

The 17th Annual Meeting of Infantile Seizure Society

International Symposium on Benign Infantile Seizures (ISBIS)

PROGRAM & ABSTRACTS



Sponsor	Infantile Seizure Society (ISS)
Co-sponsor	Japan Epilepsy Society
Support Organizations	Japanese Society of Child Neurology Asian & Oceanian Child Neurology Association (AOCNA) International League Against Epilepsy (ILAE) Commission on Asian and Oceanian Affairs



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WELCOME MESSAGE



Dear friends and colleagues,

On behalf of the organizing committee of the 17th Infantile Seizure Society (ISS), it is with great pleasure to welcome you to Tokyo. This congress has been organized by the Infantile Seizure Society under the endorsement of ILAE & pediatrics commission.

We, along with our Scientific Organizing Committee and Scientific Advisory Committee colleagues, have built a scientific program that would be of great interest to all, encompassing recent scientific, clinical and social developments in the field of benign infantile seizures. This program has a comprehensive range of main, post main and several sessions as well as practical videos and lively debates.

On the second day of the congress, we have prepared a memorial ceremony for Prof. Yukio Fukuyama, our 'father' and the founder of the Infantile Seizure Society, who passed away on July 17th, 2014.

Tokyo is a beautiful cosmopolitan city dotted with high-rise buildings and historical gardens. The city is populated by people with a diverse range of ethnicities with many different cultures, cuisine and religions. It is a city rich in contrast and color.

We are very glad with your participation in what promises to be an infantile seizure meeting of excellent quality.

Hitoshi Yamamoto

Hitoshi Yamamoto
President, ISBIS 2015



Prof. Yukio Fukuyama
Honorary Chairperson,
Board of Councils,
Infantile Seizure Society



Prof. Makiko Osawa
President of the Infantile Seizure Society,
Previous president of the Japan Society of
Child Neurology,
President of the Japan Epilepsy Society,
Emeritus Professor of Tokyo Women's
Medical University

ORGANIZATION

Organizing Committee

Congress President	Hitoshi Yamamoto
Secretary General	Yusaku Miyamoto

Program Committee

Shinichiro Hamano (Saitama, Japan)
Shinichi Hirose (Fukuoka, Japan)
Shinichi Nijima (Tokyo, Japan)
Hirokazu Oguni (Tokyo, Japan)
Akihisa Okumura (Nagoya, Japan)
Toshiyuki Yamamoto (Tokyo, Japan)
Hideo Yamanouchi (Saitama, Japan)

Advisory Board

Kai-Ping Chang (Taipei, Taiwan)
Yong-Seung Hwang (Seoul, Korea)
Hian-tat Ong (Singapore, Singapore)
Marilyn Ortiz (Manila, Philippines)
Haluk Topaloglu (Ankara, Turkey) President of Infantile Seizure Society 2014
Suad AL-Yamani (Riyadh, Saudi Arabia)
Makiko Osawa (Tokyo, Japan)

Host organizations

Infantile Seizure Society (ISS)
Fully endorsed by International League Against Epilepsy (ILAE)
Pediatrics Commission and Commission on Asian and Oceanian Affairs (CAOA)

Sponsoring Organization

Sponsor	Infantile Seizure Society (ISS), Japan
Support Organization	Japan Epilepsy Society Japanese Society of Child Neurology Asian & Oceanian Child Neurology Association

ACKNOWLEDGEMENT

Seminar Co-sponsors

Eisai Co., Ltd.
GlaxoSmithKline K.K.
UCB Japan Co., Ltd. / Otsuka Pharmaceutical Co., Ltd.

Donations

Yokohama General Hospital
Kyowa Hakko Kirin Co., Ltd.
Genzyme Japan K.K.
Fukuyama Foundation
St. Marianna University School of Medicine
Kawano Masanori Memorial Public Interest Incorporated Foundation for Promotion of Pediatrics
Nakajima Clinic
The Japanese Society of Child Neurology
Tsurukawa Kinen Hospital
MSD K.K.
JCR Pharmaceuticals Co., Ltd.
Keihin General Hospital
SRL, Inc.
Astellas Pharma Inc.

Advertisements

Alfresa Pharma Corporation
NIHON KOHDEN KANSAI CORPORATION
Eli Lilly Japan K.K.
Actelion Pharmaceuticals Japan Ltd.
Bayer HealthCare
JCR Pharmaceuticals Co., Ltd.
CSL Behring K.K.
Japan Blood Products Organization
NIHON KOHDEN MINAMIKANTOU CORPORATION
NobelPharma Co., Ltd.
Otsuka Pharmaceutical Factory, Inc.
Alexion Pharma

Exhibitors

KINOKUNIYA COMPANY LTD.
CLINICO CO., LTD.

(As of August 31, 2015)

GENERAL INFORMATION

1. Main topics

Photosensitive epilepsy, benign infantile convulsion, benign familial infantile convulsion, benign familial neonatal convulsion, benign myoclonic epilepsy in infancy, benign non-familial neonatal convulsion, benign convulsions with mild gastroenteritis, familial infantile convulsion and paroxysmal choreoathetosis, and others

2. Target attendees

Pediatricians, neurologists, neurosurgeons, epileptologists, basic and clinical researchers who are interested in epilepsy and patient care in children

3. Official language

English only

4. Visa application

To visit Japan, you must carry a valid passport. A visa is required for citizens of countries which do not have visa-exempt agreements with Japan. Please contact the nearest Japanese Embassy or Consulate for visa application.

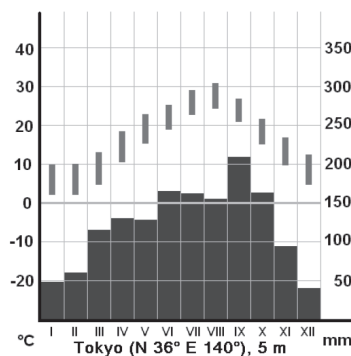
Ministry of Foreign Affairs of Japan:

http://www.mofa.go.jp/j_info/visit/Visa/index.html

5. Climate

The temperature in late September can be slightly on the higher side but getting cool day by day in Tokyo. Consider bring light clothes and a jacket since meeting room temperatures and personal comfort levels vary.

Average temperature in September in Tokyo: Average 23.8 °C, Highest 26.9°C, Lowest 19.7°C



<https://ja.wikipedia.org/wiki/%E9%9B%A8%E6%B8%A9%E5%9B%B3#/media/File:ClimateTokyoJapan.png>

(Accessed Aug. 3rd)

6. Currency exchange

Japanese yen cash or major credit cards are acceptable at regular stores and restaurants.

7. Electricity

Electric current is uniformly 100 volts, AC, throughout Japan.

8. Official Certificate for Attendance and CME Points

An official certificate for attendance at the ISBIS will be prepared for all participants. To Japanese colleagues, authorized CME units will be rewarded by three societies as following CME Points.

Society	Attendance	Authorship	
		Presenter	Co-author
Japan Pediatric Society	3u	0u	0u
Japan Epilepsy Society	5u	20u	0u
Japanese Society of Child Neurology	8u	4u	1u

max sum up to 12 units

u=unit

9. Liabilities

All participants and accompanying persons should be responsible for their own medical, accident and other necessary insurance.

REGISTRATION FEE AND CATEGORY

1. Registration Fee

Category	Early Registration (Before June 20, 2015)	Late Registration (After June 21, 2015)
Infantile Seizure Society Member AOCNA Member	JPY 18,000-	JPY 21,000-
Non Member	JPY 22,000-	JPY 25,000-
Co-Medical	JPY 5,000-	JPY 7,000-
Junior Physician /Resident*** Student	JPY 4,000-	JPY 5,000-
Accompanying Person	FREE	
Social Party	FREE	

- i. AOCNA=Asian & Oceanian Child Neurology Association
- ii. Junior Physician/Resident*** =under 35 years of age. Students of post-graduate course are also eligible to this category.
- iii. Copy of official documents such as a student's identification or a certificate will be required.
- iv. Admission fee for Social Party is FREE (participants need to show the name badge).

2. Entitlements

【Participants】

Conference registrants are entitled for the followings:

Access to all scientific sessions, poster presentations and exhibition

Daily coffee/ tea breaks, lunches for 2 days

Opening ceremony, closing ceremony, memorial ceremony for Prof. Fukuyama,

Social party, farewell party,

Conference bag with program, abstract and related information, Conference badge

【Accompanying Persons】

Registered accompanying persons are entitled for the followings:

Opening ceremony, closing ceremony, memorial ceremony for Prof. Fukuyama,

Social party, farewell party

Access to poster presentations and exhibition but not to any scientific sessions

Conference badge

3. On-site Registration

Registration desk will open at

Day 1: Friday, September 25 9:00-16:30

Day 2: Saturday, September 26 8:45-16:30

Please come to the Registration desk, located in front of the entrance of the conference venue to register.

Payment must be made in **Japanese Yen only.**

4. Social Program

Social Party

Date: Friday, September 25 17:45-20:00

Venue: Meeting Room, 2nd Floor, NII
(2-1-2 Hitotsubashi, Chiyoda-ku, Tokyo /Tel: +81-3-3261-1101)

Registration Fee: Free of charge

Farewell Party

Date: Saturday, September 26 18:00-20:00

Venue: Cafeteria, 3rd Floor, NII
(2-1-1 Hitotsubashi, Chiyoda-ku, Tokyo /Tel: +81-3-3261-1101)

Registration Fee: Free of charge

5. Conference Venue

Hitotsubashi Hall

(National Center of Sciences Building/ National Institute of Informatics)

2-1-2 Hitotsubashi, Chiyoda-ku, Tokyo / Tel: +81-3-4212-6000

Access: <http://www.nii.ac.jp/en/about/access/>

6. Conference Program and Abstracts

Price: 1,000 JPY

INSTRUCTIONS FOR ORAL AND POSTER PRESENTATIONS

Instructions for Oral Presentations

1. Every speaker is requested to finish up an arrangement necessary for data project one hour before the respective presentation at the latest, by contacting the staff of the PC Center (PC Data Registration desk), located in front of the Conference Room, 2nd floor. It is suggested you to save your final slides in a USB stick or CD-R and bring to the PC Center.
2. All speakers are requested to strictly observe the allotted presentation time. Since the conference schedule is tight, session chairpersons will strictly enforce the timing. The staff will press the buzzer for time-reminding.
3. It is required to use the laptop prepared by the conference for stable computer system connection. For any reason that you must use your own laptop, please inform the PC Center staff in advance.
4. The conference will have a laptop set up at the podium for all presenters. A remote control for changing the slides will be prepared; the presenter can control the slides on his/her own.
5. All presentation slides should be prepared by "Microsoft Office PowerPoint 2007, 2010 or 2013."
6. A single projection will be available. Windows-operated computers will be prepared by the organizer. If your slides are prepared by Mac system, the data may deform after its transfer to the Windows system. Please check and correct this possible deformation at the PC Registration Desk.
7. Video tape presentation is not available. If you need to use video records, please transfer them to the computer in a digital form (Windows Media player). The projection does not support Full HD video mode, please avoid this kind of file format. If you prepare to use a Mac laptop, please bring the Apple DVI to VGA display adapter. The connector of the projector is D-SUB, be sure the correct adapter is brought with you.
8. Please note the time allocated for each presentation as follows:
Allotted time by the organizer followed by 5 minutes of discussion for invited speakers.

Instructions for Discussion

1. Active discussions from the floor are encouraged as far as the time is available.
2. All aspects of discussion session shall be ordered by due consideration of chairpersons.
3. Those who wish to raise a question/discussion may raise their hands and wait to be called by the chairperson. To begin discussion, please identify oneself first.

Next Chairpersons and Next Speakers

The seats for "Next Speakers" and "Next Chairpersons" are prepared in the front row of the conference room.

Please be seated 15 minutes prior to your presentation/session.

Instructions for Poster Presentations

- Poster Exhibit Hours: Friday, September 25 10:30 to Saturday, September 26 13:30
 - Poster set-up time : Friday, September 25 09:00 ~ 13:30
 - Poster removal time : Saturday, September 26 13:30 ~ 16:30
 - Location: Poster Session Rooms, 2nd floor, Hitotsubashi Hall
 - Poster Tour time
 - Poster Tour 1: Friday, September 25 14:30-15:30 at Poster Session Room 1
 - Poster Tour 2: Saturday, September 26 11:00-12:00 at Poster Session Room 2
- *Please stand by 5 minutes before the session starts.

1. Necessary office supplies will be provided on-site. Stapler are prohibited for mounting. Conference will provide free pins for poster presenters.
2. The staff will remove posters not removed after 16:30 on September 26 without further notice.
3. All poster boards have a surface of 90 cm wide and 210 cm high. Top corner space will be used to place the poster number, pre-fixed by the secretariat.
4. Poster judges will evaluate all posters. Presenters are suggested to stand ready at the site of their respective posters for answering questions during the Poster Tour time.
5. The conference will present awards at the Closing Ceremony on September 26th. We strongly encourage all poster presenters to attend the ceremony.

Poster Award

(Supported by Japan Society of Child Neurology)

Poster Awards for participants from foreign countries.

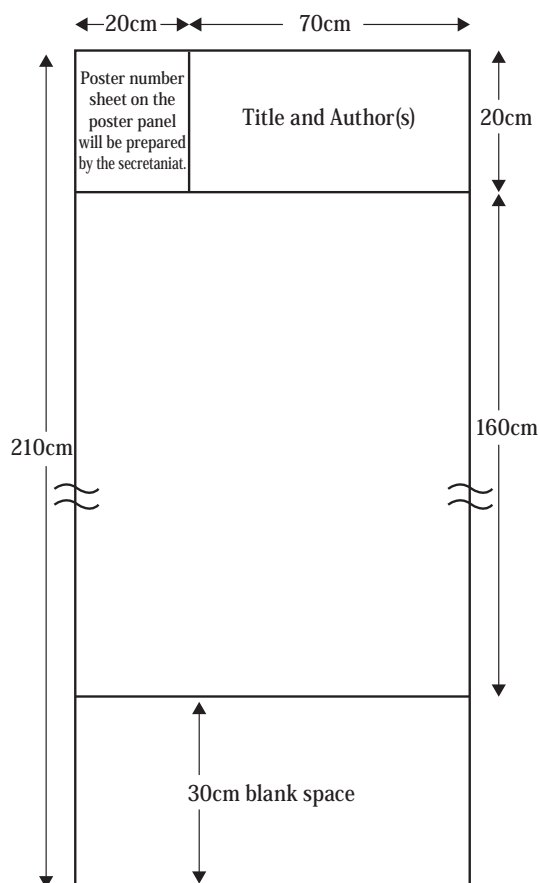
The ISBIS Award Committee will provide the best poster presentation awards based on the quality.

The Awardees will receive the certificates and award money (JPY).

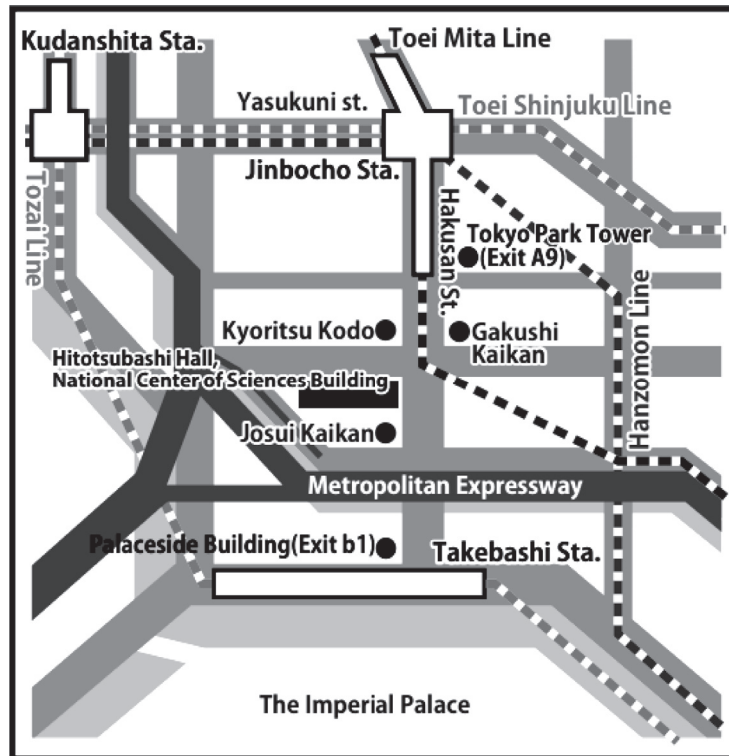
Platinum. (50,000JPY) for 3 persons

Gold. (30,000JPY) for 3 persons

Silver. (20,000JPY) for 3 persons



VENUE



(http://www.hit-u.ac.jp/hall/file/menu-016/file_02.pdf , Accessed Aug.10)

Hitotsubashi Hall

(National Center of Sciences Building/ National Institute of Informatics)

National Center of Sciences Building 2F,
2-1-2 Hitotsubashi, Chiyoda-ku, Tokyo 101-8439

● By train(Subway)

3-5 minutes walk from JIMBOCHO station and TAKEBASHI station

1. "JIMBOCHO" station (3 subway lines available)

Exit A8, A9

Station number:

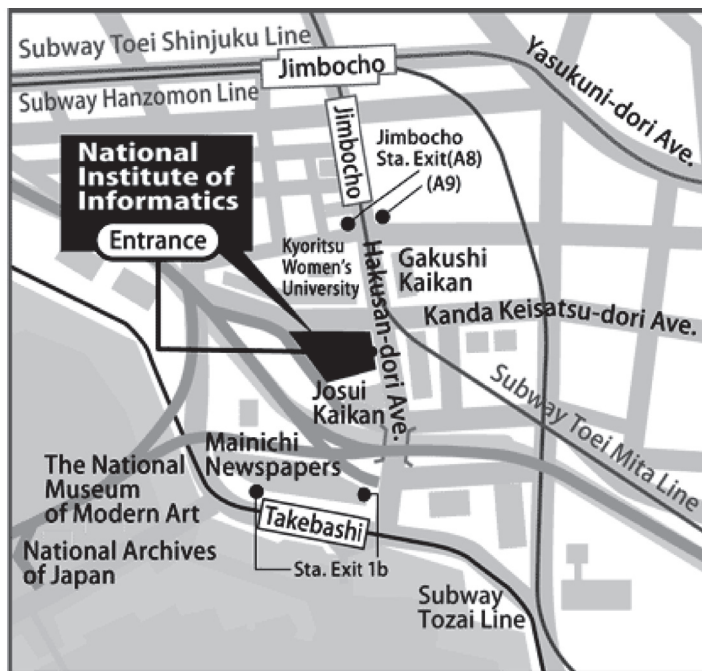
- Z-07 on Hanzomon Line of Tokyo Metro
- I-10 on Mita Line of Toei Subway
- S-06 on Shinjuku Line of Toei Subway

2. "TAKEBASHI" station

Exit 1b

Station number:

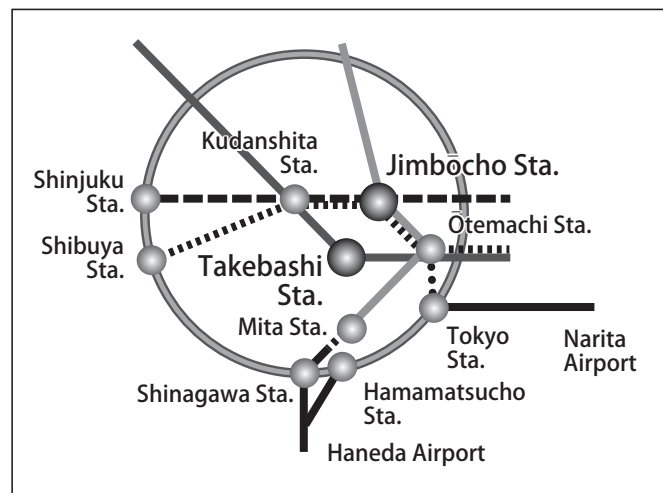
- T-08 on Tozai Line of Tokyo Metro



Inter-University Research Institute Corporation
Research Organization of Information and Systems
National Institute of Informatics

2-1-2 Hitotsubashi, Chiyoda-ku, Tokyo
101-8430
Tel: +81-3-4212-2000 (Exchange)

By Train (Subway)
Tokyo Metro Hanzomon Line / Toei Mita
Line / Toei Shinjuku Line
"JIMBOCHO" Exit A9
Toyko Metro Tozai Line "TAKEBASHI"
Exit 1b
3-5 minutes walk from the stations

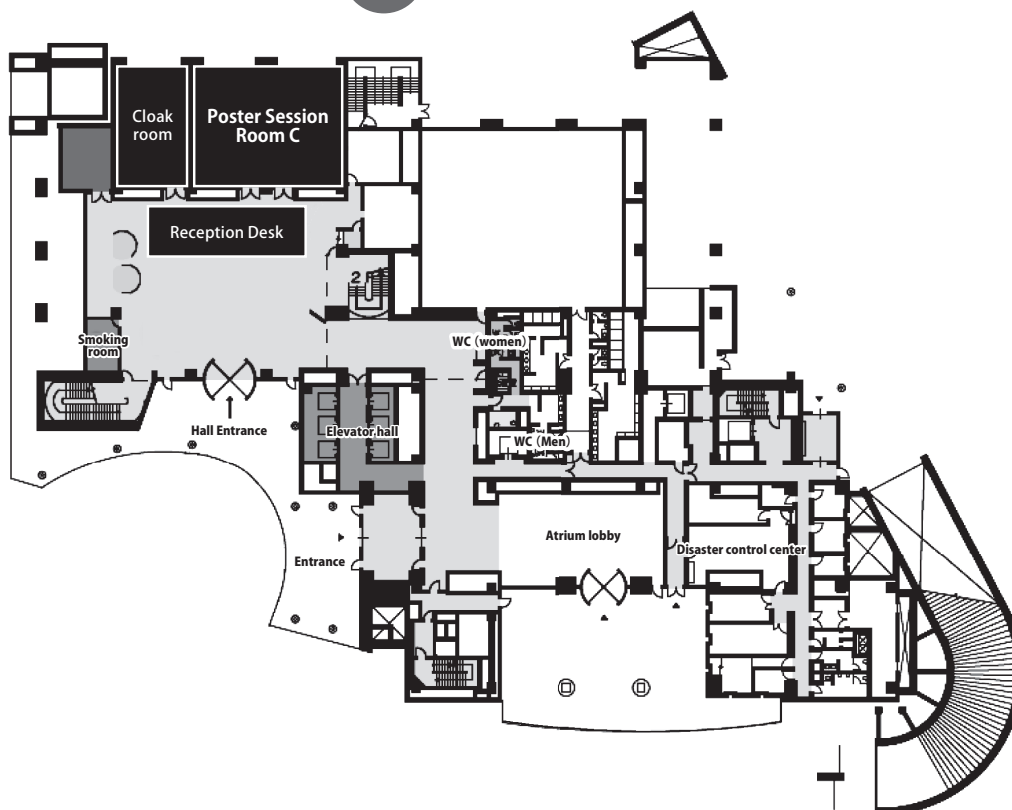


— Subway Toei Shinjuku Line	— Subway Tozai Line
..... Subway Hanzomon Line Subway Marunouchi Line
— Subway Toei Mita Line	— Yamanote Line

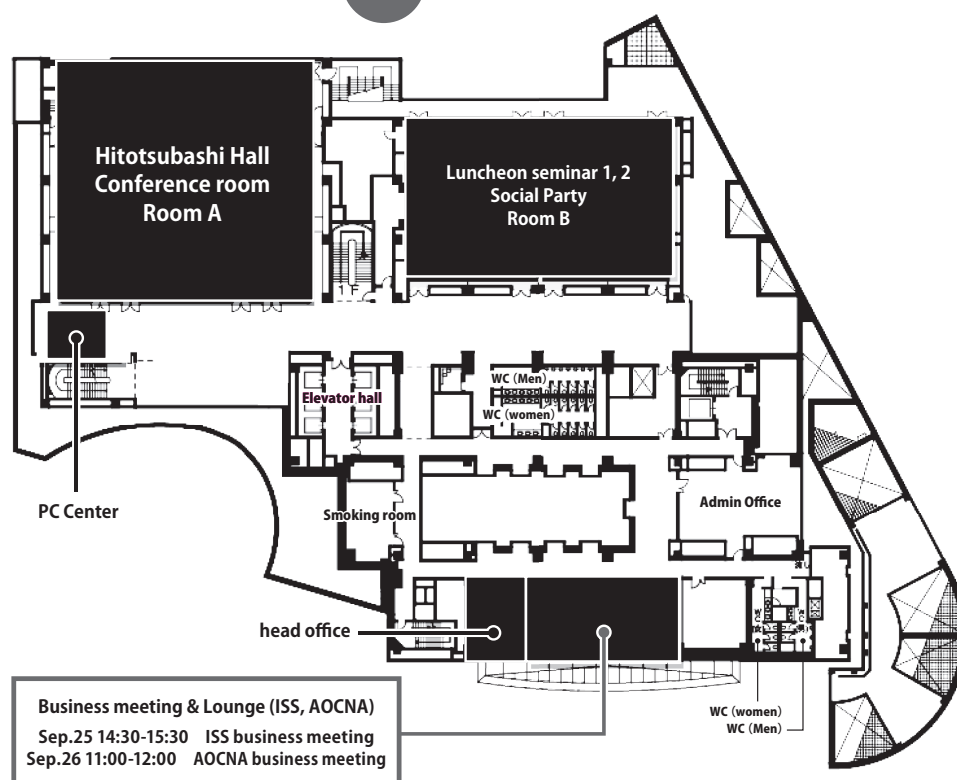
Please refer to the URL below for further details of Access.
<http://www.nii.ac.jp/en/about/access/>
(<http://www.nii.ac.jp/en/about/access/>, Accessed Aug.10)

FLOOR PLAN

National Center of Sciences 1F



National Center of Sciences 2F



OVERVIEW of DAILY PROGRAM

Time	Day 1 Sep 25(Fri)	Day 2 Sep 26 (Sat)	Time
9:00	Registration Desk open	Registration Desk open	9:00
		Morning Seminar L10 Harvey Sarnat	9:20
9:45	Opening Ceremony		9:50
10:00		Session 4 L11 Phillip Pearl	9:50
10:10	Keynote Lecture 1 sponsored by Eisai Co., Ltd. L01 Federico Vigevano	L12 Hiroshi Ohtsubo	10:20
			10:20
11:00			10:50
11:00	Session 1 L02 Nicola Specchio	Poster Session 2 (Room C)	11:00
11:30		AOCNA Business Meeting	
11:30	L03 John Millichap		
12:00			1200
12:10	Luncheon Seminar 1 (Room B) sponsored by UCB Japan Co., Ltd. and Otsuka Pharmaceutical Co., Ltd. L04 Alexis Arzimanoglou	Luncheon Seminar 2 (Room B) sponsored by GlaxoSmithKline K.K. L13 Ingrid Scheffer	12:10
13:10			1310
13:20	Session 2 L05 Shinichi Hirose	Session 5 L14 Yukitoshi Takahashi	13:20
13:50			13:50
13:50	L06 Susumu Ito	L15 Andrew Lux	13:50
14:20			14:20
		L16 Jong Rho	14:20
14:30	Poster Session 1 (Room C)	Free Discussion	15:00
	Infantile Seizure Society Business Meeting		15:00
15:30		Keynote Lecture 2 L17 Akihisa Okumura	15:20
			16:10
15:40	Session 3 L07 Toshiyuki Yamamoto		
16:10		Special Program Prof.Fukuyama memorial Raman Sankar Harvey Sarnat Haluk Topaloglu Kai-ping Chang Phillip Pearl (Piano play)	16:20
16:10	L08 Kenjiro Kikuchi		17:10
16:40	L09 Masanori Takeoka	Closing Ceremony Poster Award	17:10
17:10			
17:10	Free Discussion		17:50
17:30			
17:45	Social Party (Room B)	Farewell Party (3F Cafeteria)	18:00
20:00			20:00

PROGRAM

The 17th Annual Meeting of Infantile Seizure Society International Symposium on Benign Infantile Seizures (ISBIS)

PROGRAM - ORAL PRESENTATIONS

DAY1, FRIDAY, SEPTEMBER 25

9:00 **Registration desk open**

9:45-10:00 **Opening ceremony**

Opening address

(1) Makiko Osawa (Chairperson, Infantile Seizure Society)

(2) Hitoshi Yamamoto (President, ISBIS)

(3) Tatsuya Tanaka (Vice President of ILAE), words for Prof Fukuyama as the founder of Infantile Seizure Society

Keynote lecture 1 (sponsored by Eisai Co., Ltd.)

Chairperson: Akihisa Okumura (Nagoya, Japan)

10:10-11:00 **L01**

THE CLINICAL SPECTRUM OF BENIGN FAMILIAL INFANTILE SEIZURES

Federico VIGEVANO

Ospedale Pediatrico Bambino Gesù, Scientific Institute, Roma, Italy

Session 1

Chairpersons: Tatsuro Izumi (Oita, Japan) , Eli Shahr (Haifa, Israel)

11:00-11:30 **L02**

BENIGN FAMILIAL NEONATAL SEIZURES

Nicola SPECCHIO

Department of Neuroscience – Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

11:30-12:00 **L03**

CLINICAL SPECTRUM OF EPILEPSY SECONDARY TO KCNQ2 VARIANTS AND GENETIC MODIFIERS

John J. MILLICHAP

Epilepsy Center, Ann & Robert H. Lurie Children's Hospital of Chicago; Departments of Pediatrics and Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL

Luncheon Seminar 1 (sponsored by UCB Japan Co., Ltd. and Otsuka Pharmaceutical Co., Ltd.)

Chairperson: Makiko Osawa (Tokyo, Japan)

- 12:10-13:10 **L04**
OPTIMIZING TREATMENT STRATEGIES IN INFANTS WITH BENIGN EPILEPSY SYNDROMES
Alexis ARZIMANOGLOU
Director of the Epilepsy, Sleep and Paediatric Neurophysiology Department,
University Hospitals of Lyon (HCL), Lyon, France

Session 2

Chairpersons: Shinichi Hirose (Fukuoka, Japan) , Kai-Ping Chang (Taipei, Taiwan)

- 13:20-13:50 **L05**
GENETIC IDENTIFIERS OF BENIGN EPILEPSY DEEPEN OUR UNDERSTANDING OF THE PATHOMECHANISMS OF EPILEPSY
Shinichi HIROSE
Department of Pediatrics, School of Medicine, Fukuoka University, Fukuoka, Japan
- 13:50-14:20 **L06**
THE SPECTRUM OF “BENIGN” MYOCLONIC EPILEPSY IN INFANCY
Susumu ITO
Department of Pediatrics, Tokyo Women’s Medical University, Tokyo, Japan

14:30-15:30 **Poster Tour 1 (Infantile Seizure Society Business Meeting)**

Session 3

**Chairpersons: Hideo Yamanouchi (Saitama, Japan) ,
Haluk Topaloglu (Ankara, Turkey)**

- 15:40-16:10 **L07**
GENETIC BASIS OF BENIGN INFANTILE EPILEPSY
Toshiyuki YAMAMOTO
Tokyo Women’s Medical University Institute for Integrated Medical Sciences, Tokyo, Japan
- 16:10-16:40 **L08**
TREATMENT FOR BENIGN CONVULSIONS WITH MILD GASTROENTERITIS
Kenjiro KIKUCHI
Department of Pediatrics, Jikei University School of Medicine, Tokyo, Japan
- 16:40-17:10 **L09**
FREQUENT SLEEP POTENTIATED SPIKES AND COGNITION IN BENIGN FOCAL EPILEPSY OF CHILDHOOD WITH CENTROTEMPORAL SPIKES; TRULY ALL BENIGN?
Masanori TAKEOKA
Boston Children’s Hospital and Harvard Medical School, Boston, USA

17:10-17:30 **Free Discussion**

17:45-20:00 **Social party at 2nd Floor**

DAY2, FRIDAY, SEPTEMBER 26

Morning Seminar

Chairperson : Kenji Sugai (Kodaira, Japan)

09:20-09:50

L10

NEUROPATHOLOGY OF BENIGN INFANTILE SEIZURES

Harvey B. SARNAT

University of Calgary and Alberta Children's Hospital Research Institute,
Calgary, Alberta, Canada

Session 4

Chairpersons : Takao Takahashi (Tokyo, Japan), Marilyn Ortiz (Manila, Philippines)

09:50-10:20

L11

BENIGN VERSUS ENCEPHALOPATHIC EARLY INFANTILE EPILEPSIES

Phillip L. PEARL

Department of Neurology, Boston Children's Hospital, Harvard Medical School,
Boston, MA, USA

10:20-10:50

L12

FAST ACTIVITY IN NEWBORN AND INFANTILE EEG

Hiroshi OTSUBO

Division of Neurology, The Hospital for Sick Children
Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada

11:00-12:00

Poster Tour 2 (Asian Oceanian Child Neurology Association Business Meeting)

Luncheon Seminar 2 (Sponsored by GlaxoSmithKline K.K.)

Chairperson : Toshisaburo Nagai (Osaka, Japan)

12:10-13:10

L13

SODIUM CHANNEL EPILEPSIES OF INFANCY: A SPECTRUM OF SELF-LIMITED AND SEVERE DISORDERS

Ingrid E. SCHEFFER

Florey Institute, Melbourne, Australia
University of Melbourne, Austin Health and Royal Children's Hospital, Melbourne,
Australia

Session 5

Chairpersons : Shinichi Nijima (Tokyo, Japan) , Raman Sankar (Los Angeles, USA)

13:20-13:50

L14

PHOTOSENSITIVITY IN POPULATION & EPILEPTIC PATIENTS

Yukitoshi TAKAHASHI

National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorder,
Shizuoka, Japan

13:50-14:20 **L15**
THE BENIGN SPECTRUM OF EPILEPTIC AND NON-EPILEPTIC SPASMS IN INFANCY

Andrew LUX

Department of Paediatric Neurology, Bristol Royal Hospital for Children, Bristol, UK

14:20-15:00 **L16**
A TRANSLATIONAL TALK ON BENIGN INFANTILE SEIZURES

Jong M. RHO

Departments of Paediatrics and Clinical Neurosciences University of Calgary, Canada

15:00-15:20 **Free Discussion**

Keynote Lecture 2

Chairperson : Nicola Specchio (Rome, Italy)

15:20-16:10 **L17**
OVERVIEW OF BENIGN INFANTILE SEIZURES

Akihisa OKUMURA

Department of Pediatrics, Aichi Medical University, Nagakute, Aichi, Japan

Prof. Yukio Fukuyama Memorial

16:20-17:10 Master of the Ceremony :
Masaharu Hayashi (Tokyo, Japan) , Anannit Visudtibhan (Bangkok, Thailand)

Raman Sankar (Los Angeles, USA)

Harvey Sarnat (Calgary, Canada)

Haluk Topaloglu (Ankara, Turkey)

Kai-ping Chang (Taipei, Taiwan)

A Requiem/ Piano Play by Phillip Pearl (Boston, USA)

17:10-17:50 **Closing Ceremony**

Best Poster Awarding : Toshisaburo Nagai (Osaka, Japan)

Closing Address

(1) Hideo Yamanouchi (President, 18th Infantile Seizure Society International Symposium)

(2) Marilyn Ortiz (President, 19th Infantile Seizure Society International Symposium)

(3) Hitoshi Yamamoto (President, 17th Infantile Seizure Society International Symposium)

18:00-20:00 **Farewell Party at 3rd Floor, Cafeteria**

PROGRAM - POSTER SESSION

P-1

THE TREATMENT OF FOCI RESECTION AND BIPOLAR ELECTRO-COAGULATION ON FUNCTIONAL CORTEX IN MULTIFOCAL EPILEPSY ASSOCIATED WITH TUBEROUS SCLEROSIS COMPLEX INVOLVING ELOQUENT CORTEX

Feng ZHAI Department of Neurosurgery, Beijing Sanbo Brain Hospital, Capital Medical University, Beijing, China

P-2

PRENATAL MULTICYSTIC ENCEPHALOPATHY IN ISOLATED SULFITE OXIDASE DEFICIENCY WITH A NOVEL MUTATION

Li-Wen CHEN, MD Department of Pediatrics, National Cheng Kung University Hospital, Tainan, Taiwan

P-3

A NOVEL PIGA MUTATION IN A FAMILY WITH X-LINKED ATYPICAL DRAVET SYNDROME

Young Ok KIM Department of Pediatrics, Chonnam National University Medical School, Gwangju, Republic of Korea

P-4

CORRELATION BETWEEN STIGMA AND EEG PAROXYSMAL ABNORMALITY IN CHILDREN WITH EPILEPSY

Hideaki KANEMURA Department of Pediatrics, Faculty of Medicine, University of Yamanashi, Yamanashi, Japan

P-5

CTLA-4 +49 A/G POLYMORPHISM AND ANTIGLUTAMIC ACID DECARBOXYLASE ANTIBODY-ASSOCIATED ENCEPHALOPATHY IN TAIWANESE CHILDREN

Kuang-Lin LIN Division of Pediatric Neurology, Chang Gung Children's Hospital and Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan
Chang Gung Children's Hospital Study Group for Children with Encephalitis/Encephalopathy Related Status Epilepticus and Epilepsy (CHEESE), Taoyuan, Taiwan

P-6

A STUDY ON SPIKE FOCUS-DEPENDENCE OF HIGH-FREQUENCY OSCILLATIONS IN BENIGN CHILDHOOD PARTIAL EPILEPSY

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

P-7

CHARACTERIZATION OF EARLY AND LATER ONSET EPILEPSY IN INDIVIDUAL WITH AUTISM.

Jun MATSUI Department of Pediatrics, Shiga University of Medical Science Department of Pediatrics, Shiga, Japan,

P-8

A CASE OF BACTERIAL MENINGITIS WITH BURST WAVES OF LOCAL ONSET ON ICTAL EEGS

Hisako YAMAMOTO Department of Pediatrics, Kawasaki Municipal Tama Hospital, Kawasaki, Japan
Department of Pediatrics, St. Marianna University School of Medicine, Kawasaki, Japan

P-9

TEMPO OF MOZART MUSIC IS NOT THE CRITICAL FACTOR IN REDUCING SEIZURE ACTIVITY

Po-Ching CHOU Department of Pediatrics, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
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P-10

CONCENTRATIONS OF AMINO ACIDS AND MONOAMINE METABOLITES IN THE CEREBROSPINAL FLUID IN INFANTS SHOWING CONVULSIVE DISORDERS

Masaharu HAYASHI Tokyo Metropolitan Institute of Medical Science
Brain Development and Neural Regeneration

P-11

MRI FINDINGS DURING ACUTE PERIOD IN BENIGN CONVULSIONS WITH GASTROENTERITIS AND BENIGN PARTIAL EPILEPSY IN INFANCY

Chikako OGAWA Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan

P-12

ROLES OF SEIZURE-INDUCED MICROGLIAL ACTIVATION IN EPILEPTOGENESIS PROCESS VIA PHAGOPTOSIS AND NEUROINFLAMMATION

Fumikazu SANO Department of Pediatrics, Faculty of Medicine, University of Yamanashi, Yamanashi, Japan

P-13

CLINICAL CHARACTERISTICS OF FEBRILE AND AFEBRILE SEIZURES WITH GASTROENTERITIS IN CHILDREN

Pin Fee CHONG Department of Pediatric Neurology, Fukuoka Children's Hospital, Fukuoka, Japan.
Department of Pediatric, Fukuoka Children's Hospital, Fukuoka, Japan.

P-14

A GIRL WITH A PRRT2 MUTATION AND INFANTILE FOCAL EPILEPSY WITH BILATERAL SPIKES

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Department of Pediatrics, Fukuoka Dental College Medical and Dental Hospital, Fukuoka, Japan

P-15

EFFECTS OF LEVETIRACETAM ON INTRACTABLE SEIZURES IN CHILDREN WITH HOLOPROSENCEPHALY

Yoshimi KAGA Department of Pediatrics, NHO Kofu National Hospital, Yamanashi, Japan,
Department of Pediatrics, Faculty of medicine, University of Yamanashi, Yamanashi, Japan

P-16

DIGEORGE SYNDROME PRESENTED WITH PERIODIC VOMITING

Pi-Lien HUNG Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

P-17

EPILEPTIC APNEA IN AN INFANT WITH RESPIRATORY SYNCYTIAL VIRUS INFECTION PROVED BY VIDEO-EEG

Jao-Shwann LIANG Department of Pediatrics, Far Eastern Memorial Hospital, Taipei, Taiwan.
R.O.C.

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CLINICAL FEATURES AND *PRRT2* GENE MUTATIONS IN FAMILIES WITH BENIGN FAMILIAL INFANTILE EPILEPSY

Xiaoling YANG Department of Pediatrics, Peking University First Hospital, Beijing, China

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PHENOTYPES AND *PRRT2* MUTATIONS IN INFANTILE CONVULSIONS WITH PAROXYSMAL CHOREOATHETOSIS

Yuehua ZHANG Department of Pediatrics, Peking University First Hospital, Beijing, China

P-20

THE ELECTROCLINICAL FEATURES OF BENIGN INFANTILE EPILEPSY IN 49 PATIENTS

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P-21

***POLG1* MUTATION IN A PATIENT PRESENTING WITH PROFOUND HYPOTONIA, REFRACTORY SEIZURES AND FACIAL DYSMORPHISM: A CLINICAL REPORT**

Ceren GUNBEY Department of Pediatrics, Pediatric Neurology Unit, Hacettepe University Faculty of Medicine, Ankara, Turkey

P-22

CLINICAL FEATURE OF SEIZURE IN EMANUEL SYNDROME: A CASE REPORT

Naomi HINO-FUKUYO Center for genetic medicine, Tohoku University Hospital

P-23

CLINICOPATHOLOGIC FEATURES OF THREE JUVENILE PATIENTS WITH EPILEPSY: DYSPLASTIC TEMPORAL LOBE LESIONS WITH AN ANGIOCENTRIC ARRANGEMENT OF IMMATURE CELLS

Naohiko SEIKE Departments of Pathology, Brain Research Institute, University of Niigata, Niigata, Japan

P-24

THE CLINICAL MANIFESTATION OF 13 PATIENTS WITH PAROXYSMAL KINESGENIC DYSKINESIA

Yu KOBAYASHI Department of Pediatrics, Epilepsy Center, Nishi-Niigata Chuo National Hospital, Niigata, Japan

P-25

***KCNQ2* MUTATION IN CHILDHOOD EPILEPSY WITHOUT AN IDENTIFIED CAUSE: EEG CHARACTERISTICS IN A CASE SERIES**

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Institute of Medicine, School of Medicine, Chung Shan Medical University, Taichung, Taiwan
Genetics Laboratory and Department of Biomedical Sciences, Chung Shan Medical University, Taichung, Taiwan

P-26

NEURONAL CEROID LIPOFUSCINOSIS-2 (CLN2) DISEASE, A TYPE OF BATTEN DISEASE CAUSED BY TPP1 ENZYME DEFICIENCY: CURRENT KNOWLEDGE OF THE NATURAL HISTORY FROM INTERNATIONAL EXPERTS

Yoshikatsu ETO Advanced Clinical Research Center, Southern Tohoku Brain Research Center, Kawasaki, Japan

P-27

REAL-WORLD EXPERIENCE IN THE DIAGNOSIS OF NEURONAL CEROID LIPOFUSCINOSIS TYPE 2 (CLN2): REPORT FROM AN INTERNATIONAL COLLABORATION OF EXPERTS

Yoshikatsu ETO Advanced Clinical Research Center, Southern Tohoku Brain Research Center, Kawasaki, Japan

P-28

SEQUENTIAL PROFILING OF SERUM CYTOKINE RESPONSE TO ACTH IN PATIENTS WITH WEST SYNDROME

Gaku YAMANAKA Department of Pediatrics, Tokyo Medical University, Tokyo, Japan

P-29

THE EFFICACY OF LIDOCAINE IN INTRACTABLE EARLY-ONSET EPILEPTIC ENCEPHALOPATHY: A CASE STUDY

Kazuhiro MURAMATSU Department of Pediatrics, Gunma University Graduate School of Medicine
Department of Child Neurology, National Center of Neurology and Psychiatry (NCNP)

P-30

BENIGN INFANTILE SEIZURE AS THE INITIAL PRESENTATION OF GLUCOSE TRANSPORTER-1 DEFICIENCY

Kumiko CHINO Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA.
Toho University School of Medicine, Tokyo, Japan

P-31

TARGETED NEXT GENERATION SEQUENCING IN CHILDREN WITH EPILEPTIC ENCEPHALOPATHY: STUDY FROM A TERTIARY CARE UNIVERSITY HOSPITAL IN SOUTH INDIA

Parayil Sankaran BINDU Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India

P-32

KETOGENIC DIET AND HIGH-DOSE INTRAVENOUS METHYLPREDNISOLONE IN THREE CASES WITH ACUTE ENCEPHALITIS WITH REFRACTORY, REPETITIVE PARTIAL SEIZURES

Tetsuhiro FUKUYAMA Division of Pediatric Neurology, Nagano Children's Hospital, Azumino, Japan

P-33

GENOTYPIC AND PHENOTYPIC FINDINGS IN A PATIENT WITH COMPOUND HETEROZYGOUS PRRT2 MUTATION: UNTANGLING THE CORRELATION.

Christelle MOUFAWAD EL ACHKAR, MD
Harvard Medical School, Boston, MA
Boston Children's Hospital, Department of Neurology, Division of Epilepsy, Boston, MA
Boston Children's Hospital, Epilepsy Genetics Program, Boston, MA

P-34

A CASE OF LOCALIZATION RELATED EPILEPSY WITH EPILEPTIC SPASMS: ICTAL VTR-EEG STUDY

Kaori SASSA Department of Pediatrics, Saitama Medical University School of Medicine

CURRICULUM VITAE

Invited Lecturers

Federico Vigeveno

■ Work experience

1978 - Assistant Neurologist, Child Neuropsychiatry Unit, Children's Hospital Bambino Gesù
1982 - Head of the Unit of Neurophysiology, Children's Hospital Bambino Gesù
1997 - Chief of U.O.C. of Neurology, Children's Hospital Bambino Gesù
2009 - Director of the Department of Neuroscience, Children's Hospital Bambino Gesù
2010- Director of the Neurosciences and Neurorehabilitation Department, at Children's Hospital Bambino Gesù;



■ Education and training

1974 Degree in Medicine and Surgery at University of Rome.
1975 Qualified to practice as a surgeon
1977 Postgraduate Diploma in Neurology and Psychiatry at the I Clinic of Nervous and Mental Diseases, University of Rome.
1977 Certification in electroencephalography at University of Marseille, France.
1989 Eligibility Primary in Neurology

■ Academic assignments

Adjunct Professor of "Neurology" University "La Sapienza" - Rome - from 2012 to date;
Adjunct Professor of "Neurology" University of Tor Vergata - Rome - from 2010 to date;
Adjunct Professor of "Pediatrics" University "La Sapienza" - Rome - from 2001 to date;
Adjunct Professor of "Neurology" Catholic University "Sacro Cuore" - Rome – from 2001 to 2005
Adjunct Professor of "Neurology" University "La Sapienza" - Rome – from 1993 to 2004.

■ Scientific assignments

1996 - 1999 Secretary of LICE.
1999 - 2002 President of the LICE
2001 - 2009 Member of the ILAE Commission of European Affairs
2001 - 2005 President of the European Advisory Council of the European Leagues Against Epilepsy
2001 - Ambassador of Epilepsy.
1999 - 2014 Advisory Board of Epileptic Disorders
2010 ~ President of the Epilepsy Foundation
Referee of the following journals: Epilepsia; Brain Development; Italian Journal of Neurological Science, Italian Journal of Paediatrics, European J. of Paediatric Neurology, Epileptic Disorders.
2014 ~ Member of the ILAE Commission on Classification and Terminology (Syndromes and Diagnostic Manual Task Force)

■ Main research topics

Pediatric Epilepsy, Drug-resistant Epilepsy, Video-EEG and Long-term monitoring in epilepsy, Coma in children, Sudden Infant Death Syndrome, Non epileptic paroxysmal manifestations, Crisis by Video-Game.
Authored or co-authored more than 130 publications

Nicola Specchio

Department of Neuroscience, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

Dr. Specchio is a medical doctor and Physician doctor, he is Head of Epilepsy Surgery Unit in the Department of Neuroscience at Bambino Gesù Children's Hospital in Rome, Italy. Dr. Specchio main activity is the diagnosis and treatment of pediatric epileptic patients, with main interest in seizure semiology, classification of epileptic seizures and syndromes. He works in the field of pre-surgical evaluation of patients with drug resistant epilepsy and in the selection of patients with genetic epilepsies. Dr. Specchio has published papers in International journals with main interest on epilepsy as Epilepsia, Epilepsy Research, Epilepsy and Behavior. Dr. Specchio currently is responsible for different clinical research projects regarding invasive monitoring of epileptic patients and the genetic etiology of epileptic encephalopathy in the first three years of life. Dr. Specchio is representative of the Italian Chapter of the International League Against Epilepsy.



Biography Updated on 05 June 2015

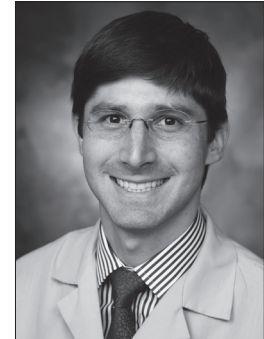
John J. Millichap

■ Present Position

Assistant Professor of Pediatrics and Neurology,
Northwestern University Feinberg School of Medicine

■ Education & Training

1993-1998 BA, Environmental Sciences, Northwestern University
2000-2004 MD, Medicine, American University of the Caribbean School of Medicine
2004-2007 Pitt County Memorial Hospital, Brody School of Medicine at East Carolina University (Internal Medicine-Pediatrics)
2007-2010 Children's Memorial Hospital, Northwestern University Feinberg School of Medicine (Child Neurology)
2010-2011 Children's Memorial Hospital, Northwestern University Feinberg School of Medicine (Clinical Neurophysiology)



■ Academic Appointments

2011-2014 Instructor, Department of Pediatrics and Neurology, Northwestern University Feinberg School of Medicine
2014- Assistant Professor, Department of Pediatrics and Neurology, Northwestern University Feinberg School of Medicine

■ Original Investigations

1. Millichap J, Ristow TA, Noskin GA, Peterson LR. Selection of *Enterococcus faecium* strains with stable and unstable resistance to the streptogramin RP 59500 using stepwise in vitro exposure. *Diagn Microbiol Infect Dis*. 1996 May;25(1):15-20.
2. Beyer R, Pestova EV, Millichap JJ, Stosor V, Noskin GA, Peterson LR. A convenient assay to estimate the possible involvement of efflux of fluoroquinolones by *Streptococcus pneumoniae* and *Staphylococcus aureus*: evidence for diminished moxifloxacin, sparfloxacin, and trovafloxacin efflux. *Antimicrob Agents Chemother*. 2000 Mar;44(3):798-801.
3. Pestova E, Millichap JJ, Noskin GA, Peterson LR. Intracellular Targets of Moxifloxacin: A Comparison with Other Fluoroquinolones. *J Antimicrob Chemother*. 2000 May;45(5):583-90.
4. Prystowsky J, Siddiqui F, Chosay J, Shinabarger DL, Millichap J, Peterson LR, Noskin GA. Resistance to linezolid: characterization of mutations in rRNA and comparison of their occurrences in vancomycin-resistant enterococci. *Antimicrob Agents Chemother*. 2001 Jul;45(7):2154-6.
5. Millichap JJ, Pestova EV, Siddiqui F, Noskin GA, Peterson LR. Fluoroquinolone Resistance Is a Poor Surrogate Marker for Type II Topoisomerase Mutations in Clinical Isolates of *Streptococcus pneumoniae*. *J Clin Microbiol*. 2001 Jul;39(7):2719-21.
6. Pestova E, Millichap JJ, Siddiqui F, Noskin GA, Peterson LR. Non-PmrA-mediated multidrug resistance in *Streptococcus pneumoniae*. *J Antimicrob Chemother*. 2002 Mar;49(3):553-6.
7. Millichap JJ, Millichap JG. Methods of investigation and management of infections causing febrile seizures. *Pediatr Neurol*. 2008 Dec;39(6):381-6.
8. Millichap JJ, Wainwright MW. Neurological Complications of Respiratory Syncytial Virus Infection: Case Series and Review of Literature. *J Child Neurol*. 2009 Dec;24(12):1499-503.
9. Millichap JJ, Stack CV, Millichap JG. Frequency of Epileptiform Discharges in the Sleep Deprived Electroencephalogram in Children Evaluated for Attention Deficit Disorders. *J Child Neurol*. 2011 Jan;26(1):6-11. Epub 2010 Aug 17.
10. Hussain SA, Kwong G, Millichap JJ, Mytinger JR, Ryan N, Matsumoto JH, Wu JY, Lerner JT, Sankar R. Hypsarrhythmia assessment exhibits poor interrater reliability: a threat to clinical trial validity. *Epilepsia*. 2015 Jan;56(1):77-81. doi: 10.1111/epi.12861.
11. Wirrell EC, Shellhaas RA, Joshi C, Keator C, Kumar S, Mitchell WG; Pediatric Epilepsy Research Consortium. How should children with West syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium. *Epilepsia*. 2015 Apr;56(4):617-25. doi: 10.1111/epi.12951.

Alexis Arzimanoglou

Director of the “Epilepsy, Sleep and Pediatric Neurophysiology” Departement at the University Hospitals of Lyon, France; Professor of Neurology and Child Neurology at the Paris College of Medicine. He serves as Editor-in-Chief of the ILAE official educational journal *Epileptic Disorders* and as Associate Editor of the *European Journal of Paediatric Neurology*.

Born in Greece, he graduated from the University of Salonica Medical School, and started his training in Neurology at the Northwick Park Hospital and at Queen Square in the UK. In 1981 he moved to Paris and completed his residency at the Hôpital de la Salpêtrière and his training in Child Neurology, as a pupil of *Jean Aicardi*, at the Hôpital des Enfants Malades. He then worked as Child Neurologist at the SALPETRIERE hospital, before becoming Consultant Child Neurologist at the Children’s University Hospital ROBERT DEBRE in Paris, in charge of the Epilepsy Program of the Department of Child Neurology and Metabolic Disorders. Since June 2008 he is heading the Pediatric Epilepsy, Sleep and Neurophysiology Dpt. at the University Children’s Hospital of Lyon (HFME).

His clinical and research activities mainly concern the pharmacological and surgical management and genetics of childhood epilepsies and issues related to cognitive function and dysfunction in children with focal epilepsies. He is involved in several European collaborative studies on neurological disorders in children and is a member of the *Brain Dynamics and Cognition* team (DYCOG) of the Lyon Neuroscience Research Center (CRNL).

Professor Arzimanoglou published more than 130 articles in peer-reviewed journals. Together with Prs. Aicardi and Guerrini, he authored the 3rd edition of one of the major epilepsy books: “*Aicardi’s Epilepsy in children*” (LWW editions). He is the co-editor of several books (John Libbey Eurotext editions), including “Cognitive Dysfunction in children with temporal lobe epilepsy” (2005), “Neuropsychology in the Care of People with epilepsy” (2011); “Outcome of Childhood Epilepsies (2012). In 2011 he co-edited with Prs. H. Cross and M. Duchowny the Raven Press book on “Pediatric Epilepsy”.

Professor Arzimanoglou is an ILAE Ambassador for Epilepsy. He chaired the organizing committee of the 26th International Epilepsy Congress held in Paris (2005) and already served as: President of the Council of the French Chapter of the ILAE; Chair of the Scientific Committee of the European Paediatric Neurology Society; Elected member of the European Commission of the ILAE; President of the Société Européenne de Neurologie Pédiatrique (French speaking).

He is an active member of the International Child Neurology Association (ICNA); Corresponding member of the American Epilepsy Society (AES); Active member of the ILAE Education Commission and the Pediatric Epilepsy Surgery Task Force; Invited member of the Executive Committee of the International League Against Epilepsy; Active member of the Advisory Board of the Infantile Seizures Society.



Shinichi Hirose

■ Present Position

Professor and Chairman, Department of Pediatrics, School of Medicine, Fukuoka University

Director, Center for Maternal, Fetal and Neonatal Medicine, Fukuoka University Hospital

■ Education:

1980 M.D. Fukuoka University, School of Medicine

1988 Ph.D. Fukuoka University, School of Medicine (Biochemistry)



■ Academic appointments:

4/1992-9/1992 Associate Physician in Pediatrics, Fukuoka University Hospital

10/1992-3/1994 Instructor in Pediatrics, Fukuoka University Hospital

4/1994-3/1997 Assistant Professor, Department of Pediatrics, School of Medicine Fukuoka University

4/1997-3/2005 Associate Professor, Department of Pediatrics, School of Medicine, Fukuoka University

4/2006-3/2010 Professor and Chairman, Department of Pediatrics, School of Medicine, Fukuoka University

Director, Center for Maternal, Fetal and Neonatal Medicine, Fukuoka University Hospital

4/2006-3/2010 Director, The Research Center for the Molecular Pathomechanisms of Epilepsy,
Fukuoka University

4/2011- Director, Central Research Institute for the Molecular Pathomechanisms of Epilepsy,
Fukuoka University

4/2014 Director, Center for Maternal, Fetal and Neonatal Medicine, Fukuoka University Hospital

Susumu Ito

■ Present Position

Assistant Professor
Department of Pediatrics, Tokyo Women's Medical University

■ Education

1996 - 2002 School of Medicine, Shinshu University
2006 - 2010 Graduate School of Medicine, Tokyo Women's Medical University

■ Work experience

2002 - Department of Pediatrics, Tokyo Women's Medical University
2007 - 2009 Laboratory for Neurogenetics, Riken Brain Science Institute
2011 - 2013 Epilepsy center, Cleveland Clinic

■ Certification

Board Certified Pediatrician, 2008 (Japan Pediatric Society)
Board Certified Pediatric Neurologist, 2009 (The Japanese Society of Child Neurology)
Board Certified Epileptologist, 2010 (The Japan Epilepsy Society)

■ Publications

1. Ito S, Oguni H, Ito Y, Ishigaki K, Ohinata J, Osawa M. Modified Atkins diet therapy for a case with glucose transporter type 1 deficiency syndrome. *Brain Dev* 2008;30:226-228.
2. Ito S, Nakayama T, Ide S, Ito Y, Oguni H, Goto Y, Osawa M. Aromatic L-amino acid decarboxylase deficiency associated with epilepsy mimicking non-epileptic involuntary movements. *Dev Med Child Neurol* 2008; 50: 876-878.
3. Ito S, Shioda M, Sasaki K, Imai K, Oguni H, Osawa M. Agranulocytosis following phenytoin-induced hypersensitivity syndrome. *Brain Dev* 2009; 31: 449-451.
4. Ito S, Oguni H, Osawa M. Benign myoclonic epilepsy in infancy with preceding afebrile generalized tonic-clonic seizures in Japan. *Brain Dev.* 2012;34:829-833.
5. Ito S, Ogiwara I, Yamada K, Miyamoto H, Hensch TK, Osawa M, Yamakawa K. Mouse with Nav1.1 haploinsufficiency, a model for Dravet syndrome, exhibits lowered sociability and learning impairment. *Neurobiol Dis* 2013;49:29-40.

■ Award

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



Toshiyuki Yamamoto

Associate Professor, Tokyo Women's Medical University Institute for Integrated Medical Sciences



■ EDUCATIONAL HISTORY

- 1989 M.D. Faculty of Medicine, Tottori University
- 1999 Ph.D. Faculty of Medicine, Tottori University

■ PROFESSIONAL BACKGROUND (EMPLOYMENT HISTORY)

- May/1989 passed the Examination of National Board
- May/1989-Mar/1990 Resident in Tottori University Hospital
- Apr/1990-Jun/1992 Medical Staff in Department of Pediatrics, Matsue Red Cross Hospital
- Jul/1992-Sep/1992 Medical Staff in Department of Pediatrics, Matsue Hospital for Disabled Children
- Oct/1992-Jun/1993 Medical Staff, Division of Child Neurology, Tottori University Hospital
- Jul/1993-Jul/1995 Research Associate, Division of Child Neurology, Institute for Neurological Sciences, Tottori University
- Jul/1995-Feb/2003 Research Associate, Gene Research Center, Tottori University
- Apr/2002-Jan/2003 Research Fellow, Centre for Medical Genetics, Laboratory of Molecular and Cytogenetics, Adelaide University, SA, AUSTRALIA
- Mar/2003- Medical Chief in Department of Medical Genetics, Kanagawa Children's Medical Center
- Jan/2006 Assistant Professor, International Research and Educational Institute for Integrated Medical Sciences (IREIIMS), Tokyo Women's Medical University (TWMU)
- Apr/2008 Associate Professor, above
- Apr/2012 Associate Professor, Tokyo Women's Medical University Institute for Integrated Medical Sciences

■ AWARDS AND HONORS

- Annual Award of Japanese Society of Child Neurology (2005)

■ MAJOR RESEARCH INTERESTS

- Molecular cytogenetic analysis for neurogenetic disorders

■ OFFICIAL POSITION

- Associate Editor of "Human Genome Variation" (Official journal of the Japan Society of Human Genetics)
- Associate Editor of "No-to-Hattatsu" (Official journal of the Japanese Society of Child Neurology)
- Asian Editor of "Journal of Pediatric Genetics"

Kenjiro Kikuchi

■ Present Position

Assistant Professor, Department of Pediatrics, Jikei University School of Medicine, Tokyo, Japan

■ Education and assignments

2000: MD. Jikei University School of Medicine, Tokyo, Japan

2013: PhD. Jikei University School of Medicine, Tokyo, Japan

2004-2008: Assistant Professor, Department of Pediatrics, Jikei University School of Medicine, Tokyo, Japan

2008-2015: Chief Physician, Division of Neurology, Saitama Children's Medical Center, Saitama, Japan

2015-: Assistant Professor, Department of Pediatrics, Jikei University School of Medicine, Tokyo, Japan



■ Selective publications:

1. Kikuchi K, Hamano S, Higurashi N, Matsuura R, Suzuki K, Tanaka M, Minamitani M. Difficulty of early diagnosis and requirement of long-term follow-up in benign infantile seizures. *Pediatr Neurol* 2015 (in press).
2. Kikuchi K, Hamano S, Mochizuki H, Ichida K, Ida H. Molybdenum cofactor deficiency mimics cerebral palsy: differentiating factors for diagnosis. *Pediatr Neurol* 2012;47:147-149.
3. Kikuchi K, Hamano S, Goto F, Takahashi A, Ida H. Epileptic focus in a case of subcortical band heterotopia: SISCOM and ictal EEG findings. *Epilepsy & Seizure* 2010;3:192-198.
4. Kikuchi K, Hamano S, Oritsu T, Koichihara R, Tanaka M, Minamitani M, Ida H. Effectiveness and safety of non-intravenous high-dose phenobarbital therapy for intractable epilepsy during childhood. *Brain Dev* 2011;33:379-383.

Masanori Takeoka

■ Education

- 1987-1989 Pre-Medicine (Japan), Keio University, Tokyo, Japan
1989-1993 M.D. Medicine, School of Medicine, Keio University, Tokyo, Japan

■ Postdoctoral Training

- 1993-1994 Resident, Pediatrics, Keio University Hospital, Tokyo, Japan
1994-1995 Resident, Pediatrics, Massachusetts General Hospital, Boston, MA
1995-1998 Resident, Child Neurology, Massachusetts General Hospital, Boston, MA
1998-2000, Clinical Fellow, Epilepsy and Clinical Neurophysiology, Boston Children's Hospital, Boston, MA

■ Faculty Academic Appointments

- 2001-2003 Instructor, Pediatrics, School of Medicine, Keio University, Tokyo, Japan
2003-2005 Instructor, Neurology, Harvard Medical School, Boston, MA
2005-present Assistant Professor, Neurology, Harvard Medical School, Boston, MA

■ Recent Selected Publications

1. Sánchez Fernández I, Peters JM, An S, Bergin AM, Takeoka M, Rotenberg A, Kothare SV, Riviello JJ Jr, Loddenkemper T. (2013) Long-term response to high-dose diazepam treatment in continuous spikes and waves during sleep. *Pediatr Neurol* 49(3): 163-170.e4.
2. Taimouri V, Akhondi-Asl A, Tomas-Fernandez X, Peters JM, Prabhu SP, Poduri A, Takeoka M, Loddenkemper T, Bergin AM, Harini C, Madsen JR, Warfield SK. (2013) Electrode localization for planning surgical resection of the epileptogenic zone in pediatric epilepsy. *Int J Comput Assist Radiol Surg*. 2013 Jun 23. [Epub ahead of print].
3. Olson H, Shen Y, Avallone J, Sheidley BR, Pinsky R, Bergin AM, Berry GT, Duffy FH, Eksioglu Y, Harris DJ, Hisama FM, Ho E, Irons M, Jacobsen CM, James P, Kothare S, Khwaja O, Lipton J, Loddenkemper T, Markowitz J, Maski K, Megerian JT, Neilan E, Raffalli PC, Robbins M, Roberts A, Roe E, Rollins C, Sahin M, Sarco D, Schonwald A, Smith SE, Soul J, Stoler JM, Takeoka M, Tan WH, Torres AR, Tsai P, Urion DK, Weissman L, Wolff R, Wu BL, Miller DT, Poduri A (2014). Copy number variation plays an important role in clinical epilepsy. *Ann Neurol*. 2014 May 9. doi: 10.1002/ana.24178. [Epub ahead of print].
4. Klehm J, Thome-Souza S, Sánchez Fernández I, Bergin AM, Bolton J, Harini C, Kadish NE, Libenson M, Peters J, Poduri A, Rotenberg A, Takeoka M, Bourgeois B, Loddenkemper T (2014). Clobazam: effect on frequency of seizures and safety profile in different subgroups of children with epilepsy. *Pediatr Neurol*. 2014 Jan 16. pii: S0887-8994(14)00027-7. doi:10.1016/j.pediatrneurol.2014.01.025. [Epub ahead of print].
5. Thome-Souza S, Kadish NE, Ramgopal S, Sanchez Fernandez I, Bergin AM, Bolton J, Harini C, Libenson M, Olson H, Peters J, Poduri A, Rotenberg A, Takeoka M, Kothare SV, Kapur K, Bourgeois BFD, Loddenkemper T (2014). Safety and retention rate if rufinamide in 300 patients: A single pediatric epilepsy center experience. *Epilepsia* 55(8):1235-44.
6. Pinto ALR, Lohan S, Bergin AM, Bourgeois BFD, Black PM, Prabhu SP, Madsen JR, Takeoka M, Poduri A (2014). Surgery for intractable epilepsy due to a unilateral brain disease: a retrospective study comparing hemispherectomy techniques. *Pediatr Neurol* 51(3):336-43.
7. Harini C, Das RR, Prabhu SP, Singh K, Haldar A, Takeoka M, Bergin AM, Loddenkemper T, Kothare SV (2014). Clinical and radiological profile of children with lesions in corpus callosum. *J Neuroimaging*. 2014 Dec 18. doi: 10.1111/jon.12190. [Epub ahead of print] .



Harvey B. Sarnat

■ Present Positions

Professor of Pediatrics, Pathology (Neuropathology) and Clinical Neuroscience,
University of Calgary Faculty of Medicine,
Paediatric Neurologist and Neuropathologist,
Alberta Children's Hospital
Alberta Children's Hospital Research Institute, Calgary, Alberta, Canada

■ Education

Degrees:

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

Postgraduate:

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

■ Research Interests

Neuroembryology and developmental neuropathology, with special reference to a) immunocytochemical markers of neuronal and glial maturation in normal human fetal and neonatal brain and in malformations; b) gradients of genetic expression in the axes of the neural tube; c) pathogenesis of Chiari malformations; d) neural tube induction of craniofacial development; e) immunocytochemical markers of neuronal and glial maturation in the fetal brain; f) heat-shock proteins as tissue markers of epileptic foci in surgical resections in children.
Mitochondrial encephalomyopathies: neuropathological/genetic correlates
Comparative neuroanatomy and evolutionary theory; primordial nervous systems in flatworms

■ Appointments

1973 -1976 Assistant Professor of Neurology and Pediatrics, St. Louis University School of Medicine
1976-1977 Lecturer and Consultant Neurologist, University of Western Australia, Perth, W.A., Australia
1977-1978 Associate Professor of Neurology and Pediatrics, St. Louis University School of Medicine
1978-1981 Associate Professor of Pediatrics, Neurology and Pathology, University of Arkansas for Medical Sciences
1981-1984 Associate Professor of Paediatrics, Pathology and Clinical Neurosciences, University of Calgary Faculty of Medicine
1984 Professor of Paediatrics, Pathology and Clinical Neurosciences, University of Calgary Faculty of Medicine
1992-2001 Professor of Pediatrics (Neurology) and Pathology (Neuropathology), University of Washington School of Medicine, Washington
1992-1998 Herman and Faye Sarkowsky Professor of Pediatric Neurology (Endowed Chair) and Head, Division of Pediatric Neurology
2001-2004 Professor of Pediatrics (Neurology) and Pathology (Neuropathology), University of California at Los Angeles (UCLA), School of Medicine, California
2004- Present Professor of Paediatrics, Pathology and Laboratory Medicine (Neuropathology) and Clinical Neurosciences, University of Calgary Faculty of Medicine



Philip L. Pearl

■ Present Position

Director of Epilepsy and Clinical Neurophysiology at Boston Children's Hospital
William G. Lennox Chair and Professor of Neurology at Harvard Medical School

■ Education and Training

1980 John Hopkins University, Baltimore, Maryland : BA (honors), Natural Sciences
1984 University of Maryland School of Medicine, Baltimore, Maryland: MD, Medicine
1984-1986 Pediatric Internship and Residency, Baylor College of Medicine, Houston, TX
1986-1989 Neurology and Child Neurology, Baylor College of Medicine, Houston, TX
1989-1990 Fellowship in Clinical Neurophysiology, Children's Hospital, Beth Israel Hospital, Harvard Medical School, Boston, MA
2003 Graduate Certificate in Leadership Development, Graduate School of Education and Human Development, George Washington University, Washington, DC



■ Positions and Employment

2002 – 2009 Associate Professor, Neurology and Pediatrics, George Washington University, Washington, DC
2002 – 2013 Director, Neurology Educational Programs, Children's National Medical Center, Washington, DC
2002 – 2013 Scholar, Master Teachers Program in Medical Education, Children's National Medical Center, GWU School of Medicine, Washington, DC
2002 – 2013 Principal Investigator, Children's Research Institute, Children's National Medical Center, Washington, DC
2006 – Visiting Associate Professor, Pediatrics, University of Virginia School of Medicine, Charlottesville, VA
2007 – 2013 Chief, Child Neurology, Children's National Medical Center, Washington, DC
2009 – 2013 Professor, Neurology and Pediatrics, George Washington University, Washington, DC
2014 – William G. Lennox Chair and Professor of Neurology, Harvard Medical School, Boston, MA
2014 – Director, Epilepsy and Clinical Neurophysiology, Boston Children's Hospital, Boston, MA

■ Recent Selected Publications

1. Bosemani T, Anghelescu C, Boltshauser E, Hoon AH, Pearl PL, Craiu D, Johnston MV, Huisman TA, Poretti A: Subthalamic nucleus involvement in children: a neuroimaging pattern-recognition approach. *Eur J Paediatr Neurol* 2014 May;18(3):249-56.
2. Vanderver A, Tonduti D, Kahn I, Schmidt JL, Livija Medne L, Vento J, Chapman K, Lanpher B, Pearl PL, Gropman A, Lourenco C, Bamforth JS, Sharpe C, Pineda M, Schallner J, Bodamer O, Orcesi S, Lesnick Oberstein SAJ, Sistermans EA, Yntema HG, Bonnemann C, Waldman AT, van der Knaap MS: Characteristic Brain Magnetic Resonance Imaging Pattern in Patients with macrocephaly and PTEN Mutations. *Am J Med Genet A* 2014 Mar;164(3):627-633.
3. Vanderver A, Simons C, Schmidt JL, Pearl PL, Bloom M, Lavenstein B, Miller D, Grimmond SM, Taft RJ: Identification of a novel de novo p.Phe932Ile KCNT1 mutation in a patient with leukoencephalopathy and severe epilepsy. *Pediatr Neurol* 2014 Jan;50(1):112-114.
4. Pearl PL, Schreiber J, Theodore WH, McCarter R, Barrios ES, Yu YJ, Wiggs E, He J, Gibson KM: Taurine trial in succinic semialdehyde dehydrogenase deficiency and elevated CNS GABA. *Neurology* 2014 Mar 18;82(11):940-944.
5. Pearl PL, Sable C, Evans S, Knight J, Cunningham P, Lotrecchiano GR, Gropman A, Stuart S, Glass P, Conway A, Ramadan I, Paiva T, Batshaw ML, Packer RJ: International Telemedicine Consultations for Neurodevelopmental Disabilities. *Telemed J E Health* 2014 Jun;20(6):559-62.

Hiroshi Otsubo

■ Present Position

Associate professor, Department of Pediatrics, University of Toronto
Director of Operations for the Neurophysiology Laboratory in the Division of Neurology, The Hospital for Sick Children, Toronto.

■ Education

1983 Graduate Shinshu University, School of Medicine

■ Postgraduate Medical Training

1988 – 1989 Research fellow, Division of Neurosurgery, The Hospital for Sick Children
1989 – 1994 EEG Fellow, EEG & Clinical Neurophysiology, Laboratory, The Hospital for Sick Children
1994 – 2008 Assistant Professor, Department of Pediatrics, University of Toronto
1997 – present Director of Operations EEG & Clinical Neurophysiology and Epilepsy Monitoring Unit (EMU)
1999 – present Project Director, Research Institute, The Hospital for Sick Children
2003 – present Visiting Professor, Department of Neurosurgery, Shinshu University, School of Medicine, Japan
2008 – present Associate professor, Department of Pediatrics, University of Toronto

■ Professional practice

Electroencephalography (EEG)
Magnetoencephalography (MEG)
Epilepsy surgery

■ Committee

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



Ingrid E. Scheffer

Chair of Paediatric Neurology Research, Departments of Medicine and Paediatrics, The University of Melbourne, Austin Health and Royal Children's Hospital, Melbourne
Senior Principal Research Fellow, The Florey Institute of Neuroscience and Mental Health

Director of Paediatrics, Austin Health, Melbourne, Australia



Professor Ingrid Scheffer is a physician-scientist whose work as a paediatric neurologist at the University of Melbourne and Florey Institute has led the field of epilepsy genetics over 20 years, with Professor Samuel Berkovic and molecular geneticists. This resulted in identification of the first epilepsy gene and many genes subsequently. Professor Scheffer has described many novel epilepsy syndromes and genotype–phenotype correlation. She recently led the first reclassification of the epilepsies in two decades as Chair of the International League Against Epilepsy Commission for Classification. Her awards include American Epilepsy Society Clinical Research Award and L'Oréal-UNESCO Women in Science Laureate for the Asia-Pacific region. In 2014, she was elected as a Fellow of the Australian Academy of Science and as inaugural Vice-President of the Australian Academy of Health and Medical Sciences. Professor Scheffer was awarded the Order of Australia and, together with Professor Berkovic, the Prime Minister's Prize for Science.

Yukitoshi Takahashi

■ Present Position:

Vice-director, National epilepsy center, Shizuoka institute of epilepsy and neurological disorders, NHO. Clinical Professor, Department of pediatrics, Gifu University School of Medicine, and Visiting Professor School of Pharmaceutical Sciences, University Shizuoka, Japan.

■ Education, Post Graduate Training and Appointment:

Dr. Takahashi has MD from Gifu University. He started the study about photosensitive mechanisms from 1991, and autoimmunity in epilepsy and encephalitis from 2000 in collaboration with Prof Mishina of Tokyo University, and published many papers concerning about photosensitivity, Rasmussen syndrome, epilepsy after acute encephalitis, and acute encephalitis. He is a member of board of Japan Neuroinfection Society; member of board of Japan Epilepsy Society; member of pharmaceutical committee of Japan Child Neurology Society; and member of board of Japan Society of Human Genetics. He received JUHN and MARY WADA Award from Japan Epilepsy Society, Japanese Society for Neuroimmunology Award, 10th Kawano Prize, The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology, and Research award of Japan Pediatric Society. His main research interests include: Mechanisms and pathogenesis of neuroimmunological diseases, particularly non-paraneoplastic acute limbic encephalitis, Rasmussen encephalitis, and epilepsy after acute encephalitis, photosensitive epilepsy.

■ Selected Publications in the field of photosensitive epilepsy:

1. Y Takahashi, et al. Self-Induced Photogenic Seizures in a Child with Severe Myoclonic Epilepsy in Infancy: Optical Investigations and Treatments, *Epilepsia* 1995; 36: 728-732.
2. Y Takahashi, et al. Wavelength Specificity of Photoparoxysmal Responses in Idiopathic Generalized Epilepsy, *Epilepsia* 1995; 36: 1084-1088.
3. Y Takahashi, et al. Wavelength Dependency of Photoparoxysmal Responses in Photosensitive Nonepileptic Subjects, *Tohoku J. Exp. Med.* 1997; 181: 311-319.
4. Y Takahashi, et al. Two different pathological conditions of photoparoxysmal responses in hereditary dentatorubral-pallidoluysian atrophy, *Brain & Development* 1997; 19: 285-289.
5. Y Takahashi, et al. Photosensitive epilepsies and pathophysiologic mechanisms of the photoparoxysmal response, *Neurology* 1999; 53: 926-932.
6. Y Takahashi, et al. Wavelength Dependence of Photoparoxysmal Responses in Photosensitive Patients with Epilepsy, *Epilepsia*, 1999; 40(suppl. 4): 23-27.
7. Y Takahashi, et al. Long-wavelength red light emission from TV and photosensitive seizures. *Acta Neurol Scand.* 2001; 103: 114-9.
8. Y Takahashi, et al. Effectiveness of broadcasting guidelines for photosensitive seizure prevention. *Neurology.* 2004; 62: 990-3.



Andrew L. Lux

■ Current posts

- 2005 Consultant Paediatric Neurologist: University Hospitals Bristol NHS Foundation Trust
- 2005 Honorary Consultant Paediatric Neurologist: North Bristol NHS Trust
- 2005 Honorary Senior Lecturer in Child Health: University of Bristol
- 2009 Honorary Consultant Paediatric Neurologist: Plymouth Hospitals NHS Trust

■ Qualifications

- 1985 Bachelor of Medical Sciences with Honours: University of Nottingham Medical School
- 1987 Bachelor of Medicine and Bachelor of Surgery: University of Nottingham Medical School
- 1989 Diploma in Child Health: Royal College of Physicians of London
- 1991 Member of the Royal College of General Practitioners: Royal College of General Practitioners, London
- 1993 Member of the Royal Colleges of Physicians (UK): Royal College of Physicians of London
- 1996 Member of the Royal College of Paediatrics and Child Health: Royal College of Paediatrics and Child Health, London
- 1997 Fellow of the Royal College of Paediatrics and Child Health: Royal College of Paediatrics and Child Health, London
- 1997 Master of Science in Medical Statistics: University of London
- 1998 Diploma of the London School of Hygiene & Tropical Medicine: University of London
- 2004 Fellowship in Clinical Neurophysiology and Pediatric Epilepsy: Washington University School of Medicine, St Louis, Missouri, USA
- 2006 Doctor of Philosophy: School for Health, University of Bath
- 2011 Master of Business Administration with Merit: The Open University

■ Recent Selected publications

1. O'Callaghan FJ, Lux AL, Darke, K., Edwards SJ, Hancock E, Johnson AL, Kennedy CR, Newton RW, Verity CM, Osborne JP.
The effect of lead time to treatment and age of onset on developmental outcome at 4 years in infantile spasms: evidence from the United Kingdom Infantile Spasms Study.
Epilepsia 2011; 52:1359-64.
2. Sinha IP, Altman DG, Beresford MW, Boers M, Clarke M, Craig J, Alberhiggi OD, Fernandes RM, Hartling L, Johnston BC, Lux A, Plint A, Tugwell P, Turner M, van der Lee JH, Offringa M, Williamson PR, Smyth RL; for the StaR Child Health Group.
Standard 5: Selection, measurement, and reporting of outcomes in clinical trials in children.
Pediatrics 2012;129(Suppl.3):S146-52.
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3. Fong CY, Osborne JP, Edwards SW, Hemingway C, Hancock E, Johnson AL, Kennedy CR, Kneen R, Likeman M, Lux AL, Mordekar SR, Murugan V, Newton RW, Pike M, Quinn M, Spinty S, Vassallo G, Verity CM, Whitney A, O'Callaghan FJ.
An investigation into the relationship between vigabatrin, movement disorders, and brain magnetic resonance imaging abnormalities in children with infantile spasms.
Developmental Medicine and Child Neurology 2013;55:862-7.
4. Peall KJ, Smith DJ, Kurian MA, Wardle M, Waite AJ, Hedderly T, Lin JP, Smith M, Whone A, Pall H, White C, Lux A, Jardine P, Bajaj N, Lynch B, Kirov G, O'Riordan S, Samuel M, King MD, Chinnery PF, Warner TT, Blake DJ, Owen MJ, Morris HR.
SGCE mutations cause psychiatric disorders: clinical and genetic characterization.
Brain 2013;136:294-303.
5. Peall KJ, Kurian MA, Wardle M, Waite AJ, Hedderly T, Lin JP, Smith M, Whone A, Pall H, White C, Lux A, Jardine P, Lynch B, Kirov G, O'Riordan S, Samuel M, Lynch T, King MD, Chinnery PF, Warner TT, Blake DJ, Owen MJ, Morris HR.
SGCE and myoclonus dystonia: Motor characteristics, diagnostic criteria and clinical predictors of genotype.
Journal of Neurology 2014;261:2296-304.



Jong M. Rho

■ Education and Training

(Post-Graduate)

1992 – 1994 Clinical Associate, Neuronal Excitability Section, Epilepsy Research Branch,

National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD

1990 – 1992 Fellow in Pediatric Neurology, Department of Pediatrics, UCLA School of Medicine, Los Angeles, CA

1989 – 1990 Resident, Department of Neurology, UCLA School of Medicine, Los Angeles, CA

Pediatric Intern & Resident, Children's Hospital of Los Angeles USC School of Medicine, Los Angeles, CA (Medical)

1983 – 1987 University of Cincinnati College of Medicine, Cincinnati, OH M.D. awarded June 1987 (Undergraduate)

1973 – 1977 Yale University, New Haven, CT, B.A. in Molecular Biophysics & Biochemistry



■ Academic Positions

2005 – 2010 Associate Professor of Clinical Neurology, University of Arizona College of Medicine, Phoenix, AZ

2007 – 2010 Adjunct Professor, Neuroscience & Behavior Program, Arizona State University, Tempe, AZ

2007 – 2010 Adjunct Professor, Harrington Department of Bioengineering, Fulton School of Engineering, Arizona State University, Tempe, AZ

2010 – Present Professor of Paediatrics & Clinical Neurosciences

Robert Haslam Chair in Child Neurology, University of Calgary Faculty of Medicine, Calgary, Alberta, Canada

■ Recent ORIGINAL PEER-REVIEWED RESEARCH PUBLICATIONS

1. Nicolini C, Ahn Y, Michalski B, Rho JM, Fahnestock M. Decreased mTOR signaling pathway in human idiopathic autism and in rats exposed to valproic acid. *Acta Neuropathol Commun* 2015; 3:3.
2. Kim DY, Abdelwahab MG, Lee SH, Thompson RJ, Duff HJ, Rho JM: Ketones prevent oxidative impairment of hippocampal synaptic integrity through KATP channels. *PLoS One* 2015; 10(4):e0119316.
3. Bello-Espinosa L, Rajapakse T, Rho JM, Buchhalter JB: Efficacy of intravenous immunoglobulin in a cohort of children with drug-resistant epilepsy, *Pediatric Neurol* 2015;52(5):509-16.
4. Lee CH, Ahn Y, Kang SM, Park Y, Jeon YJ, Rho JM, Kim SW: Stoichiometric expression of mtHsp40 and mtHsp70 modulates mitochondrial morphology and cristae structure via Opa1L cleavage, *Mol Biol Cell* 2015; 26(12):2156-67.
5. Wallace E, Kim DY, Kim KM, Chen S, Braden BB, Williams J, Jasso K, Garcia A, Rho JM, Bimonte- Nelson H, Maganti R: Effects of acute and chronic sleep fragmentation on spatial learning and synaptic plasticity in pubertal mice. *Brain Res* 2015; 1615:116-28.
6. Kim DY, Simeone TA, Simeone KA, Pandya JD, Wilke JC, Ahn Y, Geddes JW, Sullivan PG, Rho JM: Ketone bodies exerts anti-seizure effects through mitochondrial permeability transition, *Ann Neurol* [Epub ahead of print].
7. Leal-Campanario R, Arribas JI, Schlegal AA, Martinez-Conde S, Rho JM, Rieiro H, Otero-Millan J, Macknik SL: A potential therapeutic pathway for neurodegeneration in epilepsy, *Proc Nat'l Acad Sci (USA)*, in review.
8. Jiang Y, Gavrilovici C, Chansard M, Liu RH, Parsons K, Park SI, Teskey CG, Rho JM, Nguyen MD: Ndel1 and Reelin maintain postnatal integrity and function in CA1 hippocampus, *Journal of Clinical Investigation*, in review.

Akihisa Okumura

■ Present Position

Professor, Department of Pediatrics, Aichi Medical University

■ Academic career

1989 Graduated from Nagoya University School of Medicine, Aichi, Japan

1989 -1990 Resident at Tokai Chuo Hospital

1991 -1992 Department of Pediatrics, Nagoya University Hospital

1992 -1998 Department of Pediatrics, Anjo Kosei Hospital

1998 - 2005 Assistant, Department of Pediatrics, Nagoya University Graduate School of Medicine

2005 -2006 Assistant professor, Department of Pediatrics, Nagoya University Graduate School of Medicine

2006 -2014 Assistant professor, Department of Pediatrics, Juntendo University Faculty of Medicine

2014 ~ Professor, Department of Pediatrics, Aichi Medical University



■ Memberships and Activities in Societies

Asian Editor, Neuropediatrics

Member of the Board of Trustee,

Japanese Society of Child Neurology

Japan Epilepsy Society

Japan Pediatric Society

Infantile Seizure Society

Japan Society of Perinatal and Neonatal Medicine

■ Fields of Major Interest

Acute Encephalopathy, Neonatal Neurology, Infantile Epilepsy

ABSTRACTS

Oral Presentation

THE CLINICAL SPECTRUM OF BENIGN FAMILIAL INFANTILE SEIZURES

Federico VIGEVANO

Ospedale Pediatrico Bambino Gesù, Scientific Institute, Roma, Italy

Fukuyama first (1963) described the existence of infantile seizures with a benign evolution. Later on Watanabe et al. (1987) published a series of infants having focal complex seizures with benign evolution; the majority were not familial. In 1992 Vigevano et al. described familial cases with cluster of seizures in infancy with benign evolution; all the five infants had one or more paternal relatives with a history of seizures occurring at the same age with benign evolution. Age at onset ranged from 4 to 7 months. Autosomal dominant familial cases have been later reported by other authors; this syndrome is included in the ILAE epilepsy classification with the term “Benign Familial Infantile Seizures” (BFIS). Usually epilepsy is limited to the occurrence of a cluster of seizures of 1-3 days and rare seizures later on. A similar form with onset between neonatal and infantile ages was reported by Kaplan and Lacey in 1983. The authors proposed the term of “Benign Familial Neonatal–Infantile Seizure” (BFNIS). Non familial cases of Benign Infantile Seizures have also been described. In 1997 Szepietowski described four French families with benign infantile convulsions and paroxysmal choreoathetosis appearing later on, thus leading to the identification of a new syndrome called Infantile Convulsions and Choreoathetosis (ICCA). In familial cases of infantile seizures a linkage has been demonstrated on chromosome 19q, but also on chromosome 16p. In 1998, genetic mutations on KCNQ2 and KCNQ3, have been described in Benign Neonatal Seizures, thus leading to the consideration of a channelopathy; later this concept also extended to BFIS and BFNIS. In 2002 two families with BFNIS were found to present a missense mutations of SCN2A gene (Heron et al.). Missense SCN2A mutations have later been described even in cases with BFIS, underlying that BFNIS and BFIS might share clinical and genetic features. More recently, PRRT2 gene mutations have been found in BFIS. These mutations have been recognized to be involved in paroxysmal choreoathetosis, with or without benign infantile seizures.

BENIGN FAMILIAL NEONATAL SEIZURES

Nicola SPECCHIO

Department of Neuroscience – Bambino Gesù Children's Hospital, IRCCS,
Rome, Italy

Benign familial neonatal seizures (BFNS) is a genetic epilepsy syndrome characterized by the occurrence of afebrile seizures in otherwise healthy newborns with onset in the first few days of life.

Prevalence is currently unknown since this disorder is possibly overlooked.

Seizure onset is usually between the second and the eighth day of life, in otherwise healthy newborns.

Psychomotor development of all newborns before the onset of seizures is absolutely normal. The occurrence of seizures in almost all cases is in cluster. These are brief (2-3 minutes) but repetitive, occurring up to 20 times per day, which very rarely reach a true status epilepticus.

Seizures can occur during wakefulness and/or sleep and are characterized by tonic posture with diffuse hypertonia, cyanosis, and unilateral limb jerks, which become bilateral and synchronous or asynchronuous.

Clinical conditions during the cluster are normal; occasionally has been reported sopor, which is probably caused by drugs. The cluster can last 1 to 3 days.

Although most patients do receive antiepileptic treatment in the neonatal period, seizures have been shown to remit spontaneously after the first months of life, and are usually not seen after the first year of life. However, about 10 to 15% of patients have febrile or afebrile seizures later in childhood. Subsequent psychomotor development is normal.

BFNS is a genetically heterogeneous disorder due to mutations in the KCNQ2 (20q13.33) and KCNQ3 (8q24) genes that both code for voltage-gated potassium channel subunits. Mutations in KCNQ2 are also responsible for KCNQ2-related epileptic encephalopathy, a severe form of neonatal epilepsy.

Interictal electroencephalogram (EEG) reveal focal interictal abnormalities, mainly over the central regions, but otherwise the EEG background is normal. The diagnosis is confirmed by genetic testing.

Differential diagnosis includes benign familial neonatal-infantile seizures and benign familial infantile epilepsy. Transmission is autosomal dominant.

Seizures in these forms could be not treated with antiepileptic medications, and only an emergency medication with benzodiazepine might be used, but, in the clinical practice is difficult not to treat these patients. At the very beginning these newborns presents seizures in cluster (seizure every 2-3 hours), which sometimes require a rapid intervention with drugs. In emergency departments rarely physicians are aware of the etiology of the seizures, which appear clearly only after EEGs monitoring and a normal neurological evaluation. For these reasons the majority of children receive an antiepileptic treatment. In cases that exhibit a familial recurrence is possible to withhold the treatment. All drugs demonstrate their efficacy in benign neonatal seizures (valproate, carbamazepine, phenobarbital and phenytoine), with apparently no differences. The treatment can be withdrawn after one year of the onset. However, it is important for clinicians and family to be aware that some patients require treatment beyond 12 months of age.

Prognosis is good. Seizures normally disappear during the first year of life and patients do not display any neurological sequelae. Later seizures have been reported, including occasional febrile seizures and idiopathic epilepsy syndromes in childhood, in particular rolandic epilepsy.

CLINICAL SPECTRUM OF EPILEPSY SECONDARY TO KCNQ2 VARIANTS AND GENETIC MODIFIERS

John J. MILLICHAP

Epilepsy Center, Ann & Robert H. Lurie Children's Hospital of Chicago; Departments of Pediatrics and Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL

Pathogenic KCNQ2 variants can result in a spectrum of epilepsy from benign to severe. Benign Familial Neonatal Epilepsy (BFNE) is characterized by frequent neonatal seizures that generally subside completely within a few months and are followed by normal cognitive development. BFNE is highly penetrant and inherited in an autosomal dominant manner. Conversely, some KCNQ2 pathogenic variants have been shown to cause a severe phenotype. The initial clinical presentation of the severe form of KCNQ2-related epilepsy is recognizable as one of the neonatal epileptic encephalopathies, typically with onset within the first week of life and characterized by tonic and myoclonic seizures with EEG background activity usually consistent with burst-suppression. Epilepsy persists after the infantile period and is accompanied by significant cognitive and motor disability. Pathogenic KCNQ2 variants in epileptic encephalopathy are usually clustered in "hot spots" known from in vitro studies to be critical for channel activity. Variable phenotypes may occur in different ways, for example, mosaic expression of a severe KCNQ2 variant may result in BFNE. Perhaps less well defined is the potential effect of 'modifier genes'. KCNQ2 is only one of many ion channels known to contribute to the development of epilepsy. Combinations of otherwise phenotypically mild pathogenic variants in more than one ion channel gene may result in variable clinical severity of epilepsy. A better understanding of the effect of genetic modifiers is essential for counseling regarding prognosis, treatment, and family planning. Development of a collaborative multi-investigator approach can help address the challenges inherent in the study of a rare cause of disease that may then be applied more broadly to all ion channel related epilepsies.

OPTIMIZING TREATMENT STRATEGIES IN INFANTS WITH BENIGN EPILEPSY SYNDROMES

Alexis ARZIMANOGLU

Director of the Epilepsy, Sleep and Paediatric Neurophysiology Department,
University Hospitals of Lyon (HCL), Lyon, France

Neonatal and infantile seizures continue to provide the greatest challenge to management in day-to-day practice. Many are just acute symptomatic in their aetiology, and consequently although acute treatment is required, chronic administration of AEDs is usually not necessary.

The first step for an optimal therapeutic approach probably relies on appropriate recognition of the epileptic nature of the paroxysmal events, as there are many mimics of epileptic seizures that need to be excluded.

The second step relies on expertise and the degree of confidence in confirming, early in their course, the diagnosis of one of the benign infantile epilepsy syndromes. In case of even minimal doubt, the presence of a brain lesion or of an underlying metabolic disorder needs to be immediately excluded. The reason is that some of those aetiologies are treatable, either by early surgery or by a targeted intervention that may profoundly alter overall prognosis.

Evidence based guidelines which clarify the optimal management of seizures in the infantile period do not exist; most are based on local preferences and expert panel opinions. In an otherwise well infant, a policy of “wait and see” is reasonable after the first afebrile seizure, provided a close monitoring, under the guidance of an experienced in epilepsies child neurologist, is available.

The active seizure period is rather short in children diagnosed as presenting with Myoclonic Epilepsy of Infancy. The syndrome is highly pharmaco-responsive. Duration of treatment is rather empirical and in the absence of prospective longitudinal studies it is still unclear to what extent epilepsy related factors, environmental and associated genetic factors impact the neuropsychological outcome of the syndrome.

In children with a firm diagnosis of benign infantile epilepsy, familial or not, and with regard to the self-limited course of the syndrome, treatment is theoretically not necessary. However, in clinical practice, the high seizure rate per cluster makes it difficult to refuse medication. Again, treatment choices are rather based on local practices. The challenges of efficacy and safety of emerging treatments for very young children remain and need to be systematically addressed in carefully designed prospective trials.

GENETIC IDENTIFIERS OF BENIGN EPILEPSY DEEPEN OUR UNDERSTANDING OF THE PATHOMECHANISMS OF EPILEPSY

Shinichi HIROSE

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

In neonates and infants there are three types of benign epilepsy in which genetic abnormalities are found: benign familial neonatal epilepsy (BFNE); benign familial neonatal infantile seizures (BFNIS); and benign familial infantile epilepsy (BFIE). They are prefixed with “benign” because of their characteristic spontaneous remission; they also share a similar seizure phenotype except that there are overlaps in age onset. While all of these are rare familial epilepsies with autosomal inheritance, they also appear in non-familial forms. In the last decade, several genes were found to be associated with these benign epilepsies including their sporadic forms. In BFNE, mutations of KCNQ2 and KCNQ3 were found as the causes. KCNQ2 and KCNQ3 encode the subunits of voltage gated potassium channels Kv7.2 and Kv7.3, respectively. These channels are believed to stabilize the membrane excitability of neurons. SCN2A mutations were found in some BFNIS cases. SCN2A encodes the $\alpha 2$ subunit of the voltage gated sodium channel Nav1.2, which generates the action potential of neurons. In BFIE, mutations of PRRT2 were identified. PRRT2 is the gene encoding proline-rich transmembrane protein 2 on the synaptic membrane, and it may play an important role in neuro-transmitter release from the synaptic vesicles. Intriguingly, recent studies have demonstrated that mutations of these genes may result in phenotypes that differ from those of benign epilepsies. For example, some mutations of KCNQ2 are found to cause early onset epileptic encephalopathy (EOEE). Similarly, mutations of SCN2A may cause EOEE. Furthermore, mutations of PRRT2, even the same mutation such as a recurrent mutation c.649dupC, result in a variety of phenotypes including BFIE, paroxysmal kinesigenic dyskinesia (PKD) and infantile convulsions with paroxysmal choreoathetosis (ICCA) syndrome. These phenotypic diversities should extend our understanding of the pathomechanisms underlying not only benign but also severer epilepsies, thus opening new avenues to novel treatments.

THE SPECTRUM OF “BENIGN” MYOCLONIC EPILEPSY IN INFANCY

Susumu ITO

Department of Pediatrics, Tokyo Women's Medical University, Tokyo, Japan

Benign myoclonic epilepsy in infancy (BMEI) is a rare idiopathic generalized epilepsy syndrome, first reported by Dravet and Bureau in 1981. It has been listed in the International Classification of Epilepsy and Epileptic Syndromes since 1989. This syndrome was originally defined as follows: myoclonic seizures in the first 3 years of life in otherwise normal infants; lack of other seizure types except for rare simple febrile seizures; and favorable seizure and cognitive outcomes. During the past three decades, the spectrum of this syndrome has gradually widened. First, some subtypes of BMEI including “reflex,” “photosensitive,” and “nocturnal” variants have been reported. Second, some cases present with other seizure types as well, including not only late-onset generalized tonic-clonic seizures (GTCS), myoclonic seizures, or absence seizures, but also preceding afebrile GTCS. Third, less favorable cognitive outcome, including mild to severe mental retardation, has been reported. Thus, the existence of refractory myoclonic seizures has been gradually recognized. Therefore, the International League Against Epilepsy Commission suggests that the term “benign” be removed from the name of BMEI in the revised classification of 2006. In this session, we discuss the spectrum of “benign” myoclonic epilepsy in infancy and the characteristics that differentiate it from other myoclonic epilepsy syndromes based on our recent experiences.

GENETIC BASIS OF BENIGN INFANTILE EPILEPSY

Toshiyuki YAMAMOTO

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Objective: In 2012, mutations in the proline-rich transmembrane protein 2 gene (*PRRT2*) have been identified in patients with benign partial epilepsy in infancy (BPEI). Many patients with BPEI exhibit symptoms of paroxysmal kinesigenic dyskinesia (PKD) in adolescence. Therefore, such a broad clinical spectrum is now recognized as infantile convulsions with choreoathetosis (ICCA) syndrome.

Methods: For better understanding of benign infantile epilepsy including BPEI, patients' genetic basis was analyzed by molecular methods.

Results: Over the half of the patients with BPEI showed *PRRT2* mutations. Among them, about 80% of the patients share an insertion, c.649dup, which is predicted to cause loss-of-function of *PRRT2*. Many patients share this variant with symptomatic or non-symptomatic parents, indicating low phenotypic penetrance; this finding is common in the world. Identification ratio of the *PRRT2* mutations in BPEI patients from Asian countries is lower than that from Western countries. As a result, there are many BPEI patients who do not exhibit *PRRT2* mutations. Clinical characteristics of the BPEI patients without *PRRT2* mutations are sporadic occurrence and no PKD phenotype. This suggests a different clinical entity of such patients. Because the genetic background of the BPEI patients without *PRRT2* mutations is unknown, we screened genomic copy number aberrations in Japanese BPEI patients without *PRRT2* mutations. 16p11.2 microdeletion was detected in a small number of the BPEI patients without *PRRT2* mutations. This would be reasonable since *PRRT2* is included in the common microdeletion of 16p11.2; however, this is not a major genetic background of the patients. Next, whole exome sequence was performed in some BPEI patients without *PRRT2* mutations. Mutations of the chloride channel voltage-sensitive 6 gene (*CLCN6*) were identified in some BPEI patients without *PRRT2* mutations; however, this does not suggest a major genetic background of the patients.

Conclusion: Genetic background is still unknown for the most BPEI patients without *PRRT2* mutations. Further studies would be required.

TREATMENT FOR BENIGN CONVULSIONS WITH MILD GASTROENTERITIS

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Benign convulsions with mild gastroenteritis (CwG) was first described in 1982 by Morooka, and has been commonly reported in eastern Asia, especially Japan. It is now widely known as a marginal syndrome of benign infantile seizures. The clinical features of CwG are: (1) afebrile seizures associated with gastroenteritis without clinical signs of dehydration or electrolyte derangement in previously healthy patients aged from 6 months to 3 years; (2) seizures often occurring in clusters; (3) normal interictal electroencephalogram; and (4) good seizure outcome and development. CwG is not formally recognized as an epileptic syndrome and is categorized as situation-related seizures or “chanced” epilepsy.

Anti-epileptic drugs (AEDs) for CwG are commonly required in the acute phase because seizures are often clustered. Benzodiazepines are often administered but their effectiveness is controversial. Some studies have shown that lidocaine, low-dose carbamazepine, phenytoin/fosphenytoin and single-dose chloral hydrate were effective for CwG. Carbamazepine acts by blocking Na⁺ channels and inhibiting the influx of Na⁺ ions into neurons; LDC and PHT/fos-PHT also have the same mechanism of action. However, it remains unknown why these Na⁺ channel blockers inhibit seizures in CwG.

Determining an appropriate of AEDs that can be effective in the short-term would be beneficial not only for the management of seizures but also for promoting normal growth and development. The unnecessary use of AEDs for CwG after the acute phase should be avoided because seizures of CwG rarely recur. Therefore, the indications and choice of AEDs for CwG should be determined.

FREQUENT SLEEP POTENTIATED SPIKES AND COGNITION IN BENIGN FOCAL EPILEPSY OF CHILDHOOD WITH CENTROTEMPORAL SPIKES; TRULY ALL BENIGN?

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Benign focal epilepsy of childhood with centrotemporal spikes (BECTS) / Benign Rolandic Epilepsy (BRE) is a common pediatric epilepsy syndrome, accounting for approximately 25% of epilepsy in school age children. The seizure outcome is considered as benign, typically 'outgrowing' seizures in the second decade of life, but it appears that this population is vulnerable to various cognitive problems. As BECTS is associated with frequent sleep potentiated spikes, this could also be considered as a model to assess the effect of these spikes on cognition.

In this session, we will discuss the clinical, electrographic, and neuropsychological profile of children with BECTS. While the overall intelligence quotient (IQ) appears to be preserved in the normal range, there are studies documenting cognitive problems in BECTS. We found that there is a large variability among the children in various aspects of cognition, such as with cognitive efficiency, affecting learning and memory.

We will also look at BECTS as relatively homogenous model of epileptic encephalopathy associated with frequent sleep potentiated spikes, to assess the association between the frequency of spikes and cognitive difficulties, and correlating with specific domains, such as effect on language function.

Overall, while BECTS is a common and "benign" epilepsy syndrome from the point of seizure prognosis, there may be associated effect on the overall brain function including various cognitive domains; recognition of such potential deficits may be necessary, and need attention during the management of children with BECTS.

This may suggest that even in benign epilepsy syndromes, although the extent could be subtle, there may be cognitive difficulties that could be detected with detailed testing. Such cognitive issues may not be limited to the more severe forms of epileptic encephalopathy.

(Key words)

Benign, centrotemporal spikes, seizure outcome, cognitive difficulties

NEUROPATHOLOGY OF BENIGN INFANTILE SEIZURES

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Neuropathological data on cerebral architecture and lesions in benign infantile epilepsies are sparse because brain biopsy or resections are not indicated and post-mortem tissues are unavailable. Specific genetic and metabolic diseases and major malformations are exclusion criteria for this clinical diagnosis, hence specific cortical alterations as seen in tuberous sclerosis complex, lissencephalies and organic acidurias are not relevant. Nevertheless, our studies on subcortical white matter abnormalities in focal cortical dysplasias (FCD) suggest that they may be a principal factor in generating seizures in benign infantile as well. These microscopic findings are presently below the resolution of neuroimaging, but epileptogenic foci may be detected by EEG. In FCD the number of subcortical white matter neurons is increased (>20/high power microscopic field), especially at the depths of sulci and in the deep centrum semiovale. Synaptophysin immunoreactivity demonstrates not only the somata but the axons of such neurons. Synaptic connections between these neurons and with the overlying cortical grey matter indicates that they are not "isolated" cells but capable of contributing to epileptic circuitry. They are excitatory glutamatergic neurons from incomplete radial migration and not GABAergic inhibitory neurons from tangential migration or from the fetal subplate zone. With brain maturation their effect may be suppressed by physiological inhibition. We present an hypothesis that these neurons form a neuroanatomical basis of benign infantile seizures.

BENIGN VERSUS ENCEPHALOPATHIC EARLY INFANTILE EPILEPSIES

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Voltage gated sodium and potassium channels are critical regulators of neuronal excitability, and their role in pediatric epilepsy syndromes has been increasingly recognized. Genes for the alpha-subunits of three of the main central nervous system sodium channel subtypes – SCN1A, SCN2A, and SCN3A – are all located on chromosome 2q24. It remains a challenge to identify what channel mutations lead to benign versus encephalopathic, transient, or reversible early infantile epilepsies. Mutations in SCN1A have had the highest correlation with epilepsy, with over 650 variants associated with Dravet Syndrome and greater than twenty associated with GEFS+. The majority of these are mutations that cause truncation of the protein. Increasingly, SCN2A variants have been found in patients with several epilepsy syndromes, including BFNIS, GEFS+, and Dravet-like disorders. Inherited missense mutations in SCN2A are associated with benign epilepsies while de novo nonsense or missense mutations tend to cause more severe disorders. Both sequence-based mutations and copy number variants involving SCN2A have been associated with an expanded phenotype, including Ohtahara syndrome, West syndrome, and unclassified EOEEs. We present a case of neonatal onset seizures not recognized until one month of life in a patient with a 1.77 Mb duplication of 2q24.3 affecting SCN2A and SCN3A but not SCN1A. Seizures included tonic, bicycling, and epileptic spasms. EEG background was discontinuous with invariant burst-suppression and multifocal spikes. Phenobarbital therapy produced immediate resolution of prolonged tonic events and later resolution of spasms and dramatic background improvement over one month. Given the reversibility of the EEG and clinical phenotype, we hypothesize that the encephalopathy is best explained as secondary to one month of uncontrolled seizures rather than an effect of the channelopathy.

FAST ACTIVITY IN NEWBORN AND INFANTILE EEG

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Digital EEG becomes providing large amount of information in neuronal activities including physiological and pathological discharges. High sampling rate of digital EEG at 1,000 Hz has been routinely applied for prolonged scalp video EEG. The higher sampling rate has an advantage to demonstrate the fast activity of neurons to understand the functional development and epileptogenicity. In the newborn era, the thin skull and scalp has more advantageous results for EEG recording because of much less resistance than adult thick skull and scalp. This talk will present the existence of fast activities detected by scalp EEG to understand their developing brain and pathophysiology of infantile spasm that is the most interesting age related and very specific seizure disorder in children.

SODIUM CHANNEL EPILEPSIES OF INFANCY: A SPECTRUM OF SELF-LIMITED AND SEVERE DISORDERS

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Since the discovery of the first sodium channel mutation in epilepsy in 1998, sodium channels have emerged as the pre-eminent group of ion channels causing genetic forms of epilepsy. Although they were first implicated in self-limited (previously referred to as benign) epilepsy syndromes such as Genetic Epilepsy with Febrile Seizures Plus (GEFS+), they rapidly were identified as causal in severe epilepsies such as the group of developmental epileptic encephalopathies.

The prototype of these disorders is Dravet syndrome where more than 80% of patients have a mutation of the alpha 1 sodium channel subunit gene SCN1A; 90% of mutations arise de novo. Although subtle differences in phenotypic severity have been correlated with different types of mutation, Dravet syndrome is a severe disorder. In the 10% of patients with Dravet syndrome and inherited mutations, affected relatives may be mildly affected with GEFS+. In cases where the parent is mosaic for the SCN1A mutation, there is a clear correlation between mutation load and phenotypic severity.

A similar pattern has recently emerged for SCN2A which was first implicated in the rare self-limited syndrome of benign familial neonatal-infantile seizures (BFNIS). SCN2A encephalopathy was first reported in single Japanese cases and now appears to be a major cause of developmental epileptic encephalopathy with more severe impairment than Dravet syndrome. It is the second most common cause of the epilepsy syndrome, epilepsy of infancy with migrating focal seizures, after the potassium channel KCNT1.

Other sodium channel genes are also implicated with SCN8A causing epileptic encephalopathy with a wide range of presentations. Interestingly SCN9A and SCN1B are clearly involved in GEFS+ and may play a rare causative or modifying role in Dravet syndrome. To add to the complexity, variants within SCN1A are being invoked in many forms of epilepsy more broadly adding to the panoply of epilepsy syndromes associated with this protein.

PHOTOSENSITIVITY IN POPULATION & EPILEPTIC PATIENTS

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Photosensitivity is one of the markers for epilepsy, and is routinely examined with intermittent photic stimulation in conventional EEG examination. Photoparoxysmal response (PPR) in EEG or photosensitive seizures suggests the existence of photosensitivity.

In 2001, we conducted nationwide survey by the questionnaire to the major hospitals in Japan, and found 652 photosensitive subjects or patients (photosensitive epilepsy patients (63.0%); pure photosensitive epilepsy patients (26.4%) ; subjects with photosensitive constitution (5.8%)). Pure photosensitive epilepsy patients have no spontaneous epileptic seizures, but only photosensitive seizures. Subjects with photosensitive constitution have no seizures, but PPR in EEG.

In 38 subjects with photosensitive constitution, male was 45.9%, and mean initial detection age of PPR was 5.6 years old (1-21 years old), and mean last detection age of PPR was 9.3 years old (2-21 years old). Their photosensitivity is benign, and rarely leads to the onset of epilepsy, except strong flash exposure like Pocket monster incident. We must be aware the existence of subjects with photosensitive constitution, also in young children.

In 172 pure photosensitive epilepsy patients, male was 56.1%, and mean initial detection age of PPR was 12.8 years old (2-69 years old), and mean last detection age of PPR was 14.6 years old (4-79 years old). Two thirds of the patients had GTC, and one fourth had CPS. Pure photosensitive epilepsy patients occupied the largest composition of patients with photosensitive seizures (39%), and the majority had only photosensitive seizure among observation period (mean 10.7 years). Therefore, they need no antiepileptic drugs, but protection measures against strong flash light. We must recognize their natural course and their possible onset before 6 years (10%).

In 411 photosensitive epilepsy patients, main epileptic syndromes were idiopathic generalized epilepsy (28.4%), symptomatic localization related epilepsy (23.6%) and symptomatic generalized epilepsy (3.2%).

THE BENIGN SPECTRUM OF EPILEPTIC AND NON-EPILEPTIC SPASMS IN INFANCY

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Infantile spasms have a reputation for being challenging to treat and having an association with subsequent epilepsies of other types. They also have a reputation for poor long-term neurodevelopmental outcomes. Where epileptic spasms are associated with hypsarrhythmia and constitute West syndrome, there is considered to be an 'epileptic encephalopathy' and arguably a form of nonconvulsive status epilepticus.

However, not all infants with epileptic spasms, even when associated with hypsarrhythmia, have poor outcomes, and authors have described a syndrome of benign non-epileptic infantile spasms, also known as benign myoclonus of early infancy, which has many similar clinical features. In addition, there is some semiological overlap between infantile spasms and conditions such as shuddering attacks and paroxysmal tonic upgaze of infancy.

In the context of the many advances in underlying genetic causes of infantile spasms, it is interesting to explore the range of semiological presentations and neurodevelopmental outcomes with which infantile spasms might be associated, and to ask if there are general or specific factors that might predict or modify neurodevelopmental outcomes. It is also interesting to explore whether neurodevelopmental outcomes are unimodal or multimodal in distribution, and whether such findings might influence treatment choices.

Although it seems unlikely that we will identify a subgroup of infants with West syndrome that have a high predictive value for normal neurodevelopmental outcome and a form of 'benign epilepsy', it is possible that we will identify genetic causes of epileptic spasms that merit less intensive treatment with immunomodulating or antiepileptic drugs. Exploring these questions will require analysis of data from large multinational studies as well as gaining a better understanding of the pathophysiological mechanisms underlying epileptic spasms, and other epilepsies or movement disorders, with onset in infancy.

A TRANSLATIONAL TALK ON BENIGN INFANTILE SEIZURES

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The field of early-onset epilepsies continues to be transformed by novel genetic discoveries over the past two decade, and increasingly their nomenclature and evolving classification are becoming more specified on the basis of individual genes. For example, one of the earliest epilepsy ion channelopathies, KCNQ2 (which encodes a voltage-gated potassium channel), was initially linked to benign familial neonatal seizures, but recently the clinical spectrum has been expanded to include a neonatal onset severe form of epilepsy now labeled as KCNQ2 encephalopathy. Despite such advances, the rapidly expanding literature in the genetics of neonatal and infantile epilepsies continues to confound our ability to understand exactly how such mutations result in unique clinical phenotypes. Indeed, the genetic concepts of variable expressivity (i.e., widely divergent clinical manifestations arising from mutations in the same gene) and locus heterogeneity (i.e., similar phenotypes arising from different genes) appear now more than ever the canonical framework of epilepsy genetics. Obviously, the genetic abnormalities themselves are often only the “tip of the iceberg”, and clinical phenotypes can be influenced heavily by epigenetic, post-transcriptional and post-translational changes, and even modifier genes (among other factors). Benign familial infantile epilepsy (BFIE; OMIM 605751) is an early infantile autosomal dominant condition with a mean onset of seizures at 6 months of age and remission by 2-3 years of age. Multiple studies have identified mutations in the PRRT2 (proline-rich repeat protein 2) gene as being causative for BFIE, although abnormalities in this gene have also been linked to infantile convulsions with choreoathetosis and paroxysmal kinesigenic dyskinesia. While the exact pathogenesis of BFIE remains unclear, recent studies have highlighted a pathogenic role for PRRT2 in excitatory neurotransmission – specifically, the role of PRRT2 in interacting with the presynaptic protein SNAP25 (Synaptosomal-Associated Protein, 25kDa) and GRIA1 (glutamate receptor 1, aka GluA1 and GLUR1) which is a protein subunit of the ligand-gated AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate) glutamate receptor. These molecular changes were further shown to enhance glutamatergic neurotransmission, consistent with enhanced neuronal excitability, one of the defining hallmarks of epilepsy.

OVERVIEW OF BENIGN INFANTILE SEIZURES

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The presence of benign epilepsy with focal seizures had not been known until late 1980s in European or American countries. In contrast, Fukuyama described a presence of so called “benign infantile seizures” in 1963. Watanabe described focal infantile epilepsies with good outcome using ictal VTR-EEG recordings in the late 1980s. Similar infantile epilepsies were reported from several other countries, benign infantile epilepsy (BIE) became a reality from a myth. BIE has been included in the ILAE classification as an established entity.

Several investigators including us studied clinical features of BIE intensely. Clinical features of BIE are including; focal onset seizure; normal psychomotor development and neurologic findings before seizure onset; normal interictal EEG; normal neuroimaging findings; and no seizures during the neonatal period. Family history of benign infantile seizures is frequent. Seizures often occur in cluster, but principally status epilepticus is not observed. Comorbidities of BIE have also been investigated. Paroxysmal kinesigenic dyskinesia (PKD) is sometimes observed in patients with BIE, especially during childhood through adolescence. Co-occurrence of infantile seizures and PKD has been known as ICCA. We found that convulsion with mild gastroenteritis (CwG) is sometimes observed in children with BIE.

Discovery of PRRT2 gene as a causative gene of BIE is a recent topic of this subject. Mutations of PRRT2 are frequently identified not only in patients with BIE but also in those with PKD, ICCA, and other paroxysmal movement disorders. Early and definite diagnosis of BIE became possible based on genetic analyses. It is interesting that PRRT2 mutations are not seen in patients with CwG, suggesting that these two entities are genetically different. The frequency of PRRT2 mutation is relatively low in Japanese patients, especially in those without family history. There will be some other causative genes in Japanese children with BIE.

ABSTRACTS

Poster Presentation

THE TREATMENT OF FOCI RESECTION AND BIPOLAR ELECTRO-COAGULATION ON FUNCTIONAL CORTEX IN MULTIFOCAL EPILEPSY ASSOCIATED WITH TUBEROUS SCLEROSIS COMPLEX INVOLVING ELOQUENT CORTEX

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Objectives: Tuberous sclerosis complex (TSC)-associated epilepsy is medically refractory seizures secondary to cortical tubers and leads to mental retardation in childhood. TSC patients are often with refractory epilepsy involving eloquent and noneloquent cortex in multiple lobes and multiple independent seizure foci which made these patients poor candidates for conventional surgery. We have previously presented that the approach of pure bipolar electro-coagulation on functional cortex (BCFC) in the treatment of unifocal epilepsy involving eloquent areas is effective, safe and easy to use. This report describes our long-term follow-up for combined resective surgery and BCFC in TSC patients with refractory epilepsy involving eloquent and noneloquent cortex.

Methods: Four patients aged from 10 to 21 years were admitted with epilepsy. The cranial computerized tomography (CT) showed cortical and subependymal calcification, magnetic resonance imaging (MRI) demonstrated multiple cortical tubers. All patients were with drug resistant epilepsy, despite treatment with two antiepileptic drugs (AEDs). Initiated combination therapy of foci resection and BCFC for epilepsy management between May 2004 and May 2011, the patients were retrospectively reviewed with regard to seizure outcome, postoperative complications.

Results: The combination therapy of foci resection and BCFC resulted in remarkable improvement in patient's ambulation and cessation of seizures. (Engel I in 2 patients and Engel II in 2 patients) In addition, all patients showed some improvement in behavior or cognitive function with no permanent neurological deficit noticed during a standard clinical examination.

Conclusions: The combination therapy of foci resection and BCFC is an effective and safe surgical approach for the treatment of TSC-associated epilepsy involving eloquent cortex.

PRENATAL MULTICYSTIC ENCEPHALOPATHY IN ISOLATED SULFITE OXIDASE DEFICIENCY WITH A NOVEL MUTATION

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Objective: A term female baby was delivered by cesarian section due to decelerated fetal heart beat. Prenatal ultrasound study revealed enlarged cisterna magna. When 14 hours old, clonic seizures with upward gaze were noted.

Methods: Survey of neonatal seizures included electroencephalogram, neuroimaging studies, and metabolic screenings.

Results: Brain ultrasound and magnetic resonance imaging showed multicystic leukoencephalopathy. Metabolic screening revealed positive urine sulfite (80mg/L) with normal serum uric acid (5.5 mg/dL). Isolated sulfite oxidase deficiency was confirmed with a maternal nonsense mutation and paternal novel missense mutation in the *SUOX* genes.

Conclusions: Our case is the first report to demonstrate severe brain destruction in a 14-hour-old neonate diagnosed of isolated sulfite oxidase deficiency, in which prenatal onset is highly suggested. Isolated sulfite oxidase deficiency should be considered in neonatal multicystic encephalopathy, especially for those without trauma, perinatal distress or congenital infections.

A NOVEL PIGA MUTATION IN A FAMILY WITH X-LINKED ATYPICAL DRAVET SYNDROME

POSTER

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Objective: Dravet syndrome (DS) is a well-known, genetic, epileptic encephalopathy. Mutations in sodium channel $\alpha 1$ subunit gene were found in 70-80% of DS patients and mutations in GABA_A receptor $\gamma 2$ subunit gene or sodium channel $\beta 1$ subunit gene were also reported. Recently, whole exome sequencing (WES) found a mutation of the gene encoding chromo-domain helicase DNA binding protein 2 from *SCN1A* negative, DS individuals. We report a family showing X-linked atypical Dravet syndrome with a mutation in the gene encoding phosphatidylinositol glycan biosynthesis class A protein (*PIGA*; *PIGA*).

Methods: The clinical, electro-physiological and neuro-imaging data in the proband were retrospectively reviewed. WES was performed in a proband and his parents. All variants in WES were prioritized through bioinformatic data analysis. The major candidate variant was verified with Sanger sequencing.

Results: A 12-year-old boy firstly presented with right hemiclonic seizures at 5 months of age and then showed multiple types of focal seizures provoked by viral illness or fever. This patient with severe intellectual disability showed normal development before recurrent status epilepticus. Electroencephalography showed focal epileptiform discharges from different parts of the brain. Brain magnetic resonance imaging was normal at 1 year, although mild bilateral hippocampal sclerosis was present at 7 years. The proband had one younger brother and two maternal uncles who were dead during childhood with a similar course of disease with him. His younger brother was diagnosed as DS without *SCN1A* mutations in other hospital. The proband and his mother had a mutation in *PIGA* (c.A427G, NM_002641.3; p.Lys143Glu, NP_002632.1).

Conclusion: After the first report of a family with less severe form of *PIGA* deficiency showing early-onset epileptic encephalopathy, a mutation of *PIGA* in this family is the second report of mild *PIGA* deficiency. *PIGA* might be meaningful in male patients or X-linked families with similar phenotypes of atypical DS.

CORRELATION BETWEEN STIGMA AND EEG PAROXYSMAL ABNORMALITY IN CHILDREN WITH EPILEPSY

POSTER

4

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Objective: Stigma is a major issue for adolescents and adults with later development of epilepsy. However, the effects of EEG abnormalities on perceived stigma in children with epilepsy have not been fully studied. We investigated the relationship between abnormal electroencephalogram (EEG) findings such as localized EEG paroxysmal abnormality (PA) and perceived stigma to determine EEG factors associated with stigma in children with epilepsy.

Methods: Participants comprised 40 patients (21 boys, 19 girls; mean age, 14.6 years) with epilepsy at enrollment. Criteria for inclusion were as follows: 1) age of 12-18 years, inclusive; 2) ≥ 6 months after epilepsy onset; 3) the ability to read and speak Japanese; and 4) the presence of EEG PA. Fifteen healthy seizure-free children were included as a control group. Participants were asked to rate how often they felt or acted in the ways described in the items of the Child Stigma Scale using a 5-point scale. EEG paroxysms were classified based on the presence of spikes, sharp waves, or spike-wave complexes, whether focal or generalized.

Results: Children with epilepsy showed significantly higher stigma scores than healthy subjects ($p < 0.01$). A higher score reflects a greater perception of stigma. The average total scores of patients presenting with EEG PA at generalized, frontal, RD, mid-temporal, and occipital regions were 2.3, 4.0, 2.4, 3.2, and 2.2, respectively. The scores of all questions were higher in the frontal group than those in other regions ($p < 0.01$). Children presenting with frontal EEG PA perceived a greater stigma than children presenting with non-frontal EEG PA ($p < 0.01$).

Conclusion: A relationship was identified between frontal EEG PA and perceived stigma. Frontal EEG PA may function as a mediator of emotional responses such as stigma in children with epilepsy. Integrated interventions that break through epilepsy stigma in children are needed.

CTLA-4 +49 A/G POLYMORPHISM AND ANTIGLUTAMIC ACID DECARBOXYLASE ANTIBODY-ASSOCIATED ENCEPHALOPATHY IN TAIWANESE CHILDREN

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Objective: Anti-glutamic acid decarboxylase antibodies are associated with encephalopathy, an autoimmune central nervous system inflammatory disease. The cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) +49 A/G polymorphism has been shown to confer genetic susceptibility to positive anti-glutamic acid decarboxylase antibodies in patients with type 1 diabetes mellitus in Japan. We aimed to investigate the association of the CTLA-4 +49 A/G (rs231775) polymorphism in Taiwanese children with anti-glutamic acid decarboxylase antibody-associated encephalopathy.

Methods: This was a case-control study from July 2011 to June 2012 performed at Chang Gung Children's Hospital in Taiwan. Genotyping of the CTLA-4 +49 A/G polymorphism was performed by polymerase chain reaction-restriction fragment length polymorphism.

Results: Seventeen patients with anti-glutamic acid decarboxylase antibody-associated encephalopathy and 97 controls were enrolled. The genotype, allele and carrier frequencies of the CTLA-4 +49 A/G polymorphism were equally distributed in the patients and controls, with no significant differences between the two groups. In addition, we found a positive trend between the level of anti-glutamic acid decarboxylase antibodies and the G allele of the CTLA-4 +49 A/G polymorphism, although this trend was not statistically significant.

Conclusion: Our results suggest that the CTLA-4 +49 A/G (rs231775) polymorphism does not confer an increased susceptibility to anti-glutamic acid decarboxylase antibody-associated encephalopathy in Taiwanese children.

A STUDY ON SPIKE FOCUS-DEPENDENCE OF HIGH-FREQUENCY OSCILLATIONS IN BENIGN CHILDHOOD PARTIAL EPILEPSY

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Purpose: Spike foci in benign epilepsy with centrotemporal spikes (BECS) are related to seizure semiologies, but such relationship is inconspicuous in Panayiotopoulos syndrome (PS). We analyzed spike-associated high-frequency oscillations (HFOs) and their relationship to spike foci in electroencephalograms (EEGs) of patients with BECS and PS in order to elucidate the pathophysiology of these syndromes.

Methods: In 35 patients with BECS and 29 patients with PS, focal spikes in scalp sleep EEGs recorded during the period of active seizure occurrence were firstly classified by clustering according to their characteristics including shapes and distributions. In each patient, at most three spike clusters were then investigated through time-frequency spectral analysis and single-dipole analysis with a realistic 3D head model to explore relationships between presence or absence of spike-associated HFOs and the distribution of estimated spike sources.

Results: A total of 159 spike clusters was analyzed (96 in BECS and 63 in PS). HFOs were detected in 73 spike clusters (76.0%) in BECS and 37 (58.7%) in PS with a statistically significant difference ($p=0.024$ by Fisher's exact test). In BECS, spikes had relatively uniform distributions, but the proportion of spikes with associated HFOs was significantly higher in the spike group with dipoles in the perirolandic area (42/49) than that with dipoles outside of the perirolandic area (23/36; $p=0.037$). In PS, The proportion of spikes with associated HFOs was significantly higher in the spike group with dipoles in the occipital lobes (20/26) than that with dipoles outside of the occipital lobes (13/33; $p=0.020$).

Conclusions: The proportion of spike-associated HFOs was higher in BECS than PS. Greater epileptogenicity was indicated in spikes with dipoles located in the perirolandic area in BECS and in spikes with dipoles in the occipital lobes in PS.

CHARACTERIZATION OF EARLY AND LATER ONSET EPILEPSY IN INDIVIDUAL WITH AUTISM.

POSTER

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Objective: The prevalence of epilepsy in patients with autism ranges from 5% to 46%. It has been reported that there are two peaks of seizure onset in autism patients in early childhood and the other in adolescence. However, the epilepsy of patients with second peak in seizure onset is not well understood. The purpose of this study is to better characterize the features of early and late-onset epilepsy in individuals with autism.

Methods: We reviewed the charts of all patients with autism referred to Shiga University Hospital between 2002 and 2012. Patients who were identified as having epilepsy were examined, and they were divided into two groups according to the age of seizure onset (younger or older than three years). When data were available, the following information was recorded: age at first visit, gender, history and type of seizure, age at seizure onset, type of epilepsy, seizure frequency, treatment response to antiepileptic drugs, neuroimaging findings.

Results: Of the 274 patients with autism, 40 individuals with epilepsy were identified. We detected two peaks of seizure onset in the patients with epilepsy, one in early childhood and one in adolescence. The most frequent epilepsy was temporal lobe epilepsy and West syndrome in the early onset epilepsy group, and temporal lobe epilepsy, frontal lobe epilepsy and other symptomatic generalized epilepsy in late onset epilepsy group. The rate of tonic spasms was higher in the early onset group than in the late onset group. On the other hand, secondarily generalized seizures were more frequent in the late onset epilepsy group.

Conclusion: The present results are closely consistent with those published previously. However, the high rate of secondarily generalized seizures in the late-onset epilepsy group of autism is herein reported for the first time.

A CASE OF BACTERIAL MENINGITIS WITH BURST WAVES OF LOCAL ONSET ON ICTAL EEGS

POSTER

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Introduction: Bacterial meningitis is a central nervous system infection and inflammation of the meninges. Common clinical symptoms of bacterial meningitis in children are not-doing-well, fever, irritability, vomiting, and seizures. Seizures often occur in children with meningitis, however there are no reports of ictal EEGs during a seizure in meningitis. We experienced the recording of focal discharge on ictal EEGs during a seizure in meningitis.

Case: The patient was a five month old female. Her perinatal histories showed nothing in particular. Her developmental history up to five months also recorded no complications. Her vaccination history included only BCG. She had convulsions with fever twice a day just before hospital admission. A neurological examination also showed normal findings. Her consciousness was clear between convulsions. The cranial magnetic resonance imaging (MRI) was also normal. The third convulsion occurred during the recording of the EEG. The paroxysmal discharges were recorded with focal onset. Cerebrospinal fluid (CSF) cell counts revealed increased leukocytes (816/3), including 33% lymphocytes and 67% neutrophils. Penicillin-susceptible *S.pneumoniae* (PSSP) was detected in the blood and in the CSF culture specimens taken on the day of admission. We diagnosed her convulsion were caused from bacterial meningitis of PSSP.

Conclusions: In spite of an inflammation of the whole brain, paroxysmal discharges on ictal EEG were of focal onset. It is presumed that the inconsistency is caused by the child's epileptogenicity, subtle inflammation, or the immaturity of the brain.

TEMPO OF MOZART MUSIC IS NOT THE CRITICAL FACTOR IN REDUCING SEIZURE ACTIVITY

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Background: Mozart effect had been reported to interfere brain function after listening to the piano pieces composed by specific musician. Some recent reports successfully decrease the seizure activity after Mozart music exposure in human and rats with epilepsy. However, the mechanisms is still unknown. Our aim is to test the tempo of Mozart music as the critical factors by the animal model.

Methods: Long Evans rat, an animal model of epilepsy presents absence-like movement while 4 months of age. Typical high-voltage rhythmic spike (HVRS) discharges during seizure activity was recorded by wireless electroencephalography (EEG) for 3 hours (before, during, and after music exposure with the duration of one hour in each stage). Mozart's Sonata for Two Pianos in D Major, K.448 was broadcasted repeatedly during the music stage. Different tempo of music broadcasting was set as 1 time, 2 times and 4 times of speed in divided groups. Spike duration and spike number were analyzed in each groups.

Results: Total 15 Long Evans rats were evenly divided into three group. The spike duration can then be identified as the duration of average 7 to 12 Hz power surpasses an appropriate threshold. The spike number during each episode was determined by the numerical method of peak detection. In seizure frequency and seizure duration, all three group decrease seizure activity after music exposure with statistical significance ($p < 0.05$). However, the reduction rate of seizure activity remain unchanged despite in different tempo of music broadcasting.

Conclusions: Seizure activity decreases as we rearrange the tempo of music broadcasting. However, there is no dose-dependent effect. Critical factors of reducing seizure activity may present in the specific pattern of "On and off" system, which needs further investigation.

CONCENTRATIONS OF AMINO ACIDS AND MONOAMINE METABOLITES IN THE CEREBROSPINAL FLUID IN INFANTS SHOWING CONVULSIVE DISORDERS

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Objectives: To determine the involvement of disturbed metabolism of neurotransmitters in infantile convulsions, we examined the concentrations of amino acids, acetylcholine, and monoamine metabolites in the cerebrospinal fluid (CSF) in infants developing convulsive disorders.

Methods: Concentrations of aspartate, glutamate, glycine, gamma-aminobutyric acid (GABA), acetylcholine, 5-hydroxyindoleacetic acid (5-HIAA), dopamine, homovanillic acid (HVA), norepinephrine, and 3-methoxy-4-hydroxyphenylethylglycol in the CSF were determined with high performance liquid chromatography in patients with West syndrome (WS), benign infantile epilepsy (BIE), acute encephalopathy due to human herpes virus-6 (HHV-6E) and benign convulsions associated with mild gastroenteritis (CwG), in addition to age-matched controls.

Results: A significant increase in concentration of GABA was found in CwG patients as compared with controls. CwG patients also showed an increased concentration in other amino acids, although the changes were not significant. A significant decrease in concentration of GABA was found in HHV-6E patients as compared with WS patients. A significant decrease in concentration of 5-HIAA, dopamine, and HVA were found in CwG patients as compared with controls. A significant decrease in concentration of 5-HIAA and dopamine was found in HHV-6E patients as compared with controls.

Conclusion: The increase of amino acids and the decrease of monoamine metabolite in the CSF are remarkable in CwG, and the altered metabolism of neurotransmitters may be taken into consideration in epileptogenesis.

MRI FINDINGS DURING ACUTE PERIOD IN BENIGN CONVULSIONS WITH GASTROENTERITIS AND BENIGN PARTIAL EPILEPSY IN INFANCY

POSTER

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Objective: To reveal the pathophysiologies of the MRI findings in benign convulsions with mild gastroenteritis (CwG) and benign partial epilepsy in infancy (BPEI).

Methods: We reviewed medical records of 33 patients with CwG and 22 patients with BPEI who had had MRI within 7 days from seizure onset between 2010 and 2015.

Results: The mean interval period between the onset and first MRI was 0.9 day in patients with CwG and 2.2 days in patients with BPEI ($p=0.02$). On MRI, diffusion-weighted images showed high intense signal in the splenium of the corpus callosum in 6 patients with CwG, and no abnormalities in patients with BPEI. The average number of seizures was 3.3 times in patients with CwG and 7.1 times in patients with BPEI ($p=0.07$). All patients with splenial lesions (SL) had MRI at the date of onset, while only 13 of 27 CwG patients without SL had MRI at the date of onset ($p<0.01$). In patients with CwG, the average number of seizures was 4.0 times in patients with SL, and 3.1 times in patients without SL ($p=0.43$). Focal seizures were seen in 1 patient with SL and 17 patients without SL, focal seizures with secondary generalization were seen in none of patients with SL and 11 patients without SL, and generalized convulsive seizures from onset were seen in 5 patients with SL and 16 patients without SL. There was no significant difference of seizure types between patients with and without SL.

Conclusion: From the correlation of the SL with the time to MRI or seizure frequency, seizure is an important factor of the transient SL. In addition to the difference of the pathophysiologies between CwG and BPEI, the delay of MRI scans may be responsible for the difference of the MRI findings between CwG and BPEI.

ROLES OF SEIZURE-INDUCED MICROGLIAL ACTIVATION IN EPILEPTOGENESIS PROCESS VIA PHAGOPTOSIS AND NEUROINFLAMMATION

POSTER

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Objective: Temporal lobe epilepsy (TLE) is the most common type of drug-resistant epilepsy, partly characterized by loss of hippocampal pyramidal neurons and gliosis. Activated microglia could be involved in these events by phagoptosis, a novel form of cell death by phagocytosis and excess inflammatory responses. However, morphological and functional properties of microglia in TLE have rarely been studied. Here, we examined the spatiotemporal pattern of microglial activation as well as neuronal loss following status epilepticus (SE) to address the role of activated microglia in the epileptogenesis in mice.

Methods: The first SE was induced in C57BL/6J male mice by the administration of pilocarpine at 8 weeks of age and the second SE was induced four weeks after the first SE. Neuronal damages and microglial changes were investigated with immunohistochemistry at 1, 3, 7 and 28 days after the first SE. Changes in mRNA levels of pro-inflammatory cytokines and purinergic receptors, both of which were relevant to microglial activation were assessed by quantitative RT-PCR.

Results: We found that fluorojade-B-positive damaged cells were evident in CA1 within one day after the first SE and pyramidal cell layer appeared thinner at day 28. Microglia turned into amoeboid form, a typical feature of activated microglia, from one to seven days after first SE. Furthermore, activated microglia with phagocytic cups were found near dead neurons within three days after the first SE. We detected a significant increase in mRNA of P2Y6 receptor (a marker for phagocytic microglia) and pro-inflammatory cytokines (IL-1 β and TNF- α) in the hippocampus at one day after the first SE. In addition, less dose of pilocarpine was required for the induction of the second SE, indicating the first SE increased seizure susceptibility.

Conclusion: These results suggest that seizure-induced microglial activation could play important roles in epileptogenesis process via phagoptosis and neuroinflammation.

CLINICAL CHARACTERISTICS OF FEBRILE AND AFEBRILE SEIZURES WITH GASTROENTERITIS IN CHILDREN

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Objective: In an attempt to differentiate between febrile and afebrile seizures with gastroenteritis in children, we evaluate the clinical characteristics of these two conditions.

Methods: A retrospective study was conducted on patients admitted with seizures accompanying symptoms of gastroenteritis to Fukuoka Children's Hospital between January 2007 and December 2014. According to the presence or absence of fever, patients were categorized into two groups, the 'febrile seizure' group (FG), and the 'afebrile seizure' group (AG). FG was defined by fever which occurred 24 hours before or after the seizures. Medical records were examined to obtain necessary data. Statistical analyses were performed using Student's *t*-test and Fischer's exact probability test.

Results: 148 patients met the inclusion criteria with FG comprised of 64 patients, and AG comprised of 84 patients. In terms of demographic characteristics which showed statistical significance, onset age of AG was younger and past medical history of febrile seizures was more frequent in FG. In regards of clinical characteristics of gastroenteritis and seizures, the average duration of gastrointestinal symptoms before seizure onset was shorter in AG. Clustering of seizures was noticed frequently in both groups, although duration of seizures was longer, and more seizures longer than 15 minutes were noticed in FG. Comparing laboratory results, serum glucose, creatinine and CRP was significantly higher in FG, while serum uric acid was higher in AG. Causative agents were determined in 67% of FG and 42% of AG. Rotavirus constituted the most number of cases in both groups. No difference was noticed in the seizure type, and both groups showed favorable prognosis.

Conclusion: FG and AG showed different clinical characteristics which suggest the need of different therapeutic approach.

A GIRL WITH A PRRT2 MUTATION AND INFANTILE FOCAL EPILEPSY WITH BILATERAL SPIKES

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Objectives: To demonstrate unique clinical manifestations of a female patient with infantile focal epilepsy who was a member of a family with infantile convulsion and paroxysmal choreoathetosis and to analyze her and her family genetically.

Patients: The proband developed partial seizures (e.g., psychomotor arrest) at age 14 months. At the time of onset, interictal EEG showed bilateral parietotemporal spikes. The results of neurologic examination and brain magnetic resonance imaging were normal. Her seizures were well controlled with carbamazepine, and she had a normal developmental outcome. EEG abnormalities, however, persisted for more than 6 years, and the spikes moved transiently to the occipital area and began to resemble the rolandic spikes recognized in benign childhood epilepsy. Her father had paroxysmal kinesigenic dyskinesia with an onset age of 6 years, and her youngest sister had typical benign infantile seizures.

Methods: After obtaining informed consent, the the proline-rich transmembrane protein-2 (*PRRT2*) gene was sequenced using DNA extracted from the peripheral blood of affected family members.

Results: In all affected members, DNA analysis demonstrated a common familial mutation of *PRRT2* gene, c.649_650insC.

Conclusions: This patient indicates that the phenotypic spectrum of infantile seizures or epilepsy with *PRRT2*-related pathology may be larger than previously expected, and that genetic investigation of the effect of *PRRT2* mutations on idiopathic seizures or epilepsy in childhood may help elucidate the pathological backgrounds of benign childhood epilepsy.

EFFECTS OF LEVETIRACETAM ON INTRACTABLE SEIZURES IN CHILDREN WITH HOLOPROSENCEPHALY

POSTER

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Objective: Holoprosencephaly (HPE) is a developmental brain malformation in which the forebrain fails to divide into two separate hemispheres and ventricles, and frequently presents with intractable epilepsy. Levetiracetam (LEV) is an antiepileptic drug (AED) currently used as adjunctive therapy for partial-onset seizures with or without secondary generalization. We evaluated the effects of LEV on intractable seizures in the three children with HPE.

Subjects: Patient 1 is a 10-year-old girl with alobar type HPE. Her seizure type was tonic seizure with strange voice and ocular nystagmus about ten times a day with 4 AEDs administration. Patients 2 is a 4-year-old boy with semilobar type. He had both spasm-like and tonic seizures about one hundred times a day with 2 AEDs administration. Patients 3 is a 5-year-old girl with semilobar type. She had stereotypic clonic seizures with abnormal eyes movement from 10 to 20 times a day with 3 AEDs administration. In all patients, interictal EEGs indicated inactive low amplitude slow wave at all hemisphere, cerebral blood flows with ^{99m}Tc-ECD SPECT were extremely reduced, and benzodiazepines receptor concentrations with ¹²³I-iomazenil SPECT were also reduced at all brains included brain stem.

Results: All three patients were administered LEV with 300 to 800 mg (29-81mg/kg) per day. Patient 1 and 2 showed a reduction of 75% in seizure frequencies. Patient 3 showed a reduction of 50% and additional AED of sulthiame showed a reduction of >75% in seizure frequencies. In all patients, adverse events were not present.

Discussion: The findings of SPECT support hypothetical mechanism as dysplasia of inhibitory neuron system with GABA-benzodiazepine. However, a previous study showed relative maintenance of excitability neurons formations in HPE. The antiepileptic effect of LEV exert to synaptic vesicle protein 2A with excitability neurons. These results suggest that administration of LEV is effective for epileptic seizures in HPE.

DIGEORGE SYNDROME PRESENTED WITH PERIODIC VOMITING

POSTER

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Objective: Chromosome 22q11 is characterized by the presence of chromosome-specific low-copy repeats or segmental duplications. It is reported in overlapping phenotypes such as : velocardiofacial syndrome, DiGeorge syndrome and conotruncal heart malformation. Several brain malformation has been described in association with 22q11.2 deletion syndrome. Bilateral polymicrogyria (PMG) is especially the indicative brain features in 22 q11.2, so that epilepsy is one of the most common neurologic signs in 22 q11.2. We present a 2 year-old boy with bilateral PMG due to 22q11.2 deletion (DiGeorge Syndrome), suffering from periodic and cyclic vomiting which is finally diagnosed as autonomic seizures.

Methods: We managed a boy diagnosed as DiGeorge syndrome, getting vigorous periodic vomiting with consciousness alteration in specific time period (from April 2013 to Feb 2015) Gastrointestinal examinations, including upper GI series, endoscope, abdominal sonography were reported negative studies. Brain MRI revealed bilateral PMG. Video EEG disclosed lateralizing delta wave over left temporal area during emesis. The inter-ictal FDG-PET/CT scan overlapped the decreased FDG uptake areas with the cortical malformation regions. We also compared the emesis frequencies and emesis-free interval before and after anticonvulsants administration.

Results: We demonstrated the emesis frequency decreased after high dose of oral phenobarbital (8mg/Kg/day) administration and ketogenic diet intervention. Based on the unique clinical presentations, EEG manifestations and his good responsive to anticonvulsants and ketogenic diet, the boy was successfully treated as autonomic seizure.

Conclusion: A GI involvement can be identified in the 58% of patients with 22q11.2 deletion. The major problems are abdominal pain, vomiting, gastroesophageal reflux and chronic constipations. However, unusual seizure type should be kept in mind in 22q11.2 deletion patients presented as GI symptoms just like our patient.

EPILEPTIC APNEA IN AN INFANT WITH RESPIRATORY SYNCYTIAL VIRUS INFECTION PROVED BY VIDEO-EEG

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Introduction: Respiratory syncytial virus (RSV) is the most common virus that causes acute lower respiratory tract infection in infants. Extrapulmonary manifestation of RSV infection is rare but life-threatening if inadequately treated. Apnea and seizure have been seen in RSV infection, but the apnea in RSV infection has never been proved to be an ictal attack of epileptiform discharges. Here we report a premature infant with RSV-related encephalopathy presenting as epileptic apnea and highlight the importance of video-electroencephalography (EEG) study in patients with RSV infection with apnea.

Patient: This six week-old preterm male infant, born at a gestational age of 30 weeks (postmenstrual age = 36 weeks old, birth body weight = 1764gm) without perinatal insults, was brought to our emergency department with the initial presentation of apnea and cyanosis. The initial symptoms included a 1-day history of non-productive cough, irritability, and reduced oral intake. He was never febrile. His elder brother had a cold a week ago. Frequent episodes of prolonged apnea (duration: 30 seconds to 2 minutes) and cyanosis (SpO₂ 30 – 50 %) occurred during hospitalization which responded poorly to nasal positive pressure ventilation. RSV antigen was detected from the nasopharyngeal swab. The cerebrospinal fluid (CSF) study and the brain MRI revealed negative findings. The Video-EEG showed brief rhythmic discharges with evolution over the left hemisphere during the apnea attacks. He required mechanical ventilator support and his apnea subsided after the commencement of antiepileptic drug. After extubation, he was treated by antiepileptic drug only. No neurologic sequel was noted after 1 year of follow-up.

Discussion: Our case report highlights the importance of video-EEG study in patients with RSV encephalopathy. Epileptic apnea should be considered in caring patients with RSV infection. Neglecting this possibility of epileptic apnea and treating with xanthine derivatives in these apneic patients with epileptiform discharges will be detrimental.

CLINICAL FEATURES AND *PRRT2* GENE MUTATIONS IN FAMILIES WITH BENIGN FAMILIAL INFANTILE EPILEPSY

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Objective: To study the clinical features and proline-rich transmembrane protein 2 (*PRRT2*) gene mutations in families with benign familial infantile epilepsy (BFIE).

Methods: All BFIE probands and their family members were collected from Peking University First Hospital between September 2006 and April 2015. Clinical data of affected members were analyzed. Genomic DNA was extracted from peripheral blood samples with standard protocol. Mutations in *PRRT2* gene were screened using PCR amplification and Sanger sequencing.

Results: Thirty-seven BFIE families were recruited in this study. In total, 127 family members were affected. The seizure onset age of these affected members was between 2 and 12 months (median: 4.5 months). All probands presented with cluster of seizures. Two probands had one seizure induced by diarrhea at 25 months and 31 months respectively. *PRRT2* mutations were found in 21 of 37 (56.8%, 21/37) BFIE families. Mutation c.649_650insC(p.R217PfsX8) was detected in 16 of 21 (76.2%, 16/21) families with *PRRT2* mutations. Mutation c.649delC(p.R217EfsX12) was identified in three families. Mutation c.323_324delCA (p.T108SfsX25) and c.904_905insG (p.D302GfsX39) were detected in one family respectively. In one family, two heterozygous mutations of c.649_650insC and c.593_594delCT(p.P198RfsX26) were found in the proband, and mutations c.649_650insC and c.593_594delCT were respectively inherited from her asymptomatic father and mother. The affected member whose onset age was two months had *PRRT2* mutation. In two BFIE families, two family members with *PRRT2* mutation manifested as febrile seizures.

Conclusion: The minimum seizure onset age was 2 months in BFIE affected members. *PRRT2* is the major causative gene of BFIE. More than fifty percent of Chinese BFIE families had *PRRT2* mutations. Mutation c.649_650insC is the hotspot mutation of *PRRT2* gene. Few affected members with *PRRT2* mutations presented with febrile seizures.

PHENOTYPES AND *PRRT2* MUTATIONS IN INFANTILE CONVULSIONS WITH PAROXYSMAL CHOREOATHETOSIS

POSTER

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Objective: To analyze the phenotypes and proline-rich transmembrane protein 2 (*PRRT2*) gene mutations in families and sporadic cases of infantile convulsions with paroxysmal choreoathetosis (ICCA).

Methods: Clinical data were collected from ICCA patients and their family members. Genomic DNA was extracted from peripheral blood samples with standard protocol. Mutations of *PRRT2* were screened using PCR amplification and Sanger sequencing.

Results: Fifteen families and one sporadic case with ICCA were recruited in our study. In 15 ICCA families, 57 family members were affected, of which 19 individuals had benign infantile convulsions (BIC) alone, 20 individuals had only paroxysmal kinesigenic dyskinesia (PKD), and 18 individuals had BIC followed by PKD. The seizure onset age of infantile convulsions was between 3 and 12 months. The onset age of PKD was ranging from 5 to 20 years old. Four affected members in two ICCA families had PKD or ICCA co-existing with migraine. The one sporadic ICCA case had seizures between 3.5 and 4 months, and developed paroxysmal twits of limbs after 4 years and 10 months of age. He had good response to treatment with oxcarbazepine. Mutations in *PRRT2* were identified in all 15 ICCA families, including six different mutations (c.649_650insC/p.R217PfsX8, c.560_561insT/p.L187LfsX5, c.1023A>T/p.X341C, c.514_517delTCTG/p.S172RfsX3, c.649delC/p.R217PfsX8 and c.859G>A/p.A287T). The most common mutation, c.649_650insC, was detected in 8 of 15 families (53.3%). *PRRT2* mutation was also found in the sporadic ICCA case, and was identified as *de novo* mutation (c.649_650insC).

Conclusion: The phenotype of PKD in ICCA families occurred in childhood or adolescence. Few affected members in some ICCA families could have migraine. *PRRT2* is the causative gene of ICCA. *PRRT2* mutation was also found in sporadic case with ICCA. The mutation c.649_650insC was the hotspot of *PRRT2* mutations.

THE ELECTROCLINICAL FEATURES OF BENIGN INFANTILE EPILEPSY IN 49 PATIENTS

POSTER

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Objective: To summarize the electroclinical features and outcome of benign infantile epilepsy (BIE).

Methods: BIE patients were collected in Pediatric department of Peking University First Hospital. The clinical and EEG data of patients were analyzed. The treatment effects and outcome of patients were followed up.

Results: In 49 BIE patients, 21 were male and 28 were female. The seizure onset age ranged from 3 months to 13 months. Partial seizures were observed in 26 patients (53.1%), secondarily generalized seizures in 23 patients (46.9%). 39 patients (76.9%) had a history of cluster seizures. All patients had no history of status epilepticus. 24 patients had a family history of seizures. 15 patients have a family history of benign familial infantile epilepsy. The interictal EEG was normal in 33 (67.3%) cases. The interictal discharges were recorded in 16 cases. Ten of sixteen cases had interictal discharges in lateral or bilateral Rolandic area. Ictal video EEG was recorded in 4 patients. Ictal discharges originated from temporal region in three patients and from occipital region in one patient. Five patients did not be treated with antiepileptic drugs, and 44 patients accepted antiepileptic monotherapy. Treatment time is ranged from 2 months to 24 months (12.5±9.9) months. All patients were followed-up over two years old, and no one had seizure relapsed.

Conclusion The features of BIE including the onset age before one year old; manifesting partial seizures or secondarily generalized seizures, and usually a cluster of seizures; normal interictal EEG or small spikes in Rolandic area; good response to antiepileptic drugs and benign outcome.

***POLG1* MUTATION IN A PATIENT PRESENTING WITH PROFOUND HYPOTONIA, REFRACTORY SEIZURES AND FACIAL DYSMORPHISM: A CLINICAL REPORT**

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Objective: Alpers-Huttenlocher syndrome (AHS) is an autosomal recessive disorder characterised by seizures, liver degeneration, and developmental regression. It is caused by mutations in *POLG1*, and has a wide range of clinical phenotype.

Methods: We report on a patient referred with hypotonia and refractory seizures in whom a compound heterozygous *POLG1* mutation was identified.

Results: The patient was born at 38 weeks of gestation with a birth weight of 2670 g. Parents were not related. The mother had a history of epilepsy, however well controlled. He required NICU for recurrent apnea and possible meningitis at day 13. He started to have generalised seizures in clusters, 4-5 times per week with occasional status epilepticus. He was referred to our center at 8 months with refractory seizures. On admission, his centiles were %90-97 in head circumference, %10 in height and %25 in weight. Broad forehead, depressed nasal root, hypertelorism and hepatomegaly were noted. Neurological examination revealed normal eye movements without visual attention and pursuit. He was not responsive to mother's voice. There was profound generalised hypotonia with preservation of deep tendon reflexes. Neurometabolic and mitochondrial diseases were considered, however, metabolic work-up and muscle biopsy to include respiratory chain enzymes were normal. He had constant but fluctuating hypertransaminasemia. Cranial MRI showed diffuse hypomyelination, cerebral and cerebellar atrophy. Video-EEG monitoring detected rhythmic, asymmetrical and low amplitude jerks. Rhythmic teta waves originated from both left and right temporal regions independently. Based on abnormal liver enzymes as a clinical clue, *POLG1* sequence analysis was performed revealing a compound heterozygous mutation c.803G>C (p.G268A) and c.1316A>T (p.Q438L). To our knowledge c.803G>C change has been reported in progressive external ophthalmoplegia but not in AHS so far.

Conclusion: *POLG1* mutations should be considered in patients presenting with profound hypotonia and refractory seizures in the presence of significantly elevated liver enzymes.

CLINICAL FEATURE OF SEIZURE IN EMANUEL SYNDROME: A CASE REPORT

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Introduction: Emanuel syndrome is characterized by multiple congenital anomalies (microcephaly, failure to thrive, preauricular tags or pits, ear anomalies, cleft or high-arched palate, micrognathia, kidney abnormalities, congenital heart defects, and genital abnormalities) and severe development disability in males. Emanuel syndrome is caused by a chromosome imbalance. Little has been published on the clinical features of this syndrome and information on natural history is limited. Seizures are reported in a few affected individuals and abnormal EEGs without clinical seizures in another small subset. So, there was no detail of seizure reported in this syndrome. We report a case with this syndrome revealed clinical seizures and abnormal EEG.

Case presentation: A 4-year-old boy from non-consanguineous parents. He was admitted due to recurrent movement of left upper extremity at 1-year old. He had been suffered from Emanuel syndrome and treated with surgical correction for anal atresia. A diagnosis of epilepsy was made by video monitoring EEG on admission. Medication of VPA and CBZ were effective to epilepsy.

Conclusion: We can provide information of seizures in Emanuel syndrome.

CLINICOPATHOLOGIC FEATURES OF THREE JUVENILE PATIENTS WITH EPILEPSY: DYSPLASTIC TEMPORAL LOBE LESIONS WITH AN ANGIOCENTRIC ARRANGEMENT OF IMMATURE CELLS

POSTER

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Objective: We describe the clinicopathologic features of three early childhood patients with intractable epilepsy, from whom the removed surgical specimens showed characteristic dysplastic features.

Patients: The first patient, a 1.5-year-old girl, suffered an initial epileptic seizure, and brain MRI demonstrated a cystic lesion involving the right inferior temporal gyrus. Magnetoencephalography revealed accumulation of dipoles behind the cyst. At the age of 3 years, the patient underwent resection of the lesion. The second patient, a 2-year-old boy, suffered an initial generalized tonic-clonic seizure. Electroencephalography (EEG) demonstrated multiple spikes and waves, and MRI revealed a cyst with cortical atrophy and myelination delay at the left temporal tip. Positron emission tomography revealed poor signal accumulation at the lesion. The patient underwent resection of the lesion at the age of 3 years. The third patient, a 3-year-old girl, suffered tonic seizures after initially demonstrating unusual vocal sound and grabbing motions. EEG demonstrated bilateral rhythmic spikes, and MRI showed a cystic lesion at the right temporal tip. The lesion was resected when the patient was 4 years old.

Histology: The temporal lesions resected from the three patients all showed similar small cells with mono- and bipolar processes arranged parallel to the long axis of capillary vessels in the dysplastic cortex. Immunohistochemically, these cells were positive for vimentin, nestin, S-100, Tuj-1, GFAP and Olig2. Double-labeling immunofluorescence demonstrated co-localized positivity for nestin and GFAP, or for nestin and Tuj-1, indicating that the cells were immature, sometimes with either glial or neuronal profiles. Ultrastructurally, the cells displayed numerous cytoplasmic expansions and contained abundant intermediate filaments, in addition to hemidesmosome-like subplasmalemmal structures and basal lamina-like structures on their processes.

Discussion: The clinicopathologic features of the present patients were quite similar and distinct. The lesions appeared to be dysplastic in nature, the immature cells showing a characteristic angiocentric arrangement.

THE CLINICAL MANIFESTATION OF 13 PATIENTS WITH PAROXYSMAL KINESGENIC DYSKINESIA

POSTER

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Objective: Paroxysmal kinesogenic dyskinesia (PKD) is characterized by recurrent and brief attacks of involuntary movements induced by the initiation of voluntary movements. Recently, *PRRT2* gene has been shown to be the major causative gene of PKD and infantile convulsions (IC) with choreoatetosis syndrome. We aim to delineate the clinical features of familial and sporadic cases of PKD.

Methods: We retrospectively reviewed 13 patients diagnosed as PKD between 1993 and 2012 in our hospital.

Results: IC was found in two patients, febrile seizures in two patients, and focal epilepsy in one patient. Five and two patients had a family history of PKD and IC respectively. The age at onset of PKD ranged from 7 to 43 years (median age 11 years). Seven patients with a family history of PKD or IC had earlier age of onset compared with other patients without it (median age: 9 vs. 13.5 years). Most attacks were triggered by sudden movement. Four patients had premonitory sensation preceding the attacks. In addition to dystonia and chorea, some patients (5/13) complained weakness of limbs during the attacks. About half of patients were misdiagnosed as epilepsy (7/13) or psychogenic disorder (2/13). All patients presented good response to low doses of carbamazepine, except for one, in whom age at onset was 43 years old. The age of most recent follow-up was 15 to 51 (median 29) years and 11 patients have continued carbamazepine. Common *PRRT2* mutations were identified in 2 of 4 patients.

Conclusion: A family history of PKD or IC was associated with a younger age of onset. PKD is a treatable movement disorder that is often misdiagnosed as other illnesses such as epilepsy or psychogenic disorder. It is important to note the distinctive clinical features to avoid unnecessary diagnostic and therapeutic intervention.

KCNQ2 MUTATION IN CHILDHOOD EPILEPSY WITHOUT AN IDENTIFIED CAUSE: EEG CHARACTERISTICS IN A CASE SERIES

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Objective: Pediatric non-lesional epilepsy caused by a *KCNQ2* gene mutation usually manifests the phenotype of a neonatal seizure during the first week of life. However, the exact mechanism, phenotype, and electroencephalographic (EEG) changes still require investigation.

Methods: We studied the clinical phenotypes, EEG changes, and neurodevelopmental outcomes of 8 family members with *KCNQ2* mutations, from 74 nonconsanguineous pediatric patients with non-lesional epilepsy. To decide whether the mutation variants were pathogenic or benign, we used computer-based algorithms and transfected mutation variants into HEK293 cells to investigate functional changes with *KCNQ2* mutation variants.

Results: All mutation variants were predicted to be deleterious by the computer-based SIFT or PolyPhen algorithms. The functional study EEG recordings showed that the mutant variants (p.Y755C, p.V543M, and p.E515D, with currents significantly [$p < 0.05$] lower than that of the wild-type) caused functional disabilities. Four patients had the c.1545G>G/C (p.E515D) variant, but their seizure outcomes were favorable; however, three had learning disabilities. Two of these patients presented with late childhood epileptic encephalopathy with continuous spike wave discharges in slow-wave sleep (CSWS); the CSWS disappeared post-treatment in one patient. Two patients with the c.2264G>G/A (p.Y755C) variant had neonatal epileptic encephalopathy: one had EEG burst suppression and the other had multiple focal spikes that evolved into CSWS at age of 6 years. One with the (p.R432C) variant presented with rolandic spikes and CSWS that remitted post-treatment. Three patients, whose EEG paroxysmal activities were in the centrotemporal region, had benign familial neonatal convulsions; one of them had subsequent recurrent childhood seizures.

Conclusions: The variation of EEG findings in *KCNQ2*-associated epilepsy might be, first, burst suppression or multiple focal spikes in newborns; second, a late-childhood epileptic encephalopathy with CSWS; or, third, non-specific focal paroxysmal discharges. Most, however, are in the centrotemporal region.

NEURONAL CEROID LIPOFUSCINOSIS-2 (CLN2) DISEASE, A TYPE OF BATTEN DISEASE CAUSED BY TPP1 ENZYME DEFICIENCY: CURRENT KNOWLEDGE OF THE NATURAL HISTORY FROM INTERNATIONAL EXPERTS

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Objective: The neuronal ceroid lipofuscinoses (NCLs) are the most common group of neurodegenerative disorders in children and adolescents. CLN2, a type of NCL caused by TPP1 enzyme deficiency, is characterized by seizures, rapid deterioration of language, cognition, motor skills and vision, and premature death. Our aim is to describe expert knowledge of CLN2 disease.

Methods: 18 international NCL experts answered a survey on CLN2 natural history.

Results: Clinical suspicion for CLN2 is low due to its rarity and non-specific presenting symptoms. A 1-4 year delay was reported between first onset of symptoms and diagnosis. Speech delay/decline, developmental delay/regression and seizures/epilepsy were identified as initial presenting symptoms. Symptom onset typically occurs between 1.5-5 years of age, but may occur later (9-12 years). Myoclonic epilepsy was the most commonly reported seizure type. Notably, seizures are refractory oftentimes requiring polytherapy. Cardiac rhythm anomalies, not previously associated with CLN2, were also identified.

Conclusion: CLN2 is a severe, progressive, pediatric-onset neurodegenerative disease. Disease awareness is low, causing delays in diagnosis. Seizures in concert with a regression of language and/or motor milestones should raise suspicion for CLN2. Knowledge of CLN2 is paramount to ensure timely diagnosis and to enable early initiation of future therapies.

REAL-WORLD EXPERIENCE IN THE DIAGNOSIS OF NEURONAL CEROID LIPOFUSCINOSIS TYPE 2 (CLN2): REPORT FROM AN INTERNATIONAL COLLABORATION OF EXPERTS

POSTER

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Objective: CLN2 disease is a lysosomal storage disorder resulting from TPP1 enzyme deficiency that causes progressive neurological degeneration and early mortality. CLN2 disease is rare and often unsuspected, leading to delays in diagnosis.

Methods: In late 2014, 18 international CLN2 experts (clinicians, academic researchers, and laboratory directors) answered a comprehensive survey on CLN2 disease and a subset met to discuss experiences, current practices and shortcomings in diagnosis of CLN2.

Results: 70% of laboratory experts considered the standard for CLN2 diagnosis to be a demonstrated decrease in TPP1 enzyme activity, with the remaining experts favoring molecular detection of pathogenic *CLN2/TPP1* mutations. Delays in the diagnosis of CLN2 were identified as a crucial concern: 82% of the group responded that patient referral to a specialist can typically take longer than one year. Laboratory experts identified the challenge in reaching a suspicion of CLN2 (50%) and lack of awareness of available tests (83%) as common reasons for delays.

Conclusion: Experts agreed that reliable techniques exist for CLN2 diagnosis and identified timely referral as a key challenge. An upcoming CLN2 expert meeting will define laboratory-based screening and diagnostic guidelines in order to establish best practices for use of biochemical genetics testing in CLN2 diagnosis.

SEQUENTIAL PROFILING OF SERUM CYTOKINE RESPONSE TO ACTH IN PATIENTS WITH WEST SYNDROME

POSTER

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Objectives: Involvement of immunological processes in the pathogenesis of epilepsy has been suggested, we reported that serum IL-1RA levels (indicator of an anticonvulsive effect) were elevated subsequent to resolution of clinical findings in patients with West syndrome (WS). The aim of this study was to evaluate various cytokine responses to ACTH in patients with WS and to clarify the mechanism of its effect in these patients.

Methods: Five Japanese patients with WS were enrolled. Serum samples were obtained prior to and at 30, 120, and 720 minutes after the injection of ACTH (0.0125 mg/kg). Using the Bio-Plex multiplex cytokine assay, we measured the following cytokines: IL-1RA, IL-1 β , IL-2, -4, -5, -6, -7, -8, -9, -10, -12, -13, -17, TNF α , IFN γ , G-CSF, MCP-1 and VEGF. The cytokine levels were categorized into early group and delayed group, and the changes in response to ACTH were analyzed in each group. The informed consent was received from their parents to use samples for clinical investigation.

Results: In the early group, serum IL-17 levels prior to injection were higher than the levels at 720 minutes after injection, IL-9 levels decreased after ACTH injection. In both early and delayed groups, MCP-1 levels decreased after ACTH injection. The fluctuations in the levels of other cytokines varied, no significant difference in serum levels of IL-1RA was observed in this study.

Conclusions: The decreased levels of IL-17 (indicator of a proconvulsive effect) were observed, some cytokines may be involved in the mechanism of action of ACTH. Further studies with a larger patient group are needed to assess whether immunological processes is concerned with the pathophysiology of WS.

THE EFFICACY OF LIDOCAINE IN INTRACTABLE EARLY-ONSET EPILEPTIC ENCEPHALOPATHY: A CASE STUDY

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Background: Early-onset epileptic encephalopathy (EOEE) is characterized by developmental impairment and intractable seizures starting from early infancy, and its categorization is still debated. Brain development in patients with EOEE is impaired by recurrent clinical seizures or remarkable interictal epileptiform discharges during the neonatal period. Several genes are related to synaptogenesis, pruning, neuronal migration and differentiation, neurotransmitter synthesis and release, and functions of receptors and transporters have been shown to be involved in the pathogenesis of EOEE.

Case: We report a case of an 11-month old girl with repetitive generalized tonic seizure with severe cyanosis, frequently developing status epilepticus.

Her initial symptom was intractable epilepsy from 1 month of age without the suppression-burst pattern of electroencephalography (EEG). The EEG showed no definitive epileptiform discharge during sleep and awake state until 11 months of age and showed a lower voltage pattern than what is appropriate for her age.

She demonstrated generalized tonic seizure following clonic seizure. She showed many developmental features, including social smiling and head control until 7 months of age, after which she regressed to not being able to smile and hold her head up because of clustering seizures, which were only arrested by intravenous lidocaine administration. We were able to discontinue lidocaine infusion therapy under high dose of phenobarbital and zonisamide administered orally. We also started lamotrigine as a third-line therapy. She had no requirement for surgical treatment because no brain lesions were observed in magnetic resonance imaging, magnetic resonance spectroscopy, magnetic resonance spectroscopy, and positron emission tomography. Moreover, no metabolic abnormalities were indicated in the blood and cerebrospinal fluid tests. Genetic analysis is ongoing.

Conclusion: We report an intractable case of EOEE without definite disease pathogenesis. The sodium channel blocker, lidocaine, was completely effective, suggesting that sodium channel function might contribute to disease pathogenesis.

BENIGN INFANTILE SEIZURE AS THE INITIAL PRESENTATION OF GLUCOSE TRANSPORTER-1 DEFICIENCY

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Glucose transporter type 1 deficiency syndrome (GLUT1-DS) results from deficits in glucose transporter type 1 (GLUT1) at the blood-brain barrier, responsible for transportation of glucose into brain tissue. Two cases with the most severe phenotype were first reported by De Vivo et al. in 1991, with infantile-onset epileptic encephalopathy, associated with hypoglycorrachia, developmental delay, acquired microcephaly, incoordination and spasticity. Recently the range of phenotypes in GLUT1-DS has significantly expanded, including milder phenotypes even without seizures.

We present a young girl diagnosed GLUT1-DS with a SLC2A1 mutation, who presented with benign infantile seizures. She initially presented with daily clusters of head drops at 5 months of age. Seizures were associated with 1-5 second bursts of 3-4 Hz generalized spike and wave complexes, when captured on video EEG monitoring. She had normal early development, as well as normal physical and neurological examination. Basic labs and MRI were unremarkable. She became seizure-free with valproic acid and subsequently she had normal serial EEGs.

Unexpectedly at 6 years of age, she developed seizure recurrence with likely prolonged clusters of absence seizures, and mild decline in cognition and behavior; additional diagnostic evaluation with genetic testing identified a missense variant in the SLC2A1 gene at c.79G>A, variant p.Gly27Ser (G27S), which was considered pathologic.

Our case demonstrates that GLUT1-DS can present with a much more "benign" presentation compared to the classical reported cases by De Vivo et al., including benign infantile seizures, with normal early development and easily controlled seizures; the symptoms in this case appear even milder than the so called "mild" cases reported so far. GLUT1-DS could be an etiology of unexplained benign infantile seizures, even if patient achieves good seizure control with normalized EEG. Early diagnosis and initiation of ketogenic diet in GLUT1-DS is recommended, which may be important for long-term seizure and cognitive outcome.

TARGETED NEXT GENERATION SEQUENCING IN CHILDREN WITH EPILEPTIC ENCEPHALOPATHY: STUDY FROM A TERTIARY CARE UNIVERSITY HOSPITAL IN SOUTH INDIA

POSTER

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Objectives: To delineate the underlying etiology of childhood epileptic encephalopathies (EE) using targeted next generation sequencing (NGS), an emerging genetic diagnostic tool.

Methods: From a large cohort of children with EE, 20 children (Mean age at evaluation: 23.9±23.2 months; age-range: 2 months to 6 years; M:F :: 1.3 :1) with varying combination of refractory seizures, developmental delay, intellectual disability and autism underwent targeted NGS, over a six-month period, based on clinical judgment and financial affordability. Evaluation for structural and metabolic abnormalities drew negative results for an etiologic diagnosis. Genetic mutations were correlated with clinical phenotypes.

Results: Mean age at seizure onset was 9.6±8.7 months (range: 20 days to 2 years). Consanguinity was noted in one. Family history of febrile and an afebrile seizure was noted in five patients each. Associated features included: movement disorder (n=7), hypotonia (n=7), spasticity (n=4), hyperactivity (n=4), ataxia (n=2), and autism (n=2). Targeted NGS revealed mutations in 17 children, majority involving recognized EE genes: *SCN2A*, *SPTAN1*, *CDKL5*, *MECP2*, *POLG1*, *HEXA*, *EARS2*, *KCNQ3*, *SLC2A1*, *PNKP*, *GLDC*, *DYNC1H1*, *FOXP1*, *GPR98*, *GABRB3*, *MBD5*, and *PRRT2*. Among these novel associations were noted in five patients: benign familial neonatal seizures associated *KCNQ3* deletion in refractory early onset absence epilepsy; *DYNC1H1* mutation hitherto described in neuromuscular disorders in early infantile EE with spastic quadriplegia; childhood absence epilepsy associated *GPR98* and mitochondrial leukoencephalopathy associated *EARS2* mutations in one patient each with myoclonic astatic epilepsy; and Tay-Sach's disease associated *HEXA* mutation in an infant diagnosed Dravet syndrome, without hexosaminidase deficiency.

Conclusion: This study highlights the spectrum of genetic mutations underlying childhood EE from south India and brings out novel genotype-phenotype associations. Targeted NGS is a useful diagnostic tool in the evaluation of childhood EE when other tests are negative and yields valuable information for comorbidities, prognosis and genetic counseling.

KETOGENIC DIET AND HIGH-DOSE INTRAVENOUS METHYLPREDNISOLONE IN THREE CASES WITH ACUTE ENCEPHALITIS WITH REFRACTORY, REPETITIVE PARTIAL SEIZURES

POSTER

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Introduction: Recent reports indicate that ketogenic diet (KD) can be effective as an acute treatment for refractory status epilepticus. Patients with febrile illness related epilepsy syndrome (FIRES) and acute encephalitis with refractory, repetitive partial seizures (AERRPS) especially seem to be good responder for the KD. FIRES and AERRPS are postulated to have an immune-mediated, inflammatory basis. Therefore immunomodulatory treatments such as high-dose intravenous methylprednisolone (HDMPSL) and intravenous immunoglobulin were also generally challenged. However, steroids might prevent the occurrence of ketone bodies and alter response to the ketogenic diet.

Case report: We report on three cases of AERRPS treated with KD and HDMPSL. Case 1, 7-year-old boy was treated with KD from day 53. HDMPSL was used concomitantly from day 44 to 46, and day 63 to 65. After 2nd HDMPSL, he could not archive strong ketosis which serum β -hydroxybutyrate level was over 3.0mmol/L. KD could not reduce his seizure frequency dramatically. Case 2, 4-year-old girl, was treated with KD from day 6. HDMPSL was used concomitantly from day 11 to 13, and day 25 to 27. She could maintain strong ketosis during KD therapy. KD could reduce her seizure frequency temporarily. Case 3, 7-year-old boy was treated with KD from day 9. HDMPSL was used concomitantly from day 1 to 3, and day 15 to 17. His serum β -hydroxybutyrate level decreased to half after 2nd HDMPSL. His seizure frequency did not change by KD. But intrathecal administration of dexamethasone could reduce his seizure frequency.

Discussion: We cannot conclude whether HDMPSL might influence efficacy of KD or not. Because treatments to AERRPS and FIRES are still challenging, we suggest the timing of immunomodulatory treatments and KD should be separated. Further studies are needed in order to define the optimal timing of immunomodulatory treatments and KD in patients with AERRPS and FIRES.

GENOTYPIC AND PHENOTYPIC FINDINGS IN A PATIENT WITH COMPOUND HETEROZYGOUS *PRRT2* MUTATION: UNTANGLING THE CORRELATION.

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Mutations in the proline-rich transmembrane protein (*PRRT2*) gene have been described in families with benign familial infantile epilepsy (BFIE), episodic ataxia (EA), paroxysmal kinesigenic dyskinesias (PKD), and hemiplegic migraines, occurring individually or in combination.

We describe the findings in a patient with probable compound heterozygous *PRRT2* mutations and infantile onset epilepsy with status epilepticus, paroxysmal dyskinesias, prolonged episodes of ataxia, with preserved global development.

Our patient is a 4 year old boy with infantile seizures starting at age 3 months occurring in frequent clusters, either spontaneously or in the settings of febrile illness, gastroenteritis, or trauma. Some met the criteria for status epilepticus and required admission to the intensive care unit. These resolved at age 2.

He experienced prolonged ataxia post-ictally and spontaneously.

He developed frequent episodes of eye deviation with facial contortion, lacking electrographic correlate on EEG and consistent with paroxysmal dyskinesias.

Genetic testing revealed a pathogenic *PRRT2* duplication at exon 2 (c3649dupC), inherited from an unaffected mother with negative family history. The second mutation, (c916G>A), was described in a patient with BFIE with no functional data and reported as a variant of unknown significance (VUS). This was inherited from the patient's father. On the paternal side, the family history includes transient hemiplegias, tremors, and episodic aphasia.

The patient's 2 year old unaffected brother carries the maternally inherited mutation.

This patient's symptoms fall in the more severe phenotypic category with a combination of at least 3 neurological symptoms: seizures and status epilepticus, prolonged episodic ataxias, and paroxysmal dyskinesias. Interestingly, he is likely a compound heterozygote with a pathogenic mutation inherited from an unaffected mother, and a VUS inherited from an affected father/paternal side. This case illustrates the complex correlation between genotype and phenotype in the *PRRT2* gene, and suggests that compound heterozygous mutations might confer a more severe phenotype.

A CASE OF LOCALIZATION RELATED EPILEPSY WITH EPILEPTIC SPASMS: ICTAL VTR-EEG STUDY

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Here we present a case of localization related epilepsy with epileptic spasms, whose ictal manifestations were comprised of focal motor seizures followed by epileptic spasms. This three-month old infant was referred and admitted to our hospital for spasms developed at the age of 20 days, occurring in cluster with increase in frequency. Her prenatal and perinatal histories were uneventful, and early milestones were normal. Neurological examination showed normal features in cranial nerves, motor systems, postural reactions and deep tendon reflexes. Ictal manifestations were comprised of tonic right upper limb in the posture of abduction and elevation for 1min, which were followed by periodic spasms seen in bilateral lower limbs with each interval of 5-10 seconds lasting for 5min. Routine blood tests and metabolic screening tests including ammonia, lactate levels, amino acid and organic acid analyses were all normal. Brain MRI showed normal configurations and normal myelinations. VTR-EEG showed rhythmic EEG discharges in the left anterior temporal area during the ictal manifestation of the focal tonic seizure in the right upper limb. The diagnosis of localization related epilepsy was made, and seizures disappeared successfully. The ictal manifestation of focal seizures followed by the periodic spasms may be interpreted as localized cortical electrical excitation running into the brain stem provoking spasms.