The 22nd Annual Meeting of

The Infantile Seizure Society

International Symposium on

Genetic Role of Neurometabolic Diseases with Infantile Epilepsy

October 22-24, 2021

Taipei, Taiwan

Taiwan Child Neurology Society

Program Book

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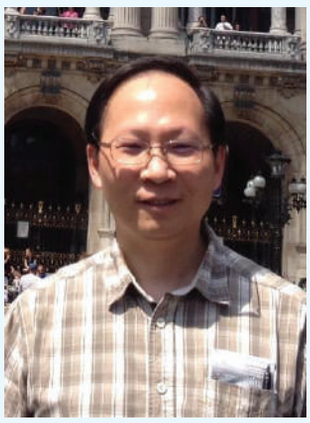
22nd ISS ISGNIE 2021

Oct 22-24, 2021 Taipei, Taiwan

Welcome Message



Dear Friends and Colleagues,

On behalf of the organizing committee, I would like to express my sincerest welcome to you for joining the International Symposium on Genetic Role of Neurometabolic Diseases with Infantile Epilepsy (ISGNIE 2021) and the 22nd Annual Meeting of Infantile Seizure Society, which is held from October 22 to 24, 2021 at Taipei International Convention Center (TICC), Taipei.

This is the second time for this significant event to be held in Taiwan again after 11 years. This gives us a great honor and prompts us to be more dedicated to organize the present Symposium. We sincerely hope you could experience a wonderful time in ISGNIE 2021!

On top of that, we are pleased to announce that this year marks the 25th Anniversary of Taiwan Child Neurology Society. We are excited to celebrate this special moment with you. This year, the Scientific Committee has made a great effort to arrange 3 keynote speeches, 42 invited speeches and more than 60 submissions from 19 countries. Unfortunately, COVID-19 situation has not yet been effectively controlled in the world, we can't get together in person in Taipei. Nonetheless, we still overcame many difficulties to share and present the latest research through hybrid meeting, which help accelerate the development of new treatment and improve the health care system.

We are confident that your participation will make this symposium both fruitful and successful, and look forward to sharing new information as well as exciting discoveries with you. Last but not least, let's hope the pandemic could be under control soon and seeing all of you together in Taipei in the near future.

Sincerely Yours,

Wang-Tso Lee, MD, PhD

President, The International Symposium on Genetic Role of Neurometabolic Diseases with Infantile Epilepsy (ISGNIE) & The 22nd Annual Meeting of Infantile Seizure Society

Professor and Chairman, Department of Pediatrics, National Taiwan University Children's Hospital, Taiwan

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Symposium Information

Symposium Venue

Taipei International Convention Center (TICC), Taipei, Taiwan

Website: http://www.ticc.com.tw

Address: 1 Hsin-Yi Rd., Sec.5, Taipei 11049, Taiwan

Tel: +886(2)2725-5200 ext.3517/3518

Map of Congress Venue & Hotels nearby

A Grand Hyatt Taipei

B AT Boutique Hotel

C Pacific Business Hotel

D Sparkle Hotel

REGISTRATION

The Registration Reception will be open at the 1F Lobby of TICC as follows:

October 22 (Friday)	07:30-18:00
October 23 (Saturday)	06:50-18:00
October 24 (Sunday)	06:50-17:30

MASK&NAME BADGE

Participants are requested to wear masks and their name badges during all the Symposium activities and social events. All staff will have the right to refuse entry to any session without a proper name badge and mask. If there is any misspelling or typographic error on your badge, please go to the information registration counter for assistance.

LANGUAGE

The official language of the Symposium is English, which will be used in all presentations and printed materials.

SYMPOSIUM POLICY

- ✓ Wear mask is requested all the time.
- ✓ Smoking is always prohibited in the meeting rooms and the entire building.
- ✓ Please switch your mobile phones off or to vibration mode during all sessions.

EXHIBITION

The exhibition will be held at the lobby and corridor of 1F in TICC during as follows:

October 22 (Friday)	08:00-17:30
October 23 (Saturday)	08:00-18:30
October 24 (Sunday)	08:00-15:30

LUNCH

Lunch box will be served at outside of Room 101AB and Room 102, 1F.

PREVIEW ROOM

Room 105 (Secretariat Room), 1F

All the Speakers / Presenters are required to use the laptops/computers provided by the organizer for presentation. Speakers / Presenters have the responsibility for their presentation functionalities, including the whole data file, the compatibility of data with the Symposium projection system, the USB flash drive, etc. Please check them prior to your presentation to make sure that they could be displayed without any problem.

Preview Room Opening Hours

October 22 (Friday)	07:30-18:00
October 23 (Saturday)	07:00-18:00
October 24 (Sunday)	07:00-17:30

SOCIAL PROGRAMS

Banquet

Date: 19:00-21:00, Saturday, October 23, 2021

Venue: 3F, Brand Ballroom II, Grand Hyatt

Fee: Physician for free / Fellow, Resident, Student and Accompanying Person: TWD 1,800

**Admission tickets are available for sale at the information registration counter.*

INSTRUCTION FOR PRESENTER

Oral Presentation

SPEAKER	PRESENTATION TIME
Keynote Speech	40 minutes
Invited Speech	20-30 minutes
Oral Presentation	8 minutes and 2 minutes for Q&A

Please arrive in the session venue no less than 20 minutes before the beginning of your session.

Presentation Notice

Please note that the computers of the Symposium are being supplied with Windows 10 and Office 2016.

If using a Power Point presentation, please note you need to bring it on a USB storage device and load it on the Symposium's laptop in the meeting room or Preview Room (Room 105) prior to your session. Our staff will assist you to save your file. You are encouraged to bring your own laptop as a back-up. If there is combining video files with your presentation, please make sure to check it in the meeting room where your session is taking place before the session starts, or during a coffee break prior to your session.

Poster Presentation

The pre-recorded presentations will be broadcasted during Poster Presentation Sessions.

The poster display will be held at Poster Presentation III. Here is the information:

Date: October 24, 2021

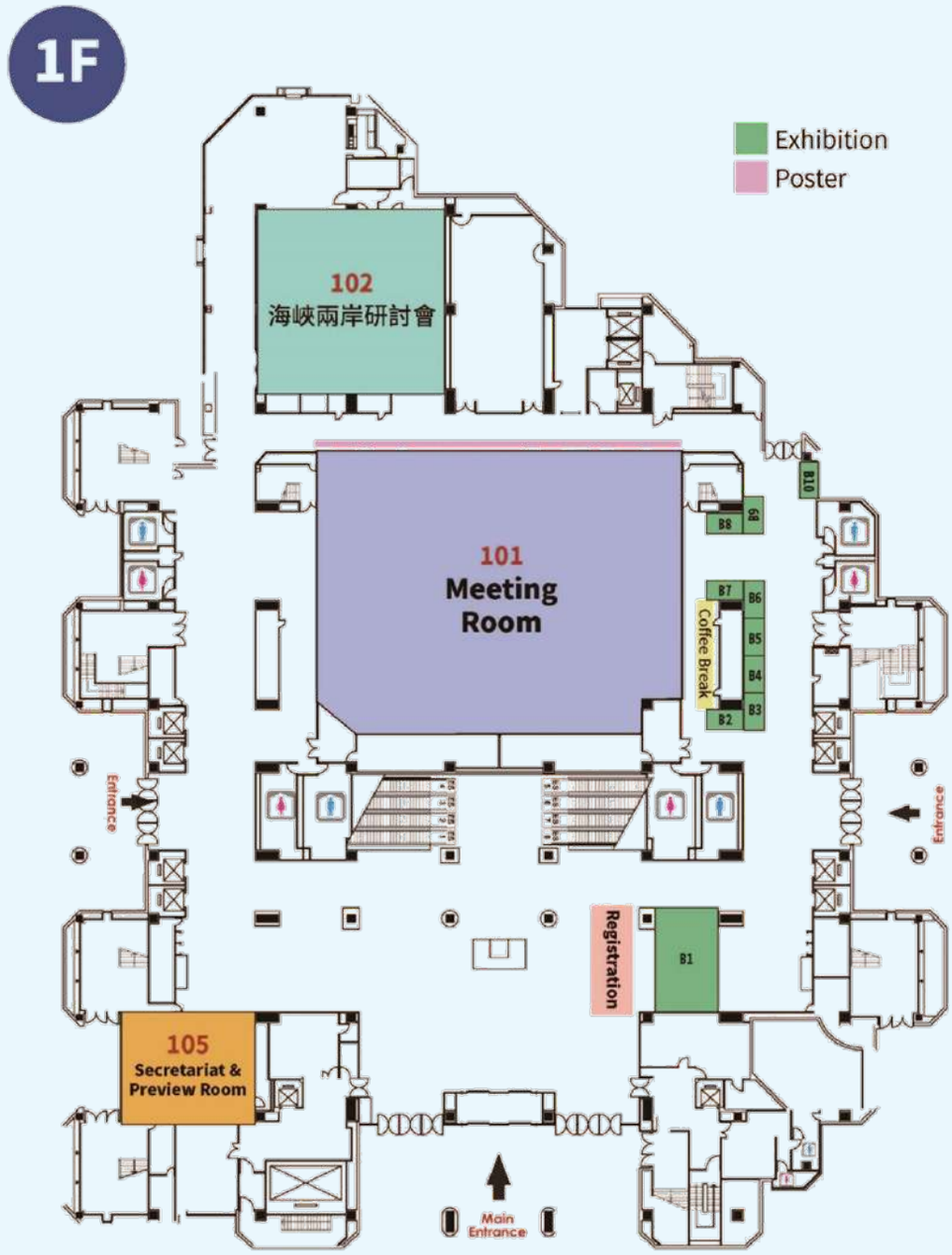
Poster Area: Corridor of Room 103, 1F

Mounting Time: 6:50-9:40

Presentation Time: 9:40-10:30

Removal Time: no later than 15:30

Floor Plan



Exhibition List

B1	Eisai 衛采製藥股份有限公司	B8	UCB Pharmaceuticals (Taiwan) Limited 台灣優時比貿易有限公司
B2-B3	GSK 荷商葛蘭素史克藥廠股份有限公司台灣分公司	B9	CSL Behring Ltd. 傑特貝林有限公司
B4-B5	Biogen 台灣百健有限公司	B10	Orient EuroPharma Co., Ltd. 友華生技醫藥股份有限公司
B6-B7	Novartis 台灣諾華股份有限公司		

Program at a Glance

Time/Date	October 22 (Fri.)		October 23 (Sat.)	
Room	101	102	101	102
06:50-07:15			Registration (Lobby, 1F)	
07:15-08:15	Registration (Lobby, 1F) (7:30-08:30)		BS1 Update in Neurophysiology	
08:15-08:30			Opening Ceremony	
08:30-09:20	PC1 Introduction of Neurometabolic Diseases in Infants and Children		K1 Keynote Speech I (8:40-9:20) Ingrid Tein	
09:20-10:00			K2 Keynote Speech II Phillip Pearl	
10:00-10:30	Coffee Break		Coffee Break	
10:30-12:00	PC2 Mitochondrial Encephalopathy		S1 Neurometabolic Diseases and Epilepsy I	
12:10-13:30	L1 Luncheon Seminar 1 Phalanx Biotech	L2 Luncheon Seminar 2 Sanofi	L3 Luncheon Seminar 3 Biogen	L4 Luncheon Seminar 4 UCB
13:30-15:00	PC3 Amino Acid Metabolic Diseases		S2 Investigations in Neurometabolic Disease	
15:00-15:30	Poster Presentation I & Coffee Break		Poster Presentation II & Coffee Break	
15:30-16:00	PC4 Miscellaneous Etiologies and Treatment (15:40-17:30)	CS1 Cross-Strait Forum	O1 Oral Presentation I	
16:00-17:30			S3 Infantile Epilepsy in Mitochondrial Disorders	
17:30-18:00	ISS Council Board Meeting		O2 Oral Presentation II	TCNS Annual Meeting
18:00-18:30				
19:00-21:00			Banquet	

Time/Date	October 24 (Sun.)	
Room	101	102
06:50-07:15	Registration (Lobby, 1F)	
07:15-08:15	BS2 Progressive Myoclonic Epilepsy in Infants and Children	
08:15-08:30		
08:30-09:20	K3 Keynote Speech III (8:30-9:10) Pratibha Singhi	
09:20-10:00	O3 Oral Presentation III (9:10-9:40)	
10:00-10:30	Poster Presentation III & Coffee Break (9:40-10:30)	
10:30-12:00	S4 Neurometabolic Diseases and Epilepsy II	
12:10-13:30	L5 Luncheon Seminar 5 Eisai	L6 Luncheon Seminar 6 GSK
13:30-15:00	S5 Neurometabolic Diseases and Epilepsy III	
15:00-15:30	Poster Presentation IV & Coffee Break	
15:30-16:00	S6 Treatable Neurometabolic Diseases and Epilepsy	
16:00-17:30		
17:30-18:00	Closing Ceremony	

Scientific Program

October 22 — Room 101

PC1

Introduction of Neurometabolic Diseases in Infants and Children

Chair: Katsuhiro Kobayashi (Japan), Chao-Ching Huang (Taiwan)

08:30-09:00 Overview of Neurometabolic Diseases in Infants
Ingrid Tein (The Hospital for Sick Children, Canada)

09:00-09:25 Mitochondrial Diseases: Infantile Epilepsy from Genetic Testing to Precision Management
Ching-Shiang Chi (Tungs' Taichung MetroHarbor Hospital, Taiwan)

09:25-09:50 Investigations in Pediatric Neurometabolic Diseases
Yann-Jang Chen (Taipei Veterans General Hospital, Taiwan)

09:50-10:10 Neurophysiological Monitoring on Neurometabolic Disorders
Douglas R. Nordli (University of Chicago, USA)

PC2

Mitochondrial Encephalopathy

Chair: Jun Natsume (Japan), Kun-Long Hung (Taiwan)

10:40-11:10 Approach to Mitochondrial Disorders in Children
Haluk Topaloglu (Hacettepe University School of Medicine, Turkey)

11:10-11:35 Mitochondrial Encephalopathy: Clinical and Genetic Features
Kei Murayama (Chiba Children's Hospital, Japan)

11:35-12:00 Molecular Basis of Neurometabolic and Neurogenetic Diseases
Henrike O. Heyne (University of Helsinki, Finland)

L1

Luncheon Symposium - Phalanx Biotech

Chair: Dar-Shong Lin (Taiwan)

12:10-13:30 Dual Analysis Application of Whole Exome Sequencing and Microarray for the Diagnosis of Developmental Delay Children
Li-Ping Tsai (Taipei Tzu Chi Hospital, Taiwan)

October 22 *Room 101*

PC3

Amino Acid Metabolic Diseases

Chair: Cheuk Wing Fung (Hong Kong), Hsiu-Fen Lee (Taiwan)

13:30-14:00 Overview of Amino Acid Metabolic Diseases: Clinical Presentations and Genetic Roles
Cheuk Wing Fung (Hong Kong Children's Hospital, Hong Kong)

14:00-14:30 MSUD and Related Disorders: Clinical Presentations in Infants and Children
Sylvia Estrada (Philippine General Hospital, Phillipines)

14:30-15:00 Sulfite Oxidase Deficiency and Related Disorders: Neuroimaging Findings and Genetic Roles
Syuan-Yu Hong (China Medical University Children's Hospital, Taiwan)

PC4

Miscellaneous Etiologies and Treatment

Chair: Jao-Shwann Liang (Taiwan), Pi-Chuan Fan (Taiwan)

15:40-16:05 Artificial Intelligence Application in EEG Analysis: A New Strategy for the Neurophysiological Management of Neurometabolic Disorders
Noboru Yoshida (Juntendo University Nerima Hospital, Japan)

16:05-16:35 Peroxisomal Disorders in Infants and Children
Hsi Chang (Taipei Medical University Hospital, Taiwan)

16:35-17:00 Metbolic Imbalances in Fatty Acid Oxidation Disorders. Implications for Pathophysiology and Treatment
Jerry Vockley (University of Pittsburgh, USA)

17:00-17:30 Lysosomal Diseases in Infancy and Children: Diagnostic Approach
Jonathan Mink (University of Rochester Medical Center, USA)

October 22 *Room 102*

L2

Luncheon Symposium - Sanofi

Chair: Wang-Tso Lee (Taiwan)

12:10-13:30 Streamlining the Diagnosis Pathway from Genotype to Phenotype in Hereditary Myopathy: Example from Pompe Disease

Andrew Kornberg (The Royal Children's Hospital, Australia)

October 23 *Room 101*

BS1

Update in Neurophysiology

Chair: Rei-Cheng Yang (Taiwan), Noboru Yoshida (Japan)

07:15-07:45 EEG Monitoring Approaches in Critically Ill Infants and Children
Nicholas S. Abend (University of Pennsylvania, USA)

07:45-08:15 Update Applications of Neurophysiological Monitoring in Neonates
Ronit Pressler (Great Ormond Street Hospital for Children, UK)

K1

Prof. Yu-Zen Shen's Memorial Lecture

Chair: Wang-Tso Lee (Taiwan)

08:40-09:20 Recent Advance in Neurometabolic Diseases: The Genetic Role in Modern Era
Ingrid Tein (The Hospital for Sick Children, Canada)

K2

Taiwan Child Neurology Society 25th Anniversary Lecture

Chair: Hideo Yamanouchi (Japan)

09:20-10:00 Recent Advances in the Treatment of Neurometabolic Diseases
Phillip Pearl (Harvard Medical School, USA)

October 23 *Room 101*

S1

Neurometabolic Diseases and Epilepsy (I)

Chair: I-Ching Chou (Taiwan), Inn-Chi Lee (Taiwan)

10:30-10:50 Ion-Channel Disorders V.S. Neurometabolic Disorders in Newborns
Inn-Chi Lee (Chung Shan Medical University Hospital, Taiwan)

10:50-11:10 Novel Treatment of Epileptic Encephalopathy in Neurometabolic Diseases
Kazuhiro Muramatsu (Jichi Medical University, Japan)

11:10-11:30 Diet Therapy for Infants with Neurometabolic Disorders and Genetic Epilepsy
Heung Dong Kim (Yonsei University College of Medicine, Korea)

11:30-12:00 Precision Medicine in Infantile Seizures
Henrike O. Heyne (University of Helsinki, Finland)

L3

Luncheon Symposium - Biogen

Chair: Wang-Tso Lee (Taiwan)

12:10-13:30 Advances in Treatment of SMA and Taiwan SPINRAZA Treatment Experience Sharing
Yuh-Jyh Jong (Kaohsiung Medical University Chung-Ho Memorial Hospital, Taiwan)

October 23 *Room 101*

S2

Investigations in Neurometabolic Disease

Chair: Yuh-Jyh Jong (Taiwan), Yung-Ting Kuo (Taiwan)

13:30-14:00 Full Genome Analysis for Rare Genetic Diseases: as Applied to Infants with Neurometabolic Diseases

Pui-Yan Kwok (Academia Sinica, Taiwan)

14:00-14:30 Pyridoxine-Dependent Epilepsy (PDE-ALDH7A1): Implications for Newborn Screening

Laura Tseng (Amsterdam University Medical Center, The Netherlands)

14:30-15:00 Neuroimaging Features in Infants with Neurometabolic Diseases

Kshitij Mankad (Great Ormond Street Hospital for Children & University College London, UK)

O1

Oral Presentation I

Chair: Marilyn H. Ortiz (Phillipines), Shyi-Jou Chen (Taiwan)

15:30-15:40 A Case Series of Varied Manifestations of Glut1 Transporter Defect

Harshuti Shah (Rajvee Hospital, India)

15:40-15:50 GNAO1-related Severe Involuntary Movements Treated with Deep Brain Stimulation

Mizuki Takagi (Aichi Medical University, Japan)

15:50-16:00 COQ4 Mutations-related Infantile-onset Mitochondrial Disorder Associated with Primary Coenzyme Q10 Deficiency

Chia-Jui Hsu (National Taiwan University Hospital Hsinchu Branch, Taiwan)

October 23 *Room 101*

S3

Infantile Epilepsy in Mitochondrial Disorders

Chair: Norimichi Higurashi (Japan), Che-Sheng Ho (Taiwan)

16:00-16:30 Mitochondrial Transplantation in MELAS Disease
Chin-San Liu (Changhua Christian Hospital, Taiwan)

16:30-16:50 Neurophysiologic Monitoring in Infants with Mitochondrial Diseases
Ronit Pressler (Great Ormond Street Hospital, UK)

16:50-17:10 Infantile Onset Epilepsy in Mitochondrial Disorder: Clinical and Genetic Insights
Jong Hee Chae (Seoul National University Hospital, Korea)

17:10-17:30 Paradigm Changes in the Genetics of the Infantile Epilepsies – Understanding the Exome and Beyond
Ingo Helbig (Children's Hospital of Philadelphia, USA)

O2

Oral Presentation II

Chair: Teik Beng Khoo (Malaysia), Yung-Ting Kuo (Taiwan)

17:30-17:40 The First Case Series of Bilateral Frontoparietal Polymicrogyria in Taiwan
Cheng-Yen Kuo (Chang-Geng Medical Foundation Linkou Chang-Geng Memorial Hospital, Taiwan)

17:40-17:50 Clinical and Electrophysiological Features of Pyridoxamine 5′ Phosphate Oxidase (PNPO) Deficiency Beyond the Neonatal Period
Lakshmi Kalband (Children's Hospital at Westmead, Australia)

17:50-18:00 Alternating Hemiplegia of Childhood: A Malaysian Tertiary Centre Experience
Lip Yuen Teng (Hospital Tunku Azizah Kuala Lumpur, Malaysia)

18:00-18:10 Focal Gyratory Seizure Associated with Ectopic Gray Matter in the Frontal Lobe
Satomi Kakuta-Ohtaki (Saitama Medical University, Japan)

18:10-18:20 Therapeutic Effects and Mechanisms of Transcranial Photobiomodulation (tPBM) on Pediatric Epilepsy
Hsi Chang (Taipei Medical University Hospital, Taiwan)

October 23 *Room 102*

L4

Luncheon Symposium - UCB

Chair: Kuang-Lin Lin (Taiwan)

12:10-13:30 A New Insight of AED Selection in Pediatric Epilepsy

Ting-Rong Hsu (Taipei Veterans General Hospital, Taiwan)

October 24 *Room 101*

BS2

Progressive Myoclonic Epilepsy in Infants and Children

Chair: Kuang-Lin Lin (Taiwan), Kazuhiro Muramatsu (Japan)

07:15-07:45 Overview of Progressive Myoclonic Epilepsy: Genetic Roles
Nicola Specchio (Bambino Gesù Children's Hospital, Italy)

07:45-08:15 Progressive Myoclonic Epilepsies. Electro-Clinical Features
Jorge Vidaurre (Nationwide Children's Hospital, USA)

K3

Prof. Yukio Fukuyama's Memorial Lecture

Chair: Ching-Shiang Chi (Taiwan)

08:30-09:10 Metabolic Epilepsy in Infancy: The Role of Genes
Pratibha Singhi (Medanta, India)

O3

Oral Presentation III

Chair: Ming-Yuh Chang (Taiwan), Sung-Tse Li (Taiwan)

09:10-09:20 Brain Age Prediction from Electroencephalographic Maturation Assessed by Deep Learning Algorithm
Shi-Bing Wong (Taipei Tzu Chi Hospital, Taiwan)

09:20-09:30 Electroencephalographic Patterns and Clinical-radiological Correlation in Children with Lissencephaly: A Case Series Report
Min-Lan Tsai (Taipei Medical University Hospital, Taiwan)

09:30-09:40 Infantile Epileptic Encephalopathy Caused by the SCN8A Variant in a Child with Citrine Deficiency
Marina Hashiguchi (Jichi Medical University, Japan)

October 24 *Room 101*

S4

Neurometabolic Diseases and Epilepsy (II)

Chair: Tung-Ming Chang (Taiwan), Julie Chi Chow (Taiwan)

10:30-10:55 SSADH Deficiency: Clinical, Genetic Role, and Treatment Strategies
Phillip Pearl (Harvard Medical School, USA)

10:55-11:20 Genetic Investigation in Lipid Metabolism with Infantile Epilepsy
Ting-Rong Hsu (Taipei Veterans General Hospital, Taiwan)

11:20-11:45 The Role of Autophagy in the Pathomechanism and Treatment of Leukodystrophy
Dar-Shong Lin (Mackay Memorial Hospital, Taiwan)

11:45-12:10 Update Treatment for Leukodystrophy and Its Associated Epilepsy in Infants
Wang-Tso Lee (National Taiwan University Children's Hospital, Taiwan)

L5

Luncheon Symposium - Eisai

Chair: Wang-Tso Lee (Taiwan)

12:10-13:30 Role of Perampanel in Early Add-on Treatment for Pediatric Patients with Epilepsy
Hsiu-Fen Lee (Taichung Veterans General Hospital, Taiwan)

Management of LGS and Rufinamide Experience Sharing
Chu-Chin Chen (Kaohsiung Veterans General Hospital, Taiwan)

October 24 *Room 101*

S5

Neurometabolic Diseases and Epilepsy (III)

Chair: Kai-Ping Chang (Taiwan), Wen-Chen Liang (Taiwan)

13:30-13:55 Congenital Disorders of Glycosylation and Infantile Epilepsy
Hsiu-Fen Lee (Taichung Veterans General Hospital, Taiwan)

13:55-14:20 Infantile Epilepsy and Carnitine Inborn Errors of Metabolism: The Role of Genes
Shinichi Hirose (Fukuoka University, Japan)

14:20-14:40 Organic Acid and Infantile Epilepsy: The Role of Genes
Yi Wang (Children's Hospital of Fudan University, China)

14:40-15:00 Diagnosis of Neurometabolic Disorders Involving Basal Ganglia based on Neuroimages
Shekeeb Mohammad (The Children's Hospital at Westmead, Australia)

S6

Treatable Neurometabolic Diseases and Epilepsy

Chair: Ting-Rong Hsu (Taiwan), Chih-Fen Hu (Taiwan)

15:30-15:55 Glucose Transporter 1 Deficiency : Past Experience, Current Status, and Future Challenges
Shin Nabatame (Osaka University, Japan)

15:55-16:20 Pyridoxine-Responsive and Dependent Epilepsy
Huei-Shyong Wang (Chang Gung Medical Center, Taiwan)

16:20-16:45 Biotinidase Deficiency and Infantile Seizures
I-Ching Chou (China Medical University Hospital, Taiwan)

16:45-17:10 Novel Treatment of Mitochondrial Disorders
Tsu-Kung Lin (Kaohsiung Chang Gung Memorial Hospital, Taiwan)

17:10-17:35 Creatine Transporter Deficiency and Epilepsy
Ming-Tao Yang (Far Eastern Memorial Hospital, Taiwan)

October 24 *Room 102*

L6

Luncheon Symposium - GSK

Chair: Huei-Shyong Wang (Taiwan)

12:10-13:30 Seizure Control in Times of Emergency: Start with a High-Risk Teratogenicity Medication for Immediate Control And Switch to a Low-Risk Teratogenicity Option Later?

Yen-Ju Chu (National Taiwan University Hospital, Taiwan)

KEYNOTE SPEAKER (K1)

Ingrid Tein

Canada

Staff Neurologist, Division of Neurology, The Hospital for Sick Children, University of Toronto, Canada

RECENT ADVANCES IN NEUROMETABOLIC DISEASES: THE GENETIC ROLE IN THE MODERN ERA

Global birth prevalence of all inborn errors of metabolism (IEMs) in children (49 studies,1980-2017) is ~50.9/100,000 live births[1]. Regional pooled birth prevalence showed higher rates in Eastern Mediterranean regions (75.7/100,000 live births) and highest in Saudi Arabia (169/100,000)[2] with higher parental consanguinity rates of ~ 60 %. Case fatality rates globally are estimated to be 33 % or higher.[1] IEMs are a group of > 600 heterogeneous disorders often presenting in newborns and infants with drug-resistant seizures and/or encephalopathy. Early diagnosis and treatments are key in the prevention of morbidity, early mortality and high lifetime health care costs, such as the early recognition of the newborn with pyridoxine- or PLP-dependent seizures.[3]

In recent years, the genetics of IEMs has been transformed by the emergence of new molecular genetic technologies. Depending on the clinical phenotype, current genetic testing may include chromosomal microarray (deletion/duplication analysis), single target gene sequencing, gene panels (sequencing & deletion/duplication analysis), DNA methylation analysis, mitochondrial nuclear gene panel and mtDNA sequencing and/or trio WES or WGS (which have reduced in costs). A meta-analysis, showed WES and epilepsy gene panels to be the most cost-effective genetic tests for unknown epilepsies versus chromosomal microarray.[4] Most recently, *rapid* genomic sequencing (RGS) has been associated with a shorter time to diagnosis (3 days) and increased diagnostic yield when compared with standard-of-care testing, including gene panels and microarrays. An RCT of rapid(r) WGS or rWES in acutely ill infants with diseases of unknown etiology in San Diego ICUs found RGS to be highly clinically useful for 77 % of 201 infants.[5] RGS changed clinical management in 28 % of infants and outcomes in 15%. An Australian study of ultra rapid exome sequencing (3.3 days) in 108 critically ill children with suspected monogenic conditions, had a molecular diagnostic yield of 51% with 20% requiring further genetic analysis.[6] In 42/55 (76%), ur exome sequencing was felt to have influenced clinical management for targeted treatments, surveillance or palliative care, however, the study could not measure differences in major clinical outcomes compared to standard care of critically ill patients. Further research is needed to understand this tool's clinical value & generalizability balanced against its high costs.

A paradigm shift is evolving from pattern- and evidence-based medicine toward algorithm-based, precision medicine targeted to individual mutations. Meticulous clinical phenotyping and pedigree analysis, combined with advances in high-throughput metabolomics, proteomics, transcriptomics (RNAseq in clinically relevant tissues), and genomics, have expedited identification of novel pathomechanisms & new therapeutic targets. Evaluation of these therapies in IEMs will depend on international registries of well characterized phenotypes in RCTs & measurement of clinically relevant endpoints.

KEYNOTE SPEAKER (K2)

Phillip Pearl
USA

Staff Physician, Division of Epilepsy and Clinical Neurophysiology,
Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

RECENT ADVANCES IN THE TREATMENT OF NEUROMETABOLIC DISEASE

The "treatabolome" has identified > 100 treatable intellectual disabilities, many with widely available, affordable, effective nutritional interventions and with increasing recent emphasis on gene-based and enzyme replacement therapies. Common clinical questions include when to upgrade from 1st-tier metabolic screens to 2nd-tier metabolic tests of CSF or enzyme assays, targeted molecular analysis, or whole exome sequencing. Circumstances that indicate a lumbar puncture include neonatal or infantile seizures of unknown etiology, dystonia or other unexplained movement disorders, progressive intellectual deterioration, severe psychiatric or behavioral phenotypes, symptoms of dopaminergic insufficiency, and to uncover therapeutic implications for neurotransmitter supplementation. The treatable metabolic epilepsies include the vitamin responsive disorders, transportopathies, amino and organic acidopathies, lysosomal storage disorders, mitochondrial disorders, purine/pyrimidine synthesis disorders, urea cycle disorders, neurotransmitter disorders, and disorders of glucose homeostasis. Vitamer B6 disorders include ALDH7A1/antiquitin deficiency of lysine metabolism, PNPO deficiency causing P5P dependency, folinic acid dependency, PROSC/PLP binding protein deficiency, hyperprolinemia type 2, and some causes of hypophosphatasia and GPI anchoring defects. Recent outcomes published for pyridoxine dependent epilepsy show abnormal neurodevelopmental outcomes despite seizure control, and lysine reduction therapy and arginine supplementation are being studied for potential benefit with early intervention. New approaches are being used for a variety of the inherited metabolic epilepsies. For example, nutritional intervention is a mainstay for phenylketonuria (PKU), but tetrahydrobiopterin and Pegvaliase, a pegylated moiety that is phe ammonia-lyase substituting for phe hydroxylase, show promise. Yet the sequencing of the human genome has ushered in a new era of treatment for neurometabolic disease. Three main approaches are gene therapy, enzyme replacement therapy (ERT), and antisense oligonucleotides (ASOs). Gene therapy involves the insertion, removal, or editing of DNA or RNA, using viral or non-viral vectors. Currently the US FDA has approved two AAV-based gene therapies: luxturna for Leber congenital amaurosis (2017) and zolgensma for SMA (2019). Gene therapy under current investigation includes intraparenchymal, both substantia nigral and putamenal, injection of AAV mediated DDC for AADC deficiency. ASOs are short (16-24 nucleotide) single-stranded nucleic acids used to alter mRNA splicing, e.g. to rescue a mis-spliced gene, or knock down target mRNAs, e.g. to suppress a mutated, toxic gene. Amenable mutations create an interfering splice site that weakens but does not destroy a required splice site. Mutations that are not amenable to ASOs destroy a splice sit, are frameshift or nonsense mutations, or are missense changes that alter a critical amino acid. Nusinersin for SMA is a breakthrough ASO intervention. ERT is FDA approved as intraventricular therapy for CLN2, and is under investigation for SSADH deficiency, the most common of the inherited disorders of GABA metabolism. We close with beautiful prose by Novel and Pulitzer Prize Laureate Pearl Buck from her book, The Child Who Never Grew, telling the story of her own daughter with PKU.

KEYNOTE SPEAKER (K3)

Pratibha Singhi
India

Director, Pediatric Neurology, Medanta Gurugram, India

METABOLIC EPILEPSY IN INFANCY: THE ROLE OF GENES

Early and precise diagnosis of Metabolic Epilepsies is important for initiating appropriate treatment, prevention, and counselling. Clinical clues are helpful in suspecting metabolic epilepsies. Considering the large number of disorders causing metabolic epilepsies, doing enzyme assays and conventional molecular tests is expensive and takes a long period of time which results in delayed treatment. Confirmation is faster and definitive by identifying the causative genes, and helps avoid further unnecessary diagnostics and may therefore help in reducing overall costs. Next generation DNA sequencing technology with comprehensive epilepsy gene panels, whole exome sequencing and at times single targeted gene studies can be used. A definitive genetic diagnosis can dictate a specific therapy and warn against giving certain therapies. Identification of the SLC2A1 gene indicates Glucose transporter deficiency (GLUT1 syndrome) and a Ketogenic diet should be tried; also, phenobarbital should not be given, as it suppresses glucose transport. Mutations in antiquitin (ALDH7A1) and PNPO genes, in infants warrant treatment with pyridoxine and Pyridoxal-5-phosphate. Mitochondrial diseases can be caused by mutations of nuclear or mitochondrial DNA (mtDNA) and many of them are associated with epilepsy. Availability of disease modifying therapies has made the genetic diagnosis of lysosomal storage disorders important. A host of other treatable metabolic epilepsies such as Biotinidase deficiency, Creatine deficiency syndromes, Serine biosynthesis, BH4 deficiency can also be confirmed by genetics. The number of metabolic disorders with seizures and epilepsy is vast and although there are guidelines on how to proceed with their diagnoses biochemically, the diagnostic process is not complete until the genetic abnormality causing the disease has been identified. It is also important to then identify all the proband's relatives who may be potential carriers of a genetic disorder, for appropriate genetic counselling.

PC1- Introduction of Neurometabolic Diseases in Infants and Children

Ingrid Tein

Canada

Staff Neurologist, Division of Neurology, The Hospital for Sick Children, University of Toronto, Canada

OVERVIEW OF NEUROMETABOLIC DISEASES IN INFANTS

Global birth prevalence of all inborn errors of metabolism (IEMs) in children (49 studies,1980-2017) is ~50.9/100,000 live births1. With NGS, all inherited metabolic disorders now comprise ~1450 disorders in 24 categories2, certain of which may present in newborns/infants with drug-resistant seizures (often myoclonic) and encephalopathy.

Many involve the CNS and can be classified pathophysiologically3 as (1) disorders of energy metabolism and (2) disorders resulting in intoxication, both resulting in neuronal death, or (3) disorders of complex molecules. Disorders of energy metabolism include disturbances of intermediary metabolism such as disorders of mitochondrial metabolism, gluconeogenesis, and fatty acid oxidation which present with recurrent life-threatening episodes of catabolic decompensation with encephalopathy and/or seizures often precipitated by infection or fever. Disorders resulting in intoxication include most disorders of intermediary metabolism and are due to accumulation of substances that cannot be further metabolized (e.g. organic acidurias, urea cycle disorders). There is often a 'free' interval of a few days between birth and symptom onset during which time there is accumulation of toxic metabolites generated by feeding. These treatable disorders must not be missed. Disorders of complex molecules (certain are treatable) include enzymatic deficiencies leading to disturbances of synthesis or catabolism of complex molecules (e.g. lysosomal & peroxisomal disorders, congenital disorders of glycosylation) and present as neurodevelopmental or neurodegenerative disorders with epilepsy and other organ involvement and may have dysmorphism or malformations. Many IEMs have nonspecific symptoms e.g. hypotonia, lethargy, poor feeding, vomiting. Most are AR in inheritance and may have prior sibs with SIDS.

Neonates with neurologic & metabolic distress can be divided into five subtypes4 namely, I: Intoxication type with primarily ketosis (MSUD); II: Intoxication with primarily ketoacidosis and hyperammonemia (organic acidurias); III: Energy deficiency, polypnea & lactic acidosis (mitochondrial, PC and PDH def,); IVa: Hyperammonemia (intoxication) with hepatic signs without ketoacidosis (urea cycle, FAO disorders); IVb: Neurologic deterioration with seizures and myoclonic jerks without ketoacidosis or hyperammonemia (neurotransmitter defects, PDE, NKH, SO ± XO, peroxisomal); IVc: Storage disorders with progressive neurologic deterioration without metabolic disturbances (GM1 gangliosidosis, Gaucher disease, MPS VII, I-cell disease); V: Hepatomegaly/dysfunction ± hypoglycemia (glycogenosis I and III, galactosemias, etc).

As it is not possible to cover this large group of disorders, certain of the treatable early onset disorders, which must not be missed, will be highlighted in which early recognition and prompt treatment intervention may have a significant impact on neurologic morbidity and mortality, such as PDE, PNPO, biotinidase, holocarboxylase synthetase, and OCTN2 (high-affinity plasmalemmal carnitine transporter) deficiencies.

PC1- Introduction of Neurometabolic Diseases in Infants and Children

Ching-Shiang Chi
Taiwan

President, Asian Oceanian Child Neurology Association

Professor, College of Life Science, National Chung Hsing University, Taichung, Taiwan

Vice superintendent, Medical Education, Tungs' Taichung MetroHarbor Hospital, Taichung, Taiwan

MITOCHONDRIAL DISEASES: INFANTILE EPILEPSY FROM GENETIC TESTING TO PRECISION MANAGEMENT

Mitochondrial diseases are a heterogeneous group of disorders affecting energy production of the body. In vivo studies demonstrate potential links between mitochondrial dysfunction and the increased neuronal excitability causing epileptiform activity are decreased intracellular adenosine triphosphate levels in neurons and alternations of neuronal calcium homeostasis. Moreover, mitochondria are involved in pathways leading to the neuronal cell death characteristic in the areas of seizure focus in human and experimental epilepsy.

Infantile onset epilepsy and epileptic syndromes can occur as a defining clinical feature or a presenting sign in some specific mitochondrial syndromes. For example, Leigh syndrome has been reported to be one of the differential diagnoses in infants with epileptic spasms. Nevertheless, infants diagnosed with nonsyndromic mitochondrial diseases are not uncommon, and epileptic seizures can manifest as the first recognized symptom or part of clinical signs of unexplained encephalomyopathies or multiorgan involvement. The existence of various epileptic phenotypes makes diagnosis of mitochondrial diseases in infants with epilepsy particularly challenging.

This speech will focus on Coenzyme Q10, a diffusible electron carrier in the mitochondrial respiratory chain and discuss the electroclinical features, neuroimaging findings, and genetic testing of primary Coenzyme Q10 deficiency related-infantile onset epilepsy.

PC1- Introduction of Neurometabolic Diseases in Infants and Children

Yann-Jang Chen

Taiwan

Director, Genetic Counseling Center, Taipei Veteran General Hospital, Taipei, Taiwan

Attending Physician, Department of Pediatrics, Taipei Veteran General Hospital, Taipei, Taiwan

Attending Physician, Department of Pediatrics, National Yang-Ming Chiao Tung University Hospital, Taipei, Taiwan

Associate Professor, Institute of Clinical Medicine & Department of Life Sciences, National Yang-Ming Chiao Tung University, Taipei, Taiwan

INVESTIGATIONS IN PEDIATRIC NEUROMETABOLIC DISEASES

Neurometabolic diseases are groups of disorders that may disrupt the metabolism pathway involving a specific chemical reaction, such as energy utilization. They usually present in newborns and infants. Neurological symptoms and signs, such as seizure, muscle weakness, mental retardation and developmental delay are the main manifestations of neurometabolic diseases. However, patients with neurometabolic diseases usually have nonspecific clinical presentations, such as poor feeding, vomiting, lethargy, seizures, and loss of consciousness when disease onset. This makes it difficult to have early accurate diagnosis. Early detection and early intervention is important for these patients with neurometabolic diseases.

Due to the nonspecific phenotypes of these patients, it is very hard to find the extract diagnosis only due to abnormal biochemical findings. Generally, amino acid analysis, urine organic analysis and tandem mass spectrometry are routine performed for these patients and some clues may be found. If candidate genes are suggested, DNA sequencing by Sanger method are then done. However, positive results are seldom found.

Next generation sequencing (NGS), whole exome sequencing (WES) and whole genome sequencing (WGS), provide a powerful tool for detecting these neurometabolic diseases. Combining deep phenotype discrimination, including metabolism screening and familial history, and WES or WGS examination, has increased the positive detection rate for diagnoses of neurometabolic diseases. Several reposts revealed the positive detection could increase to near 70%.

The neurometabolic diseases may be treatable mostly. Early detection and early intervention is important. WES and deep phenotyping provide a powerful approach to manage these disorders correctly.

PC1- Introduction of Neurometabolic Diseases in Infants and Children

Douglas R. Nordli
USA

Professor and Chief, Child Neurology,
University of Chicago, Chicago, USA

NEUROPHYSIOLOGICAL MONITORING ON NEUROMETABOLIC DISORDERS

Taken individually inborn errors of metabolism (IEM) are relatively rare causes of early life epilepsy, but when considered in aggregate they may account for as much as 3 to 7% of cases. While clinical features such as myoclonia, spasms and focal tonic postures can offer some clues to the presence of an IEM the impact is limited due to the restricted repertoire of seizure semiology in infants. EEG features may be helpful in directing a thoughtful evaluation, particularly when combined with clinical information. EEG features including background slowing, multifocal pleomorphic epileptiform discharges, and background discontinuity are commonly seen in patients with IEM (Type 4 EEG). In very rare circumstances specific EEG features may suggest the precise cause. In this presentation, a simplified approach to the rational evaluation of children with early life epilepsies will be presented, highlighting the role of clinical neurophysiology in the process, using a categorization scheme for EEG abnormalities. In brief, patient with no clear cause for their epilepsy with EEGs classified as type 4 are candidates for testing for genetic disorders and IEMs.

PC2- Mitochondrial Encephalopathy

Haluk Topaloglu
Turkey

Professor, Department of Pediatrics,
Yeditepe University, Istanbul, Turkey

APPROACH TO MITOCHONDRIAL DISORDERS IN CHILDREN

Mitochondria is present in every cell in at least hundreds of copies. There is dual control of mitochondrial genome and autosomes. Main functions are related to life: fundamental role in cellular energy metabolism, fatty acid oxidation, the urea cycle, and the respiratory chain leading to ATP production for survival. There is a vast spectrum of clinical presentations which are all progressive and cumulative. In children disorders caused by autosomal genome more common. From the molecular anatomy perspective, the abnormalities can originate from the following sites: oxidative phosphorylation defects, assembly of proteins, mtDNA maintenance, mRNA translation, membrane integrity, and mitochondrial dynamics. Typical red flags in children are failure to thrive, progressive external ophthalmoplegia, hearing loss, axonal neuropathy, cardiomyopathy, renal tubular acidosis, and diabetes. The hallmark of laboratory is elevation of lactate in plasmai CSF or urine. Biochemistry of respiratory chain is mandatory especially in children with suspected mitochondrial disease. Leigh syndrome is a typical mitochondrial syndrome with all known forms of genetic inheritance to include X-linked recessive. Treatment is ambulatory, however new trends are approaching.

PC2- Mitochondrial Encephalopathy

Kei Murayama

Japan

President, Center for Medical Genetics and Department of Metabolism,
Chiba Children's Hospital, Chiba, Japan

MITOCHONDRIAL ENCEPHALOPATHY: CLINICAL AND GENETIC FEATURES

"Mitochondrial disease" is a collective term for various clinical disorders characterized by a failure of mitochondrial function and energy production. Mitochondria are intracellular organelles with a double membrane. Mitochondria play an essential role in cells in the biosynthesis of adenosine triphosphate (ATP) via oxidative phosphorylation (OXPHOS). ATP is produced by the ATP-synthase complex, which is driven by the proton-motive force created by the respiratory chain complexes (complexes I, III, and IV). Impairment of OXPHOS leads to organ damage. This is referred to as mitochondrial respiratory chain disorder, which is considered to occur at a frequency of 1 in 5000 births.

Leigh syndrome is a major phenotype of mitochondrial encephalopathy in children. It is known as a 'subacute necrotizing encephalopathy' and is a genetically heterogeneous disease that primarily affects the central nervous system. With new therapeutic options being proposed, assessing the mortality and clinical condition of Leigh syndrome patients is crucial for evaluating therapeutics. We have published the data on mortality in Leigh syndrome patients concerning effects of age at onset and genetic diagnosis in 2020 (Ogawa E et al. J Inherit Metab Dis. 2020).

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is also a phenotype with encephalopathy in childhood. m.3243A>G is the most common mtDNA mutation that can cause MELAS. The administration of oral and intravenous L-arginine, a precursor of nitric oxide, has improved the clinical symptoms of stroke-like episodes in MELAS and decreased the frequency and severity of stroke. Taurine supplementation is also a specific treatment for MELAS with m.3243A>G, which has been covered by medical insurance in Japan since 2019. Taurine can restore the taurine modification in MELAS patients with m.3243A>G mutation and promote the maturation of tRNALeu (UUR).

In this lecture, the clinical and genetic features, including novel treatment, of mitochondrial encephalopathy in children are focused.

PC2- Mitochondrial Encephalopathy

Henrike O. Heyne
Finland

Postdoctoral Research Fellow, University of Helsinki,
Institute for Molecular Medicine Finland: FIMM, Helsinki, Finland, Mark Daly lab

MOLECULAR BASIS OF NEUROMETABOLIC AND NEUROGENETIC DISEASES

While childhood epilepsy including infantile spasms can also be caused by acquired conditions such as brain injury or infection, the majority of cases are due to genetic influences. In about half of cases specific genetic causes can be found. Particularly in more severe cases, these newly arise in the child (= de novo) not being present in the parents and are usually not passed on to the next generation. The frequent co-occurence of severe childhood epilepsy and intellectual disability is reflected in their common genetic causes with a large overlap in genes associated with epilepsy syndromes but also intellectual disability without epilepsy illustrating a large genetic heterogeneity. Recessively inherited diseases are often metabolic and more rare explaining ca. 1% of cases. Specific genes such as ion channel genes and types of mutations such as missense, as well as severity of intellectual disability are associated with development of epilepsy. The combined small effects of thousands of common genetic variants as polygenic risk scores is emerging as a possible additional contributor to this heterogeneous group of diseases.

PC3- Amino Acid Metabolic Diseases

Cheuk Wing Fung
Hong Kong

Associate Consultant, Neuology Team,
Department of Paediatrics and Adolescent Medicine, Hong Kong Children's Hospotial (HKCH), Hong Kong

OVERVIEW OF AMINO ACID METABOLIC DISEASES: CLINICAL PRESENTATIONS AND GENETIC ROLES

Disorders of amino acid metabolism refer to a huge category of inborn errors of metabolism which may usually be identified by conventional metabolic tests including amino and organic acid analyses. Deficiencies of the enzymes involved would lead to accumulation of toxic compounds causing tissue damage. Acute symptoms are often caused by breakdown of endogenous proteins during catabolism. These could result in encephalopathy with variable neurological involvement including seizures, and abnormal muscle tone, liver failure and / or cholestatic jaundice, cardiomyopathy and / or arrhythmias etc.

Examples of amino acid metabolic diseases include:

- Hyperphenylalaninaemia
- Disorders of tyrosine metabolism
- Branched-chain organic acidaemias
- Disorders of urea cycle and related enzymes
- Disorders of sulfur amino acid metabolism
- Disorders of ornithine and proline metabolism
- Cerebral organic acid disorders and other disorders of lysine catabolism
- Glycine encephalopathy
- Disorders of glutamine, serine and asparagine metabolism
- Disorders of amino acid transport

Mendelian inheritance remains the underlying molecular basis within these groups of disorders. However, genetics may play a role causing phenotypic variation amongst individuals. The clinical presentations with genetic roles would be discussed using some specific disorders. Various molecular diagnostic strategies would be explored.

PC3- Amino Acid Metabolic Diseases

Sylvia Estrada

Philippines

Clinical Professor, Department of Pediatrics (Division of Pediatric Endocrinology and Genetics), UP College, Medicine-Philippine General Hospital, Manila, Philippines

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Head and Training Officer, Division of Pediatric Endocrinology and Metabolism, UP College, Medicine-Philippine General Hospital, Manila, Philippines

National Coordinator for Short Term Follow-Up, Philippine Newborn Screening Program (DOH), Newborn Screening Reference Center-NIH

MSUD AND RELATED DISORDERS: DIFFERENT PRESENTATIONS IN INFANTS AND CHILDREN

Maple syrup urine disease (MSUD) is an amino acid disorder that results from a deficiency of or diminished function of the enzyme, branched chain alpha ketoacid dehydrogenase (BCKD). This results in the accumulation of the branched chain amino acids (BCAA) leucine, isoleucine and valine. MSUD has 5 clinical phenotypes: Classical, intermediate, intermittent, thiamine responsive and E3-deficient MSUD.

Classical MSUD will present with acute encephalopathy which rapidly progresses to a comatose state in the neonatal period. A characteristic sweet odor resembling maple syrup can be appreciated in the cerumen, sweat and urine of the neonate. The milder forms may present later in infancy or childhood with non-specific symptoms: poor feeding, anorexia, growth failure, developmental delays or seizures. Some may present acutely with lethargy and deepening encephalopathy when stressed with infection, dehydration or trauma. The underlying neuropathology is a cerebral deficiency of amino acid precursors important for the formation of dopamine, serotonin, norepinephrine and histamine; as well as S-adenosylmethionine, the major methyl donor in the brain. This deficiency results from the elevated leucine which interferes with the transport of these amino acids across the blood brain barrier.

In neonates presenting with acute encephalopathy, other metabolic disorders must be ruled out such as: urea cycle defects, propionic acidemia, MMA and glycine encephalopathy. Early recognition of MSUD is important in order to initiate prompt and appropriate treatment.

PC3- Amino Acid Metabolic Diseases

Syuan-Yu Hong
Taiwan

Attending Physician, Child Neurology, Division of Pediatric Neurology,
China Medical University Children's Hospital, Taichung, Taiwan

SULFITE OXIDASE DEFICIENCY AND RELATED DISORDERS: NEUROIMAGING FINDINGS AND GENETIC ROLES

Objective

To define the phenotypic spectrum of isolated sulfite oxidase (ISOD) and the related disorders, aiming to promote timely diagnosis

Methods

We analyzed clinical, radiographic, biochemical, and genetic data from in the literature and the patient in our hospital

Results

According to existing publications, we classified patients with isolated sulfite oxidase (ISOD) and the related disorders into 2 phenotypic subgroups based on their clinical and radiographic characteristics. In 1st group, the symptoms manifested in early life (age 1–50 days) with acute onset of neurologic symptoms and development of diffuse brain injury with cystic leukomalacia. In 2nd group, patients' symptoms emerged later in life (age 30 days–23 years), followed by remarkable movement abnormalities and selective injury of the basal ganglia and cerebellum. We also made a comparison between ISOD (mainly 2nd group) and the classical mitochondrial disorder - Leigh Syndrome

Conclusions

An appropriate classification of isolated sulfite oxidase (ISOD) and the related disorders may help benefit accurate diagnosis, prognosis, and aid in the design of future clinical trials.

PC4- Miscellaneous Etiologies and Treatment

Noboru Yoshida

Japan

Assistant, Department of Pediatrics,
Juntendo University Nerima Hospital, Japan

ARTIFICIAL INTELLIGENCE APPLICATION IN EEG ANALYSIS: A NEW STRATEGY FOR THE NEUROPHYSIOLOGICAL MANAGEMENT OF NEUROMETABOLIC DISORDERS

A diagnosis of epilepsy is based on the patient's seizure symptoms and electroencephalogram (EEG) findings. However, EEG evaluation is often difficult because reading results requires an experienced clinical neurophysiologist. The need for experience aside, other challenges of EEG analysis faced by physicians include recognizing paroxysmal discharges or spike noise as well as drastic changes in basal waveforms, which depend on the patient's sleep state or age.

EEG auto analysis has been developed in decades. The first application was to display the result of mathematical procedures. Since the year 2012, the third-generation artificial intelligence (AI) technique has been emerging. We developed several machine learning models those detect EEG anomaly. To recognize paroxysmal discharge on EEG, we choose a convolutional neural network (CNN) model as a model. Its detectability was 95% or higher, which means the model can be a candidate of EEG analysis supporting tool.

West syndrome is an epileptic syndrome that may be caused by several etiology including neurometabolic disorders. Hypsarrhythmia on EEG is a key finding of West syndrome, however, sometimes EEG reading is difficult. The feature of hypsarrhythmia is "chaotic" EEG waveforms which make quantitative analysis difficult. The proposed CNN model showed a possibility of recognizing hypsarrhythmia. On the other hand, it could not recognize the etiology of West syndrome.

In this presentation, we overview the history of AI and machine learning and a part of current progress.

PC4- Miscellaneous Etiologies and Treatment

Hsi Chang
Taiwan

Director, Department of Pediatrics, School of Medicine,
College of Medicine, Taipei Medical University, Taipei, Taiwan

Associate Professor, Department of Pediatrics,
Taipei Medical University Hospital, Taipei, Taiwan

PEROXISOMAL DISORDERS IN INFANTS AND CHILDREN

The peroxisomal disorders (PDs) represent a group of genetic diseases in which there is an impairment in peroxisome biogenesis or one of the metabolic functions of peroxisomes. These peroxisome biogenesis disorders could further divided into four different groups that include Zellweger syndrome (ZS), neonatal adrenoleukodystrophy (NALD), infantile Refsum disease (IRD), and rhizomelic chondrodysplasia punctata (RCDP). ZS, NALD, and IRD are clearly distinct from RCDP and are usually referred to as the Zellweger spectrum with ZS being the most severe type.

In this presentation a general knowledge about the classification and the underlying pathomechanism of the PDs will be introduced. In addition, the current state of knowledge about the genetic and molecular aspects of peroxisome biogenesis disorders will also be discussed.

PC4- Miscellaneous Etiologies and Treatment

Jerry Vockley

USA

Cleveland Family Endowed Chair in Pediatric Research & Professor of Human Genetics, University of Pittsburgh, USA

Chief of Genetic and Genomic Medicine & Director of the Center for Rare Disease Therapy UPMC Children's Hospital of Pittsburgh, USA

METBOLIC IMBALANCES IN FATTY ACID OXIDATION DISORDERS. IMPLICATIONS FOR PATHOPHYSIOLOGY AND TREATMENT

Inborn errors of fatty acid oxidation (FAO) have emerged as an increasing health problem. They comprise the most common group of disorders identified through expanded newborn screening mandated in all 50 states in the US, affecting ~1/9,000 babies born nationwide. While some of the morbidity in FAO disorders (FAODs) can be reduced if identified through screening, a significant gap remains between our ability to diagnose these disorders early, our understanding of the biological and clinical relevance of the spectrum of mutations found in patients, and the ability to treat them effectively. Common symptoms in long chain FAODs in the first week of life include cardiac arrhythmias, hypoglycemia, and sudden death. Symptoms later in infancy and early childhood may relate to the liver or cardiac or skeletal muscle dysfunction, and include fasting or stress-related hypoketotic hypoglycemia or Reye-like syndrome, conduction abnormalities, arrhythmias, dilated or hypertrophic cardiomyopathy, and muscle weakness or fasting- and exercise-induced rhabdomyolysis. In adolescent or adult-onset disease, muscular symptoms, including rhabdomyolysis, and cardiomyopathy predominate. Genotype/phenotype correlations are imprecise and do not allow decisions to be made on the need for therapy or counseling on outcome.

My lab has recently identified, purified, and characterized a multifunctional fatty acid oxidation complex that contains all of the enzymes involved in long chain FAOD (LC-FAOD). We also demonstrated that this complex interacts functionally with the mitochondrial electron transfer chain (ETC) in a multifunctional energy complex (MEPC) establishing a new paradigm for understanding the effects of mutations in these pathways on energy metabolism. This finding has led to the novel recognition of secondary defects in metabolic balance and mitochondrial stress including dramatically elevated mitochondrial reactive oxygen species in patient cells, amenable to development of next generation therapeutic agents. Cell and mouse studies have identified a deficiency in TCA cycle intermediates in LC-FAODs, thought to be due to a depletion of odd chain carbon compounds in patients treated with a predominantly MCT fat source. Triheptanoin (Dojolvi, Ultragenyx Pharmaceuticals) is chemically composed of three heptanoate (a seven-carbon fatty acid) molecules linked to glycerol through ester bonds that has the potential to replete TCA cycle intermediates through production of both acetyl-CoA and propionyl-CoA through medium chain FAO. Compassionate use, retrospective, and prospective studies demonstrated significant reduction of hypoglycemic events and improved cardiac function in LC-FAOD patients, but a less dramatic effect on muscle symptoms. We have also demonstrated a deep remodeling of mitochondrial cardiolipins. The aberrant phosphatidylcholine/ phosphatidylethanolamine ratio and the increased content of plasmalogens and of lysophospholipids support the theory of an inflammatory phenotype in lc-FAOD. This lecture will review studies on recently FDA approved triheptanoin and new compounds currently in development including:

- Triheptanoin for long and medium chain fatty acid oxidation disorders
- Therapeutic mRNA for VLCAD
- Mitochondrial targeted anti-oxidants
- Chemical chaperonins for long and medium chain fatty acid oxidation disorders
- Alternative anaplerotic compounds

PC4- Miscellaneous Etiologies and Treatment

Jonathan Mink

USA

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LYSOSOMAL DISEASES IN INFANCY AND CHILDREN: DIAGNOSTIC APPROACH

Lysosomal diseases (LDs) represent a heterogeneous group of rare multisystem genetic disorders with onset mostly in infancy and childhood. Sometimes referred to as "lysosomal storage diseases" (LSDs), many are characterized by accumulation of incompletely degraded biological materials within the lysosome. In some disorders, those materials exert a toxic effect on cells. In others, the accumulated material is a marker of lysosome dysfunction but is not directly toxic. In still others, impaired lysosomal function is not consistently accompanied by accumulation of a storage material. Many LDs affect the peripheral and/or central nervous system and some appear to impact the nervous system without involvement of other organs.

The cellular and molecular pathogenesis of LDs is complex. The full spectrum of lysosome and related autophagosome function is not fully understood, nor is the full spectrum of disease. Impaired autophagy is increasingly recognized in both child- and adult-onset diseases. Some disorders result from genetic variants that alter enzyme synthesis or function. Others result from genetic variants that alter lysosomal or endosomal membrane proteins. These may impair acidification of the lysosome, trafficking of the endosome, lysosome, or autophagosome, or a combination.

With the increasing availability of enzyme-replacement therapies and the emerging development of genetic-medicines for LDs, early and accurate diagnosis is increasingly important. Improved diagnostic methods have facilitated diagnosis and have led to the implementation of extensive newborn screening (NBS) programs in many countries. Even with the growth of NBS and the widespread availability of genomic diagnostic approaches, clinical suspicion and a systematic and logical approach to diagnosis is essential. The rarity of each disease and the non-specificity of early signs and symptoms presents a diagnostic challenge to even the most experienced clinician. The typical diagnostic evaluation for LDs with neurologic involvement includes taking a detailed history on the clinical presentation(s) and course of disease, detailed neurological examination, genetic testing (chromosomal microarray, exome/genome sequencing), biochemical and enzyme activity testing (leukocytes, fibroblasts, urine), neuroimaging (MRI preferred), EEG, and ophthalmologic evaluation. When results are ambiguous, including DNA sequence variations of uncertain significance (VUS), the time-intensity profile of symptom and sign development and the clinical phenotype are essential for interpretation.

In this presentation, an overview of the diagnostic approach will be followed by specific examples from the neuronal ceroid lipofuscinoses to illustrate the challenges and strategies to overcome those challenges in the diagnosis of LDs.

BS1 - Update in Neurophysiology

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EEG MONITORING APPROACHES IN CRITICALLY ILL INFANTS AND CHILDREN

Guidelines and consensus statements recommend that critically ill children and neonates with acute encephalopathy undergo 24-48 hours of continuous EEG monitoring (CEEG). These recommendations are driven by data that indicate electroencephalographic seizures (ES) occur in 10-40% of monitored patients, most ES are not identifiable by clinical observation, ES can often be treated safely with standard anti-seizure medications, and high ES exposure is associated with unfavorable neurobehavioral outcomes. Thus, an increasing number of critically ill children undergo CEEG which is resource-intense. However, CEEG is resource intense given equipment and staffing. Thus, for CEEG to be implemented in a feasible manner, approaches are needed to target CEEG to the patients most likely to benefit from CEEG-guided management. This lecture will address the use of CEEG in critically ill neonates and children, the epidemiology of ES in these patients, and focus on recent models which aim to target CEEG to patients at high risk for ES for the appropriate duration. Implementation of these models would reduce CEEG utilization while identifying most patients experiencing ES, thereby helping establish the viability of CEEG-guided management as a potential neuroprotective strategy.

BS1 - Update in Neurophysiology

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UPDATE APPLICATIONS OF NEUROPHYSIOLOGICAL MONITORING IN NEONATES

Neonatal EEG is one of the few objective methods measuring the functional integrity of the immature cortex and its connections. It can assist in determining brain maturation, evaluate acute neonatal brain injury and diagnosing seizures. Electrographic seizures and status epilepticus are common in critically ill neonates including those with hypoxic-ischemic brain injury, traumatic brain injury, and underlying epilepsy. They are often only identifiable using EEG monitoring, and associated with less favorable neurobehavioral outcomes even after adjusting for brain injury type and severity. Implementation of Neurocritical care protocols with continuous EEG has been shown to be associated with improved seizure detection, better treatment success and shorter stay on NICU. As a result, recent practice statements have advocated for EEG monitoring and surveys indicate expanding use of EEG monitoring. Although continuous EEG monition is a limited resource, advance technologies such as automatic seizure detection, seizure prediction models and remote access for expert review can improve availability and implementation of EEG monitoring for the management of critically ill neonates.

S1 - Neurometabolic Diseases and Epilepsy (I)

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ION-CHANNEL DISORDERS V.S. NEUROMETABOLIC DISORDERS IN NEWBORNS

Ion channel disorders can affect any tissue in newborn infants, and affect skeletal muscle or the central nervous system. Seizures is one of the presentations with the channelopathies in newborns. The early-onset seizure can mimic the signs of newborn infants with neurometabolic disorders. The seizures in channelopathies can cause focal and generalized seizure, which range in severity from benign course to epileptic encephalopathies that lead to developmental regression and premature death. The presenting symptoms of ion channel disorder are challenging to clinicians to make by extensive diagnosis survey by widely step by step diagnosis. Early diagnosis for the disease either by ion channel disorder or neurometabolic disorders is important to the long-term neurodevelopmental outcome.

Keywords Ion channel disorders; neurometabolic disorders; newborns; seizures

S1 - Neurometabolic Diseases and Epilepsy (I)

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NOVEL TREATMENT OF EPILEPTIC ENCEPHALOPATHY IN NEUROMETABOLIC DISEASES

Neurometabolic diseases (NMD) are a rare cause of epilepsy. However, intractable epilepsy occurs frequently in patients with NMD, since these disorders are associated with hereditary enzyme deficiencies, which impact both metabolic and biochemical pathways. This impairment of complex cellular homeostasis results in epileptogenesis, which would be specific to each gene in NMD. Autophagy is an extremely essential and conserved catabolic system in all organisms that mediate the degradation of dispensable intra/extra cellular molecules and organelles in lysosomes. Recent studies (Brain. 2016, EMBO J. 2017, Neuron. 2017, etc.) show that single gene disorders related to autophagy are critical for post-mitotic and metabolically active cells such as those in the central nervous system, giving rise to a novel group of inborn metabolic errors. Epileptic encephalopathy in NMD, particularly in diseases related to autophagy, is intractable because of unavailability of any specific fundamental treatments. Therefore, development of novel treatment methods is required. However, this is difficult, since the pathophysiology of epilepsy in diseases related to autophagy is still unknown at present. We conduct the elucidation of disease mechanisms by using molecular and cellular biology approaches. In this time, we review the current conditions of developing a treatment strategy and studying pathophysiology of epileptic encephalopathy in NMD.

S1 - Neurometabolic Diseases and Epilepsy (I)

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DIET THERAPY FOR INFANTS WITH NEUROMETABOLIC DISORDERS AND GENETIC EPILEPSY

Genetic and neurometabolic causes of epilepsy have early age of onset, compounding progression, and resistance to anti-seizure medications (ASM). As more knowledge is gained on the genetic causes and subsequent molecular mechanisms of these epilepsies, the greater opportunity for targeted therapy instead of ASM. As genes are being identified for the cause of many epilepsies, the knowledge allows targeting the specific DNA region, RNA transcript, or protein. Targeting a specific gene, transcript, or polypeptide allows for more precise treatment, including gene therapy, protein replacement, small molecules such as inhibitors or enhancers of protein/enzyme function, and dietary nutrient modification.

Altered metabolism has been implicated in the pathogenesis of diverse neurodegenerative progresses, including epilepsies arising from dysfunction of mitochondria; epilepsies associated with metabolic dysfunction; and metabolism-based therapeutic approaches. Non-mitochondrial mutations that impair brain metabolic homeostasis and give rise to seizures. These can be the defective glucose transport, proper functioning of voltage-gated ion channels, and antioxidant defense systems as well as metabolic dysfunctions associated with acquired epileptic phenotypes.

One of the earliest treatments for epilepsy—the ketogenic diet (KD)—has experienced a resurgence of both clinical and research interest in the past few decades. Dietary therapies are also valuable for certain metabolic epilepsies, specifically glucose transporter type 1 (GLUT1) deficiency, pyruvate dehydrogenase (PDH) deficiency, and mitochondrial disorders. For these conditions, the KD may improve biochemical defects, not only for seizures but also cognitive outcomes, and provide the long- term energy sources.

In this talk, the clinical and genetic spectrum of infantile epilepsy from genetic and metabolic causes and the possibility of intervention from ketogenic dietary treatment, will be discussed.

S1 - Neurometabolic Diseases and Epilepsy (I)

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PRECISION MEDICINE IN INFANTILE SEIZURES

Severe childhood epilepsy is frequently caused by genetic variants in ion channels with top genes SCN1A, SCN2A and KCNQ2 encoding for voltage-gated sodium and potassium channels. Many of these genetic variants can be pharmacologically targeted giving rise to many successful examples of precision medicine as ion channels are very well studied so that existing drugs can often be repurposed. We estimated ca. 5% of genetic variants in childhood epilepsy such as infantile seizures have treatment consequences. As trials with new drugs are underway, we hope that this number will increase in the future. Treatment is only successful when the medication targets the molecular effects of disease-causing variants correctly. As an example, treatment with sodium channel blockers improves epilepsy in individuals carrying gain-of-function variants in SCN2A or SCN8A but can dramatically worsen epilepsy in individuals with loss-of-function variants in SCN2A or SCN1A. Knowing a genetic variant's functional effect is therefore essential for the success of precision therapy. As experimental approaches to determine variants' functional effects are laborious and difficult to scale up, we present alternatives such as a machine learning method that predicts functional effects of genetic variants in voltage-gated sodium and calcium channels.

S2 - Investigations in Neurometabolic Disease

Pui-Yan Kwok

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Henry Bachrach Distinguished Professor,
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FULL GENOME ANALYSIS FOR RARE GENETIC DISEASES - ESPECIALLY IN INFANTS WITH NEUROMETABOLIC DISEASES

Whole genome sequencing has been used successfully in diagnosing rare genetic diseases, including those affecting the neurological system. Despite the best efforts, however, the majority of the cases remain undiagnosed due to technical and other issues. A new approach, named full genome analysis, combines long-read whole genome sequencing and whole genome mapping can overcome some of the limitations of whole genome sequencing and improve the yield of rare genetic disease diagnosis significantly. In this presentation, representative cases of rare genetic diseases diagnosed by the full genome analysis approach will be used to illustrate the approach.

S2 - Investigations in Neurometabolic Disease

Laura Tseng
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Amsterdam UMC, University of Amsterdam, Pediatric Metabolic Diseases, Emma Children's Hospital and Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, The Netherlands

On behalf of United for Metabolic Diseases, Amsterdam, The Netherlands

PYRIDOXINE-DEPENDENT EPILEPSY (PDE-ALDH7A1): IMPLICATIONS FOR NEWBORN SCREENING

Background: Since a decade, adjunct lysine reduction therapies (LRT) have emerged as treatment options for pyridoxine-dependent epilepsy due to antiquitin deficiency (PDE-ALDH7A1). This neurometabolic disorder of lysine degradation causes developmental delay and intellectual disability in more than 75% of the patients, and is characterized by (neonatal) seizures responsive to pyridoxine. Adjunct LRT aim on lowering putative neurotoxic intermediates via substrate inhibition (a lysine-restricted diet) and competitive inhibition of lysine (arginine supplementation). Previous literature showed promising results, however larger studies were needed for validation and to evaluate timing of treatment. Early therapy leading to significantly improved outcomes is one of the criteria a disorder should meet for inclusion in newborn screening programs.

Methods: The international PDE consortium collaborates on research in PDE-ALDH7A1, and with the use of the international PDE registry, two large studies focusing on the efficacy and timing of treatment on neurodevelopmental outcomes were conducted. In the first study the relation between developmental test score (full-scale intelligence quotient; IQ) and treatment was evaluated using a linear mixed effects model in 112 test results from 60 patients. In addition, a sub-analysis was performed in patients who started adjunct LRT before the age of six months. In the second study, timing of treatment was evaluated in 18 families with PDE-ALDH7A1. Neurodevelopment was clinically assessed over seven domains and compared between affected siblings.

Results: Results showed a modest increase in IQ in favor of adjunct LRT versus pyridoxine alone, and a significant increase of 22 IQ points (95% CI 1.7-42.0) when adjunct LRT were initiated before the age of six months. In the sibling study, no differences were noted between siblings on pyridoxine monotherapy, however for the siblings on adjunct LRT, the majority of early treated siblings performed better than their late treated sibling on overall neurodevelopment, cognition, fine motor function and behavior/psychiatry.

Discussion & conclusion: Early initiation of adjunct LRT can significantly improve neurodevelopmental outcomes and should therefore be initiated in all newborns and infants as stated by the recent PDE Consortium consensus guidelines. Together with pyridoxine therapy leading to seizure control, PDE-ALDH7A1 is considered a treatable disorder. However, not all outcomes have been completely normal, and new treatment strategies are currently studied. As natural history of PDE-ALDH7A1 is largely known, and a novel biomarker is currently validated for the purpose of implementation in newborn screening, PDE-ALDH7A1 is well underway to future inclusion in newborn screening programs.

S2 - Investigations in Neurometabolic Disease

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UK

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NEUROIMAGING FEATURES IN INFANTS WITH NEUROMETABOLIC DISEASES

This lecture will cover the spectrum of early onset neurometabolic disorders with relevant clinical, biochemical and genetic correlations.

A basic and adaptable neuroimaging protocol will be suggested at the outset.

A comprehensive review of the neuroimaging features will follow of disorders relating to entities related to toxic accumulation, energey depletion disorders and storage disorders . A practical clinico-radiological algorithmic approach will also be presented to the delegates as a summary of the session.

Finally I will touch upon neonatal metabolic screening, the disparities in this practice across the world and the importance of optimised and timely imaging when suspecting these entities to direct targeted biochemical and genetic testing.

S3 - Infantile Epilepsy in Mitochondrial Disorders

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MITOCHONDRIAL TRANSPLANTATION IN MELAS DISEASE

The cell penetrating peptide, Pep-1, has been shown to facilitate cellular uptake of foreign mitochondria but further research is required to evaluate the use of Pep-1-mediated mitochondrial delivery (PMD) in treating mitochondrial defects. Presently, we sought to determine whether mitochondrial transplantation rescue mitochondrial function in a cybrid cell model of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) disease. Following PMD, recipient cells had internalized donor mitochondria after 1 h, and expressed higher levels of normal mitochondrial DNA, particularly at the end of the treatment and 11 days later. After 4 days, mitochondrial respiratory function had recovered and biogenesis was evident in the Pep-1 and PMD groups, compared to the untreated MELAS group. However, only PMD was able to reverse the fusion-to-fission ratio of mitochondrial morphology, and mitochondria shaping proteins resembled the normal pattern seen in the control group. Cell survival following hydrogen peroxide-induced oxidative stress was also improved in the PMD group. Finally, we also demonstrated the possible routes of PMD including subcutaneous, peritoneal or intranasal injection.

S3 - Infantile Epilepsy in Mitochondrial Disorders

Ronit Pressler
UK

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NEUROPHYSIOLOGIC MONITORING IN INFANTS WITH MITOCHONDRIAL DISEASES

Mitochondrial disorders are a heterogeneous group of disorders that can affect virtually any organ and system with a predilection toward the central nervous system. Seizures constitute one of the most frequent manifestations of mitochondrial dysfunction but are also identified as a trigger for further neuronal cell death by increasing energy demands of neurons that are already metabolically challenged which in turn can provoke more seizure activity, becoming a self-perpetuating cycle. Therefore, timely diagnosis and management of seizures is an important part in the management of mitochondrial disorders. Seizure onset in infancy is seen in the most severe forms of MD with a poor prognosis.

There is no typical EEG trace in MD. The background activity in abnormal in most infants, even without clinical symptoms, mostly in form of background slowing, asymmetries and lack of posterior dominant rhythm. These abnormalities worsen progressively over time. Epileptiform abnormalities in infants are nearly always focal or multifocal, or show hypsarrhythmia. In contrast to older children generalized discharges are typically not seen. Most frequently, seizures are propagated from the occipital lobe and posterior quadrant of temporal and parietal lobes. Typical neurophysiological findings in the most common forms of MD disorders with onset in infancy will be discussed including Alpers–Huttenlocher, Leigh syndrome and Mitochondrial DNA depletion syndrome.

S3 - Infantile Epilepsy in Mitochondrial Disorders

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Korea

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INFANTILE ONSET EPILEPSY IN MITOCHONDRIAL DISORDER: CLINICAL AND GENETIC INSIGHTS

Mitochondrial Disorders have a wide range of clinical features, predominantly affecting organs with high energy metabolic demand such as brain. Epilepsy is the most frequent clinical features in mitochondrial disorders, particularly in children. The current prevalence of childhood onset mitochondrial disorders has been known to be 5-15 cases per 10,000 but the prevalence of mitochondrial epilepsy is children including infancy is still unknown. Although its exact prevalence is unknown, seizures are commonly reported in 20-60% of biochemically or genetically confirmed mitochondrial disorders.

The presentation of epilepsy in children including early infancy can be highly variable from infantile spasms, generalized seizures, focal seizures, myoclonic epilepsy to refractory epilepticus. In most of patients with mitochondrial disorders other features such as developmental delay, hypotonia, muscle weakness precede the 1st attack of seizures. In addition the genetic etiology in mitochondrial disorders are extremely heterogeneous ranging from mitochondrial DNA itself to nuclear genome. Recent advance technology including next generation sequencing make it possible to make early diagnosis and discover newer genes in mitochondrial disorders, which can also broaden the knowledge how to affect mitochondrial pathways to generate the seizures. However the exact diagnosis and treatment of mitochondrial epilepsy is still challenge in clinical practice.

Here I will summarize the clinical features of mitochondrial epilepsy, focusing on pediatrics including infancy and present the genetic advances based on recent genome technology

S3 - Infantile Epilepsy in Mitochondrial Disorders

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USA

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PARADIGM CHANGES IN THE GENETICS OF THE INFANTILE EPILEPSIES – UNDERSTANDING THE EXOME AND BEYOND

The last decade has seen an unprecedented pace of discovery with respect to the genetic basis of human epilepsies and as of 2020, more than 200 genetic etiologies are known to be causes of seizure disorders. The pace of scientific discovery has largely been fueled by technological developments, namely the wide-ranging application of next-generation sequencing approaches. This technological paradigm shift has helped transform a group or rare and virtually unknown genetic etiologies into well-recognized entities that are targets of current developments in the field of precision medicine. In this presentation, I will review the past of epilepsy genetics, highlighting the major breakthroughs in the field prior to the genomic revolution, including major insights into the clinical genetics of the epilepsies and family studies. I will then review our current understanding of epilepsy genetics, most prominently the genetic of the developmental and epileptic encephalopathies (DEE) where monogenic causes can be identified in up to 30% of individuals. Finally, I will highlight how the insight into the genetic basis has highlighted both new possibilities for treatments, but also gaps with regards to understanding the natural history of many of the genetic causes of human epilepsies. I will finish my presentation by emphasizing new possibilities that enable the "phenome" to catch up to the "genome", allowing for a better understanding and treatment of the many rare genetic etiologies that are identified in childhood epilepsies.

BS2 - Progressive Myoclonic Epilepsy in Infants and Children

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OVERVIEW OF PROGRESSIVE MYOCLONIC EPILEPSY: GENETIC ROLES

Progressive Myoclonic Epilepsies (PMEs) include a group of rare, heterogeneous genetic (mainly autosomal recessive) disorders, characterized by cortical myoclonus, other types of epileptic seizures, and progressive neurocognitive impairment. PMEs usually present in late childhood or adolescence. Recent advances have clarified molecular genetic basis, biological basis, and natural history, and have also provided a rational approach to diagnosis; however, despite the advances in molecular medicine, etiology remains undetermined in a substantial proportion of patients. To date, based on their relative frequency, five forms are considered as major (Lafora disease, Unverricht-Lunborg disease, myoclonic epilepsy with ragged red fibers, neuronal ceroidolipofuscinosis and sialidosis) compared to other rare or sporadic ones. Treatment of PMEs remains essentially symptomatic of seizures and myoclonus, together with palliative, supportive, and rehabilitative measures. Some potential targeted treatments have been identified and applied. The future effort of the research must be to identify new drugs against specific pathogenic mechanisms, or a specific action of mutated proteins, up to a gene replacement therapy

BS2 - Progressive Myoclonic Epilepsy in Infants and Children

Jorge Vidaurre

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PROGRESSIVE MYOCLONIC EPILEPSIES. ELECTRO-CLINICAL FEATURES

Characteristics:

1. Main feature is myoclonic seizures but they can be associated with bilateral tonic clonic seizures
2. Progressive neurological deterioration, usually with ataxia and dementia
3. Occurrence is rare. Usually 1% of all epileptic syndromes
4. Heterogeneous etiology
5. Thy are transmitted mainly by autosomal recessive inheritance
6. Treatment usually palliative.

Here we will describe some of the most common progressive myoclonus epilepsies (PME)

Unverricht-Lundborg disease (EPM1)

This is the most common of the PMEs. Age of presentation is usually in late childhood or adolescence ULD is a recessive disorder due to mutations in the CTSB (cystatin B) gene, located in 21q22.3. with Seizures are distal myoclonus, triggered by action or sensory stimulation. Myoclonus progress to become movement related, affecting normal activities of daily living and causing disability. BTC seizures during awakening or sleep (Less frequent with advancing age. EEG demonstrated slow background with generalized fast spikes, polyspikes and photosensitivity. Cognitive impairment is variable, from mild to moderate. The outcome varies from an independent life to bed ridden living

Lafora disease (EPM2)

Autosomal recessive disorder with mutations in 2 genes: Laforin (chromosome 6q24) or EPM2A and Malin ubiquitin E3 ligase (chromosome 6p22.3) or EPM2B Onset in adolescence (8–19 years. Maximal incidence: 14–16 years). Myoclonus, which can be massive and typical positive –negative myoclonus is observed. Occipital seizures are also characteristic of the disorder and can produce hallucinations or blindness, Dysarthria, dementia, ataxia and psychosis are associated features. EEG is slow with generalized fast spikes/polyspikes. Occipital spies are the hallmark of the disease.

Neuronal ceroid lipofuscinosis (NCLs)

Recessively inherited monogenic lethal disorders. It is the most common cause of dementia in children with onset in infancy or childhood. 14 genes have been described. There is progressive neuronal degeneration and glial activation. There is phenotypic overlap between all genes. Seizures (myoclonus and BTC seizures) are characteristic of the late infantile, followed by cognitive deterioration, blindness and ataxia, while hypotonia and motor problems precede myoclonus in the infantile type. Time locked occipital or generalized spikes at 1 Hz photic stimuli is characteristic and should trigger an investigation, since enzymatic replacement is available for CNL2 patients.

Mithoicondrial disorders, such as Myoclonic epilepsy and ragged red fiber a can present with myoclonus aggravated by action and stimuli. Alpers-Huttenlocher syndrome due to POLG mutations can produce myoclonus or Epilepsia partialis continua with brain atrophy and liver failure.

S4 - Neurometabolic Diseases and Epilepsy (II)

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USA

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SSADH DEFICIENCY: CLINICAL, GENETIC ROLE, AND TREATMENT STRATEGIES

Succinic semialdehyde dehydrogenase deficiency (SSADHD) is an autosomal recessively inherited disorder of GABA (gamma aminobutyric acid) degradation associated with the accumulation of the byproduct gamma hydroxybutyrate (GHB). Described nearly 40 years ago (Jakobs and Gibson 1983), there are an estimated 500-750 cases although < 200 could be documented in the literature (2017). The phenotype is generally that of hypotonia, developmental delay, severe expressive language impairment, intellectual deficiency, epilepsy with high SUDEP rate (15%), and myriad neuropsychiatric impairments, most notably anxiety disorder and obsessive compulsive disorder. Imaging shows abnormal MR signal in the globus pallidi, cerebellar dentate nuclei, and subthalamic nuclei, as well as cerebellar atrophy. Key milestones in SSADH research include ALDH5A1 genetic degradation murine model development and testing (2001), downregulation of GABA(A) and (B) receptors in the homozygous animal model (2006) and clinically (2009), and trial of the GABA(B) receptor antagonist SGS-742 (negative results, 2020). We are currently conducting a natural history study of patients compared to age-matched controls and disease controls with GABA transaminase deficiency (NICHD NCT03758521). This includes neurological and neuropsychological examinations, MRI/MR spectroscopy, EEG/high density EEG, TMS (transcranial magnetic stimulation), and laboratory specimens for a biorepository including skin biopsies for fibroblast derived iPSC generation. Average IQ scores are 49-56 but with a range of 30-95. While there is no overall phenotype-genotype correlation, a missense variant c.1294A>C has been associated with a very severe phenotype, whereas the novel missense variant c.1321G>A may be associated with a mild phenotype. MRS shows elevated GABA peaks in all regions studied in 100% of patients versus controls. High density EEG preliminary analysis suggests decreased gamma frequency range, correlating with downregulation of GABA receptors. Potential targeted treatment strategies include antisense oligonucleotides for a few splice site variants that may be amenable and enzyme replacement therapy (ERT). An animal model is under development to allow controllable SSADH re-expression, testing the optimal rate and timing of ERT. Restoration of GABA activity in a developmental disease with elevated [GABA] and decreased GABA receptors may involve critical aspects of timing. A post knock-out model using Cre-recombination and reversible Dox-dependent SSADH expression, utilizing a tetracycline responsive promoter element, demonstrates preliminary success at P16 in restoring enzymatic activity. Approaches include both whole brain intervention with AAV-mediated vector infusion, and therapy directed at parvalbumin interneurons specifically. While SSADHD pathophysiology is complex and current treatments remain symptomatic, on-going work is focused on developing an inducible SSADH mouse model and the clinical natural history study.

S4 - Neurometabolic Diseases and Epilepsy (II)

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GENETIC INVESTIGATION IN LIPID METABOLISM WITH INFANTILE EPILEPSY

Lipid are necessary for both energy supply and energy storage, and including triglyceride, fatty acid, cholesterol, bile acid, phospholipid, and so on. Disorders of lipid metabolism include sphingolipidoses (Krabbe disease, metachromatic leukodystrophy, Niemann Pick A and B, Fabry disease and Gaucher disease), peroxisomal disorders (adrenomyeloneuropathy, Refsum disease, disorders of pristanic acid metabolism, peroxisome biogenesis disorders), sterols disorders (cerebrotendinous xanthomatosis, Niemann-Pick C, spastic paraplegia type 5 and Tangier disease) and the newly described group of metabolic diseases affecting the synthesis and remodeling of phospholipids and sphingolipids.

Given the great proportion of lipids in the nervous system, these diseases can produce almost all kinds of symptoms, such as spastic paraparesis, psychotic symptoms, epilepsy, etc. In a patient with epilepsy, several clinical features suggest an inborn error disorders, such as atypical epilepsy; progressive myoclonic epilepsy; combined with other neurological impairments (cerebellar, pyramidal, unexplained mental retardation, or with other organ disorders; inefficacy of or worsening with classic antiepileptic drugs, which lead to further evaluation and study.

The important cost reduction and the possibility to considerably accelerate diagnosis make next generation sequencing (NGS) more and more attractive among the complex journey of patients with such rare disorders. Some centers have even implemented these techniques as first-line biological investigations as soon as a genetic disease is suspected in a patient. Other centers have elected to pursue performing metabolic investigations before targeting one candidate gene or several candidate genes, often grouped in the so-called gene panels. Although gene panels allow the analysis of a more restrictive number of genes than whole exome approaches, they do not preclude the use of standard genetic validation approaches, especially the analysis of variants frequency in the general population, the analysis of variants segregation in the family and functional analyses when possible. Moreover, some biochemical investigations should remain first-line tools for certain clinical presentations as they are cheap to perform and very sensitive to diagnosis. Of importance, the interpretation of the large-amount data obtained by NGS requires the access to advanced bioinformatics pipelines.

S4 - Neurometabolic Diseases and Epilepsy (II)

Dar-Shong Lin

Taiwan

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THE ROLE OF AUTOPHAGY IN THE PATHOMECHANISM AND TREATMENT OF LEUKODYSTROPHY

White matter diseases (WMD) are composed of neurological diseases with myeline damages as a consequence of primary or acquired events. Among the entity of WMD, Leukodystrophies are inherited disorders caused by molecular deficit in neuroglia cells affecting myeline sheath formation, maintenance and repairment. During this conference, much of the presented material is relative to X-linked adrenoleukodystrophy (X-ALD) and globoid cell leukodystrophy (GLD), which are the most devastating demyelinating disorders among children. X-ALD and GLD are caused by peroxisomal and lysosomal defects, respectively, leading to accumulation of toxic metabolites destabilizing myeline and inducing death of oligodendrocytes. Recently, autophagy dysfunction, a common pathological mechanism of proteinopathies, is also unveiled as the underlying pathogenesis of X-ALD and GLD. Both *in vivo* and *in vitro* evidence of autophagy dysfunction in X-ALD and GLD based on the literatures and our studies are presented and the efficacy and therapeutic potential of small molecules targeting the autophagy in the approaches of these specific leukodystrophies is discussed in this conference.

S4 - Neurometabolic Diseases and Epilepsy (II)

Wang-Tso Lee
Taiwan

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UPDATE TREATMENT FOR LEUKODYSTROPHY AND ITS ASSOCIATED EPILEPSY IN INFANTS

Leukodystrophies are not uncommon neurological diseases in children. They may result from abnormalities of the oligodendrocyte or other supporting cells or tissues. We can make the diagnosis of leukodystrophy based on clinical presentations and neuroimage findings. With the advance of genetic analysis, more and more atypical leukodystrophies have been diagnosed. Epilepsy can develop in early stage or late stage of leukodystrophies. Epilepsy may be common in some leukodystrophies while may be uncommon in some leukodsytrophies. Although an understanding of pathogenesis is still evolving, more and more new therapy, including gene therapy, has been designed to stop the progression of leukodystrophy. Therefore, we have to face a new era of treatment in leukodystrophy and their related epilepsy.

S5 - Neurometabolic Diseases and Epilepsy (III)

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CONGENITAL DISORDERS OF GLYCOSYLATION AND INFANTILE EPILEPSY

Glycosylation is the process of adding sugar residues to proteins and lipids in different cellular pathways. Congenital disorders of glycosylation (CDG) are a genetically and clinically heterogeneous group of over a hundred diseases caused by defects in various steps along glycan synthesis or modification pathways.

Congenital disorders of glycosylation are usually multisystem diseases, and in the majority of patients, there is an important neurological involvement comprising psychomotor disability, hypotonia, ataxia, seizures, stroke-like episodes, and peripheral neuropathy. Infantile epilepsy is a challenging condition and may have different origins (anoxic–ischemic events, intracranial bleeding, infections, brain malformations, genetic/metabolic defects, drugs abstinence) although the cause is not always identified. Among inborn errors of metabolism, CDG are a rapidly growing group of genetic defects of glycoprotein and glycolipid glycan synthesis. Seizures have been reported in almost all types of CDG.

This talk emphasizes the importance of increased awareness that among subjects with infantile epilepsy, patients with CDG may be detected.

S5 - Neurometabolic Diseases and Epilepsy (III)

Shinichi Hirose

Japan

General Medical Research Center, School of Medicine,
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INFANTILE EPILEPSY AND CARNITINE INBORN ERRORS OF METABOLISM: THE ROLE OF GENES

Carnitine is an amino acid, which is derived mainly from diet but is also bio-synthesized in the body. Still, carnitine is considered a vitamin-like nutrient, thus conditionally essential specifically in infants. Carnitine plays physiological roles in energy production via fatty acid oxidation, maintaining the intracellular free CoA level, excreting harmful organic acids from the body such as in organic aciduria, and potentiating biological antioxidative and anti-inflammatory functions. Among them, in the context of infantile epilepsy, the roles of carnitine in both fatty acid oxidation disorders and organic aciduria are crucial. There are several inborn errors associating directly with carnitine metabolisms though no genetic abnormalities in the carnitine biosynthesis have been reported as a cause of epilepsy. Such inborn errors affect the carnitine uptake of the cell and so-called "carnitine shuttle" that is a sequential process where carnitine transports long-chain fatty acids into the mitochondrial matrix from the cytosol and carnitine returns to the cytosol via the same cascade but in the opposite direction. These disorders can lead to energy depletion specifically under starvation. In newborns and infants, this energy depletion may cause profound hypoglycemia but also serious consequences such as Reye-like syndrome, acute encephalopathy, and sudden death. Thus, this lecture focuses on the autosomal recessive disorders caused by genetic abnormalities of the transporter and the enzymes in the carnitine shuttle. Genetic abnormalities of *OCTN2* encoding organic cation/carnitine transporter novel type2 cause primary systemic carnitine deficiency. This condition may present with the phenotype affecting the CNS in young children and also with cardiomegaly in later life. It is noteworthy that neonates born to a mother with this deficiency could develop seizures. Genetic abnormalities of one of *CPT1*, *CACT*, and *CPT2*, which encode the enzymes underpinning the carnitine shuttle, namely carnitine palmitoyltransferase I, and carnitine-acylcarnitine translocase, and carnitine palmitoyltransferase II, respectively, can also present with phenotypes exhibiting epilepsy. Intriguingly, some polymorphisms of *CPT2*, which are known to lead to thermolability of the corresponding enzyme, are known to be associated with the development of encephalopathy in influenza infection. Some of the described genetic abnormalities can be identified by tandem-mass spectrometry newborn screening followed by genetic analyses and the serious consequences hence might be evitable. Thus, early recognition of these genetic abnormalities is a key to a better outcome of these otherwise life-threatening disorders.

S5 - Neurometabolic Diseases and Epilepsy (III)

Yi Wang
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ORGANIC ACID AND INFANTILE EPILEPSY: THE ROLE OF GENES

Organic acids are intermediate products of metabolism of amino acids, fatty acids, steroids, carbohydrates or certain drugs in the body. The accumulation of intermediate and bypass metabolites due to genetic mutations and/or functional defects of certain enzymes in their metabolic pathways can cause metabolic acidosis and damage to brain, liver, kidney, heart, bone marrow and other organ functions. In addition to the accumulation of precursors, the bypass metabolites increase, and so does the production of other related organic acids. Organic aciduria is a group of diseases caused by intermediate metabolic disorders, characterized by accumulation of carboxylic acids, and can be diagnosed by urine gas chromatography-mass spectrometryd metabolite analysis. The vast majority of patients have predominantly systemic symptoms (classic organic aciduria), but some patients present only with brain damage. The most common form of organic aciduria is due to impaired metabolism of complex branched chain amino acids. Clinical features include progressive ataxia, extrapyramidal signs, acute (epileptic) encephalopathy, macrocephaly, and sometimes manifest non-specific intellectual impairment. Organic aciduria that can cause neurological symptoms include methylmalonic aciduria (MMA), glutaric aciduria type I (GA1), propionic acidemia (PA). The incidence of organic aciduria epilepsy is around 20-40%, epilepsy can start at all ages (8 days-11 years), and seizure types include various seizure forms such as focal seizures, generalized tonic-clonic seizures, tonic seizures, myoclonic seizures and epileptic spasms, and sometimes a combination of multiple seizure forms, with focal seizures being the most common. The EEG often combines slowed background activity (62%), focal or multifocal paroxysmal discharges in 59% of patients, all-conductor paroxysmal discharges in 15% of patients, high arrhythmias in 7% of patients, and a suppressed burst pattern in 4% of patients. 52% of cranial MRI scans show bilateral brain atrophy, 44% increased T2 signal intensity in white matter, 7% corpus callosum hypoplasia and bilateral basal ganglia T2 signal intensity increased or necrosis, and 4% cerebellar atrophy. Most of organic acidemias are inherited in an autosomal recessive manner. MMUT gene is recommended for carrier screening as an effort to move the test earlier as a part of the primary prevention of birth defects. A number of new genomic therapies, which include canonical adeno-associated virus gene addition, genome editing, and systemic mRNA therapy, have shown great promise in murine models of MMA.

Keywords: Organic acidemia, Epilepsy, gene

S5 - Neurometabolic Diseases and Epilepsy (III)

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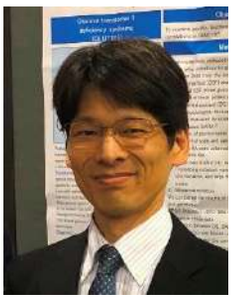
DIAGNOSIS OF NEUROMETABOLIC DISORDERS INVOLVING BASAL GANGLIA BASED ON NEUROIMAGES

Bilateral basal ganglia abnormalities on MRI are observed in a wide variety of childhood disorders. MRI pattern recognition can enable rationalisation of investigations and also complement clinical and molecular findings, particularly confirming genomic findings and also enabling new gene discovery. Some disorders seem to have a neostriatal predilection and some others have a pallidal predilection in MRI changes. The MRI patterns for certain disorders such as MEGDEL, Wilson's disease, thiamine responsive basal ganglia disease and hypermanganesemia are very distinctive and can guide early choice of empiric treatments. This presentation will outline Basal ganglia MRI patterns in various early childhood onset neurometabolic disorders to provide visual examples to aid diagnostic testing and clinical decision making. In addition, MRI patterns for some common acquired disorders will be presented to contrast with the neurometabolic disorders in order to enable better recognition and avoid expensive neurometabolic and genetic testing.

S6 - Treatable Neurometabolic Diseases and Epilepsy



Shin Nabatame

Japan

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GLUCOSE TRANSPORTER 1 DEFICIENCY: PAST EXPERIENCE, CURRENT STATUS, AND FUTURE CHALLENGES

Glucose is the essential source of energy for the brain. Glucose transporter 1 (Glut1) is the sole glucose transporter expressed on the blood–brain barrier, and its functional decline leads to Glut1 deficiency syndrome (Glut1DS), a condition that comprises various neurological disorders, including developmental delay, refractory epilepsy, ataxia, and fatigability. Starvation, fatigue, and long-lasting exertion aggravate these symptoms. In the cerebrospinal fluid, a low glucose level is the representative laboratory finding. Mutation of the *SLC2A1* gene is necessary for the diagnosis; however, approximately 10%–20% of affected patients do not have this mutation. Therefore, typical symptoms and hypoglycorrhachia are the alternative diagnostic standards. The ketogenic diet is the principal treatment of Glut1DS. It provides the brain with ketone bodies as the alternative source of energy and ameliorates epilepsy, movement disorder, and cognitive disorders. Therefore, the ketogenic diet should be initiated as early as possible.

The ketogenic diet is the basic framework for the clinical treatment of Glut1DS. However, many clinical questions remain unanswered: the clue to early diagnosis, appropriate duration of the ketogenic diet, and safety of long-term adherence to the ketogenic diet. I will present a lecture on related issues.

S6 - Treatable Neurometabolic Diseases and Epilepsy

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Professor, Department of Pediatrics
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PYRIDOXINE-RESPONSIVE AND DEPENDENT EPILEPSY

Pyridoxine (one of 6 natural forms of vitamin B6) deficiency may cause seizures due to lack of GABA synthesis. Occasionally, seizures could not be controlled without an extra amount or form of vitamin B6. The therapeutic role of pyridoxal phosphate (PLP), the only active form of vitamin B6, may not be replaced with other forms of vitamin B6 in treatment. Until now, five inborn errors of metabolism are known to affect PLP concentrations in the brain (the number in the parenthesis behind the followings indicate the possible year each gene defect was documented):

(1) Pyridoxine dependent epilepsy, NIM#266100 (ALDH7A1, 2006),

(2) Hyperprolinemia type 2, NIM#239510 (ALDH4A1, 1998),

(3) Pyridoxine phosphate oxidase deficiency, NIM#610090 (PNPO, 2005),

(4) Congenital hypophosphatasia, NIM#171760 (ALPL, 1998,1992),

(5) Pyridoxal phosphate binding protein deficiency, NIM#604436 (PLPBP, 2016), and.

(6) Mitochondrial glutamate oxaloacetate transaminase mutation (EC 2.6.1.1, 2018).

All patients with these conditions may present with early-onset epilepsy that is resistant to conventional antiepileptics. Patients may respond to any form of vitamin B6, except those with PNPO deficiency respond only to PLP. Besides CNS disorders, liver, bone, or other organs may have specific problems.

There are still some gaps in the understanding of PLP homeostasis and else. I have successfully treated some patients without the above 6 disorders with vitamin B6 through unknown mechanisms. Maybe you'll find them for me in the near future?

S6 - Treatable Neurometabolic Diseases and Epilepsy

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Medical Doctor, Division of Pediatric Neurology,
China Medical University Children's Hospital, Taichung Taiwan

BIOTINIDASE DEFICIENCY AND INFANTILE SEIZURES

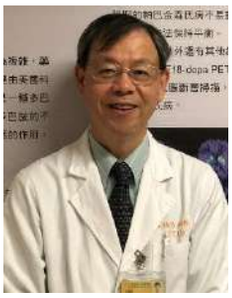
Biotin is a water-soluble vitamin and a cofactor of all four carboxylase enzymes: pyruvate carboxylase, acetyl CoA caroxylase, propionyl CoA carboxylase, and 3-methylcrotonyl-CoA-carboxylase. There are two key enzymes for biotin metabolism in humans. One is holocarboxylase synthetase (HCS), which is the enzyme responsible for attaching biotin to mammalian mitochondrial carboxylases, and the other is biotinidase, which hydrolyses biocytin to biotin and lysine, thereby recycling the vitamin. Both HCS deficiency and biotinidase deficiency result in reduced activity in multiple carboxylases.

Biotinidase deficiency can be profound (<10% enzyme level) or partial (10-30% enzyme level). Clinical presentation depends on the severity of enzymatic defect. Profound defects usually manifest between 3 and 6 months of age, with neurological manifestations (seizures, hypotonia and developmental delay), skin manifestations (eczematous skin rash, seborrheic dermatitis, alopecia) and respiratory problems.

The diagnosis of biotinidase deficiency still relies on urine organic acid analysis. Because measuring the activities of each of the carboxylases is difficult and not widely available, therapeutic trials should be performed before the final diagnosis is made. A molecular genetic approach is very helpful to establish the definitive diagnosis in most inherited metabolic diseases. Biotinidase deficiency may be detected on screening of the newborn.

A high index of suspicion for timely diagnosis and treatment is very important, since most patients can be treated readily with biotin. This disorder should be considered in children with infantile seizures, especially in the presence of other characteristic neurological or cutaneous features.

S6 - Treatable Neurometabolic Diseases and Epilepsy



Tsu-Kung Lin
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NOVEL TREATMENT OF MITOCHONDRIAL DISORDERS

The cellular power plants mitochondria possess their own genome. Alterations in mitochondrial DNA (mtDNA) causes mitochondrial bioenergetic dysfunction, decrease ATP supply which lead to many human diseases. A large scale (usually 4,977-base pairs) deletion in mtDNA is the common cause of several sporadic diseases including Pearson's syndrome, Kearns-Sayre syndrome (KSS) and chronic progressive external ophthalmoplegia (CPEO). Point mutation in mt-tRNALys (mt.3243A>G) and mt-tRNALeu (mt.8344A>G) lead to mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) and myoclonic epilepsy with ragged-red fibers (MERRF), respectively. For now, there is still no curable treatment for mitochondrial diseases. There are a number of approaches aiming to modulate mitochondrial function in mitochondrial diseases, including antioxidants supplement, exposure to hypoxia, stem cell therapies, replacing defective mtDNA in an oocyte and supplementation of a tissue with exogenous mitochondria through mitochondrial transplantation. Furthermore, there are potential therapeutic strategies trying to correct mutated point mutations utilizing gene editing therapies.

Recently our serial studies focusing on mitochondrial transplantation therapy (MTT) may pave a new way to developing effective therapy. We have demonstrated that human Wharton’s jelly mesenchymal stem cells (WJMSCs) can transfer healthy mitochondria to disease cells harboring mtDNA deletion or mutation and effectively reduce mtDNA mutation burden as well as improve mitochondrial bioenergetics. Our preliminary results present that WJMSCs-conducted MTT also reduce large-scale deletion of mtDNA in KSS patient’s fibroblasts. In this talk, we will share our data of WJMSCs-based MTT and discuss the potential therapeutic strategy of MTT for the enhancement of mitochondrial function in diseases relevant to mitochondrial disorder.

S6 - Treatable Neurometabolic Diseases and Epilepsy

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CREATINE TRANSPORTER DEFICIENCY AND EPILEPSY

Creatine metabolism plays essential roles in energy homeostasis especially in tissues with high or fluctuating energy demands, such as muscle and brain. Creatine is fundamental to normal brain development and function. A variety of cells take up creatine from the extracellular fluid by a high affinity Na^+/Cl^-dependent creatine transporter. Creatine transporter deficiency (CTD), an X-linked disease first reported in 2001, predominantly impacts the male population. The clinical manifestations of CTD include developmental delay, language impairment, mental retardation, seizures, failure to thrive, behavioral abnormalities, and muscular hypotonia. The epileptic disorder observed in CTD is generally described as mild with infrequent seizures and favorable response to common antiepileptic drugs. The seizure onset is usually in the second year of life. Atypical febrile seizures or partial status epilepticus present initially, and then turn into generalized tonic-clonic seizures later. Refractory seizures are uncommon but have been reported. Diagnostic approaches include magnetic resonance spectroscopy; levels of creatine, creatinine, and guanidinoacetate in urine, plasma and cerebrospinal fluid; and genetics. None of the treatment strategies explored to date have been effective in the long-term management of CTD. Oral supplement with creatine or creatine precursors (i.e., arginine and glycine) improved the symptoms in some patients with mild CTD symptoms, and this therapy appeared beneficial only in patients up to 9 years of age. Putative therapeutic strategies for handling CTD include modifying the creatine molecule and pharmacochaperoning. In conclusion, CTD is associated nonspecific neurologic symptoms, so pediatrician should consider CTD as one of the differential diagnoses in children with unexplained and frequently poorly controlled seizure episodes. Early diagnosis and treatment helps these children with treatable inborn error of metabolism.

Poster Presentation

Developmental Disorders

Chair: Pi-Lien Hung (Taiwan), Ming-Tao Yang (Taiwan)

Poster Number	Title & Presenter
PA-01	Pathological Gait in Patients with Rett Syndrome: Quantitative Evaluation Using Three-Dimensional Gait Analysis *Takeshi Suzuki (Nagoya University Graduate School of Medicine, Japan)*

Genetics

Poster Number	Title & Presenter
PB-01	Molecular Aspect of PRRT2 Gene Variation with Paroxysmal Kinesigenic Dyskinesia Patients in Central Taiwan *Wei-De Lin (China Medical University Hospital / China Medical University, Taiwan)*
PB-02	Two Siblings with Refractory Infantile Epilepsy were Sharing the Same Mutations in TBC1D24 *Chih-Wei Lin (Kaohsiung Veterans General Hospital Pingtung Branch, Taiwan)*
PB-03	Next Generation Sequencing Contributes to Genetic Diagnosis of Infantile-Onset Drug Resistant Epilepsy: VGHTPE experience *Ting-Rong Hsu (Taipei Veterans General Hospital / National Yang Ming Chiao Tung University, Taiwan)*
PB-04	A Case of Methylenetetrahydrofolate Reductase Deficiency Presenting as Microcephaly and Hydrocephalus *Yi-Ting Kuo (National Taiwan University Children Hospital, Taiwan)*
PB-05	Novel Mutations in KDM5C Gene Causing X-linked Intellectual Disability *Po-Ming Wu (National Cheng Kung University, Taiwan)*
PB-06	De Novo Deletion Variants in the IRF2BPL is Associated with Developmental Epileptic Encephalopathy *Wei-De Lin (China Medical University Hospital, Taiwan)*
PB-07	Use of Quinidine in Two Siblings with KCNT1-Related Epilepsy *Pou-Leng Cheong (National Taiwan University Hospital Hsin-Chu Branch, Taiwan)*
PB-08	Whole Exome Sequencing Identifies Novel Homozygous Mutation of ERCC6 Gene in a Taiwanese Boy *Ching-Ming Lin (National Defense Medical Center / Kaohsiung Armed Forces General Hospital, Taiwan)*
PB-09	Ultrarare Genetic Cause to a Wide-Spectrum of Genetic Disorders Causing Severe Childhood Epilepsy in Taiwan *Inn-Chi Lee (Chung Shan Medical University Hospital, Taiwan)*
PB-10	Maternal Inheritance of Deletion of Chromosome 18 q21.3 *Hueng-Chuen Fan (Tungs' Taichung Metroharbor Hospital / Jen-Teh Junior College of Medicine, Taiwan)*

Poster Number	Title & Presenter
PB-11	A Neurodevelopemental Degenerative Female with Refractory Epilepsy Caused by MECP2 Duplication Syndrome *Zhao-Qing Lin (Taipei Medical University-Shuang Ho Hospital, Taiwan)*
PB-12	Dravet-Like Syndrome with PCDH19 Mutation in Taiwan—A Multicenter Study *Yi-Hsuan Liu (Chang Gung Children's Hospital and Chang Gung Memorial Hospital, Taoyuan Taiwan*
PB-13	A Case with NADPHX Dehydratase Deficiency: A Newly Defined Mutation in a Novel Neurodegenerative Disorder *Gökçen ÖZ Tunçer (Ondokuz Mayıs University, Turkey)*
PB-14	A Case of FBXL4-Related Mitochondrial Disease Presenting with a Mild Phenotype *Mayu Tahara (The Jikei University School of Medicine, Japan)*
PB-15	The Time-Course Changes of Electroencephalogram Findings in a Girl with a Nonsense Variant in SMC1A *Kazuhiko Hashimoto (National Center of Neurology and Psychiatry, Japan)*
PB-16	The Phenotype of Seizure in Ring Chromosome 13: A Case Report *Naomi Hino-Fukuyo (Tohoku Medical and Pharmaceutical, Japan)*

Infection/Immunology

Poster Number	Title & Presenter
PC-01	Diffuse Cutaneous Mastocytosis of an Infant with Refractory Epilepsy: A Case Report *Ting-Rong Hsu (Taipei Veterans General Hospital / National Yang Ming Chiao Tung University, Taiwan)*
PC-02	Case Report: Arterial Spin Labeling Might Be Useful to Predict Mild Encephalopathy Associated with Excitotoxicity *Yuki Nakajima (Showa General Hospital, Japan)*
PC-03	Midbrain Abnormality in a Patient with Acute Encephalopathy with Biphasic Seizures and Late Reduced Diffusion *Sayaka Ishihara (Showa General Hospital, Japan)*

Metabolic Disorders

Poster Number	Title & Presenter
PD-01	Leigh Syndrome Presenting with Nonconvulsive Status Epilepticus *Sheng-Shing Lin (China Medical University Children's Hospital, Taiwan)*
PD-02	Isolated Sulfite Oxidase Deficiency with Refractory Neonatal Seizures Mimicking Neonatal Hypoxic-Ischaemic Encephalopathy *Janardhan Krishnappa (KK Women's and Children's Hospital, Singapore)*

Poster Number	Title & Presenter
PD-03	A Case of Late-Onset Pyridoxine-Dependent Epilepsy Detected by Urine Metabolomics *Takuzo Marukane (Okayama University Hospital, Japan)*
PD-04	The Effect of Dietary Protein Restriction in a Case of Molybdenum Cofactor Deficiency *Yu Abe (Tohoku University School of Medicine, Japan)*

Neonatal Seizures/Epilepsy

Poster Number	Title & Presenter
PE-01	Neonatal Alexander Disease: Case Report and Review of Literature *Xiao-Ru Ji (National Taiwan University Children's Hospital, Taiwan)*
PE-02	SCN8A Encephalopathy *Hueng-Chuen Fan (Tungs' Taichung Metrohabor Hospital, Taiwan)*
PE-03	Premature Maybe the Risk Factor for Subsequent Epilepsy, ASD and ADHD in Children with FS *Chien-Heng Lin (China Medical University Children's Hospital / China Medical University, Taiwan)*
PE-04	Ketogenic Diet Therapy for Infantile Epilepsy Aged Less Than 2 Years Old *Tzu-Yun Hsieh (Kaohsiung Chang Gung Memorial Hospital / Chang Gung University College of Medicine, Taiwan)*
PE-05	Paroxysmal Kinesigenic Dyskinesia in Clinical Practice *Kun-Long Hung (Fu-Jen Catholic University Hospital / Cathay General Hospital, Taiwan)*
PE-06	Neonatal Seizure in a Late Preterm Infant with Accidental Finding of Periventricular Leukomalacia *Chun-Hao Chu (Tri-Service General Hospital / Kaohsiung Armed Forces General Hospital Zuoying Branch, Taiwan)*
PE-07	Tubulinopathy Presenting as Developmental Epileptic Encephalopathy *Kun-Long Hung (Fu-Jen Catholic University Hospital / Cathay General Hospital, Taiwan)*
PE-08	The Mitochondria Related Epilepsy: A Retrospective Study in One Tertiary Center *Hsin-Pei Wang (National Taiwan University Hospital Yunlin Branch, Taiwan)*
PE-09	Genetic Factors and the Risk of Drug-Resistant Epilepsy in Young Children with Epilepsy *Po-Yen Wu (China Medical University Children's Hospital, Taiwan)*
PE-10	ERGENT: Early Recognition of Genetic Epilepsy in Neonates *John Millichap (Northwestern University Feinberg School of Medicine, USA)*

Poster Number	Title & Presenter
PE-11	The Etiology and Genetic Related Causes of Seizure in Term Newborn *Yonlalit Neetiwatanapong (Chulalongkorn University, Thailand)*
PE-12	Atypical Presentation of Pyridoxine-Dependent Epilepsy in a Child *Eric Ma (KK Women's and Children's Hospital, Singapore)*
PE-13	A Hospital-Based Comparative Study on Serum Perampanel Concentrations between Children and Adults with Epilepsy *Ryo Goshima (Osaka Women's and Children's Hospital, Japan)*
PE-14	Epileptic Focus Estimation in Children with Tuberous Sclerosis Complex Using EEG-fMRI Combined with FDG-PET *Yuki Maki (Nagoya University Graduate School of Medicine / Nagoya University, Japan)*

Neuroimaging

Poster Number	Title & Presenter
PF-01	Febrile Seizures Reduce Hippocampal Subfield Volumes but not Cortical Thickness in Children with Focal Seizures *Min-Lan Tsai (Taipei Medical University Hospital, Taiwan)*

Neurophysiology

Poster Number	Title & Presenter
PG-01	Protective Effect of Fluvastatin Against NMDA-Induced Seizure and Underlying Mechanism *Ya-Jean Wang (National Health Research Institutes / Minghsin University of Science and Technology, Taiwan)*
PG-02	Prognosis of Neuropsychological Development in Patient with Agenesis of Corpus Callosum *Po-Yen Wu (China Medical University Children's Hospital, Taiwan)*
PG-03	Analyses on Ictal Scalp EEG May Predict Outcomes of Corpus Callosotomy for Epileptic Spasms *Sotaro Kanai (Tottori University, Japan)*
PG-04	Analysis of EEG Changes in 2 Cases of Doose Syndrome Treated with Long-Term ACTH Therapy *Ayami Yoshikane (Fujita Health University School of Medicine, Japan)*

Others

Poster Number	Title & Presenter
PH-01	Intracranial Cerebral Artery Dissection Associated with a Competitive Basketball Match: A Pediatric Case Report *Ann-Ching Wang (Taoyuan Armed Forces General Hospital, Taiwan)*
PH-02	The Exercise Effects on the Symptoms and Behaviors in People with Epilepsy: The Systematic Review *Shiau-Chian Jeng (Chang Gung University / National Keelung Special Education School, Taiwan)*
PH-03	ACTH in Epileptic Spasms: A Follow up Study in New Taipei City, Taiwan *Zhao-Qing Lin (Taipei Medical University, Taiwan)*
PH-04	Retrospective Analysis of Motor Progression in DD with and without Intellectual Disability Receiving Rehabilitation Therapy *Hueng-Chuen Fan (Tungs' Taichung Metroharbor Hospital / Jen-Teh Junior College of Medicine, Taiwan)*
PH-05	Therapeutic Hypothermia is Effective for Status Epilepticus of Acute Encephalopathy in Dravet Syndrome *Anna Shiraki (Nagoya University Graduate School of Medicine, Japan)*
PH-06	A Successful Solo Treatment of Valproic Acid in West Syndrome *Hisako Yamamoto (Kawasaki Municipal Tama Hospital / St. Marianna University School of Medicine, Japan)*

Oral & Poster Presentation Abstracts

O1-1

A Case Series of Varied Manifestations of Glut1 Transporter Defect

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Purpose:

1.To identify the various manifestations of glut1 transporter defect

2.To establish genotypic phenotypic corelation if any

Methods:

All patients with refractory epilepsy or paroxysmal manifestations with borderline developmental delay were screened for glut1 transporter defect.

3 patients were identified in the span of 2015-2020

Screening was done by CSF examination after 2 hours of fasting. Random blood sugar was tested immediately before CSF examination. Lactate was also estimated from CSF samples.

Ratio of CSF/RBS <0.44 (used by MeSH,pubmed)was diagnostic for glut1 defect.

All patients were evaluated for SLC2A1 mutation by exome sequencing

EEG for epileptiform discharges and MRI was done in all positive patients.

Immediately after diagnosis, patients were put on ketogenic diet using CHO:fat ratio of 1:3

They were monitored for ketones measured twice a day using ketostix.

Patients were monitored for control of seizures and neurodevelopment

Results:

There were 3 patients with M:F2;1

All patients had seizures refractory to AEDS

All patients responded to ketogenic diet, Younger patient responded within 48 hours and infants responded within 1 week

All needed supplementation with oxarbamazepine for breakthrough seizures.

All patients were slc2a1 negative

Conclusion:

Glut1 transporter defect is a rare condition with varied manifestations like refractory seizures, paroxysmal dyskinesias, spastic diplegia with normal neuroimaging is .[1,2]

Low CSF glucose in absence of sepsis and low CSF glucose/RBS ratio<0.44 (used by MeSH,pubmed)is diagnostic for glut1 transporter defect.

Mutation for SLc2A was negative suggesting that factors other than mutation seem to be responsible for phenotypic characteristic of glut1 defect [3,4] .

Response to alternative fuel like ketogenic diet is remarkable in epilepsy.

All patients may not need life long ketogenic diet.

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O1-2

GNAO1-related Severe Involuntary Movements Treated with Deep Brain Stimulation

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ABSTRACT

Background: *GNAO1* gene, encoding the alpha-subunit of heterotrimeric guanine nucleotide-binding protein, is associated with early onset epileptic encephalopathy and movement disorders. Progressive hyperkinetic movements are often refractory to most medication, and brain stimulation of the globus pallidus internus (GPi-DBS) is recently reported to be effective.

Case: The patient was an 8-year-old girl who was the first child of non-consanguineous healthy parents. She was referred to our hospital because of psychomotor delay at 6 months of age. Her perinatal and family histories were unremarkable. She showed hypotonia and decreased spontaneous movements. Epileptic seizures were not observed. Whole-exome sequencing revealed a de novo mutation in *GNAO1*, c.709G>A:p.(E237K). At 5 years of age, her involuntary movements developed, which were brief, asynchronous, and irregular movements of the upper and lower limbs. They were repetitive and often lasted for about 10 minutes. At 6 years of age, her involuntary movements worsened after her hip dislocation surgery, lasting for one week. Gabapentin, clonazepam, and pregabalin were partially effective. At the age of 8 years, her involuntary movements worsened, triggered by acute upper respiratory infection. Continuous involuntary movements and insufficient oral intake made her exhausted. After the hospitalization, the patient was sedated with phenobarbital and midazolam. Her sleep-wake rhythm improved, but the involuntary movements occurred throughout when she was awake. Increased dose of gabapentin was not effective. Two weeks later, we decided to perform GPi-DBS. After the GPi-DBS, her involuntary movements ameliorated drastically, to the extent in which her involuntary movements were only seen when she is in stress such as blood sampling.

Conclusion: DBS can be effective to the *GNAO1*-related severe involuntary movements. We should not hesitate to adopt DBS when we encounter rapidly deteriorating movement disorders associated with *GNAO1*.

O1-3

COQ4 Mutations-related Infantile-onset Mitochondrial Disorder Associated with Primary Coenzyme Q10 Deficiency

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Background: Mitochondrial disease is a neurometabolic, multi-systemic disorder with variable clinical phenotypes. Numerous genetic mutations were proven to result in mitochondrial diseases. At presence, whole exome sequencing becomes more affordable and feasible in clinical practice. More novel genetic mutations leading to this disease could be identified. The COQ4 gene is involved in the production of coenzyme Q10, which plays critical role in oxidative phosphorylation in mitochondria. COQ4 mutation is one of the etiologies of primary coenzyme Q10 deficiency.

Case report: We identified total 6 patients of primary coenzyme Q10 deficiency, age ranged from 3 to 11 years old so far, via whole exome sequencing and the most common genotype is COQ4 homozygous c.370G>A mutation. All the subjects had multi-systemic involvement in their clinical presentations, severe global developmental delay and lactic acidosis. Some of those patients had epileptic encephalopathy or cardiomyopathy since early infancy. Brain MRI showed thin corpus callosum and diffuse brain volume loss, including cerebellum and brainstem. Currently, all of surviving patients had severe hypotonia and global developmental delay and most of them had refractory epilepsy with daily seizure. The clinical seizures become stabilized after supplementation of high-dose CoQ10.

Conclusion: COQ4 mutations cause early-onset mitochondrial diseases that are associated with CoQ10 deficiency. Homozygous COQ4 mutation c.370G>A, p.(Gly124Ser) may be one of the relative common genotypes in Asian papulation. Subjects with COQ4 mutations may benefit from high-dose CoQ10 supplementation.

O2-1

The First Case Series of Bilateral Frontoparietal Polymicrogyria in Taiwan

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Introduction

Bilateral frontoparietal polymicrogyria (BFPP) was one kind of polymicrogyria, first be described in 2000, as frontoparietal distribution of polymicrogyria on brain MRI, and further be confirmed related to genetic mutation on chromosome 16q12.2-21, which encodes an orphan G protein-coupled receptor (GPCR). The clinical features are including hypotonia during infancy, developmental delay, cognitive impairment, childhood onset epilepsy, and Lennox-Gastaut syndrome.

Methods

We reviewed the medical records of three cases of BFPP in a single family including one elder girl and two identical twin boys from birth to adult. The clinical symptoms, electroencephalography (EEG), brain MRI, whole exome sequencing, and treatment records including medications, neuromodulation, and epilepsy surgery, clinical outcome were reviewed.

Results

The elder girl was 21-year-old, and the twin boys were 19-year-old now. All of them presented with hypotonia, global developmental delay initially, and further intelligent disability. The seizure appeared since childhood with tonic seizure initially, following with multiple type seizures, including myoclonic, generalize tonic-clonic, dialeptic, and finally epileptic falling appeared around 18-year-old. Their epilepsies were refractory to anti-epileptic drugs polytherapy, and vagus nerve stimulation, but responded well to callosotomy.

Conclusion

We reported the first BFPP family with genetic confirmed in Taiwan, and demonstrated the efficacy of epilepsy surgery in genetic epilepsy.

O2-2

Clinical and Electrophysiological Features of Pyridoxamine 5' Phosphate Oxidase (PNPO) Deficiency Beyond the Neonatal Period

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Abstract:

Background: Pyridoxamine 5'-Phosphate Oxidase (PNPO) deficiency (OMIM 6032870) is a rare autosomal recessive, treatable cause of early onset epileptic encephalopathy. There is little information regarding clinical features and EEG findings beyond the neonatal period in this disorder. In this report, we describe the symptoms of Pyridoxal 5' Phosphate (PLP) deficiency, seizures and EEG findings over a 16-year period in a patient with PNPO deficiency who developed cirrhosis and hepatocellular carcinoma necessitating liver transplantation at the age of 15.

Methods: PNPO deficiency was diagnosed in this 27-day old neonate after resolution of seizures and encephalopathy with therapeutic doses of PLP. He was subsequently found to be heterozygous for a missense mutation, D33V (c.98A>T) and a single base pair deletion (c.246delT) in the PNPO gene. The patient was monitored with video EEG during the multiple admissions over the years from infancy to adolescence, especially during the prolonged admission for liver transplantation.

Symptoms of deficiency were recorded at clinic visits. About 4800 hours of EEG (and nearly as much video EEG data), performed between ages of 21 months and 16 years were analyzed.

Results: The patient was intellectually normal and was able to report symptoms of deficiency by 6 years of age. These typically involved visual/ ocular disturbance (eyes feeling bigger than sockets, seeing unusual colours, transient amaurosis) often associated with anxiety, mood changes and autonomic features.

Posteriorly dominant 3.5 – 4 Hz spike and wave discharges of brief duration (0.5 – 1 seconds) were seen several minutes (range 0 to 32.02) prior to clinical symptom onset. They increased in frequency and duration with time and were noted to become diffuse if deficiency progressed untreated. Discharges were present for variable periods after the correction of deficiency, disappearing earliest after intravenous replacement (within seconds) versus intranasal or oral correction (several seconds to minutes). These observations were first seen in the recording performed at the age of 3 years and persisted until the last follow-up (16 years). These EEG features were only noted in association with periods of PLP deficiency. Seizures, both electrographic and clinical convulsive episodes, were recorded. Electrographic features of deficiency disappeared during sleep.

Conclusions: In PNPO deficiency, the EEG shows distinct findings during periods of PLP deficiency, the rapid resolution of which occurs after correction of deficiency. EEG is a useful non-invasive tool for recording the deficiency state. The almost complete absence of EEG changes as sleep ensues suggests that the metabolic need of the brain for PLP is reduced in the sleep state.

O2-3

Alternating Hemiplegia of Childhood: A Malaysian Tertiary Centre Experience

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ABSTRACT

Background:

Alternating hemiplegia of childhood (AHC) is a very rare neurological disorder. To our best knowledge, there is no paediatric literature published from Malaysia. We reported a cross-sectional study of children with AHC from a paediatric neurology referral centre in Malaysia.

Methods:

It was a retrospective, cross-sectional study of children with alternating hemiplegia of childhood who was followed up in Women and Children Hospital Kuala Lumpur from 2019-2021. All their medical records were reviewed for data extraction and analysis.

Results:

Seven patients met the inclusion criteria. All fulfilled the AHC clinical diagnosis. Five patients (71.4%) had AHC genetic panel tested, among whom 4 (80%) had ATP1A3 mutation detected and 1 (20%) had no identifiable gene mutation. Six patients (86%) from our cohort had manifestation of classic AHC while 1 (14%) had relatively later onset with normal development. Our cohort of patients had a median age of 4 months at disease onset and 2.96 years at diagnosis. 85.7% of patients had developmental delay, 42.9% movement disorder, 42.9% epilepsy, 28.6% headache, 71.4% behavioural/mood disorders, 14.3% sleep disorder and 42.9% gastrointestinal manifestation. All patients were started on flunarizine as preventive treatment; 4 (57.1%) on topiramate; 3 (42.9%) on clonazepam and 2 (28.6%) on acetazolamide with 85.7%, 50%, 100% and 50% of patients reported improvement after drug initiation, respectively. However, none had complete resolution.

Conclusion:

The clinical profiles of our AHC patients were comparable to other centres worldwide with similar challenges in AHC management: delayed diagnosis and lack of effective preventive treatment. Most drugs are of low evidence level except flunarizine. Even for flunarizine, its complete response rate is extremely low. Further understanding of the disease, particularly pathophysiology, is essential in the development of future precision medicine for alternating hemiplegia of childhood.

O2-4

Focal Gyratory Seizure Associated with Ectopic Gray Matter in the Frontal lobe

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Gyratory seizure is a rarely described seizure characterized by a paroxysmal rotation around the body axis. We present a gyratory seizure found in a 12-year-old girl with ectopic gray matter in the frontal lobe. She was referred to our hospital for sudden-onset rotative movements of the body. She was well-nourished and normally developed girl with history of a single febrile seizure in her one year of age. Her family history is not eventful. This rotative movement was characterized by paroxysmal counterclockwise rotation on her body axis with impairment of consciousness for over several minutes, sometimes followed by motor seizure with tonic flexed upper-limbs and extended lower-limbs. Brain MRI study showed ectopic gray matter in the deep white matter of the right frontal lobe. Conventional interictal EEG showed spike-and-wave discharge as well as 6 Hz rhythmic theta wave burst in the frontopolar, frontal, and anterior temporal areas during awake and sleep periods. A long-term video EEG revealed that an ictal event with paroxysmal counterclockwise rotation was correlated with abrupt provocation of 11Hz rhythmic low voltage alpha wave burst over the right frontopolar area, followed by irregular 2Hz delta wave burst superimposed with irregular 8 Hz wave in the right central-parietal area. 99mTcECD-SPECT showed decrease of regional blood flow in the right frontal area. FDG-PET exhibited hypometabolism in the cerebral cortex of the right frontal lobe as well as hypermetabolic area corresponding to the heterotopic gray matter in the right frontal lobe, where MEG spikes sources were not clearly clustered. Because of the intractability to the anticonvulsant medication with levetiracetam, lacosamide and lamotrigine, surgical resection of the lesion in the right frontal lobe is under consideration.

O2-5

Therapeutic Effects and Mechanisms of Transcranial Photobiomodulation (tPBM) on Pediatric Epilepsy

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ABSTRACT

Convulsive status epilepticus (CSE) is the most common neurological emergency in children and adolescents, yet the response to antiepileptic drugs (AEDs) was merely 72-76%. Due to the refractory pediatric CSE to AEDs, developing effective and safe non-pharmacological treatments for pediatric CSE is urgently needed. Clinically, Depakine (sodium valproate, valproic acid, VPA) is one of the most frequent used AEDs for pediatric CSE. Nevertheless, there is the dose-dependent hepatotoxicity in VPA. Therefore, it would be a good news for patients suffered from pediatric CSE if add-on therapy to VPA could reduce the dose of VPA while maintaining or even increase the anticonvulsive effects so that the hepatotoxicity would be reduced. Considering the mechanic similarities between tPBM and VPA, tPBM is a potential candidate for add-on therapy to VPA. However, there effects of tPBM add-on therapy to VPA was unknown. Transcranial photobiomodulation (tPBM) had been shown to have neuroprotective effects in numerous neurological diseases. In this study, near infrared laser with a wavelength 808 nm was applied transcranially to peripubertal rats received pentylenetetrazole (PTZ) for acute seizure induction. The tPBM was served as monotherapy and add-on therapy (combination therapy or polytherapy) to valproic acid. We evaluated the therapeutic effects and explored the underlying mechanisms. Lastly, the effects of tPBM preconditioning on PTZ-induced seizures was examined.

In conclusion, tPBM with wavelength 808 nm served as monotherapy and add-on therapy to VPA had anticonvulsive effects on PTZ-induced seizures and SE. Particularly, the tPBM add-on therapy to low-dose VPA had trend of synergistic effects yet without statistical significance, while off-set effects occurred when tPBM was added-on to high-dose VPA. Lastly, tPBM preconditioning in the setting of tPBM 1hr before PTZ injection didn't have anticonvulsive effects. Our study might provide insights to future application of tPBM to pediatric epilepsy in particularly pediatric CSE.

O3-1

Brain Age Prediction from Electroencephalographic Maturation Assessed by Deep Learning Algorithm

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ABSTRACT

Scalp electroencephalography (EEG) reflects cortical neuronal activities and undergoes profound changes from ages of infancy to teenage years. The deep learning (DL) approaches have revealed decent classification and prediction capabilities for varies tasks and provide a novel tool for analyzing EEG maturation. In this study, we aimed to develop a deep learning algorithm to predict brain age from EEG data. We collected 10-second eye-open resting state EEG recordings from 481 neurotypical individuals at 1 to 18 years-old from Taipei Tzu Chi Hospital from 2018 to 2020. Among the recordings, 322 samples were used for DL algorithm training and 159 samples were used for evaluation. We explored the prediction accuracy of two different DL algorithms including long-short term memory (LSTM) and bidirectional-LSTM (BLSTM). The BLSTM yielded a better prediction accuracy than the LSTM algorithm. While dividing the individuals chronological age into two groups (1-12 years-old vs. 12-18 years-old), the BLSTM algorithm reached a prediction accuracy to 86.7%. In conclusion, the individuals' brain age predicted from EEG maturation assessed by BLSTM algorithm was highly consistent with chronological age. Therefore, EEG maturation could potentially be served as a marker to monitor neurodevelopment from infancy to teenage years.

O3-2

Electroencephalographic Patterns and Clinical-Radiological Correlation in Children with Lissencephaly: A Case Series Report

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ABSTRACT

Objectives: Lissencephaly is a rare, heterogeneous group of brain malformations caused by mutations of many different genes. Most research focused on radiologic and genetic aspect of pathologic findings. Correlation between EEGs with clinical-radiologic findings is less emphasized.

Methods: The EEG and neuroimaging findings together with gene report and clinical manifestations were reviewed in 9 children with classic form of lissencephaly diagnosed by MRI. We used 3 patterns of EEG for classification: pattern 1 is diffuse bi-hemispheric high-voltage alpha with intermixed with beta fast waves; pattern 2 is bi-hemispheric distribution of 1.5-2.5 slow waves with sharp waves and pattern 3 is high-voltage generalized or bisynchronous sharp waves or epileptiform discharges (EDs).

Results: Among 9 children with neuroimaging diagnosed as lissencephaly, 3 were DCX, 1 LIS gene, 1 DYNC1H1, 1 ARX gene mutation and 3 were unknown. Two patients were posterior more severe than anterior (p>a), 3 patients were anterior more severe than posterior (a>p) and 4 patients were diffuse form. We found most common EEG findings were high-voltage bisynchronous or focal EDs (pattern 3) in 5 patients, diffuse bi-hemispheric high-voltage alpha with intermixed with beta fast waves in 2 and bi-hemispheric distribution of 1.5-2.5 Hz slow waves with sharp contoured wave in 2. Extreme or prolonged spindle oscillations were found in 7 patients. EEG pattern 1 and 2 were correlated with more diffuse pachygyria and have poor clinical prognosis.

Conclusions:

We concluded that EEG characteristics are one of the useful tools to correlate the MRI and clinical manifestations in patients with classic lissencephaly. Diffuse bi-hemispheric high-voltage alpha or fast activity in EEGs were correlated with more diffuse pachygyria and indicated poor prognosis. The results may be related to the abnormal organization and orientation of cortical layers of abnormal neurons.

O3-3

Infantile Epileptic Encephalopathy Caused by the *SCN8A* Variant in a Child with Citrine Deficiency

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ABSTRACT

【Introduction】Citrine deficiency is an autosomal recessive disorder caused by mutations in the *SLC25A13* gene and leads to neonatal intrahepatic cholestasis. It is rarely associated with intractable epilepsy in infancy. Here we report a case of intractable epilepsy in an infant with *SCN8A* variant combined with citrine deficiency.

【Case】A 1-year-old boy was born at full term, weighed 2985g at birth, without birth asphyxia. From days 2and 3, he showed the generalized onset of tonic-clonic seizures. In addition, he showed metabolic acidosis with hyper citrullinemia and cholestatic jaundice. Following these observations, we diagnosed him with citrine deficiency in the boy based on the homozygous *SLC25A13* variants (p.Met285Pro fs*2). From 1 month of age, he showed frequently intractable status epilepticus with cardiacarrest. Although phenytoin (PHT) was effective, we ceased PHT due to severe hepatic dysfunction. Since epilepsy is rare phenotype of citrine deficiency, whole exome sequencing (WES) was conducted, and a de novo heterozygous *SCN8A* (p.Ala1491Val) variant was detected. At 11 months of age, the boy showed no head control, without smiling and word. Subsequently, the signs of cholestatic jaundice improved, and PHT treatment was resumed. While PHT is only effective, the seizures remained intractable, even though combined treatment with clobazam, phenobarbital, topiramate, lamotrigine, and ketogenic diet therapy was initiated.

【Discussion】Intractable epilepsy cases with SCN8A variant might present with autonomic symptoms, such as marked bradycardia and apnea during seizures. While PHT has undesirable side effects, several cases show favorable response to phenytoin in status epilepticus are reported (Neurology 2018, Epilepsia open 2017, etc.). Because cholestatic jaundice is known to improve after infancy in children with citrine deficiency, PHT treatment can be resumed. Actually, reinitiation of PHT, seizures decreased compared to before cessation and his hepatic dysfunction is not shown.

PA-01

Pathological Gait in Patients with Rett Syndrome: Quantitative Evaluation Using Three-Dimensional Gait Analysis

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[Purpose] Patients with Rett syndrome exhibit developmental regression, epileptic seizures, and a variety of movement disorders represented by stereotyped movement, ataxia, tremor, and dystonia. Most patients with Rett syndrome show gait disability and around half of them cannot walk independently. Previous studies based on direct or video observations have reported 'ataxic rigid gait' as the characteristic gait pattern in Rett syndrome. The aim of this study is to evaluate gait deviations in Rett syndrome quantitatively using three-dimensional gait analysis (3DGA).

[Methods] We performed 3DGA in five ambulatory patients with Rett syndrome aged between 5 and 17 years. Twenty-four retro-reflective markers were placed on lower extremities and eight optical cameras were used for motion capture. We investigated their clinical features, gait parameters, and kinematics of lower extremities including gait deviation index (GDI), which is a commonly used comprehensive index of gait pathology.

[Results] All patients had pathogenic mutations in MECP2 gene and showed severe intellectual disability and stereotyped hand movement. All patients also had epilepsy and took antiepileptic drugs. Out of five patients, all five showed pes planovalgus and ataxia, four showed restriction of ankle dorsiflexion, two showed hypotonia while another two showed hypertonia. No patients showed scoliosis. Three patients had slow gait speed and short stride length. Four patients showed low value of GDI. All patients showed wide step width due to 'ataxic' gait. On the other hand, only two patients showed restricted range of motion (ROM) in knee joint indicating 'rigid' gait. Four patients showed restricted ROM in ankle joint, which caused rocker dysfunction. Two patients showed bilateral asymmetry caused by the abnormal pelvic rotation, and one patient showed excessive anterior pelvic tilt.

[Conclusions] We demonstrated various gait patterns with a core gait characteristic of 'ataxic' gait in patients with Rett syndrome using 3DGA. Kinematics of the entire lower extremities in addition to the gait parameters should be evaluated carefully to provide appropriate intervention for gait problems in Rett syndrome.

PB-01

Molecular Aspect of *PRRT2* Gene Variation with Paroxysmal Kinesigenic Dyskinesia Patients in Central Taiwan

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ABSTRACT

Background: Paroxysmal kinesigenic dyskinesia (PKD) is a rare paroxysmal movement disorder and is often misdiagnosed clinically as epilepsy. It is characterized by recurrent, brief attacks of dyskinesia that are triggered by sudden voluntary movement. Mutations in the proline-rich transmembrane protein 2 (*PRRT2*) have recently been reported in patients with PKD. To extend these recent genetic reports, we investigated the frequency and identified of *PRRT2* mutations in central Taiwanese patients.

Methods: A total of 48 patients from 35 unrelated families were identified according to PKD criteria. Among them, 21 patients from 8 families had familial PKD, and 27 were apparently sporadic cases. The complete *PRRT2* coding regions, including the intron/exon boundaries, were sequenced on PKD patients.

Results: After *PRRT2* sequencing analysis, two disease-caused mutations were identified. One was c.625insC (p.R217Pfs7X). It was observed in six familial cases (17 patients) and two sporadic patients. The other was c.272delC (p.P91Qfs24X), which was observed in one sporadic patient. Two single nucleotide polymorphisms were found in this study, they were c.412C>G (p.P138A) and c.623C>A (p.S208Y).

Conclusion: Our results demonstrated that the *PRRT2* mutation was major disease related gene in familial PKD cases (6 out of 8 families, 75%), but minor in sporadic cases (3 out of 27 patients). However, considering the limitation of directed DNA sequencing, it does not exclude the possibility of other mutation types in *PRRT2* gene, such as inversions, translocations, mutations within the introns and promoter. Meanwhile, other genes mutations correlated with PKD cannot rule-out. Further investigation is required for *PRRT2* negative-finding cases.

PB-02

Two Siblings with Refractory Infantile Epilepsy were Sharing the Same Mutations in TBC1D24

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ABSTRACT

Infantile-onset drug-resistant epilepsy is a severe neurological disorder, which leads to impaired motor, cognitive, and sensory development. Genetic tools play an important role for these groups of patients.

We reported two siblings who had early onset of focal clonic and myoclonic astatic epilepsy at about 5-month-old without significantly abnormal findings in their brain MRI. No remarkable development delay before seizure onset, but language delay then was found with the following of development regression. Besides, non-convulsive status epileptics was also noted as the disease was developing at around 1-year-old. The electroencephalography showed multifocal epileptiform discharges with diffuse slow wave background. No abnormal finding in the initial lab data of amino acid analysis and urine organic acid analysis, except the two siblings showed intermittent elevated lactate. Under the impression of mitochondrial disease, the whole mitochondrial DNA sequencing was done initially, but no point mutation was noted. Then, muscle biopsy and function of mitochondria were done. His muscle biopsy showed mild degeneration and fibrosis but electron microscope did not show significant mitochondrial pathologic change. Dysfunction of mitochondria was noted with relative low activities in complex I+III and IV in the mitochondria function test. The result was compatible with the better control of epilepsy after the patient used Ubiquinone. Finally, the whole exome sequencing was done which showed the two siblings shared the same homozygous mutations of TBC1D24 and their parents were heterozygous mutations, all were conformed by sanger sequencing later.

In conclusion, we demonstrate two siblings with TBC1D24 genetic mutation and clinically were compatible with early infantile epileptic encephalopathy. In addition, mitochondrial dysfunction was noted on these patients. Next generation sequencing tool and comprehensive clinical information are important for diagnosis of these patients.

PB-03

Next Generation Sequencing Contributes to Genetic Diagnosis of Infantile-Onset Drug Resistant Epilepsy: VGHTPE Experience

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ABSTRACT

Infantile-onset drug-resistant epilepsy (DRE) is a severe neurological disorder, which leads to severe delayed development. Recent advancement has documented genetic variations are a major etiology for this group of patients. This study is aimed to establish a systemic genetic diagnostic pipeline for infantile-onset epilepsy by utilizing different designs of next generation sequencing technology.

We enrolled 57 patients with DRE and the seizure onset was within the first year of age at Taipei Veterans General Hospital since 2016. Chromosomal aberrations have been excluded. Next generation sequencing including the targeted panel sequencing (TS) of focusing on epilepsy genes and whole exome sequencing (WES) and/or whole genome sequencing (WGS) were applied. Genetic diagnosis has been achieved in a total of 45 patients with the hit rate of 78.9% (45/57), all compatible with ClinVar database or ACMG 2015 criteria. All above genetic variants have been validated by Sanger sequencing and compatible with clinical manifestations. TS could quickly identify genetic variants and account for 19.3% (11/57) in our diagnosed cases. WES/WGS helped the diagnosis of the other 59.5% (34/57) cases, including Family-based WES and trio-based WGS.

For the 45 patients, including 27 male, the mean antiepileptic drugs are 2.67. Thirty-six patients (63%) have developmental delay or mental retardation. *SCN1A* variations are the most common etiology (*N*=11). Other variants were identified in many genes, like *ALDH5A1, ASH1L, CASK, CDKL5, CLCN6, CNTN2, DNM1, FAT4, FLNA, GABRB3, GFAP, HNRNPU, KCNV2, MTMR11, PDE1A, SLC26A1, SCN2A, SCN5A, SCN8A, SUOX*, *SYNGAP1, TBC1D24, and TUBA1A*.

In conclusion, our results documented genetic variation is a major etiology in infantile-onset DRE and showed high genetic heterogenicity. Comprehensive clinical information, including neurophysiology, brain imaging, neuropathology, and a matured genetic and bioinformatic analysis, will be the key to determine the yield rate of NGS.

PB-04

A Case of Methylenetetrahydrofolate Reductase Deficiency Presenting as Microcephaly and Hydrocephalus

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Background and Purpose:

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme involved in the remethylation of homocysteine to methionine. It reduces 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (5-MTHF), the primary biologically active form of folate. MTHFR deficiency is a heterogeneous autosomal recessive metabolic disorder characterized by hypomethionenemia with concomitant hyperhomocysteinemia. It usually leads to neurological manifestations such as seizure, poor feeding, hypotonia, developmental delay and cerebrovascular event. This report described a typical presentation of MTHFR deficiency with prompt diagnosis which resulted in a better prognosis.

Summary of case:

We report a 2-month-old female baby referred to us for surgical intervention due to severe hydrocephalus. She had growth retardation with body weight, body height and head circumference all below third percentile. Tense and bulging anterior fontanelle, craniosynostosis with sunset eyes were found on physical examination. Prominent hypotonia was also noticed. Brain magnetic resonance imaging (MRI) showed reduced cerebral volume with hypomyelination over frontal lobes despite hydrocephalus. Biochemical investigation revealed low plasma methionine (5.54 μmol/L) and markedly elevated plasma homocysteine level (161.27 μmol/L), leading to a preliminary diagnosis of MTHFR deficiency. The subsequent whole exome sequence showed biallelic MTHFR mutation ([c.1709T>G, p.L570R] + [c.646G>A, p.A216T]) inherited from her parents. She commenced taking oral 5-MTHF, betaine, vitamin B6 and vitamin B12. Ventriculo-peritoneal shunt was implanted afterwards. Notably, the plasma level of homocysteine (53.93 μmol/L) decreased significantly and methionine level (21.54 μmol/L) increased to normal range after supplement for 2 weeks. Furthermore, her activity, muscle tone and feeding condition gradually improved.

Conclusion:

Taken together, these statistical and clinical changes under early treatment are shown to improve the clinical course in MTHFR deficiency. Hence, the possibility of an MTHFR deficiency should always be considered if an infant has idiopathic hydrocephalus, brain atrophy and neurological impairment.

PB-05

Novel mutations in KDM5C gene causing X-linked intellectual disability

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Objectives

To investigate the pathogenicity of two novel KDM5C mutations, report the clinical and neuroimaging findings, and review the available literature.

Methods

Physical examinations, structural neuroimaging studies, and exome sequence analysis were carried out. KDM5C constructs were used to study the effect of the mutations in transfected cells.

Results

We identified two novel mutations c.2233C>G and c.3392_3393delAG in the KDM5C gene harboring from two Chinese families with X-linked intellectual disability. The affected male patients exhibited severe intellectual disability, short status, and facial dysmorphism. The one with c.3392_3393delAG additionally had epilepsy and autistic spectrum disorder (ASD). Transiently transfected mutant KDM5C constructs both reduced protein expression and stability and decreased histone demethylase activities in cells. Reviewing the available literature, we found that the associated ASD tended to occur in patients with mutations near the C-terminus of KDM5C.

Conclusions

We report the clinical, molecular genetic, and pathological features in patients with novel mutations of KDM5C. The variability of the clinical phenotype in addition to an intellectual disability may associate with altered particular parts of KDM5C.

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PB-06

De novo Deletion Variants in the *IRF2BPL* is Associated with Developmental Epileptic Encephalopathy

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ABSTRACT

The cause of neurodevelopmental disorders (ND) can vary and can include multifactorial causes, prenatal exposures, maternal disease, and single genes. Epilepsy and severe intellectual disability (ID) are frequent comorbid conditions, with epilepsy affecting more than half of individuals with severe ID. Developmental and epileptic encephalopathy (DEE) defines a group of conditions characterized by the cooccurrence of epilepsy and ID, typically with developmental plateau or regression associated with frequent epileptiform activity. In a recent study, 42% of ND cases have *de novo* mutation in their coding region of genes. The phenotypic and genomic heterogeneity of ND, ID, and DEE can pose a diagnostic challenge.

Herein we reported a 1.5-year old boy who was the first child of healthy nonconsanguineous Taiwanese parents. He could not sit and no speech development. Neurologic examination revealed poor neck controlled, dystonia, and choreoathetosis. Seizures were noted at 12-month-old. MRI of brain showed periventricular leudodystrophy of the white matter in the bilateral occipital lobes, bilateral corona radiate and centrum semiovale. The DNA was extracted from patient's peripheral blood and subjected to whole exome sequencing. A 82-bp deletion was found in his *IRF2BPL* gene (c.224_305del, p.Pro75Argfs49X) and confirmed by Sanger sequencing. This mutation occurred *de novo* which was not found in his parents and absent in the ExAC, geomAD, and Taiwan Biobank databases.

The *IRF2BPL* is an intronless gene and encodes a protein that is expressed in many organs, including the central nervous system. Animal study reveals that the *IRF2BPL* gene is involved in both neurologic development and neuronal maintenance. Heterozygous mutation in the *IRF2BPL* gene has been considered to cause neurodevelopmental disorder with regression, abnormal movements, loss of speech, and seizures (NEDAMSS). Our patient's diagnosis was compatible with the NEDAMSS and extend the genotype spectrum of this gene analysis.

PB-07

Use of Quinidine in Two Siblings with KCNT1-related Epilepsy

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ABSTRACT

OBJECTIVE: To show the occurrence of KCNT1-related epilepsy with the same mutation and similar clinical manifestations in 2 siblings of a family and the need of early diagnosis of genetic epilepsy with early use of quinidine and its efficacy in KCNT1-related epilepsy.

METHODS: The medical records and electroencephalograms and epilepsy gene panel results of these two siblings were checked.

RESULTS: The elder brother has laryngomalacia, hypotonia, psychomotor retardation and progressive seizures since 6 months old while the younger sibling has even earlier seizure onset since neonatal period with similar clinical manifestations. They have been given vigabatrin, carbamazepam, clobazam, phenobarbital and levetiracetam and even ketogenic diet and their seizure frequency was >10 times/day. Their EEG exam both showed multifocal epileptiform discharges. We used the gene panel for refractory epilepsies and found them to have the same KCNT1 mutation (c.2719A>G; p.Thr907Ala). After adding quinidine, their seizure frequency and duration markedly decreased but they were left severely psychomotor retarded.

CONCLUSIONS: Though KCNT1-related epilepsy is inherited in an autosomal dominant manner, it is not reported to have a family with two siblings with the same genetic mutation and similar clinical manifestations. The use of quinidine is effective in stopping their seizures and its possible earlier use might result in a better neurodevelopmental outcome due to reduction of seizure frequency and duration. This shows the importance to early inform parents about genetic tests in patients with refractory epilepsies for a better treatment plan and outcome.

PB-08

Whole Exome Sequencing Identifies Novel Homozygous Mutation of ERCC6 Gene in a Taiwanese Boy: A Case Report And Literature Review

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ABSTRACT

Cockayne syndrome (CS), rare autosomal recessive disorder, is characterized by progressive growth failure, neurologic abnormality, and premature pathological aging. Mutations of the ERCC6 and ERCC8 genes can cause of Cockayne syndrome A and Cockayne syndrome B. The ERCC6 gene mutation is present in approximately 65% to 75% in all CS cases. We described a Taiwanese boy with Cockayne syndrome with homozygous missense mutation c.1607T>G (p.Leu536Trp) in ERCC6 gene which has not been reported yet. In addition, the patients' father and mother carried a heterozygous allele at the same location of the ERCC6 gene, which was confirmed by Sanger DNA sequencing. This missense mutation is located in the highly conserved motif I of ATPase domain. This region provides energy for its association with chromatin, is very important in biologic function. Notably, mutations in this domain, especially motif I and II, respectively, can completely inactivate the ATPase activity of CSB. While this missense mutation is now characterized as "likely pathogenic" via ACMG classification. We believed that this case of CS with homozygous mutation c.1607T>G (p.Leu536Trp) in ERCC6 gene can enrich the genetic database of this disease and provide more evidence to prove the pathogenicity of this missense mutation in Cockayne syndrome B.

PB-09

Ultrarare Genetic cause to a Wide Spectrum of Genetic Disorders Causing Severe Childhood Epilepsy

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ABSTRACT

Background: Pediatric epileptic encephalopathy or severe neurological disorders comprise a group of heterogenous diseases. We used whole-exome sequencing (WES) to identify genetic defects in pediatric patients. **Methods:** Patients with refractory seizures using ≥2 antiepileptic drugs (AEDs); receiving one AED and having neurodevelopmental regression; or having severe neurological or neuromuscular disorders with unidentified causes were enrolled. Fifty-four patients fulfilling the inclusion criteria were enrolled and underwent WES. **Results:** Genetic diagnoses were confirmed in 24 patients. In the seizure group, *KCNQ2, SCN1A, TBCID 24, GRIN1, IRF2BPL, MECP2, OSGEP, P*ACS1, *PIGA, PPP1CB, SMARCA4, SUOX,* SZT2, *UBE3A,* 16p13.11 microdeletion, [4p16.3p16.1(68,345–7,739,782)X1, 17q25.1q25.3(73,608,322–81,041,938)X3], and *LAMA2* were identified. In the nonseizure group, *SCN2A, SPTBN2, DMD*, and *FBN1* were identified. Ten novel mutations were identified. The recurrent genes included *SCN1A, KCNQ2,* and *TBCID24.* Male pediatric patients had a significantly higher [57% vs. 29%; $p < 0.05$, odds ratio = 3.18] yield than their female counterparts. Seventeen genes were identified from the seizure groups, of which 82% were rare genetic etiologies for childhood seizure and did not appear recurrently in the case series. **Conclusions:** Wide genetic variation was identified for severe childhood seizures by WES. WES had a high yield, particularly in male infantile patients.

PB-10

Maternal Inheritance of Deletion of Chromosome 18 q21.3

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ABSTRACT

The 18q deletion syndrome is a rare chromosomal disorder. The phenotype is highly variable but is characterized by central nervous system abnormalities, head and neck dysmorphisms, cardiac anomalies, bone deformities, and cognitive and immune impairment. On chromosome structure analysis, the most common breakpoint of the long arm of the chromosome 18 is at q21.3, and most cases are paternally inherited. However, case reports regarding the specific 18q21.3 deletion are quite few. We report the clinical manifestations in a case of a male infant with 18q21.3 deletion, wherein his and his mother's cytogenetic findings showed a terminal deletion of the long arm of chromosome 18, whereas his father's karyotype was normal. Whole-blood chromosome analysis revealed significant information that narrowed down a possible diagnosis, and genetic information from the parents' karyotypes shed light on the inheritance pattern of the disease.

Key words: 18q deletion syndrome, paternal and maternal inheritance

PB-11

A Neurodevelopemental Degenerative Female with Refractory Epilepsy Caused by MECP2 Duplication Syndrome

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Background

MECP2 duplication syndrome is a rare genetic neurodevelopmental disorder characterized by a wide variety of symptoms including hypotonia, intellectual disability, developmental delays, recurrent respiratory infections, and intractable seizures. MECP2 duplication syndrome mostly inherits in an X-linked manner and affects predominantly males, which is caused by the duplication of genetic material on a specific region on the X chromosome (Xq28). Here we present a female case of MECP2 duplication syndrome.

Methods

Review of clinical data, pathology and image report.

Results

A 13-year-old female had microcephalus and psychomotor developmental delay. Her newborn screening, organic, fatty and amino acid survey were all negative. She had variable seizure patterns since four years old. The seizure patterns included: 1) internal strabismus followed by hand automatism, 2) blinking, 3) smiling, crying and flushing with shortness of breath. The neurological examination showed progressive spasticity with walking disability after 10 years old. The EEG showed diffuse epileptiform activities mainly, and rare localized foci over right centro-middle temporal and left frontoparietal-middle temporal areas with diffuse cortical dysfunction. The brain MRA presented generalized hypoplasia of brainstem and cerebellum with enlarged 4th ventricle, vermian hypoplasia and a huge cyst occupying lower half of posterior fossa with communication with 4th ventricle, favoring Dandy-Walker variant. The HD array gene study revealed MECP2 (methyl-CpG binding protein 2) duplication. At the same time, she received anti-epileptic drugs and ketogenic diet for seizure control. PEG was performed due to swallowing difficulties and recurrent aspiration.

Conclusions

We reported a rare female case of MECP2 duplication experienced more severe clinical course than Rett syndrome. The MECP2 duplication usually shows poor prognosis. Approximately half of affected people pass away before age 25 years.

PB-12

Dravet-like Syndrome with PCDH19 Mutation in Taiwan— A Multicenter Study

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Objective: PCDH19 epilepsy is a rare epilepsy syndrome with early onset seizures, cognitive and sensory delays, and behavioral problems, which was first described in 1971, although without known genetic cause at that time as epilepsy and mental retardation limited to females (EFMR). It is caused by a change or mutation of the PCDH19 gene found on the X chromosome. A recent study has demonstrated that 16% of SCN1A-negative patients with Dravet-like phenotype have a mutation in PCDH19, the gene encoding protocadherin-19. The aim of this case series was to characterize the phenotype of epileptic patients with PCDH19 mutations, and analysis antiseizure medications and brain images on those patients in Taiwan.

Methods: From July 2017 to December 2020, medical records of 15 patients with epilepsy due to PCDH19 mutation were retrospectively reviewed for clinical profiles, antiseizure medications and brain imaging findings from a multicenter cooperation in Taiwan.

Results: Twelve female patients were enrolled, aged 3 to 23 years. Seizure onset was at 6-month-old to 2-year-7-month-old with generalized tonic-clonic seizures or dialeptic seizures. 10 (66.7%) patients presented febrile seizure for the first attack and 2 (13.3%) with hemiclonic seizure. 13 of patients are fever sensitivity but lack of photosensitivity, and seizure frequency trends in clusters as opposed to single longer seizures. Eleven (73.3%) displayed varying degrees of intellectual disability but 4 had no impairment. 3 patients (20%) had abnormal brain images including mesial temporal sclerosis, subcortical and periventricular white matter lesion. On average, the patients received 4 different antiseizure medications (range 3–6). 9 patients received levetiracetam to control seizure currently and 6 patients use phenobarbital.
8 patients became seizure free at least 6 months before the last visit. Four 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 20% patients with abnormal brain MRI findings in our study, which is compatible with the role of protocadherin 19 during brain development and PCDH19 mutations leading to brain structural malformations.

PB-13

A Case with NADPHX Dehydratase (NAXD) Deficiency: A Newly Defined Mutation in a Novel Neurodegenerative Disorder

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Nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) are required redox equivalents for essential biochemical reactions. Their hydrated forms named NADHX and NADPHX are inhibitors of several dehydrogenases and cause harmful side-products(1). NADPHX dehydratase (NAXD) and NADPHX epimerase (NAXE) create nicotinamide repair system together, which eliminates accumulating side-products to prevent toxic environment(2). Just a few cases with NAXD deficiency have been described(3). Here, we report an infant presenting with NAXD deficiency.

A 7-month-old boy was admitted due to myoclonic seizures, impaired consciousness and rapid loss of head control. There was no previous history of infection or fever. He was born to healthy parents, first-degree cousins. His birth and postnatal development history were unremarkable, but one of his siblings regressed after a febrile seizure and died at 7 months. Upon admission, he had lethargy, axial hypotonia. Skin lesions and organomegaly were not noted. Basal metabolic tests were within normal limits except serum and CSF lactate levels, which were mildly elevated. Electroencephalography revealed epileptic activity originating from the posterior regions and abnormal background activity. Cranial MRI showed global cerebral atrophy and corpus callosum hypoplasia. Mitochondrial cocktail was added to the antiepileptic treatment with suspicion of mitochondrial disease. Whole exome sequencing showed a novel homozygous mutation (c.247G> A) in the NAXD gene. His parents were found to carry this mutation heterozygously. His seizures stopped within a few weeks. However, his neuromotor development had stopped completely and he died at the age of 18 months.

The prominent features in NAXD deficiency were progressive neurological detoriation after fever, cardiomyopathy, skin lesions, and premature death(3). Unlike the cases reported in the literature, our patient had neither preceding fever nor skin lesion during follow-up. It appears that the cases show phenotypic diversity. There is a need for further functional studies about this novel disease.

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PB-14

A case of *FBXL4*-related mitochondrial disease presenting with a mild phenotype

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ABSTRACT

Introduction: F-box and leucine-rich repeat protein 4 (*FBXL4*) plays an important role in maintaining mitochondrial DNA function. It has been reported to be the causative gene of mitochondrial DNA depletion syndrome-13 (MTDPS13). MTDPS13 is characterized by lactic acidosis, severe neurodevelopmental delay, hypotonia, and fatal encephalopathy. Herein, we report a rare case of non-progressive *FBXL4*-related MTDPS13 with laryngomalacia, hearing loss, neurodevelopmental delay, hyperlactacidemia, and abnormal brain MRI findings.

Case: A 4-month-old boy was admitted to the hospital for wheezing and severe respiratory distress. He was born at 37 weeks' gestation, weighing 2560 g, and was found to have hearing loss during newborn screening. A bronchoscopic examination revealed laryngomalacia, and auditory brainstem response showed severe sensorineural hearing loss. There was no apparent external malformation, cardiac function was normal, and chromosome karyotype was 46 and XY. Brain MRI showed extensive atrophy of the cerebrum and strong diffusion restriction in the optic radiation and central tegmental tract. In addition, the elevation of lactate and pyruvate in blood and cerebrospinal fluid (cerebrospinal fluid lactate 45.5 mg/dL, pyruvate 2.07 mg/dL, L/P ratio 22.0) was observed. Subsequently, the whole exome sequencing identified compound heterozygous mutations in *FBXL4* gene (NM_001278716.1:c.616C > T [p.Arg206*]; NM_001278716.1:c.647A > G [p.Tyr216 Cys]). At 3 years old, his MRI abnormalities, respiratory impairment, and hearing loss improved, allowing him to be weaned from the ventilator and hearing aid. At 4 years old, he was able to walk with support. He is now 5 years old, and although his speech is limited, he can communicate with others.

Discussion: Previous studies on MTDPS13 have shown a progressive course of ataxia, developmental delay, hypotonia, encephalopathy, and lactic acidosis, with a poor neurological prognosis. Contrary to most of the reported cases, this is not a mutation in the Leucine-rich repeats domain. This may have contributed to the difference in the severity of the disease.

PB-15

The Time-Course Changes of Electroencephalogram Findings in a Girl with a Nonsense Variant in *SMC1A*

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[Introduction] Pathogenic variants in *SMC1A* located on chr.Xp11.2, are known to cause infantile-onset epilepsy and severe intellectual disability in girls. Several studies reported the correlation between *SMC1A* truncating variants and seizures clustering, but characteristic electroencephalogram (EEG) patterns have been largely unknown. [Case presentation] The patient was an 11-year-old girl. She exhibited severe intellectual disability and global developmental delay from her infancy. She developed epilepsy at the age of 4 months. Her seizures were comprised of generalized tonic-clonic seizures that occurred in cluster, often progressed to status epilepticus, and were refractory to antiepileptic medications. Typical clinical features of Cornelia de Lange syndrome were not observed except for short stature. Brain MRI revealed mild cerebral atrophy, thinning of the corpus callosum, and an infratentorial arachnoid cyst. Her interictal EEG at the age of 2 years showed occasional high-voltage slow waves on left frontotemporal region in awake state, whereas epileptiform discharges were scarce. Subsequently, EEG findings changed as follows; at the age of 5 years, sharp waves appeared in bilateral frontal region; at the age of 9 years, continuous 1.5Hz delta activities were observed in bilateral temporal region; at the age of 11 years, bilateral-synchronous, continuous spike-and-wave discharges appeared in bilateral temporal region. Despite the deterioration of her EEG, from the age of 9 years, she did not develop seizure clustering. Whole genome sequencing revealed a *de novo* known nonsense variant in *SMC1A* (c.2923C>T, p.R975*). [Discussion] To our knowledge, the course of EEG findings of patients with *SMC1A* truncating variant has not been reported. Our case presented interictal EEG of early phase were mild considering frequent seizure clustering and status epilepticus. It was also noteworthy that her EEG findings gradually deteriorated over time, which was discrepant to the amelioration of seizures clustering.

PB-16

The Phenotype of Seizure in Ring Chromosome 13: A case report

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ABSTRACT

INTRODUCTION: Ring chromosome 13 (r (13)) is a rare cytogenetic disorder and is relatively uncommon, with an estimated incidence of 1/58,000 in live birth. The most consisted findings of individuals with r (13) are, intellectual disability ranging from moderate to severe, marked short stature and small for gestational age, frequently associated with neural tube, brain and heart defects, microcephaly, genital malformations and dysmorphic features. The hearing and speech delay in a relatively common birth defect. Although little is known about its epilepsy. The report of epilepsy complicated with r (13) is only 4 cases, and detailed seizures are not listed. We present here the description of seizure of a 7-year-old girl with r (13).

CASE: She was the first child to healthy and unrelated parents. She was born at 39 weeks of gestation by vaginal delivery with birth weight of 1,964 g (−3.1 SD); length 46.0 cm (−1.6 SD); head circumference 30.0 cm (−2.4 SD). The face showed dysmorphic features including a microcephaly, hypertelorism, upslanting palpebral fissures, broad nasal root, and short philtrum. The milestones were delayed, with head control by 1yr and sitting independently by 2 yr. Cytogenic analysis showed 46 chromosomes including a small ring chromosome 13. The karyotype was 46, XY, r (13)(p11.2q33.2). Additional imaging studies showed normal kidneys, normal heart, and eyes. She presented with her first episode of afebrile seizure at 3 years of age. Clonic seizure of the patient's right hand, followed by loss of consciousness. The seizure activity had persisted for 10 min. EEG and MRI were normal at that time. She experienced tonic seizure with high fever at 4 year of age. EEG was normal at 5 years old. She is now 7 years old and has acquired standing up with support and reply with a single sound. She has been seizure free without antiepileptic drugs since 4 years old.

DISCUSSION: The karyotype of 4 reported cases with epilepsy were r (13) (p11q34) (3 cases) and r(13)(p12q33) . It is supposed that epilepsy in r (13) seemed to depend on the location of the deleted segment.

PC-01

Diffuse Cutaneous Mastocytosis of an Infant with Refractory Epilepsy: A Case Report

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ABSTRACT

Mastocytosis is characterized by an excessive number of apparently normal mast cells in the skin. However, systemic mastocytosis is rare.

We reported one pediatric case with mastocytosis and central nervous system involvement. Now he is 6 years of age, and he was born to a healthy mother of Gravida 3 Para 3 (G3P3), 34 weeks of gestational age via normal spontaneous delivery and the birth body weight was 2100 gm. No perinatal insult was noted. No specific family history was disclosed. Since birth, many well-defined brown to black flat skin papule was noted over whole body. First seizure was noted at 5 months of age and consisted of brief eye staring and unresponsiveness. He was referred to our hospital due to seizure control, persisted hypotonia, regression of speech, and just can obey simple orders when he was 3 years of age. Phenobarbital and topiramate were used for seizure control. Typical urticaria pigmentosa was presented and the lesion becomes swelling and redness when scratching the papule. Electroencephalography showed diffuse cortical dysfunction, abundant multifocal spikes and electroencephalographic seizure. Magnetic resonance image showed marked decreased of white matter, ventricular dilatation with irregular border, and several high T2-weighted signal patch over periventricular white matter. Systemic mastocytosis with central nervous system involved was suspected. Skin biopsy confirmed the diagnosis of mastocytosis. Since then, prescription drug included antihistamine and anti inflammation medication. Gradually, the condition showed improving including less seizure, more increased muscle strength leading to walk independently, and improving cognition. Following up MRI showed no interval change of decreased white mater but mild progression of small high T2-weighted lesion one year later, which might be indicative of the progression of disease.

In conclusion, we report a rare case of mastocytosis with central nervous system involved. Our case showed progressive course of disease with developmental delay, generalized hypotonia, and multifocal epilepsy. Antihistamine and anti-inflammation drugs showed good response to our patient. It is important to recognize the disease for further aggressive treatment to get a better prognosis.

PC-02

Case Report: Arterial Spin Labeling Might be Useful to Predict Mild Encephalopathy Associated with Excitotoxicity

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Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is the most frequent pediatric acute encephalopathy in Japan. AESD typically shows biphasic seizures, a prolonged febrile seizure on day 1, followed by partial seizures on day 4 to 6, and radiologically reveals delayed reduced diffusion in subcortical area, the so-called 'bright tree appearance (BTA)' on day 3 to 9. In the acute stage (within 24 hours) of AESD, arterial spin labeling (ASL) showed decreased cerebral blood flow in the frontal region, increased cerebral blood flow when BTA appeared, suggesting that ASL may be useful for early diagnosis of AESD. In addition, proton MR spectroscopy (MRS) has been reported that glutamate (Glu) is elevated from 1 to 4 days in AESD and is replaced by glutamine (Gln) elevation from 4 to 12 days. These findings support the theory that delayed cell death due to excitotoxicity is the pathogenesis of AESD, and indicate that the astroglial cells convert excess Glu, an excitatory neurotransmitter, to Gln. Mild encephalopathy associated with excitotoxicity (MEEX) has been described as a group of mild encephalopathy with transient elevation of Gln in MRS as well as in AESD, but without clinical biphasic course and no abnormalities including BTA in MRI images. The usefulness of ASL for AESD has been reported, but not confirmed in patients with MEEX. In this report, we describe our experience with a 4-year-old girl who was diagnosed with MEEX.

The patient was a 4-year-old girl. She was brought to the emergency room with a febrile status epilepticus. Because of the possibility of AESD, a vitamin therapy was administered. The ASL of the brain MRI performed on the second day showed increased blood flow in frontal, temporal, and occipital regions, but spared central sulcus which was reminiscent of central sparing of AESD, so the patient was treated as AESD including pulse steroid therapy and immunoglobulin therapy from the third day. The patient remained unconscious but gradually became conscious on the 7th day without any seizures. Brain MRI performed on the 8th day did not show any findings characteristic of AESD such as BTA. However, Gln elevation was observed in the MRS, and together with the clinical course, it was considered to be MEEX.

In conclusion, ASL may be useful in the early diagnosis of MEEX as well as AESD, which allows us to start early intervention.

PC-03

Midbrain Abnormality in a Patient with Acute Encephalopathy with Biphasic Seizures and Late Reduced Diffusion

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ABSTRACT

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is the most common cause of pediatric encephalopathy in Japan. Typical AESD is characterized by febrile status epilepticus on the first day, followed by a cluster of secondary seizures on day 4-6. In addition to biphasic seizures, the MRI findings which shows a reduced diffusion in the subcortical white matter, or a 'bright tree' appearance is well recognized and required to make the diagnosis of AESD. Furthermore, some reports mention that MRI findings might be useful to predict the severity of AESD. However, midbrain abnormality in patients with AESD has never been reported.

We report the case of a one-year-old boy who was admitted to our hospital due to febrile status epilepticus. After seizure was terminated, he still had mild disturbance of consciousness on day 2-4. A cluster of secondary seizures were developed on the day 4 and EEG showed generalized high voltage slow. Brain MRI was performed on the day 5 and high signals on diffusion-weighted imaging (DWI) were observed in subcortical matter, deep white matter, genu of corpus callosum, tegmentum and tectum mesencephali, and bilateral pulvinar. In the same regions, low signals on apparent diffusion coefficient mapping were also confirmed. We diagnosed him with AESD by clinical course and the findings of brain MRI. The patient was treated by steroid pulse, vitamin, and immunoglobulin. He was intubated and sedated to control seizures from days 5-10. Since he did not react to noise, we performed auditory brainstem response on the day 13 to evaluate the function of midbrain, which showed no abnormalities. Brain MRI on the day 24 showed generalized atrophy in the cerebrum, but no atrophy is seen in midbrain. His neurological symptoms were gradually improved and he was discharged from the hospital on the day 31. He did not show any abnormalities in his eyes and ears, and could walk without support, but showed asymmetric muscle weakness and increased deep tendon reflex at 1 year and 3 months of age, suggesting that his neurological sequelae are mild.

We experienced a case with AESD complicating midbrain abnormality on DWI. He did not show any sequalae related to midbrain lesion, suggesting that midbrain abnormality on DWI might not cause irreversible damage.

PD-01

Leigh Syndrome Presenting with Nonconvulsive Status Epilepticus

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Background: Leigh syndrome is a rare mitochondrial disease, characterized by degeneration of central nervous system. One of the main neurological manifestations is metabolic epilepsy. These epileptic seizures are more frequently of posterior quadrant and occipital lobe onset, more likely to present with non-convulsive status epilepticus which may last months and be more resistant to treatment from the onset. We presented a patient with Leigh syndrome, who presented with non-convulsive status epilepticus.

Methods: A 9-month-old male infant was born to non-consanguineous healthy parents. At 5 months old, the mother noticed that he could not roll over. At 9 months of age, he was hospitalized due to fever for 3 days. Family history disclosed diseases in several maternal relatives. One younger sister of mother has mental retardation. The mother had another two siblings both died at 5 months old with suspicion of mitochondrial disease. Maternal grandmother had two siblings with mental retardation. The father and paternal relatives had no major disease. His body height, weight, and head circumference were within 15^{th} to 50^{th} percentile. Physical examination showed head lag on traction response. General hypotonia and weak deep tendon reflex was observed. On seventh hospital day, he had choking, aspiration pneumonia, and subsequent respiratory failure. Patient was intubated with mechanical ventilator support. Seizure occurred on eleventh hospital day and was controlled by levetiracetam. Three weeks later, seizure episodes increased despite of add-on anticonvulsant treatment.

Results: Electroencephalogram revealed nonconvulsive status epilepticus and intravenous loading with Levetiracetam was prescribed. Brain MRI showed multifocal T2 hyperintensity in basal ganglia, thalamus, peduncles and callosal splenium. MR spectroscopy showed elevated lactate. The lactate was also high in serum and cerebrospinal fluid. Mitochondrial mtDNA sequence showed MT-ATP6 gene c.467T>G mutation. Therefore, Leigh syndrome was diagnosed

Conclusion: There are no specific curative treatments for mitochondrial epilepsy. Generally, the epileptic seizures should be managed by specialist neurologist with appropriate use of anticonvulsants. Early recognition and diagnosis of Leigh syndrome may help to communicate about the prognosis. Genetic counseling is very important, especially when the family want to have another baby.

PD-02

Severe Isolated Sulfite Oxidase Deficiency with Refractory Neonatal Seizures Mimicking Neonatal Hypoxic-Ischaemic Encephalopathy: Clinical and Biochemical Clues Aid Diagnosis

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Introduction: Isolated sulfite oxidase deficiency (ISOD) is a rare devastating, autosomal recessive neurometabolic disorder caused by mutations in the *SUOX* gene, which is important for catabolic pathway for sulphur containing amino acids. Patients present in the neonatal period with seizures refractory to anticonvulsants, abnormal muscle tone, abnormal movements and marked developmental delay and prognosis is extremely guarded. Clinical and radiological features mimic hypoxic-ischemic encephalopathy. We present a case of refractory neonatal seizures and progressive encephalopathy with neuroradiological features mimicking hypoxic-ischaemic encephalopathy.

Case: A term male infant was born by emergency caesarean section. APGAR scores were 9 at both 1 min and 5 min of life. Birth weight was 3.855 kg, head circumference was 37 cm and length was 54cm. He presented on day 1 of life with poor feeding, myoclonic jerks and cycling movements. Neurology examination was grossly abnormal with clinical dysmorphism - low set ears, flat nasal bridge, flat philtrum, bilateral 5th clinodactyly, left simian crease. Clinical & electrographic seizures were confirmed on CFM and EEG and required treatment with phenobarbitone, levetiracetam, topiramate, pyridoxine and midazolam infusion. MRI brain demonstrated diffuse restricted effusion along the cortices of bilateral cerebral and cerebellar hemispheres, appearing more subcortical in frontal lobes, likely involving the subcortical white matter.

There was no history of fetal distress or perinatal difficulties. Diagnostic work-up therefore encompassed differential diagnoses of inborn error of metabolism and hypoxic-ischemic-encephalopathy. Serum homocysteine level was very low and uric acid was low. Amino acid profile revealed low cysteine and elevated sulfo-cysteine level. In view of 1.) neonatal seizures without a clear hypoxic-ischaemic event, 2.) biochemical findings of very low homocysteine, low cysteine level and elevated sulfo-cysteine level and 3.) global grey matter swelling on MRI, clinical suspicion was for sulfite oxidase deficiency or molybdenum cofactor deficiency. Low uric acid was supportive of sulfite oxidase deficiency, DNA testing for sulfite oxidase deficiency was performed and dietary protein was restricted. The patient deteriorated with bradycardia, desaturation and hypotension despite inotropic support .In view of poor prognosis parents decide to withdraw care and eventually passed away. The gene test result later confirmed the diagnosis of isolated sulfite oxidase deficiency.

Discussion: Isolated sulfite oxidase deficiency (ISOD) is a life-threatening disease characterized by severe neurological impairment mimicking profound hypoxic ischemic encephalopathy clinically and radiologically. The absence of hypoxic-ischaemic events should raise suspicion of ISOD. Homocysteine and uric acid are useful in screening for ISOD or Molybdenum cofactor deficiency in such patients before genetic results become available.

PD-03

A Case of Late-Onset Pyridoxine-Dependent Epilepsy Detected by Urine Metabolomics

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Introduction: Pyridoxine-dependent epilepsy (PDE) typically presents during the neonatal period. PDE is refractory to conventional antiepileptic drugs but responds to vitamin B6 (VB6). We describe the case of a patient with epilepsy who mainly has seizures with consciousness impairment that started at 2 years of age, and PDE was diagnosed using urine metabolomics at 9 years of age.

Case Report: A 9-year-old girl had no abnormalities in her perinatal or developmental history. At 2 years of age, she had generalized convulsions with fever and left hemiconvulsive status epilepticus lasting for 1 hour while taking theophylline. Electroencephalogram (EEG) showed multifocal epileptic discharges. At 3 years and 2 months of age, the patient had a seizure with discomfort and impairment of consciousness, and valproic acid was initiated. She was admitted to Okayama University Hospital after lamotrigine was added without effect. Long-term video-EEG monitoring showed generalized 3–4 Hz spike-wave discharges with right frontal leading lasting approximately 10 seconds several dozen times a day. Some of these discharges were accompanied by impaired consciousness and resembled absence seizures. There were no abnormalities in brain magnetic resonance imaging or blood and cerebrospinal fluid test results. The Wechsler Intelligence Scale for Children-IV showed a full-scale intelligence quotient of 95. Urine metabolomics revealed an increase of 6-oxopipecolic acid, which was not detected in healthy subjects, and high serum alpha-aminoadipic semialdehyde, which led to the diagnosis of PDE. After oral pyridoxal 5'-phosphate administration (300 mg/day), the clinical seizures disappeared and the epileptic discharges were markedly reduced on EEG. Genetics testing revealed a c.1016A>G (p.H339R) homozygous mutation in the ALDH7A1 gene (NM00182.5). **Conclusion**: For refractory epilepsy of unknown etiology, it is necessary to perform metabolic screening such as urine metabolomics regardless of the age of onset to avoid overlooking treatable diseases such as PDE.

PD-04

The Effect of Dietary Protein Restriction in a Case of Molybdenum Cofactor Deficiency

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ABSTRACT

Molybdenum cofactor deficiency (MoCD) is an autosomal recessive inborn error of metabolism that results from mutations in genes involved in molybdenum cofactor (Moco) biosynthesis. MoCD is characterized clinically by intractable seizures and severe, rapidly progressing neurodegeneration leading to death in early childhood in the majority of known cases. We report on a patient with an unusual late disease onset and mild phenotype, characterized by delayed development and a decline triggered by a febrile illness and a subsequent dystonic movement disorder. Magnetic resonance imaging showed abnormal signal intensities of the bilateral basal ganglia. Blood and urine chemistry tests demonstrated remarkably low serum and urinary uric acid levels. A urine sulfite test was positive. Specific diagnostic workup showed elevated levels of xanthine and hypoxanthine in serum with increased urinary sulfocysteine (SSC) levels. Genetic analysis revealed a homozygous missense mutation at c.1510C>T (p.504R>W) in exon 10 of the *MOCS1* in isoform 7 (rs1387934803). At age 1 year 4 months, the patient was placed on a low protein diet to reduce cysteine load and accumulation of sulfite and SCC in tissues. At 3 months after introduction of protein restriction, the urine sulfite test became negative and the urine SCC level was decreased. After starting the protein restriction diet, dystonic movement improved, and the patient's course progressed without regression and seizures. Electroencephalogram findings were remarkably improved. This finding demonstrates that the dietary protein restriction suppresses disease progression in mild cases of MoCD and suggests the effectiveness of dietary therapy in MoCD.

PE-01

Neonatal Alexander Disease: Case Report and Review of Literature

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Background: Alexander disease (AxD) is a rare progressive leukoencephalopathy, which is an autosomal dominant genetic disease caused by mutation of GFAP gene encoding glial fibrillary acidic protein. Two distinctive types had been proposed according to the age of onset and clinical manifestations: type I (onset age<4 years) , and type II has late onse. Among the statistical data from literature review, neonatal onset AxD has less been reported. Using the next generation sequencing technique, we were able to detect pathogenic mutation in a 1-month-old boy with clinically refractory epilepsy and leukodystrophy.

Summary of case: We report a 1-month-old male neonate, who had his first seizure attack in 26-days-old, presenting with erratic myoclonic jerks and bilateral clonic seizure, accompanied with desaturation and unconsciousness. The EEG revealed generalized and multifocal epileptiform discharges. Brain MRI showed extensive signal changes over both basal ganglia, thalami, frontal, occipital areas areas in T2-weighted sequences, suggesting leukodystrophy. AxD was confirmed by whole exome sequencing, which revealed missense mutation in exon 6 of the GFAP gene, c.1106 T>C, producing a 369 Leu>Pro change in the GFAP protein. The patient's clinical status deteriorated, and bulbar dysfunction involving respiration and swallowing were also found.

Conclusion: AxD is a myelin degenerative disorder presenting with seizures, spastic paresis, progressive psychomotor deficiency and grave clinical consequence. Neonatal onset AxD had manifestation atypical from the majorities of infant or juvenile onset form. Current next generation sequencing technique could provide earlier and detailed information about the etiology of refractory neonatal epilepsy.

PE-02

SCN8A Encephalopathy: Case Report

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Epileptic encephalopathy is a condition resulting from extreme forms of intractable childhood epilepsy. The disease can cause severe delays in cognitive, sensory, and motor function development, in addition to being fatal in some cases. Missense mutations of *SCN8A*, which encodes Nav1.6, one of the main voltage-gated sodium channel subunits in neurons and muscles, have been linked to early infantile SCN8A encephalopathy. Herein, we report the case of a 5-month-old girl with SCN8A encephalopathy with a novel missense mutation. Apart from intractable seizures and autistic phenotypes, the results of blood and biochemical tests, electroencephalogram (EEG) results, and brain magnetic resonance imaging (MRI) results were all normal. As the phenotypes caused by these mutations cannot be identified by any clinical, neuroimaging, or electrophysiological features, genetic sequencing should be considered to identify the underlying genetic causes. Although phenytoin is recommended as a last-resort treatment for SCN8A encephalopathy, the administration of the oxcarbazepine, instead of phenytoin, mitigated this patient's intractable seizures.

PE-03

Premature Maybe the Risk Factor for Subsequent Epilepsy, Autism Spectrum Disorders and Attention Deficit Hyperactivity Disorder in Children with Febrile Seizure

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Background: Febrile seizure (FS) is the most prevalent childhood seizure; it is significantly related to subsequent epilepsy and has possible links to autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). Premature also increases the risks of ASD and ADHD. Therefore, this study investigated whether premature is the risk factor for subsequent epilepsy, ASD, and ADHD in children with FS.

Methods: We retrospectively collected data for children with FS aged < 5years from January 1, 2005, to December 31, 2013. We divided these children into two groups: premature group and full-term group, and compared their incidence rates of epilepsy, ASD, and ADHD.

Results: Data of 426 patients with FS were retrospectively collected. The premature group had 108 patients and the full-term group had 318 patients. The overall epilepsy risk in the premature group was higher than that in the full-term group (odds ratio [OR], 2.52; 95% confidence interval [CI], 0.63–9.97; p = 0.01). The overall risk of ASD in the premature group had 16.9 time as higher than that in the full-term group (95% CI, 4.79–59.7; p = 0.001). In addition, premature group had higher odds of having ADHD (OR, 6.41; 95% CI, 2.13–19.26; p = 0.001) compared with full-term group.

Conclusions: Premature may be the risk factor for subsequent epilepsy, ASD, and ADHD in children with FS

Keywords: Premature; epilepsy; autism spectrum disorder; attention deficit hyperactivity disorder

PE-04

Ketogenic Diet Therapy for Infantile Epilepsy Aged Less Than 2 Years Old

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Background

Infants aged less than 2 years old is the important period for neurodevelopment and the seizure would increase the risk of poor developmental outcome in the long term. However, many antiepileptic drugs (AEDs) have no FDA-proved in this young age group. Studies about ketogenic diet (KD) for controlling seizures in this age group are scanty. This prospective study attempted to disclose the achievability, tolerability, efficacy and safety of KD therapy in infantile epilepsy aged less than 2 years old.

Materials and Method

Children younger than two years old with drug-resistant epilepsy (DRE) were enrolled at Kaohsiung Chang Gung Memorial Hospital from December 2017 to November 2019. Classic ketogenic diet (cKD) was initiated with non-fasting, gradual KD initiation protocol (GRAD-KD) protocol for 5-day of admission. Finger sugar, blood β-hydroxybutyrate (βHB) level, and urine ketone concentration were obtained during admission and at monthly outpatient clinic visit. The correlation between finger sugar, ketone body concentration from blood & urine, and seizure reduction rate were assessed by Spearman's correlation.

Results

Nine patients with mean aged of 9.7 months old were enrolled in this study. The leading epileptic etiologies were genetic defect (3/9, 30%). The most common seizure type was epileptic spasm (5/9, 55%). After 6 months of KD therapy, 44% of the study subjects were responders. Finger sugar showed negatively correlated to blood βHB and urine ketone concentration during 5-day admission at KD initiation, however, it was not correlated to neither blood βHB nor urine ketone concentration at 3 and 6 months of KD therapy. The blood βHB level was not correlated to KD efficacy. There were no symptomatic adverse effects in all of the study subjects.

Conclusion

KD is a safe and effective alternative therapy for treating infantile epilepsy less than 2 years old. Neither blood βHB level nor urine ketone concentration was correlated to KD efficacy in this study. Further exploring another biochemical parameters to predict the KD efficacy in this age group is mandatory.

PE-05

Paroxysmal Kinesigenic Dyskinesia in Clinical Practice

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Paroxysmal kinesigenic Dyskinesia (PKD) is a hyperkinetic movement disorder characterized by episodic involuntary movement attacks triggered by sudden voluntary movement, change in the direction of movement, or startle. It can be misdiagnosed as seizure or other psychogenic disorders and results in delayed diagnosis and in-proper treatment. Here we report our case series experience in recent 2 years.

Totally 4 patients were collected from our out-patient clinic of pediatric neurology. All were female. Their age ranged from 6 to 12 years (mean: 10.3 years). The presenting symptoms were sudden onset of limb dyskinesia in 2 patients, gait apraxia in 2 and standstill in 2, while they tried to walk or move their bodies. No consciousness loss was noted during the episodes. The duration were mostly 5 to 10 seconds. Three patients showed daily attacks and the other occurred weekly. All the EEG recordings showed negative results. Two patients had history of infantile seizures (generalized tonic-clonic type) which were treated well with phenobarbital and discontinued after 2-3 years' medication. The family history showed positive PKD members in 2 cases. All patients were treated with low dose of oxcarbazepine (mean: 9.3mg/kg/d) and the responses were satisfactory. One case had PKD symptom recurrence while lapse of medication. Another case showed true seizure occurrence while tapering her dosage. The duration of the delay in diagnosis ranged from 1-4 years (mean: 2.3years). The gene study revealed positive proline-rich transmembrane protein 2 (PRRT2) mutation in 2, and negative in the others. Interestingly, all two patients with positive PKD family history demonstrated positive PRRT2 gene mutation. The metabolic testing was basically normal.

PKD is a relativity benign disease, yet the symptom can bother the affected children and lead to inadequate treatment. Low-dose sodium channel blockers are effective to control the symptoms and improve the quality of life. PKD should be kept in mind in clinical practice when facing a patient with brief dyskinetic movement disorder without loss of consciousness. The prognosis is usually guarded. Mutations in PRRT2 are commonly implicated in patients with PKD. Though not attributing to seizure disorder, PKD can accompany true seizures in affected patients in the lifetime.

PE-06

Neonatal Seizure in A Late Preterm Infant with Accidental Finding of Periventricular Leukomalacia

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Periventricular leukomalacia (PVL) is defined as white matter injury caused by neonatal hypoxic events with or without brain hemorrhage over periventricular area, and usually occurred in the population of early preterm (gestational age (GA) before 32 weeks) and birth weight below 1500 grams. The most common symptom of PVL is neonatal seizure, in addition, the incidence of PVL should be disproportionate to GA of preterm infants.

However, we present a late preterm female infant delivered at GA 36 4/7 weeks who had history of maternal exposure of aspirin during pregnancy due to Protein S deficiency and this case suffered from neonatal seizure with accidental finding of PVL at age of 1.5 months old.

In summary, previous aspirin exposure during pregnancy may be a plausible etiology of PVL leading to neonatal seizure.

PE-07

Tubulinopathy Presenting as Developmental Epileptic Encephalopathy

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Tubulin proteins play a key role in the cortical development during neuronal proliferation, migration, differentiation and cortical lamination. Mutations in the tubulin genes typically affect patients with complex malformations of cortical, commissural and posterior fossa development and varying degrees of ventriculomegaly. The present report describes two cases of epileptic encephalopathy and malformation of the brain due to tubulinopathy.

Case 1. This 26-year-old boy was born to unrelated healthy parents. He was found to have brain malformation with moderate ventriculomegaly prenatally. Hypotonia was noted at birth. Seizures were noted on the 1st day of life with multifocal discharges on the EEGs, which became intractable to many anticonvulsants later. Brain MRI showed marked dilated ventricles with dysgenesis of corpus callosum, poor configuration of cortical gyri suspected pachy/polymicrogyri. He had other systemic problems including pseudo-obstruction of lower GI (megacolon) and received partial colectomy, colostomy, and gastrostomy at 2 years old. He became a victim of epileptic encephalopathy with severe motor and mental handicap. A de novo mutation in TUBB2B (c.629T > A; p.Ile210Asn) was later proven through next-generation sequencing (NGS).

Case 2. A mature male baby born to unrelated healthy parents began to have myoclonic jerks of arms and legs 4 hours after birth. Several episodes of apnea with cyanosis were also noted. EEG showed focal sharp waves from bilateral central & temporal regions. Brain CT showed lissencephaly, type I, which was also confirmed in the following MRI study. The seizures became refractory to anticonvulsants with phenobarbital, valproic acid and levetiractam, and finally better controlled by lacosamide. He showed motor delay at 4 months of age. A de novo mutation in TUBA1A (c.629A>G; p.Tyr210Cys) was proven at the 6th week of life through NGS.

Tubulinopathies associate with mutations in the α- , β- and γ- tubulin genes, related to the functional area of the protein involved, lead to a complex and wide spectrum of cerebral malformations including lissencephaly, pachy/polymicrogyri, basal ganglia dysmorphisms and commissural anomalies. The clinical features of the tubulinopathies include motor delay, intellectual disabilities, epilepsy, and other deficits, of various severity. Our presenting cases demonstrated the severe form of tubulinopathy due to different tubulin gene mutations. The newly developed NGS technique makes possible the early identification of genetic etiology, clinical and prognostic evaluation.

PE-08

The Mitochondria Related Epilepsy: A Retrospective Study in One Tertiary Center

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ABSTRACT

Mitochondria disorders usually presents with neurodegenerative and multiple organ involvement. Epilepsy is a common presentation. The mitochondria diseases can be defined as mutations related to the proteins involved in mitochondria structure or functions, mutations, deletions or mitochondria depletion syndrome.

We retrospectively collected patients with confirmed mitochondria disorder by genetic method in National Taiwan University Hospital during 2011 to 2021 and to evaluate the clinical diagnosis and features of epilepsy.

RESULTS

Total 57 patients confirmed with mitochondria gene mutations. 22 of them (39%, M: F =5:17) have epilepsy history. 10 cases are MELAS with m.3243 A>G mutations (8/23) and twin patients with m. 10158; COQ4 mutation (4/23), other gene mutation including NARS2, COQ6, POLG (Leigh), m.8344 (MERRF), m.8945, m.9592, m.15401, and FARS2.

Of the 10 MELAS patients, the seizure onset ages are older, ranging from 12-52 years old. The stroke and seizure events as the first presentation in 4/10, others present with WPW syndrome, hearing impairment, DM, retinal disorders, or cognitive decline before the seizure onset. The seizure is drug resistance in 3 patients as disease progression and during follow up, 1 is bedridden and 1 died. The patient diagnosed MERRF disease developing myoclonic seizure at 45 years old and proximal myopathy 3 years later. Multiple lipomas (Medelung's disease) and type 2 DM were also noted.

7 patients had seizure onset before one year old; 4 are COQ4 mutations and 1 is NARS2 mutation (Asparaginyl-tRNA synthetase 2, Mitochondrial) and all are infantile spasms. 1 patient with m.9592 mutation present with generalized tonic seizure, 1 FARS2 gene (Phenylalanyl-tRNA synthetase 2, mitochondrial) mutation.

CONCLUSION

Those gene mutations involved in mitochondria respiratory enzymes synthesis or respiratory trains oxidation (COQ4) are prone to have seizure at early ages and many are infantile spasms. For those with MELAS and MERRF, seizure onsets are at older ages. The seizure may develop after other symptoms, as WPW syndrome and hearing loss are mostly encountered. MRI are usually had abnormal signal changes when first seizure.

PE-09

Genetic Factors and the Risk of Drug-resistant Epilepsy in Young Children with Epilepsy and Neurodevelopment Disability: A Prospective Study and Updated Meta-Analysis

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Background: Drug-resistant epilepsy (DRE) affects 7%–20% of children with epilepsy. Although some risk factors for DRE have been identified, the results have not been consistent. Moreover, data regarding the risk factors for epilepsy and its seizure outcome in the first 2 years of life are limited.

Methods: We analyzed data for children aged 0–2 years with epilepsy andneurodevelopmental disability (NDD) from January, 2013, through December, 2017. These patients were followed up to compare the risk of DRE in patients with genetic defect (genetic group) with that without genetic defect (nongenetic group) . Additionally, we conducted a meta-analysis to identify the pooled prevalence of genetic factors in children with DRE

Results: A total of 96 patients were enrolled. A total of 68 patients were enrolled in the nongenetic group, whereas 28 patients were enrolled in the genetic group. The overall DRE risk in the genetic group was 6.5 times (95% confidence interval [CI], 2.15–19.6; p = 0.03) higher than that in the nongenetic group. Separately, a total of 1308 DRE patients were participated in the meta-analysis. The pooled prevalence of these patients with genetic factors was 22.8% (95% CI 17.4–29.3)

Conclusions: The genetic defect plays a crucial role in the development of DRE in younger children with epilepsy and NDD. The results can serve as a reference for further studies of epilepsy panel design and may also assist in the development of improved treatments and prevention strategies for DRE.

PE-11

The Etiology and Genetic Related Causes of Seizure in Term Newborn

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Background: Neonatal seizures are common in the newborn period and can be associated with significant morbidity and mortality. Because of the neonatal brain is relatively easy to develop seizure and there are different etiologies of neonatal seizures varying in medical center.

Objective: The aim of this study is to describe the etiologies and clinical features of neonatal seizures in King Chulalongkorn Memorial hospital

Methods: Full-term neonates who developed seizure within 4 weeks of life, admitted to King Chulalongkorn memorial hospital from January 2015 till December 2019 were enrolled and retrospectively reviewed their medical records.

Results: 66 neonates with seizure, of which 41 (62.10%) were referred from primary care hospitals. 39 cases (59.0%) were male. The frequencies of etiologies of neonatal seizures were classified into 8 categories: hypoxic-ischemic encephalopathy (HIE) (*n* = 18; 27.27%), transient metabolic or electrolyte imbalances (*n* = 11; 16.67%), cerebrovascular events including neonatal ischemic stroke and intracranial hemorrhage (*n* = 9; 13.64%), genetic epilepsy (*n* = 8; 12.12%), inborn errors of metabolism (IBEM) (*n* = 6; 9.10%), central nervous system infection and developmental brain malformation were equally (*n* = 5; 7.57%) and unknown etiology (n = 4; 4.54%). The most common seizure semiology was subtle seizure (32.05%). Subtle, focal clonic or generalized tonic seizures are predominantly seen in the patients with acute symptomatic seizures. On the other hands, the patients with IEM and genetic epilepsy had more frequent presentations with multifocal clonic seizures and myoclonic seizure semiologies.

Conclusion: Even though the common etiologies of neonatal seizures are HIE and transient metabolic or electrolyte disturbances. A genetically proven etiologies diagnosis by next generation sequencing (NGS) should be considered in especially case of epileptic encephalopathy and difficult controlled seizure.

PE-12

Atypical presentation of Pyridoxine-Dependent Epilepsy in a Child

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ABSTRACT

Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive epileptic condition that is characterized by resistance to standard anticonvulsive therapy and is responsive to pyridoxine therapy. Classic PDE presents early in neonatal period with refractory epileptic encephalopathy while atypical PDE may present with late-onset seizures that may respond initially to anticonvulsants then become intractable. We present an atypical presentation of PDE in a 4-year-old child diagnosed through genetic testing which showed inheritance of pathogenic variants in ALDH7A1. This case demonstrates the utility of gene panel testing in the diagnosis of PDE and a reminder to consider atypical presentations of pyridoxine-dependent epilepsy.

PE-13

A Hospital-Based Comparative Study on Serum Perampanel Concentrations Between Children and Adults with Epilepsy

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Background: Perampanel (PER) is a novel antiepileptic drug that functions as a selective, non-competitive AMPA receptor antagonist and is mainly metabolized by CYP3A4. Enzyme-inducing antiepileptic drugs (EIAED) taken concomitantly with PER influence serum PER concentrations. Although there are few reports on PER pharmacokinetics in children, the current package insert indicates the same daily dose of PER for children and adults.

Methods: A total of 228 steady-state PER concentrations were obtained from 83 patients (4-37 years old) who received PER between 2016 and 2021. We compared PER doses, serum concentrations, and concentration to dose (CD) ratios between children (< 16 years old, 90 samples) and adult (138 samples) groups. In this study, the CD ratio was defined as the concentration divided by daily dose (mg/day) instead of the concentration divided by dose per body weight (mg/kg/day).

Results: In both children and adult groups, serum PER concentrations were positively correlated with the PER dose. In addition, patients who took EIAED had lower CD ratios than those who did not. In patients overall and who did not take EIAED, a significantly (overall; $p=0.045$, without EIAED; $p=0.003$) higher mean CD ratio was observed in children than in adults. Although not significant, children taking EIAED also had higher CD ratios than adults taking EIAED. Seizure control was achieved in 9 adults. The responders were widely distributed across PER concentrations (70-1390 ng/ml). Side effects, such as irritability and somnolence, developed in 53 patients (20 children) at PER levels between 20 and 3280 ng/ml.

Conclusions: Children had higher CD ratios than adults, suggesting that the same PER dose in adults produces a high concentration in children. The pediatric PER dose should be reconsidered.

PE-14

Epileptic Focus Estimation in Children with Tuberous Sclerosis Complex Using EEG-fMRI Combined with FDG-PET

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Background and Objective: In patients with tuberous sclerosis complex (TSC), epileptic focus estimation is difficult because of multiple cortical tubers, all of which may have epileptogenicity. This difficulty is related to poor seizure prognosis after epilepsy surgery. The aim of this study is to improve the accuracy of epileptic focus estimation using EEG-fMRI combined with FDG-PET.

Methods: Three children underwent EEG-fMRI scans. One child underwent EEG-fMRI scans twice, at the onset of West syndrome (WS) and for focal epilepsy, the other one only at the onset of WS, and the last one only for focal epilepsy. The acquired data from these four scans were analyzed using event-related design. Intermittent hypsarrhythmia bursts during sleep were regarded as events with duration at the onset of WS, and the onsets of epileptiform discharges were regarded as events in focal epilepsy. The results were compared with FDG-PET, which were scanned close to EEG-fMRI scans.

Results: On FDG-PET, all 4 scans showed multiple hypometabolic areas which corresponded to cortical tubers. For EEG-fMRI, both children at the onset of WS showed positive BOLD responses (P-BOLDs) which were located on multiple neocortices as well as in the brainstem, hippocampus, and thalamus. In one child, P-BOLDs of almost equivalent *t*-values were located beside the three cortical tubers. In another child, P-BOLDs did not correspond to cortical tubers. In both children with focal epilepsy, P-BOLDs were located on the neocortex beside single cortical tuber, and their glucose metabolism was higher than the tuber core but lower than normal neocortex.

Conclusion: In children with TSC-associated WS, EEG-fMRI did not help to estimate cortical tuber most related to epileptogenicity. On the other hand, in children with TSC-associated focal epilepsy, the utility of EEG-fMRI in epileptic focus estimation was suggested when EEG-fMRI was combined with FDG-PET. Our results also indicated that neocortex around cortical tuber, which has decreased activity than normal neocortex, most contributes to epileptogenicity in children with TSC-associated focal epilepsy.

PF-01

Febrile Seizures Reduce Hippocampal Subfield Volumes But Not Cortical Thickness in Children With Focal Onset Seizures

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Objectives: Whether febrile seizures (FS) produced long-term injury to the hippocampus or other brain structures is a critical question concerning focal onset seizures in children. Our aims were to evaluate the effect of FS on subfields of the hippocampus, thalamic nuclei, cortical thickness, and surface areas of the cortex in children with FS who later developed focal seizures and to identify biomarkers based on MRI structures. *Methods:* Children who had focal onset seizures with or without previous FS and normal 3-T MRI findings were included retrospectively. Age-matched controls were also recruited. Ratios of hippocampal subfields volumes and thalamic subfields, amygdala volumes, cortical thickness, and surface area ratios in individual cortical regions were calculated by FreeSurfer version 7.1.1. We compared measurements of volumetric data between children with focal seizures with or without FS and controls, and correlated these findings with clinical parameters. *Results:* Children with FS and focal seizures exhibited a significantly smaller left cornu ammonis (CA) 2/3 compared to those without FS and age-matched controls ($p < 0.05$). A smaller left granular-molecular cell layer in the dentate gyrus was found in children with FS and focal seizures compared to age-matched controls ($p < 0.05$). A larger hippocampal fissure was also found in FS with focal seizures compared to controls ($p < 0.001$). There were no statistically significant differences in the ratios of each nucleus of the thalamus, amygdala volume, cortical thickness, and surface areas ratios of each cortical region among the three groups. A negative correlation was found between the frequency of FS and the left and right CA1 ratios ($p = 0.027$, $r = –0.471$ and $p = 0.028$, $r = –0.468$, respectively). *Conclusions:* We concluded that multiple episodes of FS can be associated with volume reduction of the left CA2/3 and an enlarged left hippocampal fissure but not with individual cortical thicknesses, surface areas, thalamus, or amygdala in children with focal onset seizures. This study highlights the hippocampal subfields CA2/3 are more vulnerable than the cortices in children with focal seizures who experienced multiple FS episodes. Further prospective studies need to be conducted to identify an association between volumetric results and neurocognitive outcomes.

PG-01

Protective Effect of Fluvastatin Against NMDA-induced Seizure and Underlying Mechanism

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Objectives: Epilepsy affects 50 million people worldwide. The present study is to delineate the effect of fluvastatin against NMDA-induced epileptic seizure and underlying mechanism. It is very much unknown whether fluvastatin was able to reduce the seizure types related to neuronal excitability and progression mediated by NMDA receptor activation, and the mechanisms involved in these actions are not completely understood so far. The present study evaluated the effects of fluvastatin on the seizures and hyperexcitable neuronal activity associated with activation of *N*-methyl-d-aspartic acid (NMDA) receptor. Methods: The effects of fluvastatin on seizure thresholds, BK_{Ca} channels, sodium channel, NMDA-mediated current, and action potentials induced by NMDA were monitored in mice and cortical neurons, respectively. Results: Our study demonstrated that fluvastatin increased the NMDA-induced seizure thresholds and suppressed the frequency of action potentials. Interestingly, the present study provides the first evidence that fluvastatin exhibits inhibitory effects on BK_{Ca} channels currents, sodium channel currents, and NMDA-mediated current in mouse cortical neurons. Discussion: These findings suggest that fluvastatin might be capable of protecting against the seizure types related to neuronal excitability and NMDA receptor activation via inhibition of BK_{Ca} channels, sodium channels, and NMDA-mediated currents.

Keywords: fluvastatin; NMDA-induced epileptic seizure; BK_{Ca} channels; sodium channel; NMDA receptor, action potential

PG-02

Prognosis of neuropsychological development in patient with agenesis of corpus callosum

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Background: Neurodevelopmental outcome for individuals with callosal abnormalities is variable. The advances in imaging techniques led detection rate increased and more earlier and makes counseling for the individuals with agenesis of corpus callosum (ACC) challenging especially in prenatal periods.

Methods: This study reviewed the basic data, clinical condition for imaging, and the further study such as electroencephalogram and psychodevelopmental test in eight individuals with agenesis of corpus callosum.

Results: In these eights patients, six patient was diagnosed ACC accidentally while performing prenatal, perinatal brain image. Two of six had clinical significant issue; one with borderline WISC-IV FSIQ and also diagnosed ADHD and preterm labor, another one had seizure episode and Rt limbs clumsy with EEG showed Intermittent L't C-F spikes, and image also revealed left side parasagittal lobulated cystic lesion. In the remaining two patients, one was presented with VSD plused failure to thrive, limbs spasticity, opisthotonus posture at 5month old and diagnosed trisomy 8; one was presented at clinic due to mental retardation and trice seizure episodes in a week.

Conclusions: The clinical outcome of ACC have great variation from asymptomatic to seizure, mental retardation or syndromic disease with other organ malformation. Advanced neuroimage let the diagnosis of ACC more common even in prenatal period. Further studies designed for predicting neurodevelopmental outcome especially in those individuals with isolated ACC as perinatal periods are needed.

PG-03

Analyses on Ictal Scalp EEG May Predict Outcomes of Corpus Callosotomy for Epileptic Spasms

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We aimed to analyze the ictal electrographic changes on scalp video-electroencephalography (EEG) in children with epileptic spasms (ES), and then identified factors associated with corpus callosotomy (CC) outcomes. We enrolled 17 patients with ES who underwent CC before 20 years of age. Post-CC Engel's classification was as follows: I in 7 patients, II in 2, III in 4, and IV in 4. First, we analyze the correlation between ictal high-voltage slow waves and CC outcomes based on the following three symmetrical indices: (1) negative peak delay: interhemispheric delay between negative peaks; (2) amplitude ratio: interhemispheric ratio of amplitude values for the highest positive peaks; and (3) duration ratio: interhemispheric ratio of slow wave duration. All these symmetrical indices were significantly higher in the unfavorable outcome group than in the favorable. Then we added computer-based analyses of ictal-EEGs as the objective approaches. The mean cross-power spectrum (CPS) in the delta, theta, and gamma frequency bands were significantly higher in the unfavorable outcome group than in the favorable. The differences in CPS tended to be significant in the frontal and temporal areas. Asymmetry and asynchrony of presurgical ictal EEGs may predict unfavorable outcomes following CC for ES.

PG-04

Analysis of EEG changes in 2 cases of Doose syndrome treated with Long-term ACTH therapy

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【Purpose】ACTH therapy is recognized as an effective treatment for intractable epilepsy such as West syndrome. Although Doose syndrome is an epileptic syndrome that develops mainly in early childhood and follows a course of drug resistance, some of them are known to respond well to ACTH therapy. Here we experienced two cases of Doose syndrome in which good seizure suppression was obtained by long-term ACTH therapy (LT-ACTH). Therefore, we analysed on the temporal changes in EEG in LT-ACTH for Doose sydrome.

【Patients and Method】Case 1 was an 8-year-old girl who received poly-antiepileptic drug therapy, ordinary ACTH therapy, and VNS therapy prior to LT-ACTH. She was diagnosed as Doose syndrome at age 2, and myoclonic and atypical absence seizures were remained refractory. Case 2 was a 5-year-old boy who received poly-antiepileptic drug therapy, intravenous immunoglobulin therapy, ketogenic diet prior to LT-ACTH. He was diagnosed as Doose syndrome at age 3, and status of atypical absence and cluster of clonic seizures are remained refractory. EEG were recorded before the LT-ACTH, and after 2 weeks, 3 weeks, 4 weeks, 5 weeks, and 6 weeks. For each case, recording time, amplitude of background EEG activity in the frontal and occipital regions, number of seizures during recording, and cognitive level at the time of recording were investigated.

【Result】In both cases, there was a significant decrease in voltage in the background EEG activity at 2 to 3 weeks. Improvements of amplitude in EEG were maintained during LT-ACTH. The number of seizures was also reduced, and the effect of treatment was confirmed.

【Discussion】Although there are several reports of long-term ACTH therapy in West syndrome, few in Doose syndrome. In Doose syndrome, it is known that the background theta activities in awake stage are extremely high and cause cognitive decline, but it was found that ACTH improved the amplitude as well as the cognition. As the form of seizure recurrence differs by the case, it is necessary to make a treatment plan while continuing the evaluation of EEG over time during the treatment period.

PH-01

Intracranial Cerebral Artery Dissection Associated with A Competitive Basketball Match: A Pediatric Case Report

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Craniocervical arterial dissection related to sport is a rarely reported arteriopathy in children. It features a high stroke rate and variable outcomes in children.

Herein, we reported a 13-year-old boy who suffered from an episode of a falling down injury during a basketball match, followed by a drowsy conscious. Physical examinations revealed a pulse of 94/min, a respiratory rate of 18/min, a pressure of 121/71 mmHg, a GCS:12, and weakness of right-side limbs. Unexpectedly, his MRI revealed multiple narrowing of left ICA, left MCA, and left ACA. Anticoagulation therapy was immediately prescribed to the patient. Stroke related to sports in children may be a rare medical event, but emergency clinicians should be aware of such an underestimated risk, particularly considering that an early diagnosis and early treatment are critical.

PH-02

The Exercise Effects on the Symptoms and Behaviors in People with Epilepsy: The Systematic Review

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Epilepsy is a disorder of the brain characterized by prolonged generating epileptic seizures. Previous studies indicated people with epilepsy have lower level of fitness, more symptoms of mental health conditions, and lower self-esteem and quality of life. Despite physical exercise is one of the easiest ways to improve health-related quality of life, people with epilepsy may be overprotected and do not have the opportunity to participate in the physical activity and exercise as compared with healthy peers. The aim of this systematic review was to assess the effects of physical exercise intervention on clinical symptoms and behavior change in the people with epilepsy. We followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. Seven electronic databases were searched. The Physiotherapy Evidence Database (PEDro) scale was used to assess the methodological quality of included studies. Out of 11 included studies, 7 (64%) were level 3 according to the Oxford 2011 Levels of Evidence, and the mean methodological quality of the included studies was poor according to PEDro scale. We pooled a total of 258 participants with epilepsy in the 11 studies for systematic review. The mean age of the participants was 33.4 years. The training period was average 13.4 weeks, 2.8 sessions per week, and 1.5 hours per session. Out of five studies investigated the seizure frequency during exercise training period, three studies showed significant decrease and the other two showed neither increase nor decrease the seizure attacks. In general, physical exercise trainings could improve the physical fitness, decrease depression, anxiety, and behavior problems, and improve the quality of life in people with epilepsy. Although only 11 studies were included in this study, the review showed that the exercise training is beneficial to the people with epilepsy in different domains. However, there is a need for further studies with good PEDro scores to establish the guideline of the physical exercise for people, especially for children, with epilepsy in the future.

PH-03

ACTH in Epileptic Spasms: A Follow Up Study in New Taipei City, Taiwan

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Background: West syndrome, a severe epileptic syndrome composed of the triad of spasms, hypsarrhythmia, and mental retardation, is usually refractory to most conventional AEDs (anti-epileptic drugs) in early infants. The American Academy of Neurology and the Child Neurology Society concluded that natural or synthetic ACTH (adrenocorticotropic hormone) therapy is probably effective for short-duration treatment and resolution of hypsarrhythmia.

Methods: We retrospectively reviewed the charts of 13 infants, between 2008 to 2018, clinically presenting with epileptic/infantile spasms and hypsarrhythmia or multifocal epileptogenicity in order to study their outcomes of short-term (< 56 days after initial ACTH) and long-term (2 years later after initial ACTH) respectively. ACTH was intramuscular administrated QD for 2 weeks and then tapering gradually.

Results: There was 13 infants enrolled (9 male and 4 female). 9 infants were classified as “symptomatic” group regarding subdural effusion, lissencephaly, microcephaly, cerebral palsy, cerebral infarction, hypoxic ischemic encephalopathy and hypotonia). Cryptogenic group (CRY) is 31% (4/13) and symptomatic group (SYM) is 69% (9/13). Mean age of onset of spasms or nodding is 5.8 m/o (months old). Before ACTH, varied AEDs had been prescribed regarding Valproic acid (62%), Levetiracetam (46%), Vigabatrin (38%), Phenobarbital (23%), and Topiramate (15%). Mean age of ACTH administration is 17.6 m/o. Mean interval between spasms or nodding onset to ACTH administration is 12.6 months. Rate of short-term half-reduction is CRY 100% (4/4) versus SYM 77.8% (7/9). Rate of short-term cessation is CRY 100% (4/4) vs. SYM 66.7% (6/9). Rate of long-term cessation is CRY 75% (3/4) vs. SYM 33.3% (2/6). Recurrent rate (2 years after cessation) is CRY 25% (1/4) vs. SYM 66.7% (4/6). Long-term psychomotor delay (motor and/or speech) is CRY 50% (2/4) vs. SYM 77.8% (7/9).

Conclusion: ACTH is an effective agent to treat epileptic/infantile spasms. Cryptogenic group has better results in both short-term and long-term outcomes.

Keywords: ACTH, West syndrome, infantile spasms, cryptogenic, symptomatic

PH-04

Retrospective Analysis Of Motor Progression In Developmental Delay With And Without Intellectual Disability Receiving Rehabilitation Therapy

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Children with development delay (DD) typically exhibit impairments in gross motor, fine motor, language, cognitive, sensory, psychological, behavioral, auditory, and/or visual development in one or more developmental domains. There are a variety of causes for DD, and many cases of DD may have multiple causes. Relatedly, while intellectual disability (ID) is among the major causes of DD, not all children with DD have ID, and since children with ID typically have underlying neurological or functional impairments, there is some questions as to whether ID limits the degree of improvement that a given rehabilitation can provide and, if so, the progress of the gross and fine motor skill development should be different between with children with concurrent DD and ID and with DD after receiving the same therapy. To answer this question, we designed a retrospective study to analyze the gross motor skills and fine motor skills treatment outcomes for children with concurrent ID and DD and children with DD alone who received at least 12 months of physical and occupational rehabilitation at the child development center of a teaching hospital.

The results indicated no significant difference in the progress of the gross and fine motor skill development of the children with concurrent DD and ID and the children with DD after receiving the therapy. As such, this study suggests that the physical and occupational therapy used in this teaching hospital is appropriate for both children with concurrent DD and ID and children with DD alone, and that both types of children should actively continue their rehabilitation to achieve the greatest possible levels of self-reliance and independence in their daily lives.

Key words: developmental delay, intellectual disability, rehabilitation, gross motor skills, fine motor skills

PH-05

Therapeutic Hypothermia is Effective for Status Epilepticus of Acute Encephalopathy in Dravet Syndrome

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Background: Dravet syndrome is an infantile-onset epileptic encephalopathy. Seizures are readily induced by fever and they often progress to status epilepticus (SE). While some patients suffer from acute encephalopathy, no specific treatments have been established. We experienced SE caused by acute encephalopathy with Dravet syndrome that stopped soon after inducing therapeutic hypothermia (TH).

Case report: A 2-year-old girl with Dravet syndrome who was taking anticonvulsants developed respiratory syncytium virus infection and SE for 1 hour. She was taken to a hospital and given diazepam and phenobarbital injections. Her consciousness cleared the next day; however, at night she developed a high fever and repeat SE. She was intubated and a continuous midazolam infusion was added. Nevertheless, the seizures were difficult to control and she was transferred to our hospital on day 4. We started continuous electroencephalography (cEEG) monitoring. On day 6, left central-onset seizures increased on cEEG to more than 5 times per hour, although her temperature had dropped to 37°C. On day 7, brain magnetic resonance imaging (MRI) and diffusion-weighted images revealed high intensity areas in part of the right occipital lobe and entire left subcortical white matter that were not present on day 4. Considering the clinical course and MRI imaging, she was diagnosed with acute encephalopathy with febrile convulsive SE and treated with methylprednisolone pulse therapy. TH was started to protect her cerebral function. As soon as the cooling started, the refractory SE disappeared. She was kept at 34°C for 72 hours without any complications. After discharge, she is well, although right hemiplegia remains.

Conclusion: Using cEEG, we could detect seizures under sedation. TH might be effective for SE due to acute encephalopathy with Dravet syndrome.

PH-06

A Successful Solo Treatment of Valproic Acid in West Syndrome

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[Introduction] West syndrome (WS) is a drug resistant infantile epilepsy, and it has poor prognosis in most cases because of intractable epileptic seizures and associated neurodevelopmental disabilities. The type of epileptic seizure in WS is infantile spasms, which in most cases are refractory to polytherapy with antiepileptic drugs. We experienced a case of WS in which VPA monotherapy relieved intractable seizures. [Case] The patient was a six-month-old female infant. Her perinatal and past histories showed nothing in particular. Her developmental history up to five months also revealed no complications. She had no family history of epilepsy. At the age of six months, she started to nod her head three to five times a day. She showed normal neurological findings. She had no major and/or minor anomaly. At the age of six months, she showed a developmental quotient (DQ) of 89. She experienced clustering spasms and contraction of flexor and neck, and individual seizure lasted for a brief period. Inter-ictal EEG showed hypsarrhythmia, and positive slow waves synchronized with spasms were observed on ictal EEG. The findings of cranial magnetic resonance imaging (MRI) were normal. Blood test including amino acid analysis showed no abnormalities. We diagnosed her with cryptogenic West syndrome, and VPA was started at 30 mg/kg/day. Her seizure stopped on day 2, and hypsarrhythmia on inter-ictal EEG was absent on day 4. She has been seizure-free for six months since the start of treatment. At the age of 10 months, she had a DQ of 80. We suggest to her parents that genomic analysis in the Initiative on Rare and Undiagnosed Diseases. [Conclusions] Polytherapy with antiepileptic drugs and hormonal therapy with corticotropin (ACTH) are the primary treatment of WS because seizures are drug-resistant in most cases of WS. It was demonstrated there are no refractory West syndrome in this case. Various causative genes of epileptic encephalopathies have been identified. Therefore, we recommended causative gene analysis in our case. If the causative gene is discovered, it will contribute to the prediction of a good or bad prognosis. The accumulation of similar cases could lead to the discovery of the causative gene of WS.

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