contribute to altered neuronal excitability. These encephalopathies are expressions of dauntingly diverse causes – for example, infantile spasms, now called epileptic spasms by the ILAE, may derive from hypoxic ischemic encephalopathy or tuberous sclerosis or mutations in the ARX gene (or numerous other causes). Further, emerging genetic knowledge has revealed rather extensive genetic heterogeneity as well as phenotypic heterogeneity (sometimes called pleiotropy) which challenges classification. It is indeed remarkable that with such diversity in etiology, we can encounter such a typical semiology and neuronal network behavior that is so characteristic of these disorders.

It is unfortunate that we are not gathering in person in Okayama to pay homage to the late Professor Ohtahara and recall his exquisite descriptions of these encephalopathies and the sequential progression from his eponymic Ohtahara syndrome to West syndrome and further onward to the Lennox-Gastaut syndrome. This presentation will remind us of his seminal work in the area and give a broad overview of what we have learned from genetics, neuroimaging, and neurophysiology. Attempts to model these disorders in animals have been especially challenging and some available models will also be described. It is hoped that some of the concepts alluded to in this overview will receive more detailed treatment by the distinguished panel of speakers at this conference.

L-03 COMPUTATIONAL EEG ANALYSIS IN EPILEPTIC ENCEPHALOPATHY

Hiroki NARIAI

Pediatric Neurology / Pediatrics, University of California, Los Angeles, USA

Electroencephalogram (EEG) has been a crucial tool to evaluate children with epileptic encephalopathy. EEG can diagnosis, identify an epileptogenic focus, and monitor treatment response. Traditional visual analysis is still the gold standard. However, one of the significant issues with visual analysis is its subjective and qualitative nature. Poor inter-rater (or intra-rater) reliability is also a concern. Introduction of digital EEG system and recent advances in computational infrastructure provide a promise in this field. Quantitative computational EEG analysis enables the objective characterization of EEGs. For example, high frequency oscillations (HFOs) (EEG activity > 80 Hz) is reported initially as a promising EEG biomarker of epileptogenic zones in invasive EEGs. Recent reports have demonstrated that such HFOs can be analyzed in non-invasive scalp EEGs. In scalp EEG, the importance of data cleaning before getting to the actual cerebral waveforms should not be underestimated. Such examples include the selection of poor-quality EEG channels and independent component analysis (ICA) to remove muscle and movement artifacts. Advanced statistical methods including machine learning may further enhance efficiency and accuracy in data cleaning and data analysis in a larger dataset. This talk will summarize the current practice of the objective computational EEG analysis in epileptic encephalopathy, focusing on West syndrome.

PIVOTAL ROLES OF NEURONAL EXCITATION-INHIBITION DYNAMICS IN EPILEPTOGENESIS OF HUMAN AND ANIMAL MODELS

L-04

Atsuo FUKUDA

Department of Neurophysiology, Hamamatsu University School of Medicine, Japan

Most of epilepsies are caused primarily by an imbalance of excitation and inhibition, both in neuronal and network levels. The next-generation DNA sequencing technology has accelerated the identification of epilepsy-associated gene mutations, especially in infantile patients with intractable epilepsy. Functional analyses of mutated products revealed that some mutants cause alterations in membrane excitability of neurons or depression of inhibition. Here I introduce our recent reports on causative gene mutations in epilepsy patients (e.g., *CNPY3, KCBN1, CAMK2A*/*B*) with experimentally-confirmed electrophysiological changes in neuronal excitability.

I also focus on *SLC12A5* encoding KCC2, a main Cl^- extruder of neurons rendering the proper inhibitory function of GABA. Because any *SLC12A5* variant could be epileptogenic by causing deteriorated inhibition and collapse of excitation-inhibition balance. Three patients of epilepsy of infancy with migrating focal seizures had compound heterozygous mutations in *SLC12A5*. Heterologous transfection of variants, mimicking the patient status, resulted in $[Cl^-]_i$ significantly higher than wildtype but less than null. Thus even mildly impaired Cl^- extrusion could be causal to epilepsy.

Phosphorylation of KCC2 at two threonine residues (Thr^{906} and Thr^{1007}), which inhibits KCC2 activity, decreases in parallel with the lowering of neuronal $[Cl^-]_i$ during brain development. Thanks to the CRISPR-Cas9 technology, we generated mice expressing missense mutations Glu^{906} and Glu^{1007} in the KCC2 alleles (*KCC2*$^{e/e}$), which mimics constitutive phosphorylation at these sites. The *KCC2*$^{e/e}$ demonstrated deteriorated ability to extrude Cl^-, being susceptible to status epilepticus by any sensory stimulation.

L-05 STUDIES ON THE PATHOMECHANISMS OF DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY USING INDUCED PLURIPOTENT STEM CELLS

Shinichi HIROSE [1,2)]

[1)] Department of Pediatrics, School of Medicine, Fukuoka University, Japan

[2)] Research Institute for the Molecular Pathomechanisms of Epilepsy, Fukuoka University, Japan

Induced pluripotent stem cells (iPSCs) are an excellent tool to study the pathomechanisms of epilepsy. Disease-specific iPSCs have been established for several genetic epilepsies. In particular, the molecular mechanisms underlying some developmental and epileptic encephalopathies (DEEs) have been revealed. These DEEs include *CDKL5* encephalopathy, *STXBP1* encephalopathy, Dravet syndrome, *PCDH19*-related epilepsy, *KCNT1* encephalopathy, and *ST3GAL3* encephalopathy. Among them, the underlying pathomechanisms have been studied most extensively for Dravet syndrome, which is caused by mutations of the *SCN1A* gene encoding the α1 subunit of the sodium channel $Na_v1.1$. Accordingly, many studies using Dravet syndrome-specific iPSCs, including ours, suggested that insufficient GABAergic neuron activity directly contributes to the pathogenesis, although early findings were conflicting. Using a high-throughput multiple electrode apparatus (MEA), we successfully demonstrated that the cardinal pathomechanism of Dravet syndrome is $Na_v1.1$ functional insufficiency in the GABAergic inhibitory neurons. Knowledge of these underlying pathomechanisms will facilitate the identification of targets for drug screening. We sought chemical compounds that can ameliorate the $Na_v1.1$ dysfunction of GABAergic inhibitory neurons in Dravet syndrome. Applying both an **in silico** pre-screening and a high-throughput screening on MEA, we identified two drug candidates out of approximately 1.3 million chemical compounds. Collectively, iPSCs can help identify the pathomechanisms of DEEs and discover novel drugs based on the pathomechanisms.

Reference: Hirose S. et al. Application of Induced Pluripotent Stem Cells in Epilepsy. *Mol. Cell. Neurosci.*, 2020 in press.

GENETICS OF NEONATAL-ONSET EPILEPTIC ENCEPHALOPATHIES: A TRIBUTE TO PROF. OHTAHARA

L-06

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Ohtahara et al. first reported a case series on the specific age-dependent epileptic syndrome termed early-infantile epileptic encephalopathy with suppression-burst, now officially designated as Ohtahara syndrome, in 1976. Aicardi and Goutieres subsequently reported another case series of neonatal myoclonic encephalopathy, now referred to as early myoclonic encephalopathy (EME), in 1978. Although the main seizure semiology of Ohtahara syndrome and EME is divided into two types, tonic and myoclonic seizures, respectively, both syndromes share certain common features, including neonatal onset, suppression-burst pattern on EEG, and poor prognosis. Ohtahara syndrome was previously classified in a syndromic group because four of the original eight patients investigated exhibited structural brain abnormalities, such as Aicardi syndrome, porencephaly, and subacute progressive encephalopathy. The disease was initially not considered to have a genetic etiology because no familial cases had been reported. However, the first causative gene for Ohtahara syndrome, *ARX*, was identified in 2007. Next-generation sequencing accelerated the discovery of genes associated with neonatal-onset epileptic encephalopathies. Among these genes, *STXBP1*, *KCNQ2, SCN2A, SCN8A, CASK, GNAO1, PIGA, SPTAN1, PLPBP,* and *CYFIP2* have been reported to cause Ohtahara syndrome while *PNPO, SLC25A22, PIGA, STXBP1,* and *ERBB4* are causative genes for EME. Several other genes are associated with unclassified neonatal-onset epileptic encephalopathies. An overview of the genetic predisposition to neonatal-onset epileptic encephalopathies will be discussed herein, drawing mainly on the results of our investigations.

L-07 NEONATAL AND INFANTILE ONSET DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY

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The concept of developmental and epileptic encephalopathy (DEE) was proposed by ILAE 2017 revision of the classification. DEE are heterogenous epilepsy disorders characterized by encephalopathy and seizures which occur early in life and impact directly in development and cognition. Clinical features, EEG characteristics, and severity of developmental delays depend on age of onset, genetic mutation, disease progression and perhaps modified by environmental factors or intervention. Advances in genetic testing help to understand better the etiologies and pathophysiology of DEE. For example, mutations in *SCN2A, KCNQ2* and *STXBP1* are the most commonly reported causes in neonatal onset DEEs. However, the cause remains unknown in many patients.

This session will focus on the clinical approaches to evaluation and diagnosis with an emphasis on early identification of etiologies of DEE to optimize likelihood of better outcomes.

ELECTROPHYSIOLOGY IN DEE

L-08

Nicola SPECCHIO

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To review the evolution of the concept of Epileptic Encephalopathy (EE) and to analyze how the current definition might impact on both clinical practice and research and to expand the use of electrophysiology in DEE.

Many biological pathways could be involved in the pathogenesis of DEEs. Epilepsy and epileptiform discharges might impact on cognition via several mechanisms, although they are not fully understood. In DEEs the cognitive impairment seems to be independent from seizure recurrence and EEG abnormalities. Epileptiform discharges can produce a transient effect on information processing in the brain has been shown in studies of spikes and slow activity in hypsarrhythmia with EEG coupled with f-MRI. Multifocal interictal spikes, and high-amplitude slow waves activity within the hypsarrhythmia are associated with the activation of different neuronal networks. Although spikes might be causing a cortical activation pattern similar to that in focal epilepsies, slow wave activity produced a hypsarrhythmia-specific activation in cortex and subcortical structures such as brainstem, thalamus, and putamen. Epileptiform discharges can produce, also, a more long-lasting effect leading to prolonged inhibition of brain areas distant from but connected to the epileptic focus. Significant activation of brainstem and thalamus (especially centro-median and anterior thalamus) associated with epileptiform discharges has been shown in patients with LGS. Also, in CSWS, it has been demonstrated that there is activation of thalamus, together with mesial temporal and parietal regions, which constitute the central hub of the network.

L-09 PHENOTYPE-GENOTYPE CORRELATIONS IN DEE

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DEEs are characterized by early-onset epilepsy, intellectual disability and autism.
A customized early treatment might improve the long-term outcome. The current approach is to diagnose such patients using genetic tests, even before the clinical phenotype is characterized. Three features should be enhanced: age at onset, electroclinical seizure, comorbidities. Seizures starting in the first day of life, we might expect *ALDH7A1*, *PROSC*, *PNPO, SLC13A5, SCN2A, KCNQ2*, *KCNA2* or *FHF1* mutations. In DEEs with onset in the first month of life, the most frequent genetic variants are *KCNQ2* and *STXBP1*, while between 1 and 3 months *SCN1A* and *CDKL5* are the major players. In the EIEE the most frequent variants are *KCNQ2, STXBP1* and *SCN2A*.Several DEEs present with tonic seizures; a severe bradycardia at seizure onset, is the hallmark of *SCN8A*. Self-induced seizures are seen in *CHD2* and *SYNGAP1*. Early-onset absence seizures are often due to *SLC2A1* mutations. Prolonged febrile or afebrile hemiclonic seizure is a hallmark of *SCN1A;* if seizures are febrile and clustered *PCDH19* should be excluded. A photoparoxysmal response during the first year of life is frequent in Dravet Syndrome; if response to lights is observed between the second and third year of life CLN2 should be considered. The analysis of comorbidities can improve our diagnostic yield; cerebellar atrophy is a typical feature of *CASK*, teeth hypoplasia is a distinctive hallmark of *SLC13A5*, deafness of *TBC1D24* andhemiplegic attacks and paroxysmal nistagmus of *ATP1A2, ATP1A3* and *SLC2A1*.

NEURONAL MATURATIONAL FACTORS CAN CHANGE EXCITATORY/ INHIBITORYSYNAPTIC RATIOS IN INFANTILE EPILEPSIES

L-10

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Background: The balance or ratio between excitatory (glutamatergic) and inhibitory (GABAergic) inputs into maturing individual cortical neurons influences their epileptic potential. Axodendritic synapses are mainly excitatory; axosomatic synapses are inhibitory. Pathological factors that alter either synaptic inputs can be demonstrated in tissue sections. Increased mitochondrial activity identifies excessively discharging neurons. Other factors of normal neuronal maturation include sprouting of neurites, ATPase pump to maintain resting membrane potential/depolarization threshold, membrane receptors and ion channels, biosynthesis and axoplasmic transport of neurotransmitters and enzymes of degradation.

Methods: Neuropathological study of surgical resections for epilepsy in 20 infants and children; and autopsy of 30 human fetuses of 13 to 38 weeks gestation were examined using immunocytochemical markers in all and electron microscopy in most surgical cases.

Results: Factors influencing afferent synaptic ratios include: *A)* proteoglycan (keratan sulfate) binds to somatic membranes but not to dendritic spines, and may be focally diminished (cerebral atrophy; schizencephaly; lissencephaly) or augmented (holoprosencephaly); *B)* satellitosis of glial cells displaces axosomatic synapses; *C)* impaired development of dendritic spines causes decreased excitation (Down syndrome); *D)* synaptic short-circuitry of fused molecular zones of adjacent gyri (polymicrogyria); *E)* peri-neuronal inflammation (tuberous sclerosis) and heat-shock proteins.

Conclusions: Neuropathological examination of surgical and post-mortem brain tissue can demonstrate subcellular changes that help explain either epilepsy or lack of seizures at a cellular level in immature brains that compliments neuroimaging, EEG, genetic and clinical findings in individual patients. Excitatory/inhibitory synaptic ratios are altered by impaired neuroblast maturation in malformations and neonatal encephalopathies and influence neuronal epileptogenesis.

L-11 INHERITED METABOLIC DISEASES IN DEVELOPMENTAL/EPILEPTIC ENCEPHALOPATHY

Tomoyuki AKIYAMA

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Inherited metabolic diseases (IMDs) are a rare cause of epilepsy. Among approximately 250 IMDs presenting with epilepsy, one third are treatable. Therefore, physicians should always include IMDs as differential diagnoses for patients with unexplained epilepsy. Initial metabolic work-up consists of "screening" tests including blood glucose, gases, ammonia, liver function tests, lactate, creatine kinase, uric acid, amino acids, acylcarnitines, urine ketones, amino acids, and organic acids. Therapeutic trials of pyridoxine, pyridoxal 5′-phosphate, and biotin are recommended. If effective, the therapy should be continued until the results of confirmatory test becomes available. After initial work-up, more specialized tests according to clinical setting are considered. Based on these results, enzymatic assays and/or genetic tests are performed to confirm diagnosis. Next-generation sequencing can be helpful in case that biochemical diagnosis could not be established or resources for specialized metabolic tests are unavailable. We also utilize a urine metabolomics-based test to screen over 130 IMDs efficiently. Our current research interest includes vitamin B6-dependent epilepsy, folate metabolism disorders, creatine metabolism disorders, and neurotransmitter disorders. I will demonstrate some results of our recent research on vitamin B6-depnedent epilepsy.

INFLAMMATION IN EPILEPSY

L-12

Derrick CHAN

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Epilepsy is common, begins suddenly and unpredictably and ranges from rare seizures to severe epileptic and developmental encephalopathy. Current pharmacological treatments aim to bring seizures under control after epilepsy is established by reducing neuronal excitability or increasing neuronal inhibition. Ideally, treatment should target epileptogenesis.

We need to deepen our understanding of the mechanisms in epileptogenesis and subsequent disease progression. There is increasing evidence for a key role of inflammation in the brain, seizures and epilepsy. Peripheral antibodies against brain neurones causes autoimmune encephalitis and autoimmune epilepsy. Other inflammatory signals such as interleukin (IL)-1β, Tumour Necrosis Factor (TNF)-α and IL-6 are found in the blood and brain of patients with seizures and epilepsy. Conventional treatments suggest immunomodulatory treatment may work in epilepsy: corticosteroids can control or improve certain epilepsies (West Syndrome and refractory epilepsy). Even treatments such as the ketogenic diet could have anti-inflammatory mechanisms.

Immune dysregulation could drive epileptogenesis through peripheral and CNS immune derangement and forms a coherent target for further research and treatment.

L-14 GENETIC ASPECTS OF DEE WITH MOVEMENT DISORDERS

Wang-Tso LEE

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Children and infants with DEE are occasionally associated with movement disorders. They are also rarely associated with eye movement disorders, and were rarely reported in the past. We investigated the movement disorders in children with DEE. Several patients with DEE and movement disorders were found, including different movement disorders. They were occasionally leading to neurological deficits. The mechanisms leading to different movement disorders in DEE may be related to the involvement of different brain regions due to genetic mutations or other unknown mechanisms. Of these movement disorders, the involvement of eye movement disorders is not difficult to find and may remain unnoticed by most neurologists. To pay attention to the presentations of these movement disorders may broaden the clinical phenotypes of children with DEE.

GENETIC STUDIES IN DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY

L-15

Chaiyos KHONGKHATITHUM

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Developmental and epileptic encephalopathies (DEE) of infancy and childhood are characterized by different seizure semiologies, frequent epileptiform discharges, and delay or regression of development.The DEE include many age-related electroclinical syndromes with intractable seizures and several EEG features.Cognitive and developmental problems in patients with DEE may result from an interaction between the underlying etiology and the effect of frequent seizures and epileptiform discharges.The genetic causes of DEE identified by recent tests such as microarray, targeted gene sequencing panels, whole exome and whole genome sequencing have increased dramatically in the recent years.The diagnostic yield of these tests is quite high in conjunction with precise clinical characteristics.Understanding of genetic etiology will provide new insights into the pathogenesis of DEE and help to develop novel targeted therapies, which are crucial to improve the seizure and developmental outcomes of these severe disorders.

L-16 A BRIDGE BETWEEN GENETICS AND ELECTROPHYSIOLOGY

Renzo GUERRINI

Neuroscience Department, Children's Hospital A. Meyer-University of Florence, Italy

A main achievement of pediatric epileptology derives from the characterisation of epilepsy syndromes, especially those for which after onset at a given age, course and outcome become relatively predictable. The advent of modern genetics has further enriched the predictive power of the diagnostic approach to early onset epilepsies by demonstrating how similar phenotypes may in fact result from different genetic causes and manifest different outcomes or that, at the opposite, even the same genetic defect, or slightly different genetic variations, may underlie profoundly divergent outcomes. In addition to information araising from these correlations, or lack of them, old and new knowledge has linked a growing number of genetic etiologies to highly distinctive electrophysiological patterns. While electrophysiological-genetic correlations have in the past been mainly valued because of their usefulness in gathering homogeneous series of patients with suspected genetic etiologies, and addressing genetic testing, they are now also exploitable for the purposes of better management. The classical observations that have linked specific electroclinical patterns to the Ring 20 chromosome, Angelman syndrome, 4p- syndrome, Aicardi syndrome and other rare conditions are now part of the historical repertoire of pediatric epileptology. More recent work has provided evidence of specific single gene epilepsies being associated with recurrent electroclinical and topographic patterns and, importantly, of the possible correlations between somatic, brain confined mutational gradient and epileptogenesis.

EPILEPTOGENIC MODULATION AND SYNCHRONIZATION IN HYPSARRYTHMIA SECONDARY TO PERINATAL MIDDLE CEREBRAL ARTERY STROKE

L-17

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Children with perinatal arterial ischemic stroke of middle cerebral artery(PS-MCA) have a potential risk for infantile spasms(IS) presenting hypsarrhythmia. Modulation index(MI) measures strength of phase-amplitude coupling(PAC) between gamma and slow waves. Synchronization likelihood(SL) measures generalized synchronization. We hypothesize that epileptogenic hemisphere in IS secondary to PS-MCA establishes epileptogenic modulation and synchronization generating hypsarrhythmia.

We selected patients with IS and focal epilepsy(FE) secondary to PS-MCA. We collected 10x2-minute epochs of sleep interictal scalp EEG. MI between gamma(30-70 Hz) and slow waves(3-4 Hz) were calculated between affected and unaffected hemispheres. SLs among all paired electrodes were analyzed in 9-frequency bands: 5-delta bands, theta, alpha, beta and gamma. We investigated SL of inter- and intra- hemispheric connectivity.

We collected video EEG in 10 IS patients(4~11month-old) with hypsarrythmia and 11 FE patients(0.9~12year-old). MIs in IS group were significantly higher than those in FE group. MIs in affected hemispheres in IS group were significantly higher than in unaffected hemispheres. The inter-hemispheric connectivity of 7-frequency bands in IS group were significantly stronger than those in FE group. The intra-hemispheric connectivity of 8-frequency bands in affected hemisphere were significantly stronger than in unaffected hemisphere in IS group, while that of only gamma band in affected hemisphere was significantly stronger in FE group.

MIs and SLs are surrogate markers to lateralize the epileptogenic hemisphere of IS secondary to PS-MCA despite of hypsarrythmia. IS secondary to PS-MCA may have epileptogenic modulations in both inter- and intra-hemispheric connections to generate hypsarrythmia.

L-18 NEUROIMAGING OF DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES

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Neuroimaging has an important role in the evaluation of developmental and epileptic encephalopathies (DEEs). Neuroimaging is not only useful for the diagnosis of underlying etiologies but also for the evaluation of developmental and encephalopathic conditions. In this presentation, I review the neuroimaging studies of West syndrome, one of the typical DEEs characterized by infantile onset of epileptic spasms, an abnormality on electroencephalography (EEG)called hypsarrhythmia, and developmental regression.

FDG-PET often reveals regional cortical hypometabolism in patients with West syndrome of unknown etiology. The findings of hypometabolism resolve along with disappearance of epileptic spasms and hypsarrhythmia by ACTH therapy in some patients. The FDG-PET findings correlate with long-term developmental outcome. Diffusion tensor imaging (DTI) at onset of West syndrome shows elevated fractional anisotropy (FA) and reduced mean diffusivity (MD) in brainstem and diffuse cerebral white matters. The elevated FA and reduced MD possibly reflect microstructural cytotoxic edema and/or inflammation during the encephalopathic period. During follow-up period, the DTI findings change to reduction of FA and elevation of MD, which may be caused by delayed maturation of the white matters. Simultaneous EEG-functional MRI (EEG-fMRI) during the state of hypsarrhythmia shows activation of brainstem and multiple cerebral cortices. The findings of EEG-fMRI suggest the involvement of widespread networks of cortical and subcortical structures in the generation of hypsarrhythmia.

Combination of these neuroimaging studies enhances our understanding of the pathophysiological mechanisms of DEEs.

NETWORK AND MOLECULAR MECHANISMS OF GENERALIZED SPIKE-WAVES IN DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES

L-19

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Absence seizure is an “iconic” clinical phenomenon that characterizes the epilepsy phenotype and guides the choice of antiepileptic drugs. Although many controversies remain unresolved, the mechanism of absence seizures has been well elucidated by showing that pathological oscillations caused by various molecular and functional imbalances within the cortico-thalamo-cortical network underlie generalized spike-wave discharges on electroencephalograms. Absence seizures may not only occur in genetic generalized epilepsies but also may appear in many developmental and epileptic encephalopathies (DEEs), such as Dravet syndrome. Absence seizures can also increase the risk of worse developmental outcomes. Therefore, it is clinically important to understand how genetic defects responsible for DEEs cause absence seizures. In this lecture, we will outline the current understanding of the network and molecular pathogenesis of absence seizures, highlighting the contribution of several DEE-responsible molecules.

L-20 BEYOND GENETIC BASIS OF MONOGENIC DEVELOPMENTAL EPILEPTIC ENCEPHALOPATHY

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Developmental epileptic encephalopathy (DEE) is cause by single gene alterations. Nevertheless, DEE cases triggered by the same gene, and even by the same specific genetic variant, can present different phenotypic manifestations. This phenotypic variability also differs within epilepsy syndrome, type of epilepsy disease, cognition involvement, and overall prognosis . Some reports have identified modifications in other genes, called modifiers, as the reason for such diversity. For example, Dravet syndrome caused by *SCN1A* gene abnormalities has been associated with a 5-fold enrichment for rare variants of *SCN9A*, whereas the presence of a variant of *CACNA1A* has been linked to an absent seizure phenotype and earlier disease onset . Nevertheless, the incidence of such single gene modifier variants is not high. In recent years, next-generation sequencing (NGS) data has provided additional evidence for the role of inner genetic modifiers, which were found to be influenced by the mosaicism rate . Additionally, exome sequencing has shown the enrichment of harmful ultra-rare variants in DEE. For instance, NGS sequencing has revealed mosaicism in about 10% of de novo Dravet syndrome patients and their asymptomatic parents. Furthermore, in terms of intellectual capacity, it has been shown that rare variants are mainly present in mild DEE cases. In this seminar, I will go beyond the role of single genes in DEE to describe endogenous genetic factors and polygenic structures.

GENETICS AND PRECISION MEDICINE IN THE DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES

L-21

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Huge inroads into understanding the genetic basis of the epilepsies have been made since the discovery of the first gene for epilepsy 25 years ago. The epilepsies are a complex group of diseases, ranging from mild self-limited disorders to severe conditions with many associated comorbidities which include intellectual disability, autism spectrum disorder, cerebral palsy and an increased mortality rate. For the most severe epilepsies, the developmental and epileptic encephalopathies, the molecular basis has been solved in 50% of cases, with the majority arising secondary to a *de novo* mutation. Pathogenic variants in more than 200 genes can cause developmental and epileptic encephalopathies. Novel mutation types are emerging which create innovative options for therapeutic targeting. For the first time, we are poised to develop precision therapies for people with epilepsy. Precision medicine takes many forms and simple precision approaches can improve care today. Gene therapy itself is yielding promising results in animal models, but there remains an enormous chasm to bridge for safe translation from mouse to man.

L-22 DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES AND NEURODEVELOPMENTAL DISORDERS

Yushiro YAMASHITA[1)], Tomoko SAIKUSA[1)], Koutarou YUGE[1),2)], Shinichiro NAGAMITSU[1),2)], Tomoyuki TAKAHASHI[1),2)], Toyojiro MATSUISHI[2),3)]

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The developmental and epileptic encephalopathies (DEE) are heterogeneous group of rare neurodevelopmentl disorders, characterized by early onset intractable seizures, EEG abnormalities, and developmental delay or regression. Examples of DEES include Ohtahara, West, Lennox-Gastaut, Landau-Kleffner, Doose, Dravet syndrome and epileptic encephalopathy with CSWS. In epileptic encephalopathy with CSWS, interictal epiletiform discharges during sleep play an important role in the cognitive function deficits. Landau-Kleffner syndrome (LKS) is a particular presentation with its core symptom of acquired aphasia. LFS is now regarded as the rare and severe end of spectrum of cognitive-behavioral symptoms and the benign end of spectrum being the more common typical rolandic epilepsy.

In the latter part of this lecture, I will talk on double syndromes and conditions with high rate of epilepsy and autistic symptomatology. A number of conditions-genetic, metabolic, and syndromes-have a high rate of several autism symptoms associated with them (i.e., Angelman syndrome, Tuberous sclerosis, and Rett syndrome). The prevalence of epilepsy in children with autism spectrum disorder (ASD) ranges from 5-38%. It remains unclear whether seizures and epileptiform activity on EEG are causative or comorbid. In tuberous sclerosis complex, infantile spasms is an independent risk factor for autism, suggesting a specific pathophysiologic role for epilepsy in development of autism. Rett syndrome is a neurodevelopmental disorder, with a cluster of clinical manifestations that includes early psychomotor regression with autistic features, and seizures. We will report the natural course and predicting factors of epilepsy in 60 Japanese patients with Rett syndrome with literature review.

COGNITIVE AND BEHAVIORAL CONSEQUENCES IN ECSWS: THE RELATIONSHIP BETWEEN SEIZURES/PAROXYSMAL EEG ABNORMALITIES AND COGNITIVE/BEHAVIORAL DISTURBANCES

L-23

Hideaki KANEMURA

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Epilepsy affects both the child himself and the family because of its psychological and social results. In developmental and epileptic encephalopathies (DEE), a condition in which cognitive and behavioral functions are altered by the epilepsy itself. Moreover, parents of children with intractable seizures may experience especially high levels of anxiety about seizures and psychological effects. Accordingly, DEE can be associated with poorer quality of life (QOL) for both child himself and the family.

Among these DEEs, epilepsy with continuous spike-waves during slow sleep (ECSWS), as a representative epileptic syndrome of electrical status epileptics during slow sleep (ESES), is characterized by impairment of neuropsychological abilities. ECSWS may affect the prefrontal cortex and leave residual mental and behavioral abnormalities. In our studies, prefrontal lobe volume revealed growth disturbance in ECSWS patients. These studies also revealed that the prefrontal lobe growth disturbances were persistent in patients with longer seizure durations and ESES periods. These findings suggest that seizure and the duration of EEG paroxysmal abnormality may be associated with prefrontal lobe growth disturbances, which are associated with neuropsychological problems. Thus, the best treatment options may be required to remit seizures and EEG paroxysmal abnormality as soon as possible to achieve optimal prognosis in ECSWS.

Modern care of children with DEE goes beyond attempts to control seizures and requires consideration of broader issues related to cognitive, behavioral, and social functioning. Optimizing the QOL for child himself and the family in children with DEE such as ESCWS needs careful assessment of these issues.

L-24 BURDEN OF DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY-AFFECTED CHILDREN ON FAMILIES, NURSERY SCHOOLING, AND EMPLOYMENT IN JAPAN

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Patients and their families with developmental and epileptic encephalopathy (DEE) face several difficulties not only due to the frequent epileptic seizures, but also because of related complications, including developmental delay, developmental disabilities, and special medical care needs.

Recently, it was found that the utilization of nursery schools by working parents is increasing because of rapidly changing social situations in Japan, and this utilization rate rose up to 42.4% in 2017. However, parents of children with epilepsy, especially those with DEE, frequently experience difficulties in utilizing in nursery schools due to their children's medical complications, and consequently, are unable to retain stable employment.

To substantiate this trend, we administered a survey on the families of children with Dravet syndrome (DS) and West syndrome (WS; infantile spasms). The results showed that the nursery school utilization rates were 25.0% and 36.8%, respectively, and 0% for patients with special medical care needs. Care-related restrictions were present in 66.7% (DS) and 19.6% (WS) of the children, and epileptic seizures during school hours were experienced in 85.0% (DS) and 44.0% (WS), especially of status epilepticus, which was seen in 20.0% (DS) and 4.5% (WS). Consequently, employment rates were lowered to 20.8% (DS) and 26.4% (WS) in mothers, compared to the overall employment rate (47.3-61.2%) of all mothers in Japan. For optimal and safer utilization of nursery schools, creating proper guidelines and establishing an in-school system of care for DEE-affected children is needed in the future.

TREATMENT OF DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY

L-25

Ki Joong KIM

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Epileptic encephalopathy was redefined by Berg et al. as where the epileptic activity itself contributes to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone. These developmental impairments are thought to be caused not only by frequent epileptic seizures but also by the abundant epileptiform activity, and the key concept here is that amelioration of the epileptiform activity may have the potential to improve the developmental consequences. Scheffer et al. added the concept of developmental encephalopathy as where developmental impairment is predominant without presence of frequent epileptic activity suggesting that developmental component can be independently caused by underlying gene mutations. So, in contrast to epilepsy in adults and adolescents, epilepsy in children, especially early onset epilepsy below the age of 1 year, has significant potential risk for developmental and cognitive problems. In this respect, more aggressive treatment is needed to avoid aggravation of epileptic processes as well as developmental outcomes. Since treatment of epileptic seizures may improve developmental outcome, so early diagnosis and proper management are essential. However, understanding that genetic etiology independently causes developmental impairment leads to the importance of application of precision medicine in developmental and epileptic encephalopathy. There is an urgent need for development of new therapeutic modalities in this field.

L-26 HOW DO INFANTILE SPASMS AND WEST SYNDROME RELATE TO THE CONCEPTS OF DEVELOPMENTAL & EPILEPTIC ENCEPHALOPATHIES?

Andrew LUX

Women's and Children's Health / Department of Paediatric Neurology, University of Bristol, UK

Infantile spasms and West syndrome have been described as a form of encephalopathy since as early as 1960. Alongside Ohtahara syndrome, Dravet syndrome, and Lennox-Gastaut syndrome, they have been considered to constitute a situation in which the epilepsy requires very close monitoring and vigorous intervention in order to prevent long-term and permanent harm. Indeed, some investigators have considered whether prophylactic antiepileptic treatment is justified in conditions, such as tuberous sclerosis complex, in which infantile spasms have a high incidence. This concept has become embedded within the new terminology and definitions of the International League Against Epilepsy, where the 2017 position paper of its Commission for Classification and Terminology recommended the term "Developmental and Epileptic Encephalopathy" in order to emphasise that, although an underlying genetic aetiology might affect development directly, associated epileptic activity might make an additional contribution to more severe cognitive and behavioural impairments. However, it has also been argued that the concept of the epileptic encephalopathy may be applied to any of the epilepsies and epilepsy syndromes, that this can affect an individual at any age, and that stopping the epileptic activity has only a limited impact on developmental outcomes. Given these nosological changes and contested concepts, is there anything distinctive about epileptic spasms, either in infancy or at older ages, that usefully informs this debate?

ABSTRACTS

Platform Sessions

G-01 PATHOLOGICAL GAIT IN PATIENTS WITH DRAVET SYNDROME: QUANTITATIVE EVALUATION USING THREE-DIMENSIONAL GAIT ANALYSIS

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Purpose: Patients with Dravet syndrome (DS) exhibit various progressive gait deviations such as crouch gait (hyperflexion of knee and hip joint in stance-phase), ataxic gait, dystonic gait, and Parkinsonian gait. Gait problems are closely associated with the deterioration of quality of life. The aim of present study is evaluating gait deviations in DS quantitatively, using three-dimensional gait analysis (3DGA).

Methods: We performed 3DGA in four ambulatory patients with DS aged between 10 and 18 years. Photoreflective markers were placed on lower extremities and infrared cameras were used for motion capture. We investigated their clinical features and kinematics including gait deviation index (GDI).

Results: All patients had pathogenic SCN1A mutation and took multiple antiepileptic drugs. One patient had an episode of acute encephalopathy six years ago and exhibited diffuse cerebral atrophy in brain MRI. All patients exhibited hypotonia, muscular weakness, pes planovalgus, restriction of ankle dorsiflexion, and intellectual disability. No patients showed dysmetria, tremor, or rigidity. Two of four patients had reduced walking speed and stride length. Three patients showed crouch gait and low value of GDI (median value = 68, range = 51-95). Two patients showed axial asymmetric pelvic kinematic abnormalities (right-frontal and left-frontal rotation respectively) during walking, that were inconsistent with symmetric muscle strength and range of motion in lower extremities at rest.

Conclusions: Three of four patients with DS exhibited crouch gait, and two also exhibited axial asymmetric kinematic abnormalities which may be related to dystonic gait. 3DGA has the potential to evaluate pathogenic gait in DS quantitatively.

CHOICE AND EFFICACY OF INTRAVENOUS ANTIEPILEPTIC DRUGS FOR STATUS EPILEPTICUS IN DRAVET SYNDROME

G-02

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Objectives: The aim of this study was to evaluate choice and efficacy of intravenous antiepileptic drugs (AEDs) for status epilepticus (SE) in Dravet syndrome.

Methods: We retrospectively reviewed medical records. SE was defined as single seizure lasting for more than 30 minutes or intermittent seizures lasting for more than 30 minutes without complete recovery of consciousness. Effectiveness of AEDs was defined as cessation of seizures for more than 24 hours after administration. In this study, buccal and intramuscular midazolam (MDL) administration were included as intravenous AEDs.

Results: Seventy-four SE episodes in nine patients (two boys, seven girls: median age, 31 months) were enrolled. SCN1A mutation was positive in five patients. Fever-induced SE was 26 episodes. Eleven SE episodes ceased without AEDs administration. MDL was administered most frequently as first-line AEDs in 36 episodes, followed by diazepam in 22, fosphenytoin/phenytoin in three. As second-line AEDs, MDL and phenobarbital were most common, followed by fosphenytoin/phenytoin and continuous MDL (cMDL), and as third-line, phenobarbital was most frequently, followed by cMDL. Effectiveness rate (effective episodes /number of administration) was as follows: cMDL (77.8%), phenobarbital (66.7%), MDL (53.1%), diazepam (44.4%), fosphenytoin/phenytoin (37.5%), and thiopental (100%). Respiratory adverse effects were found in thiopental (100%), followed by PB (41.7%), MDL (34.6%), fosphenytoin/phenytoin (33.3%), and cMDL (14.3%).

Conclusions: We consider that MDL may be practical as first-line AEDs for SE in Dravet syndrome and that cMDL and phenobarbital may be the second-line AEDs. Fosphenytoin/phenytoin may not be effective for SE in Dravet syndrome.

G-03 LONGITUDINAL CORRESPONDENCE OF EPILEPSY AND SCALP EEG FAST (40 - 200HZ) OSCILLATIONS IN PEDIATRIC PATIENTS WITH TUBEROUS SCLEROSIS COMPLEX

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Introduction: Epilepsy associated with tuberous sclerosis complex (TSC) has very complex clinical characteristics. Recently, scalp electroencephalogram (EEG) fast (40 - 200Hz) oscillations (FOs) are suggested to indicate epilepsy severity. However, age-dependent longitudinal changes of epileptic FOs in individual patients are yet fully clarified. We therefore investigated the correspondence between complex clinical courses and FOs according to age in pediatric patients with TSC-associated epilepsy.

Subjects and Methods: The inclusion criteria of the participants of the present study were pediatric patients with TSC who were born after January 1, 2000 and visited Okayama University Hospital before May 31, 2018. We manually selected a 60-second-long EEG data section in each individual NREM sleep record, and semi-automatically detected FOs.

Results: Twenty-three children (15 boys, 8 girls) with TSC who had both EEG data and detailed clinical information during infancy and/or young children < 10 years of age were eligible and selected for the study. The number of FOs associated with spikes per patient was significantly greater than those unassociated with spikes (p=0.0001). In the eight patients who had West syndrome (WS) in infancy, the number of FOs associated with spikes was significantly greater during the period of WS before ACTH therapy than during the post-WS period (p=0.0078). There were no apparent age-related changes in FO frequency and duration.

Conclusions: It was suggested that the number of FOs associated with spikes might be related to the state of epilepsy, and age-dependent changes might provide a cue to the pathophysiological mechanism of epilepsy.

EVALUATION OF EPILEPTIC BRAIN ACTIVITY AT THE ONSET OF WEST SYNDROME USING SIMULTANEOUS EEG-fMRI

G-04

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Background: Diffusion tensor imaging and FDG-PET studies have found occult neocortical lesions and a network involving the brainstem and basal ganglia at the onset of West syndrome (WS). We evaluated epileptic brain activity at the onset of WS using simultaneous EEG-fMRI.

Method: We performed EEG-fMRI in six infants (one case with tuberous sclerosis (TSC) and five of unknown etiology) at the onset of WS [median age, 7 months (range: 3-9 months)] between January 2016 and September 2019, using a 3-Tesla scanner. The median interval between the onset of epileptic spasms and the scan was 17 days (range: 4-43 days). Each intermittent hypsarrhythmia burst during sleep was considered an event and the BOLD response related to the event was analyzed using an event-related design.

Results: All infants had positive BOLD responses (P-BOLDs) in widespread neocortices, the bilateral hippocampi, basal ganglia, and brainstem. P-BOLDs were also seen in the bilateral thalami in all but one infant of unknown etiology. The maximum t-value was in the neocortices in three infants, brainstem in two, and left hippocampus in one. The five cases of unknown etiology had bilateral diffuse P-BOLDs in the neocortices; in the infant with TSC, the P-BOLDs in the neocortices did not correspond to cortical tubers. Group analysis revealed P-BOLDs in the left hippocampus and thalamus.

Significance: We demonstrated hippocampal and thalamic involvement, in addition to brainstem and basal ganglia involvement, in hypsarrhythmia. EEG-fMRI did not help to detect neocortical lesions at the onset of WS.

G-05 FACTORS ASSOCIATED WITH TREATMENT LAG AND OUTCOMES OF INFANTILE SPASMS IN MALAYSIA - A MULTICENTRE PROSPECTIVE STUDY

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Aim: The aim of this study was to evaluate the factors causing delay in the diagnosis and treatment of infantile spasms and their impact on the course of the disease.

Methods: We carried out a prospective study in 5 tertiary centres in Malaysia with paediatric neurologist for 2 years duration. A total of 50 infants, 28 females (56%) and 22 males (44%), with infantile spasms were identified, of which 37 (74%) of them were symptomatic in nature. They were aged between 2 to 16 months (median 6 months, mean 6.6, SD 3.18) at first symptoms. The participants included had to exhibit a combination of clinical symptoms of infantile spasms, with onset between 1 to 24 months and characteristic electroencephalographic (EEG) with hypsarrhythmia or modified hypsarrhythmia based on International League Against Epilepsy (ILAE) criteria.

Results: The mean time from appearance of first symptom to first visit to a medical practitioner was 8.9 weeks (median 2.9 weeks). Only 22/50 (44%) were diagnosed and treated appropriately within 14 days of onset of spasms. The diagnosis was missed at first visit in 84% of the cases, with the incorrect diagnosis of either normal baby movement, abdominal colic or gastro-oesophageal reflux. The time lag between first presentation and diagnosis was significantly longer for individuals presenting to general practitioners. Response to treatment was better in those who were diagnosed and treated earlier.

Conclusion: Creating awareness and providing education to medical practitioners and parents may be crucial to reduce this catastrophic time lag and improve outcomes in future.

AN EFFECTIVENESS OF TRICLOFOS SODIUM ON TWO PATIENTS WITH OHTAHARA SYNDROME

G-06

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Introduction: Ohtahara Syndrome (OS) is one of the most refractory epileptic encephalopathy. Here we illustrate two patients with OS, whose epileptic spasms (ES) were improved after the administration of triclofos sodium, the sedative drug.

Patient 1: was referred to our hospital for focal tonic seizures appeared at the 3rd day after birth, as well as frequent spasms developed thereafter. MRI exhibited focal cortical dysplasia in the left parietal and occipital lobes. At four months of age, she was diagnosed as OS based on the video EEG records illustrating interictal suppression-burst pattern (SBP) as well as ictal ES. PB, ZNS, vitB6, LEV, ACTH, VGB and LCM were ineffective for ES. However, the frequency of ES was reduced by approximately 30% after the administration of final dose of 400mg t.i.d. triclofos sodium.

Patient 2: was reported in elsewhere. In brief, lactic acidosis and hypoglycemia as well as focal tonic seizure were noted in neonatal period, and diagnosed as pontocerebellar hypoplasia type 6 (PCH6). Genetic study showed homozygous mutation in mitochondrial arginyl-tRNA synthetase 2 **(***RARS2*) gene, namely c.944G>C (p.R315P). Video EEG at 4 months of age exhibited interictal SBP as well as ES. Although PB, ZNS, NZP, LEV and vitB6 were ineffective to ES, the administration of triclofos sodium at the final dose of 400mg t.i.d. totally disappeared ES.

Conclusion: We have found the effectiveness of triclofos sodium in two patients with OS. It may be suggested that triclofos sodium is one of optional choice for the treatment of OS.

G-07 TWO CASES OF DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY CAUSED BY *CYFIP2* GENE MUTATION

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Introduction: *CYFIP2* encodes one of the component proteins which are assembled with other four protein, regulate actin dynamics in dendric spinal morphology and synaptic plasticity. It has been recently reported that *CYFIP2* mutation causes severe developmental and epileptic encephalopathy.

Case1: A 18 months-old boy, was suffering from first focal seizures at 3 months old. He developed to West syndrome at 7 months. Although treatments of ACTH, valproate, zonisamide and ketogenic diet were done, series spasms continued, and he could not pursuit and laugh. After administration of vigabatrine since 14 months old, spasm was improved, and he could laugh. His Brain MRI showed mild dysgenesis of the cerebellar gyrus and a small congenital defect of scalp. Interictal EEG showed right parietal dominant focal spikes and generalized spike and waves. Whole exome analysis revealed a heterozygous missense mutation in *CYFIP2*, c.260G>T (p.Arg87Leu).

Case 2: A 13-years-old boy, developed early infantile epileptic encephalopathy at 2 months. ACTH and multiple antiepileptic drugs were not effective. Corpus callosotomy was performed at 22 months of age which was partially effective in seizure frequency. He also showed choreic movements since his early childhood. Brain MRI indicates mild atrophy of cerebrum. Interictal EEG showed multifocal spikes and generalized spikes. Whole exome analysis revealed *CYFIP2* mutation, c.259 C>T (p.Arg87Cys).

Conclusion: The *CYFIP2* mutation should be regarded as among the causative gene for severe developmental and epileptic encephalopathy. While ACTH and anti-epileptic drugs were not effective, vigabatrine might be an effective medication for spasms and developmental impairments.

COMBINATION THERAPY WITH TOPIRAMATE AND GABAPENTIN IN A CHILD WITH *CACNA1E*-ENCEPHALOPATHY

G-08

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Introduction: *De novo* variants in *CACNA1E* cause a developmental and epileptic encephalopathy (DEE) presenting with congenital contractures, macrocephaly, and dyskinesias, which is registered as EIEE69 on OMIM. We report a patient with EIEE69 and discuss the pharmacological effectiveness on this.

Case: A 9-year-old boy, born after an uneventful delivery with contractures of the extremities, had an initial seizure at the age of 5 days followed by infantile spasms and focal seizures resistant to treatment with multiple antiepileptic drugs, ACTH therapy, and ketogenic diet. The electroencephalogram changed from modified hypsarrhythmia to extremely high voltage multifocal spikes. He also demonstrated macrocephaly, hypotonia, abnormal involuntary movements such as abrupt dystonic posture and myoclonus, profound intellectual disability, respiratory impairment, and feeding difficulty. Genetic analysis identified a *de novo* missense variant in the *CACNA1E* gene (c.2104G>A:p.(Ala702Thr)), which is recurrently reported in 6 patients showing epileptic spasms. After diagnosis, along with topiramate which was partially effective, an addition of gabapentin remarkably reduced myoclonic seizures with no improvement of electroencephalographic pattern.

Discussion: *CACNA1E* encodes the α_1-subunit of the voltage-gated $Ca_V2.3$ channel, which conducts high-voltage-activated R-type calcium currents. According to a previous study, topiramate, which blocks R-type calcium channels, is expected to be effective for seizures in this DEE. On the other hand, gabapentin binds to the $\alpha_2\delta$ subunit of calcium channels including $Ca_V2.3$ channel and modulates Ca channel function. Therefore, a combination therapy with topiramate and gabapentin may have an additive effect, and the therapeutic benefit in this *CACNA1E*-encephalopathy.

G-09 SEIZURE OUTCOME AND COMPLICATIONS IN SURGICAL TREATMENT OF INFANTILE EPILEPSY

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Introduction: Intractable epilepsy can develop early in infancy and becomes an indication of surgical treatment. However, comprehensive reports on infantile epilepsy surgery are still rare. In this study, we report our experience on infantile epilepsy surgery.

Subjects and methods: This study included 66 consecutive patients with intractable epilepsy who underwent surgical treatment in our institution under 2 years of age between 2006 and 2017. The clinical picture, surgical complications, seizure / developmental outcomes were investigated retrospectively.

Results: The median age and body weight at the time of surgery was 6.5 months and 8.42 kg. 33 patients developed epilepsy within one month of birth. The etiology included 30 cases of cortical dysplasia, 17 of hemimegalencephaly, and 9 of tumors. The surgical procedure included 24 cases of hemispherotomy and 13 of posterior quadrantectomy. Ventricular or subdural drainage was placed postoperatively in 29 cases. 10 patients (15.2%) required re-operation for hydrocephalus or post-operative cyst formation. Seizure free rate at post-operative one year and at the last follow-up were 85.9% and 68.8% (mean follow-up period: 56 months). The mean developmental index was 71.7 before surgery, 61.1 for one year after surgery, and 53.5 at the last follow-up. No clear association was found between seizure / developmental outcomes and surgical complications.

Conclusion: Epilepsy surgery in early infancy is an effective treatment with a high chance of seizure freedom. However, major complications requiring re-operation are not rare. The development of minimally invasive procedures and the teamwork of experienced doctors are important to perform infantile epilepsy surgery.

ABSTRACTS

Talking Poster Sessions

P-01 THE ROLE OF INFLAMMATION ON EPILEPTOGENESIS AFTER NEONATAL HYPOXIC-ISCHEMIC BRAIN INJURY

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Rationale: Hypoxic-ischemic encephalopathy (HIE) is the most common cause of death and disability in human neonates. The reported rate of epilepsy after HIE ranges from 9 to 33%. The accurate mechanisms leaded to epilepsy after HIE were noted clearly known. In this study, the role of inflammation on epileptogenesis after neonatal hypoxic-ischemic (HI) brain injury would be explored.

Methods: A rat model of HI-induced spontaneous epilepsy was established. HI was induced on postnatal day 7 by ligating right common carotid artery followed by hypoxia for 2 hours. Lipopolysaccharides (LPS, 0.01mg/kg) or vehicle (normal saline) was administered intraperitoneally weakly after HI for 8 weeks. Spontaneous seizures were recorded by continuous electroencephalography (EEG) monitor at 20-21wks of age.

Results: Compared with vehicle group (HI-V), LPS group (HI-LPS) increased discharge frequency and duration at right hemisphere ($P = 0.001$), but not at left hemisphere. In addition, HI-LPS group slightly increased total brain infarct volume but significantly reduced hippocampus infarct volume (P=0.023). Although total cell numbers in right side hippocampus were similar in both groups, HI-LPS group reduced cell loss at CA1 but exaggerated cell loss at dentate gyrus of right side hippocampus compared to left side hippocampus ($P = 0.028$). The Timm score in right side hippocampus of HI-LPS group was significantly higher than HI-V group ($P = 0.028$).

Conclusions: LPS-treated HI rats increased seizure potency and showed enhanced Mossy fibers at ipsilateral hippocampus of HI injury compared to vehicle-treated HI rats. The inflammation plays a role on epileptogeneisis after HIE.

POLYMICROGYRIA WITH CALCIFICATION IN PALLISTER-KILLIAN SYNDROME DETECTED BY MICROARRAY ANALYSIS

P-02

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Background: Pallister-Killian syndrome (PKS) is a rare disorder caused by the mosaic tetrasomy of chromosome 12p and is characterized by facial dysmorphism, pigmentary skin anomalies, developmental delay, hypotonia and seizures. Recently, association of PKS and neuronal migration abnormality was reported. We report a boy patient with PKS showing unique polymicrogyria with calcification on neuroimaging.

Case & Results: A boy patient, the first child of healthy unrelated parents, was born at 36 weeks gestational age by cesarean section with normal body weight and length. At 6-months of age, he was noticed to have developmental delay with dysmorphic features including coarse face, frontal bossing, hypertelorism, and high arched palate. He presented epileptic spasms without typical hypsarrhythmia at one-year of age. His seizure was controlled after ACTH treatment. His development was severely delayed: he could not sit alone and could not speak at three-years of age. Brain neuroimaging revealed asymmetric polymicrogyria with calcification, predominantly affected at right side. Routine laboratory tests gave normal results, including extensive examinations for metabolism or intrauterine infections. Result of chromosome G-band was 46,XY, however, array-CGH analysis showed mosaic duplication of chromosome 12p. The supernumerary isochromosome 12p was detected in 58% of buccal mucosa cells by the interphase FISH analysis using D12Z3 probe, indicating PKS.

Conclusions: His neuroimaging initially suspected the mosaic pattern of some cause, and finally proved to originated from PKS. This report describes that array-CGH can lead to diagnose PKS, and would provide an additional clue for differential diagnosis regarding structural brain anomaly with calcification.

P-03 AGE-RELATED CHANGES IN GLUTAMATE AND GLUTAMINE CONCENTRATIONS OBSERVED ON MR SPECTROSCOPY

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Purpose: Disturbance in the glutamate (Glu) - glutamine (Gln) cycle in the brain plays an important role in the pathogenesis of epilepsy. There have been only a few reports of changes in Glu and Gln concentrations in the brain with age, we evaluated the age-related changes observed on MR spectroscopy (MRS).

Methods: 65 children (from 1 month to 15 years) were enrolled in this study, who were studied to evaluate disorders such as mild retardation, history of febrile seizures, headache or an enlarged head circumference, and had no MRI abnormality. Single voxel MR spectroscopy (PRESS, TR/TE/NEX = 5000/30/32) with a 3.0T scanner was acquired from the fronto-perietal white matter (VOI = 15x20x15mm). Glu and Gln was quantified by LCModel (water scaling method, PD = 35.88M, corrected by R=1.3 [0-6 month], 1.2 [6-12 Mo], 1.1 [12-24 Mo]).
This study was approved by IRB of Tokyo Women's Medical University (#3535R, 3123R4).

Results: There is a significant correlation between age and Gln concentration (Spearman's $\rho = -0.714$, $p < 0.0001$), and age and Glu concentration (Spearman's $\rho = -0.792$, $p < 0.0001$).

Conclusion: This MRS study reveals decrement in Glu and Gln concentration with age. Gln concentration decreases with age, from over 4.0 mM under 3-month-old to around 1.8 mM after 10-year-old. Glu concentration also shows age-related decrease, from around 7.0 mM under 2-year-old, to around 6.0 mM over 4-year-old.

AN INFANT WITH PERSISTENT PERIVENTRICULAR HYPER-ECHOGENICITY WITH NO OTHER SYMPTOMS AND RADIOGRAPHIC ABNORMALITIES

P-04

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Periventricular hyper-echogenicity in preterm infants is usually seen as preceding lesions of periventricular leukomalacia. However, this finding can be seen in rare cases with several disorders. Here, we report an undiagnosed infant with persistent periventricular hyper-echogenicity. This girl was born as the second baby to non-consanguineous Japanese parents at 34 weeks 0 day of gestational age. No family history of neurological disorders was noted. Her birth weight, length, and head circumference were 1822g, 44cm, and 30cm, respectively. Apgar scores at 1 min and 5 min were 8 and 9, respectively. She had no sign of bacterial infection on admission, and she did not need respiratory support. No abnormal findings were noted by physical examination. However, she showed bilateral periventricular hyper-echogenicity, which extended to subcortical white matter, immediately after birth. Diffusion-weighted imaging at 3 days of age did not show decreased ADC values in the lesions. This sonographic finding persisted for more than 10 months, and no cystic change in hyper-echogenic lesions were detected. No significant abnormality was detected by means of blood tests (including the analysis of ammonium, amino acids, very long chain fatty acid, lactate, pyruvate, intact-PTH and chromosome), urine analyses (including the analysis of CMV-DNA, organic acids and sulfite), cerebrospinal fluid tests, brain MRI/CT and whole body plain X-rays. EEG at term-equivalent age showed disorganized pattern transiently. Currently she is 11 month old with favorable development, and recent MRI and EEG showed no abnormal findings. However, periventricular hyper-echogenicity remains.

P-05 USEFULNESS OF VIDEO ELECTROENCEPHALOGRAPHY RECORDING FOR THE DIAGNOSIS OF DEXMEDETOMIDINE WITHDRAWAL IN TWO PATIENTS WITH INTRACTABLE EPILEPSY

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Introduction: Dexmedetomidine (DEX) is an alpha-2 adrenergic receptor agonist, which has both sedative and mild analgesic effects with rapid onset and offset action. Several clinical reports have exhibited the withdrawal symptoms such as agitation, fever and/or vomiting in pediatric series. Here we report DEX withdrawal found in two patients with intractable epilepsy, the symptoms of which were closely resemble to epileptic seizures but differentiated from epileptic seizures using video electroencephalography (VEEG).

Patient 1: This one-year-old girl had been diagnosed as trisomy 13 associated with intractable combined generalized and focal epilepsy with tonic and myoclonic seizures. DEX was administrated during the surgical operation of cleft lip and cleft palate. Persisting elevation of upper limbs with vibratory movements as well as tachycardia developed two hours after the discontinuation of DEX. VEEG exhibited no epileptic ictal discharge during these abnormal movements, leading the diagnosis of DEX withdrawal.

Patient 2: This eleven-month-old boy had been diagnosed as cerebral palsy as well as intractable focal epilepsy with focal motor onset seizure. DEX was infused at the resuscitation for acute respiratory failure. The elevating and stiffening right upper limb were intermittently seen along with increased blood pressure 15 hours after the discontinuation of DEX, during which episodes no epileptic ictal discharge were exhibited on VEEG, leading the diagnosis of DEX withdrawal.

Conclusion: The symptoms of DEX withdrawal found in these two patients were resemble to epileptic seizure. VEEG was useful for the differentiation between DEX withdrawal and epileptic seizure.

EVOLUTIONAL PROCESS OF EPILEPSY ASSOCIATED WITH TUBEROUS SCLEROSIS COMPLEX (TSC) DURING INFANCY

P-06

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Purpose: We intended to clarify the evolutional process of epilepsy associated with tuberous sclerosis complex (TSC) during infancy.

Subjects and Methods: Seven patients who visited Okayama University Hospital were diagnosed with TSC during infancy. We retrospectively investigated the evolution of epilepsy in these patients, particularly focusing on the chronological and topographical changes of epileptic discharge in electroencephalogram (EEG) before the onset of epilepsy including West syndrome (WS). These results were compared to our previous findings on EEG changes prior to the onset of symptomatic WS in high-risk premature infants.

Results: All of the patients developed WS. Two (one with epileptic spasms and the other with only partial seizures) showed hypsarrhythmia in EEG at the first visit at 6 months of age. In the remaining five patients, EEG was recorded prior to the onset of WS at ages ranging from 2 to 6 months (median 2 months). Their EEGs showed multifocal spikes in various areas with a tendency toward predominance of one hemisphere. Their EEG then developed into hypsarrhythmia at around 6 months of age. Three of these five patients had partial seizures before the development of hypsarrhythmia and/or spasms.

Conclusion: A high proportion of infantile patients with partial seizures associated with TSC were found to subsequently develop WS. The infants with TSC who initially exhibited multifocal epileptic discharges in EEG differed from the premature infants who initially exhibited discharges in the occipital area prior to the development of WS at a median age of 4 months.

P-07 FIVE-DIMENSIONAL MAPPING OF AUDITORY LANGUAGE FUNCTION

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Introduction: Using whole-brain 4D mapping of language function based upon event-related modulation of electrocorticography (ECoG) signals, we investigated how language-related neural dynamics would alter throughout development, by delineating the effect of development on high-gamma activity at a given space and time.

Methods: Patients estimated to have right-hemispheric language dominance were excluded. Thus, this study included 103 patients (age: 4-20 years, 9297 artifact-free nonepileptic electrodes) with focal epilepsy who underwent two-stage epilepsy surgery with extraoperative ECoG recording. Linear and non-linear mixed model analysis determined the developmental effects on naming-related high-gamma activity, with multiple co-variates including 'response time' and 'proximity of seizure onset zone' incorporated.

Results: Positive age effects on high-gamma activity were noted 1) in the posterior superior/middle temporal areas immediately following stimulus onset, 2) in the left inferior-precentral regions at 120-480 ms following stimulus onset, 3) in the left middle-frontal region at 120-340 ms following stimulus offset, and 4) in the posterior cingulate area at 90 ms and 140 ms prior to stimulus offset. Better positive age effect was observed in the linear analysis than non-linear one. Negative age effects were noted in right inferior-parietal, left inferior-frontal regions, and left anterior-temporal areas relative to stimulus offset.

Conclusions: Our 5D brain maps revealed alteration of dynamic cortical activities associated with language function across age.The developmental trajectory of high-gamma modulations might demonstrate developmental consolida tion of language network.

EVOLUTION OF SEIZURES AND EEGS AMONG CHILDREN WITH BILATERAL BASAL GANGLIA AND THALAMIC LESION

P-08

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To establish the adequate medical practice for epilepsy in dyskinetic cerebral palsy (DCP) due to bilateral basal ganglia and thalamic lesion (BGTL). Methods: Clinical manifestations and evolution of seizures and EEGs were retrospectively investigated in 114 children (M:F = 66:48, 2-21y) with DCP due to BGTL. Results: Forty-two children developed epilepsy. Thirteen showed epileptic spasms (ES), 6 myoclonic seizures (MS), and 28 focal seizures (FS), respectively. Six had ES/MS along with FS. Precise electro-clinical course was investigated in 8 children. In 3 children with ES/MS and FS, ES/MS appeared in infancy and disappeared after administration of ACTH or oral antiepileptic drugs. FS appeared 1 to 5 years later and disappeared or decreased gradually before adolescence. Two children had status epilepticus. EEGs showed hypsarrhythmia or occipital discharges during ES/MS-positive period, improved during seizure-free period, and showed frequent multifocal spikes in peri-rolandic areas during FS-positive period. Those peri-rolandic discharges diminished with age in one child, but remained and shifted to frontal areas in two children. In 5 children with FS alone, the onset was between 2 and 9 years. Two children still had seizures at the time of evaluation.Three children had status epilepticus. EEGs were normal before the onset, showed frequent peri-rolandic spikes after the onset, and improved after the disappearance of seizures. Discussion: It would be necessary to continue medical intervention for epilepsy even if EEG was normal or improved after the disappearance of ES or MS among children with DCP due to BGTL.

P-09 EXPRESSION OF INTRACELLULAR CYTOKINES IN TWINS WITH INTRACTABLE EPILEPSY ASSOCIATED WITH LISSENCEPHALY

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Objective: This study determined whether immune system dysfunction was exhibited by twins presenting with intractable epilepsy who - despite sharing a common diagnosis of lissencephaly and the same genetic mutation - had different developmental prognoses: Twin A, severe developmental delay; Twin B, moderate developmental delay.

Method: We examined the intracellular cytokine profiles of peripheral blood mononuclear cells (PBMCs) collected from the twins through flow cytometry and their plasma cytokine levels in reference to age-matched controls.

Results: The twins had a higher percentage of interleukin (IL)-1β-positive CD14+ monocytes than did the controls. Twin A had higher percentages of IL -1 receptor antagonist (IL-1RA) and TNF-α positive CD14+ monocytes than did Twin B and the control. The plasma cytokine levels of IL-1β, IL-1RA, and TNF-α were lower in Twin A than in Twin B and the control. Concerning the CD3+CD4+ T cells, Twin A had more IFN-g positive cells than Twin B and the control. Regarding CD3+CD8+ T cells, while cells positive for IL-4, IL-10, or IL-17 were barely detectable, Twin A had lower cytokine levels of IFN-g than did Twin B and the control. No remarkable differences in the levels of IL-4, IL-10, or IL-17 were observed between the three groups. Our results indicate a lack of correlation between the proportions of positive cells for the considered cytokines and the plasma cytokine levels in the affected patients.

Conclusion: The dysregulation of the quantity of cytokine-producing cells can vary among patients with intractable epilepsy associated with lissencephaly.

A BOY WITH SEVERE EARLY-ONSET DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY ASSOCIATED WITH A CASK VARIANT INHERITED FROM HIS MOTHER WITH MILD INTELLECTUAL DISABILITY

P-10

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The phenotypes with a *CASK* mutation in males are classified into three groups (i) microcephaly with pontine and cerebellar hypoplasia (MICPCH) with severe epileptic encephalopathy, with a loss-of-function mutation, (ii) MICPCH and a severe developmental disorder but without epilepsy, with inactivating alternations in the mosaic state, and (iii) mild to severe intellectual disability (ID), with missense/splicing mutations that leave the CASK protein intact but likely alter its function. We report on a boy with severe early-onset developmental and epileptic encephalopathy associated with a *CASK* missense variant inherited from his mother with mild ID. The proband is a 1-year-old Japanese boy. Both parents have ID. The boy was born by vaginal delivery without asphyxia. At birth he had a weight of 3722 g (+1.8SD) and OFC 32.6 cm (-0.6SD). After birth he showed hypotonia and needed tube feeding. Brain MRI demonstrated prominent pontocerebellar hypoplasia. At three months of age, he showed epileptic spasms, and EEG showed a suppression-burst pattern. EEG at four months demonstrated hypsarrhythmia. His seizure was refractory, and his development was severely delayed with bedridden and no eye pursuits. We performed whole exome sequencing on the proband, and identified a hemizygous single nucleotide substitution in *CASK* (c.764G>A: p.Arg255His). His mother with ID carries the same substitution. His mother demonstrated random X inactivation pattern. The *CASK* mutation found in our patient is possibly a loss-of-function mutation in view of his severe phenotype, but the functional consequences of this alteration have not been investigated.

P-11 *ST3GAL5* MUTATION IN TWO CHINESE SISTERS WITH EPILEPSY, DEVELOPMENTAL DELAY, AND INVOLUNTARY MOVEMENTS

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ST3GAL5 mutation causes GM3 synthase deficiency which is a rare neurometabolic disorder. GM3 synthase deficiency was first reported within Amish population of the Northeastern United States in 2004. In Asia, there is only one case report of Korean siblings to date. Here we present two Chinese sisters with a novel *ST3GAL5* mutation.

Patient 1 (currently 23-year-old female)
She had no perinatal abnormalities. She began to vomit frequently at the first month of life. Growth failure and neurodevelopmental delay were observed. At 1 year of age, involuntary movements appeared. She also had epileptic seizures. EEG showed multifocal spikes. Involuntary movements deteriorated as she grew up, and she was treated with deep brain stimulation at 9 years.

Patient 2 (currently 16-year-old female)
She began to vomit at the first month. Epileptic seizures were recognized at 7 months. She had acute encephalopathy at 9 months. Afterwards, she exhibited spastic paralysis and refractory epilepsy.

Although their current symptoms are different, both patients have epilepsy, severe developmental delay, sensorineural hearing loss, and visual impairment. We performed whole exome sequencing, and a novel, compound heterozygous mutation in *ST3GAL5* was detected in both patients.

GM3 synthase deficiency due to *ST3GAL5* mutation may possibly be identified in patients with refractory epilepsy, developmental delay, and involuntary movements.

RETROSPECTIVE STUDY OF SEIZURE CONTROL IN WOLF-HIRSCHHORN SYNDROME: A SINGLE CENTER EXPERIENCE FROM JAPAN

P-12

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Background: Wolf-Hirschhorn syndrome (WHS), a syndrome caused by partial deletion of short arm of chromosome 4, presents refractory seizures during infancy. We were interested in frequency of convulsive status epilepticus and the effects of antiepileptic medications.

Methods: We retrospectively reviewed the medical records of 9 patients with WHS from 1993 to 2018 in our center. WHS was diagnosed from both clinical presentation and results of either the karyotype, fluorescence in situ hybridization or cytogenomic microarray.

Result: The median age of seizure onset was 9 months after birth (range 7 -32 month). Fever frequently triggered seizure in 7 out of 9 patients. Status epilepticus presented in 8 out of 9 patients; the frequency of status epilepticus during infancy was monthly in 6 and yearly in 2 patients.

Antiepileptic medications were effective to reduce the frequency of status epilepticus in 3 out of 6 for valproic acid, 2 out of 2 for potassium bromide, 1 out of 1 for topiramate; phenytoin, phenobarbital, clobazam, and zonisamide did not show significant effect. The median age at follow-up visit was 12 years old (range 1-19 years). Status epilepticus disappeared in 6 out of 7 patients who were followed over 5 years old; three patients were seizure-free and antiepileptic medications were weaned off.

Conclusion: Most of the status epilepticus disappeared after the age of 5 years. Potassium bromide were effective to reduce the frequency of status epilepticus in patients with refractory epilepsy, which was consistent with the previous reports.

P-13 EXAMINATION OF CAKUTHED DIAGNOSED BASED ON INTELLECTUAL DISABILITY IN WHICH A NEW PATHOGENIC VARIANT WAS IDENTIFIED

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Congenital Anomalies of Kidney and Urinary Tract Syndrome with or without Hearing Loss, Abnormal Ears or Developmental Delay (CAKUTHED) is characterized by facial dysmorphology and external ear anomalies in addition to renal lesions. Its incidence is unclear, and no case report has been published in Japan.

Case presentation: A 4-year-old girl was born at the gestational age 37 weeks by cesarean section due to pelvic presentation. At the age of 8 months, a short stature, characteristic face, and external ear anomalies were observed. Developmental quotient (DQ) was 60 and rough movement values were significantly low. Cerebral MRI at the age of 1 year-3 months revealed a bilateral frontal lobe atrophy. Furthermore, abdominal MRI showed a bilateral high intensity of renal cortex, renal atrophy and pyelectasia. An auditory brainstem response (ABR) indicated hearing impairment of the right ear, and bronchoscopy led to a diagnosis of pharyngeal malacia. Differential G staining showed a normal mutation (46,XX inv(9)(P1-12q13)). Although nephropathy had been progressive, leading to renal failure on stage3 at the age of 2 years. At the age of 4 years-2 months, Whole-exome sequencing indicated NM 002585:exon4:c.566delC:p.T189f, leading to a diagnosis of CAKUTHED. This patient was considered to have a new pathogenic variant in reference to previous reports.

Conclusion: CAKUTHED is a new disease entity registered on the Online Mendelian Inheritance in Man in 2017. If chronic renal failure or hearing impairment is present in children with idiopathic growth retardation, Whole-exome sequencing should be positively performed, considering the possibility of this disease.

ALTERED PTERIDINE AND SEROTONIN METABOLISM IN *GNAO1*-RELATED CHILDHOOD-ONSET HYPERKINETIC MOVEMENT DISORDER: A CASE REPORT

P-14

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Background: *GNAO1* encodes the alpha-o subunit (Gαo) of G-proteins. Gαo is the most abundant alpha subunit of G-proteins in brain tissue, particularly in neuronal synapses. They regulate multiple intracellular effectors and associated signaling cascades. A heterozygous gain-of-function mutation of *GNAO1* results in a distinct autosomal dominant neurodevelopmental encephalopathy called *GNAO1*-related childhood-onset hyperkinetic movement disorder (*GNAO1*-MD). To date, research has been limited regarding the molecular and neurological mechanisms that link the gene mutation to patients' symptoms.

Subject: A Japanese female with *GNAO1* p.Arg209Cys mutation. She showed chorea with moderate developmental delay from infancy and began to exhibit recurrent flares of hyperkinetic status requiring intensive care at 11 years old. She did not have epilepsy. Bilateral deep brain stimulation to the internal globus pallidus (GPi-DPS) at 14 years old ameliorated her hyperkinetic involuntary movements.

Methods: 5-Hydroxytryptamine (5-HT), 5-Hydroxyindoleacetic acid (5-HIAA), neopterin and biopterin levels of cerebrospinal fluids were measured twice, before (11 years old) and after (13 years old) her episodic flares of hyperkinetic status began.

Results: Low 5HT, low 5-HIAA, and low biopterin concentrations were found in both measurements. Neopterin concentration was normal in the first measurement but was low in the second.

Discussion: The results suggest that *GNAO1* gain-of-function lowers the CSF pteridine and serotonin levels. These changes might contribute to the disease pathophysiology. Further research is needed to confirm our results and to delineate the precise molecular pathophysiology of *GNAO1*-MD.

P-15 A CASE OF DEVELOPMENTAL EPILEPTIC ENCEPHALOPATHY WITH *PPP3CA* MUTATION

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Introduction: The genetic background of developmental epileptic encephalopathy (DEE) is diverse, and many responsible genes have been identified. We experienced a case of severe DEE and identified a mutation in the calcineurin-related gene *PPP3CA*.

Case: The case was a 4-year-old girl with normal perinatal history. At 6 months, she developed spasms in cluster. Head MRI did not show any notable findings, and hypsarrhythmia was observed in interictal EEG. The child was diagnosed with infantile spasms and treated with ACTH. ACTH was effective but the spasm recurred soon. At 9 months, a focal seizure of approximately 1 minute with eyes deviation to the right or the left and tonic convulsions in the ipsilateral upper limb appeared. She was treated with ACTH again, but the spasm recurred and was resistant to several antiepileptic drugs and pyridoxal. Ketogenic diet resolved the spasm. At present, focal seizures remain on a weekly basis. Although fixation and pursuit and turning over are possible, there is no language understanding. Whole exome analysis identified a de novo single nucleotide insertion c.1290dupC (p.Met431Hisfs * 20) in *PPP3CA* gene.

Discussion: The *PPP3CA* gene is highly expressed in the central nervous system and encodes a calcium-dependent subunit of serine / threonine phosphatase. It is thought that the mutation impairs intracellular signal transmission and causes neurological symptoms. It is becoming possible to select a treatment that is tailored to the genetic background. Accumulation of case information is important for the further development of personalized treatment.

LONG-TERM FOLLOW-UP STUDY OF MALAN SYNDROME WITH WEST SYNDROME : A CASE REPORT

P-16

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Malan syndrome is a recently introduced clinical entity characterized by overgrowth, marcocephaly with a prominent forehead, and developmental delay. This syndrome has been associated with the *NFIX* gene mutation located on chromosome 19p13.2. Recently, we identified a de novo 19p13.2 deletion in a male with west syndrome (HINO-FUKUYO, et al. hum genet 2015). We present a long-term follow-up study of this case who was considered as having malan syndrome and west syndrome.

P-17 CAPABILITY OF DIFFERENT PREDICTION ALGORITHMS TO CLASSIFY PHENOTYPE AS BENIGN NEONATAL EPILEPSY OR DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY

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Objective: Pathogenic variants of the *KCNQ2* gene can cause benign (familial) neonatal epilepsy (B(F)NE) or *KCNQ2* developmental and epileptic encephalopathy (*KCNQ2* DEE). We analyzed the characteristics of their prediction algorithms.

Methods: *KCNQ2* pathogenic variants were collected from in-house data and two large disease databases (The RIKEE project and EpilepsyGene) with their clinical phenotypes. Non-pathogenic *KCNQ2* missense variants were obtained from the Genome Aggregation Database (gnomAD). Several algorithms for predicting pathogenicity from these genetic variants were evaluated.

Results: The Protein Variation Effect Analyzer (PROVEAN) was the most effective algorithm for predicting whether a *KCNQ2* variant would be pathogenic. In the *KCNQ2* protein region between S3 and helix A, the PROVEAN scores for the B(F)NE and *KCNQ2* DEE variants were significantly lower than that for gnomAD non-pathogenic variants. In the same region, the Percent Accepted Mutation (PAM) 30 scores of the *KCNQ2* DEE variants were significantly lower than those of B(F)NE variants and gnomAD variants. In the S1 S3 protein region, PAM30 scores of the B(F)NE variants were significantly lower than those of gnomAD variants and *KCNQ2* DEE variants.

Conclusion: Using these regional specificities, PROVEAN is a useful tool for predicting the pathogenicity of novel *KCNQ2* sequence variants. PAM30 scores can be further used to distinguish whether a novel *KCNQ2* variant is might cause the B(F)NE or *KCNQ2* DEE.

A PATIENT WITH WEST SYNDROME AND AUTISTIC SPECTRUM DISORDER WITH *SCN2A* GENE DELETION WITHOUT *SCN1A* INVOLVEMENT

P-18

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Introduction: Chromosomal anomalies have been associated with West syndrome (WS), especially those involving voltage-gated sodium channels (VGSCs). The chromosome 2q24.3 region is important since it harbors three VGSC genes (*SCN1A*, *SCN2A*, *SCN3A*), although the pathogenicity is thought to be mainly due to loss-of-function of *SCN1A*.

Method & Results: The proband was a 2-year-old boy who showed limited eye contact and social smile at 4 months, motor delay at 9 months, and developed clusters of epileptic spasms at 10 months. Facial features consisted of upslanted palpebral fissure and hypertelorism, and physical examination revealed generalized muscular hypotonia, dystonia-like involuntary movement, and stereotypic movements. At 10 months, interictal EEG demonstrated hypsarrthythmic pattern during sleep and awake. Intramuscular low-dose adrenocorticotropic hormone was effective, and subsequent seizure control was achieved by topiramate. Development was evaluated to be 8 months at 21 months, and he was also diagnosed with autism spectrum disorders (ASD). Chromosomal analysis (G-banding) revealed a normal male karyotype. Whole-exome sequencing did not reveal any causative *de novo* point mutations in previously known developmental and epileptic encephalopathy-associated genes. eXome Hidden Markov Model detected a microdeletion encompassing a 1,102-kb region of chromosome 2q24.3. Further analysis showed a *de novo* microdeletion of *SCN2A* and *SCN3A*, without concomitant involvement of *SCN1A*.

Conclusions: Although three previous literatures reported microdeletions including *SCN2A* without *SCN1A* involvement in patients with ASD and mental retardation, only one had unclassified infantile seizure. Our case suggests *SCN2A* as a probable genetic cause in the development of ASD and WS.

P-19 A CASE OF DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY WITH INVOLUNTARY MOVEMENTS DUE TO MUTATION OF THE *SCN2A* GENE

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Mutations of *SCN2A* were originally described in a patient with benign familial neonatal-infantile seizures. Recent studies have expanded the clinical phenotypes. We report a patient with infantile-onset developmental and epileptic encephalopathy who presented with episodic involuntary movements.

Case report: A 24-year-old Japanese woman was born to healthy parents after uneventful pregnancy. On day 1, she presented with focal seizures (< 1 minute), manifesting as eye deviation, stiffening of the limbs, and crying. Nonepileptic myoclonus also developed on day 4. Inter-ictal EEG revealed the suppression-burst pattern. There were no abnormalities on MRI. Blood, urine, and CSF tests were all negative. Although transient epileptic spasms in series were observed at one month of age, she was diagnosed with early myoclonic encephalopathy of unknown etiology. Her focal seizures, sometimes evolving to clusters, were refractory to several antiepileptic drugs, but markedly responded to lidocaine. At 20 years of age, episodic choreoathetotic movements of her face and extremities developed. Whole exosome sequencing identified a *de novo* missense mutation in the *SCN2A* gene (c.2994G>A p.Glu999Lys). At the final evaluation, she was bed-ridden with severe mental disability. Her seizures have been controlled by antiepileptic treatment (PHT and NZP) for over 20 years.

Conclusions: Our patient, carrying a missense *SCN2A* mutation, presented with epileptic encephalopathy during early infancy and subsequently developed episodic involuntary movements in early adulthood.

COMPARATIVE CHARACTERIZATION OF *PCDH19* MISSENSE AND TRUNCATING VARIANTS IN *PCDH19*-RELATED EPILEPSY

P-20

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PCDH19-related epilepsy is clinically characterized by the occurrence of seizures in girls at the mean age of 9 months. Seizures can be convulsive, focal or tonic; development can be normal but regression often happens with severe intellectual disability, autistic features and/or psychiatric disorders. It is caused by pathogenic variants of the *PCDH19* gene encoding protocadherin 19. *PCDH19* pathogenic variants can be divided into two types: missense or truncating, which produce proteins carrying a single amino acid substitution or shortened/degraded proteins, respectively. The aim of study was to investigate the distributional characteristics and the clinical implication of each type of *PCDH19* pathogenic variants.

We collected novel 34 pathogenic variants in our cohort and compared the distribution of variants between missense and truncating, after including previously reported variants. The distribution of missense variants was uniform throughout the extracellular (EC) domain (which consists of highly conserved six domains). On the other hand, truncating variants showed two types of distributions: 1) uniform from EC domain 1 to EC domain 4, and 2) uniform from EC domain 5 to the upstream region of the last exon. Furthermore, we also found that the intellectual disability associated with the second type of truncating variants was milder than that with the other types of variants. These findings provide the first evidence that there are two types of truncating variants in the *PCDH19* gene in their distribution as well as in their resultant clinical phenotype.

P-21 ASSESSMENT OF ACUTE ENCEPHALOPATHY WITH BIPHASIC SEIZURES AND LATE REDUCED DIFFUSION FROM FEBRILE STATUS EPILEPTICS AND FEBRILE SEIZURE USING EEG SPECTRUM ANALYSIS

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Objective: To assess the progress of acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) by power spectrum analysis of EEG data.

Methods: We retrospectively collected EEG data of 8 pediatric patients with status epilepticus who underwent EEG. The patients with a final diagnosis of AESD (n=4) and febrile seizure (FS) (n=4) were included and their EEG data with bipolar montages (Fp1-F3, Fp2-F4, F3-C3, F4-C4, C3-P3, C4-P4, P3-O1, P4-O2, C3-T3, C4-T4, Fp1-Fp2, F3-F4, C3-C4, P3-P4, and O1-O2) were analyzed. Artifact-free 60-second epochs were selected from each record and the average power values were calculated between electrodes for each patient. When the three EEG measurements were recorded in the acute phase, biphasic seizures were observed, and after biphasic seizures which were used for analyzing the AESD group. The EEG data of the FS group were also collected doing the same period. Results: The power values of the beta and gamma bands during acute phase and after biphasic seizure in the AESD group were relatively lower than those in the FS group. All EEGs of the AESD group showed encephalopathy characterized by dominant widespread regular/irregular delta activity. MRI showed centro-occipital sparing in 2 patients, predominantly affecting the bilateral frontal lobes in one patient and diffuse injury in another patient.

Conclusions: The power values in the beta and gamma bands using EEG data with bipolar montage may help distinguish AESD from FS before biphasic seizure.

A CASE OF INFANTILE SPASMS SUSPECTED OF METABOLIC BRAIN ABNORMALITY IN RESPONSE TO VIGABATRIN

P-22

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Introduction: Epileptic encephalopathy is caused by various diseases, which include brain malformation, perinatal abnormalities, brain tumors, metabolic abnormalities, chromosomal abnormalities, and genetic abnormalities. We report a case of infantile spasms with characteristic brain images and therapeutic effects of vigabatrin (VGB).

Case: The patient was born full term with normal delivery. She had myoclonus and poor weight gain at 3 months of age. She developed spasms at 4 months of age. EEG showed diffuse irregular spike and waves. She was diagnosed infantile spasms. However ACTH therapy, ketogenic diet, and some anticonvulsants did not control seizures. She had severe motor and mental developmental delay. MRI showed abnormal findings in the periventricular to subcortical white matter, posterior limb of internal capsule, tractus tegmentalis centralis, and red nucleus. MRS detected the increase peak of Glx (Glu + Gln). The concentration of GABA in the CSF was normal. She started the treatment of VGB at 9 months, seizure frequency was relieved, and a social smile appeared. Her seizure was controlled at 15 months of age.

Discussion: Disorders of GABA metabolism are rare and manifest prominent neurological sequelae. We report a case in which VGB was successful, suspected of abnormal GABA metabolism from brain imaging.

P-23 INCIDENCE AND RISK FACTORS OF ACUTE ENCEPHALOPATHY WITH BIPHASIC SEIZURES AND LATE REDUCED DIFFUSION IN CHILDREN WITH PROLONGED FEBRILE SEIZURE

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Objective: To clarify the incidence and risk factors of acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) among pediatric patients with prolonged febrile seizures (PFS).

Methods: We retrospectively surveyed the number of patients with PFS (≥ 20 minutes and ≥ 40 minutes) and AESD under 6 years old. The survey period was two years from January 2016. For the primary survey, we mailed the questionnaire to 1123 hospitals with pediatric department nationwide in Japan. Then, we sent the secondary questionnaire about clinical data for the patients with PFS over 40 minutes and those with AESD. We analyzed the clinical data in comparison with the PFS group and the AESD group.

Results: The recovery rate of the primary survey was 42.3%. The incidence of AESD was 4.3% in PFS ≥ 20 min and 7.1% in PFS ≥ 40 min. In the univariate analysis, the following factors showed significant difference between the PFS group and the AESD group; pH, AST, ALT, LD, CK, NH3, Procalcitonin(PCT), uric acids, BUN, Cr, lactate. The multivariate analysis for stratified values showed high PCT and high glucose as risk factors for AESD. Above 3 points of the prediction score using the following variables, AST ≥ 40 (1 point), Cr ≥ 0.35 (1 point), PCT ≥ 1.7 (2 points), glucose ≥ 200 (2 points), had 80.0% of sensitivity and 72.3% of specificity.

Conclusion: The incidence and the prediction score for AESD would be useful for future intervention trials for AESD.

A COMPARISON OF CLINICAL FEATURES OF ACUTE ENCEPHALOPATHY WITH BIPHASIC SEIZURES AND LATE REDUCED DIFFUSION BETWEEN SHORT AND PROLONGED FIRST SEIZURE DURATION

P-24

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Background: Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) typically shows biphasic seizures followed by prolonged first seizures (general status epilepticus), with hyperintensities in the subcortical white matter on diffusion-weighted magnetic resonance imaging (MRI) on days 3-14 after onset. Although AESD cases after a short seizure have been reported sporadically, the characteristic differences between short and prolonged first seizures are unknown.

Objective: We compared the clinical characteristics of patients with short (less than 30 minutes) and prolonged first seizures (more than 30 minutes) using a single-center consecutive cohort.

Method: We retrospectively reviewed the database of Hyogo Prefectural Children's Hospital from October 1, 2002, to September 30, 2019. Forty-three pediatric patients under 18 years of age met the AESD diagnostic criteria of the Japanese Acute Encephalopathy Guidelines 2016. The clinical characteristics were compared between the short (n = 9) and prolonged first seizure groups (n = 34).

Result: The patients in the short first seizure group tended to be younger (14.0 vs. 19.8 months) and had a better neurological prognosis (pediatric cerebral performance scale 1 vs 2; follow-up at 1 month, 6 months, 1 year, and 2 years). A high-intensity area on the diffusion-weighted MR images was mainly observed in the frontal region in the short first seizure group and spread beyond the frontal lobe in the prolonged first seizure group.

Conclusion: AESD is not necessarily caused by a prolonged first seizure. More extensive brain damage and poor neurological prognosis are associated with prolonged first seizures.

P-25 FIVE YEARS FOLLOW UP OF SCN8A DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY

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Introduction: Developmental and epileptic encephalopathy (DEE) is characterized by early-onset intractable seizures and developmental delay. The SCN8A mutation has been reported as one of the causes of DEE.

Patient: From one month after birth, the patient had status epileptics monthly with cyanosis required oxygen over 30 minutes. There were spike rarely on EEG, and no cortical dysplasia was found on MRI. The seizures were drug-resistant, with the exception of lidocaine. ACTH therapy was effective only for a short time. The de novo heterozygous SCN8A mutation (p.Arg1872Trp) was identified at 1 year of age. Daily generalized onset tonic seizures (GTS) persisted without lidocaine, yet GTS were slightly reduced with high doses of PB (over 40 ug/ml) and PHT. When the effectiveness of lidocaine declined, total callosotomy was performed to treat GTS at 2 year of age. However, the GTS were still repetitive; Ketogenic diet (KD) therapy was partially effective. VNS reduced the seizures to weekly GTS and daily focal onset clonic seizure in the limbs. The patient is currently bedridden, unable to speak, and with tube feeding.

Discussion: A wide range of phenotypic variation is associated with SCN8A mutations. In many cases, the seizure status and efficacy of AEDs change with age. It is important to evaluate genotype-phenotype correlations. In this case, channelopathy was considered to be lidocaine-dependent. Early diagnosis was useful for developing an appropriate therapeutic strategy. If the seizures are resistant to AEDs and KD, palliative surgery might be considered for improving prognosis even in channelopathy.

MOVEMENT DISORDERS IN CHILDREN WITH GENETIC EARLY INFANTILE EPILEPTIC ENCEPHALOPATHIES

P-26

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Background: Early onset encephalopathies are a heterogenous group of diseases characterized by severe dysfunction of cognitive, sensory and motor development. The aetiology included various genetic defects that disrupt brain function or its normal structure and development. In recent years the occurrence of movement disorder in early infantile epileptic encephalopathies (EIEEs) has been increasingly recognized and became core feature of several EIEEs.

Aims: To describe the phenomenology and spectrum of movement disorder in children with genetic EIEEs seen at our hospital between 2019 till January 2020. Evaluation of the movement disorders evolution and response to treatment were also described. The overall neurodevelopmental outcome of these children was highlighted as well.

Results: Eleven of 17 patients followed up under our hospital with genetically confirmed EIEE were found to have movement disorders. The genetic EIEEs with prominent movement disorders were CDKL5, FRRS1L, GRIN2A, KCNQ2, KCNT1, SCN1A, SCN8A, SLC2A1, STXBP1 and TBC1D24. The most common type of movement disorders seen in our cohort was dystonia followed by myoclonus. One of the patients with KCNQ2 had status dystonicus that responded well with only Gabapentin. Other forms of movement disorders did not warrant specific treatment. Details of the time course of the movement will be further elucidated.

Conclusion: Variable types of movement disorder can occur in children with genetic EIEE. The movement disorders tend to manifest as early as neonatal period. Further evaluation would be beneficial to recognize these non-epileptic movement disorders which could be a more predominant feature in these patients.

P-27 ATYPICAL EVOLUTION OF SELF-LIMITED IDIOPATHIC FOCAL EPILEPSIES

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Self-limited focal epilepsies, i.e. Benign Childhood Epilepsy with Centro-Temporal spikes (BCECT) and Panayiotopoulos Syndrome (PS) are known to rarely evolve into Encephalopathy related to Status Epilepticus during slow Sleep, or ESES (Dalla Bernadina, et al. 1991). ESES syndrome is characterized by variable seizures, neurological deterioration, involving cognitive, behavioral and/or motor domains, and typical EEG findings that extremely high spike & wave index (or status epilepticus) during NREM sleep (Tassinari, et al. 2019). We have experienced 4 such patients out of 10 from 2017 to 2019. 2 patients are male PS, and 2 patients are BCECT. 2 PS patients have been prescribed carbamazepine, and 2 BCECT patients have been administered levetiracetam. In 3 patients, the seizure frequencies have been increased, and the other patient has come to show negative myoclonus and speech difficulties. We review the literatures and discuss about the history, pathomechanisms, diagnostic criteria, prognosis, genetics and treatment of ESES.

PANAYIOTOPOULOS SYNDROME-LIKE EPILEPSY IN PEDIATRIC PATIENTS WITH HYPOPLASTIC LEFT HEART SYNDROME

P-28

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Introduction: There are few in-depth studies on the characteristics and actual prevalence of epilepsies associated with severe congenital heart disease (CHD). Herein, we report that a disproportionally high number of patients with hypoplastic left heart syndrome (HLHS), a type of severe CHD, developed Panayiotopoulos syndrome-like epilepsy.

Methods: Children with HLHS who were born between January 2006 and March 2016 and underwent cardiac surgery at Okayama University Hospital were investigated. We retrospectively examined the number of patients with epilepsy and their clinical characteristics, including seizure types, EEG, neuroimaging studies, clinical course, and treatment response. Patients who died before one year of age were excluded from the study.

Results: The subjects were 79 children with HLHS, and comorbid epilepsy was confirmed in 10 patients (12.7%). The age of epilepsy onset ranged from 11 months to 7 years, 2 months. Eight of these ten patients exhibited focal seizures with autonomic symptoms such as vomiting during the clinical course. Interictal EEG showed occipital spikes at least once during the clinical course in eight patients. Five patients had more than ten seizures, while three had only one seizure. In neuroimaging, five patients exhibited mild abnormalities. In regard to development, mild to moderate delay was observed in four patients.

Discussion: The rate of children with HLHS and comorbid epilepsy is high at 12.7% and many of them exhibited characteristics similar to Panayiotopoulos syndrome in this study. This phenomenon may be related to the high sensitivity of the autonomic nervous center in young children.

P-29 EPILEPSY CHARACTERISTICS AND EFFICACY OF TREATMENT IN JAPANESE PATIENTS WITH DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY DUE TO *CDKL5* MUTATIONS

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Purpose: Mutations in the cyclin-dependent kinase-like-5 (*CDKL5*) gene cause an early onset developmental and epileptic encephalopathy. We investigated epilepsy characteristics and the efficacy of antiepileptic drugs (AEDs) in Japanese patients with *CDKL5* mutations.

Method: Twenty-nine patients (female 21, male 8) with putative pathogenic *CDKL5* mutations were included. We retrospectively evaluated each patient's clinical date and antiepileptic medication, including age at onset, epilepsy types, seizures types, neuropsychological status, electroencephalography (EEG), and the effectiveness of AEDs.

Results: The mean age of onset of epilepsy were 3.3 months (4 days to 26 months). Eighteen (18/29, 62%) were diagnosed as West syndrome, 12/29 (41%) as unclassified early onset epileptic encephalopathy and 2/29 (7%) as Ohtahara syndrome. Hypsarrhythmia was observed in 19 patients, who had spasms all. AEDs with higher percentage for achieving more than 25% reduction in seizure frequency were VPA, TPM, CZP, STM and VGB. Conversely, CBZ, GBP, PHT and KBr were less effective. LTG (4/21) aggravated epileptic seizures. ACTH was the most effective of all treatment, however its effect had lasted temporarily. Ketogenic diet could not help improve seizure frequency in most patient, but was remarkably effective in one patient.

Conclusion: Although ACTH was temporally effective, patients with *CDKL5*-related epileptic encephalopathy had drug resistant seizures. Further studies are required to find more effective treatment.

SUSPECTED AUTONOMIC DYSFUNCTION IN INFANTS WITH APNEIC SEIZURES RELATED INSULA

P-30

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Objective: Apnea in infants can be caused by various pathophysiological mechanisms. The apneic seizure is rarely captured on routine EEG. Critical conditions of apnea can be life-threatening events. Recently, focal onset seizures from insula have been reported to provoke apnea on prolonged video EEG. We suspect that the focus of autonomic seizures including apnea may be insula. The aim of the present study is to expertise the possibility that focus of apneic seizure in infants is insular cortex.

Methods: We collected nine infants including 2 neonates with apneic seizures from January 2010 to October 2019 in The Hospital for Sick Children, Toronto. Clinical data and video EEG findings were retrospective analyzed. And we evaluated the sympathetic and parasympathetic activities in the patients by analyze the heart rate variability (HRV): low frequency (LF) power; high frequency (HF) power; LF/HF ratio; and root mean square of successive differences (RMSSD) using ECG during video EEG monitoring. Interictal, preictal and postictal HRV was measured at 5 minutes.

Results: The vEEGs were performed from 3 day to 13 month-old. We captured 18 of apneic seizures. Prolonged 17-71 hours video-EEG captured 1-3 apneic events. Ictal EEG showed rhythmic activities before apneic events. The interictal RMSSD was significantly lower than controls. The increase of RMSSD change from interictal to preictal in bradycardia group during seizures was significantly higher than those of the others.

Conclusions: Ictal EEG findings and HRV might indicate deep seated focal onset autonomic seizures from insula in a subset of infants with apneic seizures.

P-31 LATERALIZATION OF THE EPILEPTOGENIC HEMISPHERE GENERATING HYPSARRHYTHMIA SECONDARY TO PERINATAL ISCHEMIC STROKE; PHASE AMPLITUDE COUPLING AND FUNCTIONAL CONNECTIVITY

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Purpose: Children with perinatal arterial ischemic stroke(PAIS) have a potential risk for infantile spasms(IS) presenting hypsarrhythmia despite focal stroke.
Modulation index(MI) measures strength of phase-amplitude coupling between gamma and slow waves. Synchronization likelihood(SL) measures degree of generalized synchronization. We hypothesized that epileptogenic hemisphere in IS patients with PAIS in middle cerebral artery territory(PAIS-MCA) establishes pathological network generating hypsarrhythmia.

Methods: We collected 10patients with IS and 11patients with focal epilepsy(FE), secondary to PAIS-MCA. We selected ten 2-minute epochs of interictal EEG. MI between gamma(30-70Hz) and slow waves(3-4Hz) were calculated. We compared MIs in affected hemispheres to in unaffected hemispheres.
SLs among all pairs of electrodes were analyzed in 9-frequency bands: 5-delta bands, theta, alpha, beta and gamma. We investigated SL matrixes of inter- and intra- hemispheric connectivity.

Results: MIs in affected hemispheres of IS patients were significantly higher than in unaffected hemispheres of IS patients and both hemispheres of FE patients. The inter-hemispheric connectivity of 8-frequency bands in IS patients were significantly stronger than in FE patients. In IS patients, the intra-hemispheric connectivity of 9-frequency bands in affected hemisphere were significantly stronger than in unaffected hemisphere.

Conclusions: MIs and SLs are surrogate markers to lateralize the epileptogenic hemisphere of IS secondary to PAIS-MCA despite hypsarrythmia. IS secondary to PAIS-MCA may have epileptic network in inter- and intra-hemispheric connections to provoke hypsarrythmia. Hypsarryhmia and IS can be generated by abnormal cortical, subcortical and transcallosal networks compared to cortical epileptic network provoking FE.

RAPID IMPROVEMENT OF ENCEPHALOPATHY IN CHILDREN WITH LENNOX-GASTAUT SYNDROME AND GENERALIZED EPILEPSY AFTER FOCAL RESECTION

P-32

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Successful epilepsy surgery in children with generalized EEG findings but with focal lesions on neuroimaging has been well-described (Willie E et al, 2007), with good long-term seizure outcome. However, data is limited on clinical and EEG improvement; this may be important for children with epileptic encephalopathies such as Lennox-Gastaut syndrome (LGS), where improvement in encephalopathy and neurocognitive comorbidities is equally important.

We describe two children seen at Boston Children's Hospital with LGS (multiple seizure types, including tonic seizures, slow spike wave complexes on EEG and developmental delay) and focal lesions on neuroimaging. Case 1 (3 year old boy with left fusiform gyrus low grade neoplasm) developed epilepsy at 15 months (epileptic spasms, atypical absence, generalized tonic clonic and myoclonic-tonic seizures), significant language and behavioral regression. Resection of the lesion resulted in seizure freedom and improvement in encephalopathy, with improved attention and behavioral regulation. Case 2 (6 year old girl MRI with right temporal neoplasm) developed frequent tonic seizures at age 3, with upper extremity extension and trunk flexion, and developed neuro-cognitive regression, becoming non-verbal, and losing skills of daily living. Resection of the lesion resulted in seizure freedom and regaining speech (able to speak a few words in 1 month, speaking in phrases by 1 year after surgery).

Surgical resection in children with epileptic encephalopathies such as LGS with focal lesions may result in good seizure control as well as improvement in clinical encephalopathy. Larger scale studies are needed to further explore the reproducibility of the findings.

P-33 THE ROLE OF FOCAL EPILEPSY FEATURES IN DEFINING SCN1A POSITIVE DRAVET SYNDROME AS GENERALIZED AND FOCAL EPILEPSY

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The recent International League Against Epilepsy proposal adopted new category of epilepsy syndrome which manifest both generalized and focal epilepsy. Dravet syndrome is suggested as the representative example of generalized and focal epilepsy syndrome. However, features of focal epilepsy have not been comprehensively illustrated. We investigated the features of focal epilepsy in 82 *SCN1A* positive Dravet syndrome patients to better define the clinical spectrum of Dravet syndrome. The focal seizures at onset and during the clinical course was found in 56.1% (46/82) and 90% (63/70). Among the 30 seizures recorded during the long-term video EEG monitoring in 21 patients, 11 seizures were confirmed as focal onset (36.7%). Bilateral tonic clonic seizures captured during the video EEG recording are more likely to be focal onset (63.6%, 7/11). Focal epileptiform discharges were found more frequently than generalized epileptiform discharges at seizure onset and during the clinical course: (13.4% vs. 3.6%, 70% vs 24.3%). The five patients (5/70, 7.1%) showed only focal epilepsy features during the clinical course. Our study provided the comprehensive focal epilepsy features of *SCN1A* positive Dravet syndrome patients. This evidence could contribute to support the concept of generalized and focal epilepsy of Dravet syndrome. Recognition of focal epilepsy features in defining the clinical spectrum of Dravet syndrome could lead to earlier genetic diagnosis.

INFANTILE EPILEPTIC ENCEPHALOPATHY ASSOCIATED WITH A KCNA2 GENE MUTATION

P-34

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We report the case of a 3-year-old boy with epileptic encephalopathy due to a mutation in the gene encoding the potassium voltage-gated channel subfamily A member 2 (KCNA2). He first exhibited focal epilepsy with secondary generalization. He was given carbamazepine treatment, and at 14 months of age, his epilepsy relapsed. These seizures took on several forms and usually occurred in response to fever or taking a bath. He also experienced developmental delay and developed truncal ataxia. Electroencephalography (EEG) revealed generalized high voltage slow waves. We initially assumed that the epileptic encephalopathy was because of an undiagnosed metabolic or neurodegenerative disease. Blood tests and brain magnetic resonance imaging (MRI) revealed no significant findings. Given his clinical course, we performed a comprehensive analysis of genes related to epilepsy, including sodium voltage-gated channel alpha subunit 1 (SCN1A). Notably, we identified a missense mutation in KCNA2. A few reports have considered the relationship between KCNA2 and epileptic encephalopathy, and it clinically resembles Dravet syndrome. We should consider possible KCNA2 gene mutations for patients with epileptic encephalopathy and ataxia since infantile period.

P-35 GENETICS AND CLINICAL CORRELATION OF DRAVET SYNDROME AND ITS MIMICS

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Objective: De novo variants of the SCN1A gene were discovered to cause most cases of Dravet syndrome (DS). In some cases, non-SCN1A genes mutation can present with a phenotype so similar to that of DS. The aim of this study was to compare the phenotype of SCN1A gene with non-SCN1A gene mutation related DS.

Methods: Thirty-six patients with DS-like phenotypes were followed at Chang Gung Memorial Hospital from July 2017 to December 2019. We retrospectively analyzed the variables of clinical profile and genetic survey.

Results: There were 36 patients with DS-like phenotype enrolled in this study. 12 patients (33.3%) with SCN1A mutation, 1 (2.8%) with SCN8A mutation and 5 females (13.9%) with PCDH 19 mutation. The median age of first seizure onset was 7 m/o in SCN1A mutation patients, 1.3 y/o in PCDH19 and 10 m/o for remaining patients. The majority of SCN1A mutation patients had status epilepticus (75% vs 40%) and fever-sensitive seizures (77% vs 31%) compared with patients of PCDH19 mutation. 3 of 5 (60%) patients with PCDH19 mutation showed brain MRI abnormalities. The 3 most commonly used antiepileptic drugs were levetiracetam, sodium valproate, and clobazam. 3 of 12 patients with SCN1A mutation used stiripentol. 27.2% genetic mutation identified patient became seizure free.

Conclusion: Patients with SCN1A mutation had high rate of fever-sensitive seizures, status epilepticus, and relatively small seizure onset age. PCDH19 mutation had a relatively high proportion of abnormal brain MRI findings. Compared with genetic mutation identified patients, the remaining patients had better seizure outcome.

DRAVET-LIKE EPILEPTIC PATIENTS WITH PCDH19 MUTATIONS IN TAIWAN AND MALAYSIA

P-36

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Objective: PCDH19 epilepsy is a rare epilepsy syndrome with early onset seizures, cognitive and sensory delays, and behavioral problems. The aim of this case series was characterizes the phenotype of epileptic patients with PCDH19 mutations, a Dravet syndrome mimic.

Methods: From July 2017 to December 2019, medical records of 6 patients with epilepsy due to PCDH19 mutation were retrospectively reviewed for clinical profiles in Taiwan and Malaysia.

Results: Six female patients were enrolled, aged 3 to 45 years. Seizure onset was at 6 month-old to 2-year-7-month-old with generalized tonic-clonic seizures or focal seizures. 4 (67%) patients presented febrile seizure for the first time attack and 2 (33%) with hemiclonic seizure. All cases (100%) are fever sensitivity but lack of photosensitivity, and seizure frequency trends in clusters as opposed to single longer seizures. Five (83%) displayed varying degrees of intellectual disability but one had no impairment. 4 patients (67%) had abnormal brain images. On average, the patients received 5 different antiepileptic drugs (range 4-6). 2 patients became seizure free at least 6 months before the last visit. Half of patients used sodium channel blockers currently and without aggravations.

Conclusions: Although presence of fever sensitivity in PCDH19 epilepsy and Dravet syndrome, differences were noted including later seizure onset, lack of photosensitivity, increased frequency of seizure clusters. Remarkably, there was a relatively high proportion of abnormal MRI findings in our patients. The role of protocadherin 19 during brain development suggests that PCDH19 mutations lead to structural malformations.

P-37 EVALUATION OF HYPOTHALOMO-PITUITARY-ADRENOCORTICAL FUNCTION AFTER SYNTHETIC ACTH THERAPY FOR INFANTILE SPASMS (WEST SYNDROME)

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Objective: Adrenal insufficiency as a side effect of hormonal therapy using natural adrenocorticotropic hormone (ACTH) for infantile spasms (West syndrome) has been previously reported. However, no study has assessed the hypothalamo-pituitary-adrenocortical function after hormonal therapy using synthetic ACTH, which is commonly used in Japan.

Methods: 37 patients with infantile spasms (West syndrome) who received synthetic ACTH therapy between April 2010 and March 2017 were retrospectively investigated. 35 patients underwent a corticotropin-releasing hormone (CRH) loading test after ACTH therapy. Patients with a peak serum cortisol concentration below 15 μg/dL were considered to be at risk for adrenal insufficiency.

Results: Of the 35 patients, four (11%) exhibited a peak cortisol concentration below 15 μg/dL. There was no significant difference in terms of age at ACTH therapy, total amount of ACTH administration, duration of ACTH administration or presence of other critical side effects besides adrenal insufficiency between the patients with and without the risk of adrenal insufficiency.

Conclusions: This is the first report examining the hypothalamo-pituitary-adrenocortical function following synthetic ACTH therapy. Clinicians should be aware that some patients exhibit an insufficient response on the CRH loading test after synthetic ACTH therapy. The predictors of the risk of adrenal insufficiency were not identified. When patients after ACTH therapy have symptoms of adrenal insufficiency, steroid hormone should be administered.

A CASE REPORT OF CEREBRAL CAVERNOUS HEMANGIOMA-ASSOCIATED HEMORRHAGE DURING THE TREATMENT OF FOCAL EPILEPSY

P-38

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We report the case of a 23-month-old girl with no significant perinatal history. At the age of 7 months, she was referred to our department with complaints of seizures with eye deviation to the right, blinking, loss of consciousness, and limb tonicity lasting less than 30 seconds. Interictal electroencephalogram (EEG) showed repeated focal spike-wave discharges in the right occipital region. Ictal EEG demonstrated rhythmic fast-wave activity spreading from the right occipital region. Magnetic resonance imaging (MRI) of the brain and technetium-99m-ethyl cysteinate dimer (99mTc-ECD) single-photon emission computed tomography (SPECT) failed to indicate a clear seizure focus. Levetiracetam (LEV) therapy was ineffective, but oral administration of valproic acid (VPA) and zonisamide (ZNS) eliminated seizures and improved EEG findings. At 23 months, repeat MRI revealed subacute hemorrhage in the white matter adjacent to the right ventricle. There were no symptoms of vomiting or paralysis. Head CT showed a slightly higher density of unclear clinical significance in the right parietal region. Blood tests showed no predisposition to bleeding. We suspected the lesion to be a cavernous hemangioma, and as the patient was asymptomatic, we decided to monitor her with regular MRI scans. The relationship between hemangiomas and epileptic seizures is unknown as the location of EEG abnormalities does not correlate with the bleeding sites. However, we believe that patients should be carefully monitored for the appearance of new lesions. We present a case report of cerebral cavernous hemangioma-associated hemorrhage during the treatment of epilepsy, which is relatively rare.

P-39 SUCCESSFUL TREATMENT OF KETOGENIC DIET IN A CASE WITH EPILEPTIC ENCEPHALOPATHY AND ALTERNATING HEMIPLEGIA WITH NOVEL *CACNA1A* MUTATION

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Introduction: Developmental epileptic encephalopathies are genetically heterogeneous severe childhood-onset epilepsies with developmental delay. Here we report a case with epileptic encephalopathy and alternating hemiplegia with novel *CACNA1A* mutation.

Case: A 6-year-old Japanese boy was born to healthy, nonconsanguineous parents. He showed severe neurodevelopmental delays, such as inability to perform eye tracking, an unstable head, and severe muscular hypotonus. He had epileptic seizures lasting more than half a day following vomiting since early infancy and was repeatedly hospitalized especially during fever. Epileptic seizures always could not be eliminated by intravenous midazolam, and intravenous phenobarbital was relatively effective. Blood and cerebrospinal fluid tests showed no obvious abnormalities, electroencephalography showed no apparent epileptic discharge, and brain MRI showed only mild brain atrophy. From 3 years, he showed hemiparesis attacks several times in his right or left upper and lower limbs. Whole-exome sequencing analysis revealed a novel de novo missense mutation (c.2131G>T) in *CACNA1A*. Administration of oral phenobarbital, zonisamide, and potassium bromide was difficult to control seizures. However, he started the ketogenic diet at 3 years, then his seizures dramatically declined about once every six months.

Discussion: A ketogenic diet has been reported to be effective for refractory epilepsy and alternating hemiplegia in patients with *ATP1A3* gene mutation, but no report has been reported for *CACNA1A*. This is the first report that patient with *CACNA1A* mutation was successfully treated by ketogenic diet for preventing hemiplegic attacks and seizures.

SPASTICITY: A SIDE EFFECT OF ADRENOCORTICOTROPIC HORMONE THERAPY ?

P-40

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We sometimes experience patients who appears or aggravate spasticity during ACTH therapy, which in not a well-known side-effect.

This retrospectively study assessed 85 patients with epileptic spasms and treated with synthetic ACTH therapy; we selected patients who presented spasticity and required initiation or increase in muscle relaxant during ACTH therapy and reviewed their clinical findings. In addition, to identify the risk of this side-effect, these findings were compared with the remaining patients (no side-effect patients).

Ten patients (11.8%) presented spasticity during ACTH therapy. Epileptic spasms presented at the median age of 4 months old (range, 1 to 7). The etiology of the patients were as follows: prior acquired injury in 5, genetic in 3, malformation of cortical development in 1, and unknown in 1. All patients showed delayed development. Three out of 8 patients had prior use of muscle relaxant. During ACTH therapy, they required commencement or modification of the median number of 2 types (range, 1 to 3) of muscle relaxants. Further, due to the exacerbation of spasticity, 3 patients showed decrease in oral intake which required administration of intravenous fluids, and 1 patient showed respiratory failure which required mandatory ventilation. Compared to the no side-effect patients, the target patients had earlier onset of epileptic spasms ($p<0.05$); they tended to show developmental delay, though not statistically significant.

Spasticity may be a side-effect for synthetic ACTH; we suspect that prior acquired injury and genetic etiology with developmental delay may be a risk, however we need more larger studies.

P-41 A CASE OF LEVETIRACETAM-RESPONSIVE POSTTRAUMATIC WEST SYNDROME

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Recently, levetiracetam (LEV) treatment have been known to be one of the primary therapeutic options for West syndrome (WS), and the reported rate of seizure disappearance is 10-40%. However, a lot of information is yet-to-be-defined, for example, preferable treatment dose, and latency period for manifestation of the effect.

We herein report a boy 11 months after birth, who developed WS caused by very severe brain injury and responded dramatically to LEV. In this case, LEV treatment was initiated at the age of 19 months at a dose of 10mg/kg/day. His seizures markedly decreased on 2 days after the onset of treatment, and disappeared on 8 days at a dose of 20mg/kg/day. EEG was also markedly improved and only focal sharp waves were left.

We considered the clinical features of LEV as a treatment drug for WS, reviewing the past reports of successful cases. Literature search indicated that the latency period for manifestation of the effect is about two weeks in successful cases. But, it was difficult to estimate the preferable dose of LEV, because the reported dose for seizure disappearance had tendency to be polarized between high and low dose.

A CASE OF COMBINED GENERALIZED AND FOCAL EPILEPSY WITH IMPAIRED HIGHER CORTICAL FUNCTION

P-42

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The patient was first seen at our hospital at the age of 1yr for repeated generalized convulsions associated with fever. EEG was unremarkable. Optimal dose of Valproate (VPA) was not effective. At 3y7m, afebrile, focal-motor seizures (Sz) developed (EEG; normal); carbamazepine (CBZ) was effective for focal Sz while it failed to control convulsions with fever. EEG showed central spikes and frequent generalized 3Hz sp-w burst (lasting approx. 10sec) at 4y5m.

At 5yr, she presented with repeated brief loss of consciousness with ictal generalized 3Hz sp-w on EEG. A diagnosis of childhood absence epilepsy (CAE) was made. However, neither VPA nor ethosuximide (ESM) was effective (with concomitant CBZ) and neither were other AEDs (levetiracetam, lamotrigine). She was also reported to suffer from mild cognitive decline.

At 10yr of age, VPA was started for the second time and remarkably effective with no seizure recurrence and normalization of EEG. It is noted that her higher cortical function in daily living and school performance has also been greatly improved.

In this case, which is diagnosed as combination of focal-onset (with awareness impaired) and generalized (started 5yr of age, i.e., CAE) epilepsy, we infer that 1) frequent generalized Sz and profound EEG abnormality were the cause of declined cognitive function and 2) VPA and ESM failed to work for the absence Sz of genialized-onset because CBZ (known to exacerbate generalized-onset Sz) was used concomitantly.

Upon selection of AEDs, particularly in case of combined generalized and focal epilepsies, drug-drug interaction must be considered.

P-43 AIMS AND OUTCOMES OF CORPUS CALLOSOTOMY IN CHILDREN WITH INTRACTABLE EPILEPSY: A SINGLE-CENTER RECENT EXPERIENCE IN JAPAN

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Background: Corpus callosotomy (CC) is performed in cases with intractable seizures, mainly in symptomatic patients, including those with developmental epileptic encephalopathy (DEE) such as Lennox-Gastaut syndrome. It is considered in patients with either generalized or multifocal refractory epilepsy, particularly with injurious drop attacks. This procedure is a type of palliative surgical therapy, while it is sometimes performed to determine the laterality of epileptic foci. Here, we examined the outcomes in pediatric patients in our department undergoing CC based on the purpose of treatment.

Method: We retrospectively surveyed the medical records of pediatric epilepsy patients undergoing CC at the Department of Pediatrics, Hiroshima University Hospital, between March 2010 and January 2019. Etiology, type and frequency of seizures, aims, efficacy, and other surgical procedures before and/or after CC were assessed.

Result: The study population consisted of 13 patients ranging in age from 4 to 16 years old. The follow-up period after CC ranged from 12 to 91 months. The primary and secondary aims of treatment were improvement of seizures and identification of laterality of epileptic foci. Reduction of seizures by > 50% or disappearance of falling due to seizures was achieved in 11 cases. No patients underwent lesionectomy after CC in this cohort.

Conclusion: CC was useful for improvement of seizures in cases of pediatric refractory epilepsy, including DEE. However, identification of resectable epileptic foci after CC is difficult in pediatric patients in whom conventional resective surgery is initially contraindicated.

RELATIONSHIP BETWEEN PROVISIONAL NEUROLOGICAL DIAGNOSIS AND ABNORMAL EEG FINDINGS

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Background: EEG is one of the important investigations for epilepsy and other neurological diseases. EEG has been increasingly used as an indicated medical tool in the different provisional diagnosis such as epilepsy, unprovoked seizure and recurrent febrile seizure

Objective: To study the relationship between provisional diagnosis which indicated for EEG and the EEG results.

Material and Methods: Retrospective cross-sectional study, data was collected among patients age from 3 months to 15 years who had EEG result since 1st Jan 2015 to 31th Dec 2017 at Pediatric department, Hatyai hospital.

Results: There were 610 patients. Mean age was 6 years 2 months and female was dominant (53.77%). Abnormal EEG were found in 142 patients (23.78%) and could be categorized into 2 groups : Generalized epileptiform feature for 9.84% and Focal epileptiform feature for 13.44%. We found most provisional diagnosis was recurrent unprovoked seizure (24.95%), epilepsy (20%), first episode unprovoked seizure (17.21%) and recurrent febrile seizure (17.05%). The relationship between abnormal EEG results and associated factors showed that male gender tended to have more abnormal EEG results than female (Odd ratio=1.654, p-value<0.05). Moreover, patients diagnosed epilepsy were more associated with abnormal EEG (Odds ratio=2.782, p-value<0.05). In the other hand, patients with recurrent febrile seizure were not likely to show abnormal EEG result (Odds ratio=0.188, p-value<0.05).

Conclusion: EEG is one of the useful medical tools which provide information for diagnose epilepsy and epileptic syndrome. However, the indication for EEG should be considered for cost-effectiveness.

PHYSIOLOGICAL ANALYSIS OF NEURONS DERIVED FROM DRAVET SYNDROME IPSCS MODELS USING MEA SYSTEM

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Dravet syndrome (DS), a devastating type of infantile-onset epilepsy that presents with cognitive deficits and autistic traits, is caused by a mutation in *SCN1A*, which encodes the α-subunit of the voltage-gated sodium channel, $Na_v1.1$. Excitatory/inhibitory (E/I) imbalance in the cerebral cortex can cause central nervous system disorders, such as DS. However, the underlying cellular disturbance remains ill-defined owing to the reliance of available knowledge on animal models that are not readily transferable to the syndrome in humans. Recently, we generated induced pluripotent stem cells (iPSCs) derived from a DS patient (D1) with a c.4933C>T substitution in *SCN1A* predicted to cause truncation in the fourth homologous domain of the protein (p.R1645*). Moreover, to elucidate the mechanism of neurodegeneration in DS caused by c.4933C>T mutation, we performed gene correction in D1 iPSCs using TALEN (transcription-activator-like effector nuclease)-mediated genome editing, generating D1 TALEN iPSCs. In this study, we generated excitatory or inhibitory neurons by employing direct in vitro conversion of iPSCs through the overexpression of specific transcription factor cocktails as a novel approach for neuronal differentiation. These cells were seeded on multi-electrode array (MEA) systems, which is a measuring device with multiple electrodes integrated in a cell culture dish, and the spontaneous neuronal activity was recorded. We present data comparing excitatory or inhibitory neurons derived from healthy (WT), DS (D1), and isogenic control (D1 TALEN) iPSCs that were measured using MEA systems.

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