

Characteristic phasic evolution of convulsive seizure in *PCDH19*-related epilepsy

Hiroko Ikeda ¹, Katsumi Imai ¹, Hitoshi Ikeda ¹, Hideo Shigematsu ¹,
Yukitoshi Takahashi ¹, Yushi Inoue ¹,
Norimichi Higurashi ^{2,3}, Shinichi Hirose ^{2,3}

1 Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Japan

2 Department of Pediatrics, Jikei University School of Medicine

3 The Central Research Institute for the Molecular Pathomechanisms of Epilepsy of Fukuoka University

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



PCDH19-related epilepsy

Epilepsy and mental retardation limited to females (EFMR)
(2008, Scheffer)

X-linked protocadherin 19 mutations (2008, Dibbens)

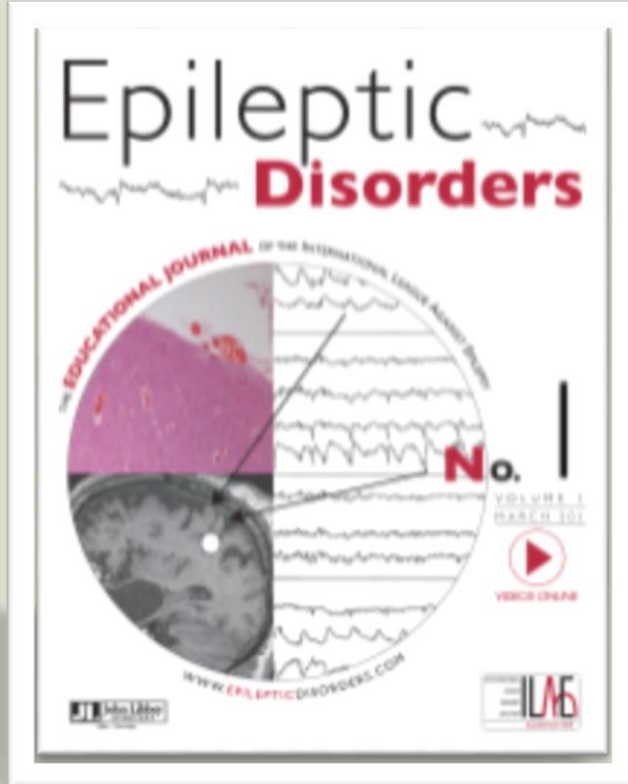
Epileptic encephalopathy caused by mutations of *PCDH19*

- Seizure onset : infantile, early childhood
- Tendency for seizure clustering
- Fever-sensitivity
- Seizure frequency: not so frequent
- Intellectual disability: 2/3
- Psychiatric features such as autism, psychosis

Reported Seizure Types

- Generalized seizures
 - Generalized Tonic Clonic seizures (GTCS)
 - Absence
 - Myoclonic
 - Tonic
 - Atonic
- Focal seizures

Volume 18, issue 1, March 2016



Epileptic Disord 2016; 18 (1): 26-33

Characteristic phasic evolution of convulsive seizure in *PCDH19*-related epilepsy*

Hiroko Ikeda¹, Katsumi Imai¹, Hitoshi Ikeda¹,
Hideo Shigematsu¹, Yukitoshi Takahashi¹, Yushi Inoue¹,
Norimichi Higurashi^{2,3}, Shinichi Hirose^{3,4}

¹ National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, NHO

² Department of Pediatrics, Jikei University School of Medicine

³ The Central Research Institute for the Molecular Pathomechanisms of Epilepsy of Fukuoka University

⁴ Department of Pediatrics, Fukuoka University, School of Medicine, Japan

Received June 12, 2015; Accepted January 04, 2016

Purpose

To elucidate the characteristic features of convulsive seizures associated with PCDH19 Related Epilepsy.

Methods

- 47 seizures in 5 patients detected on Video EEG
 - 26 convulsive seizures from 3 patients on Video-EEG
- Semiological analysis of convulsive seizures
- Reviewed from medical records
 - family history
 - precipitation by fever
 - frequency and duration of seizures
 - interictal EEG
 - brain imaging
 - Treatments
 - cognitive and behavioural assessments
- Genetic analyses; Fukuoka University

- The patients and their parents agreed to participate in this study and allowed their video to be used.
- The *PCDH19* and *SCN1A* genetic tests were approved by the institutional ethical committee.

Patient 1

- 14-year-old female
- Perinatal; mother suffered severe toxemia
- Past history; unremarkable
- Psychomotor development;
 - Normal before, delayed after seizures onset (10m)
 - Mild intellectual disability at 11y
 - IQ62 (VIQ72,PIQ58)
- MRI/CT; slight diffuse brain atrophy

Family history

Mother (47y)

intellectual disability

Epilepsy

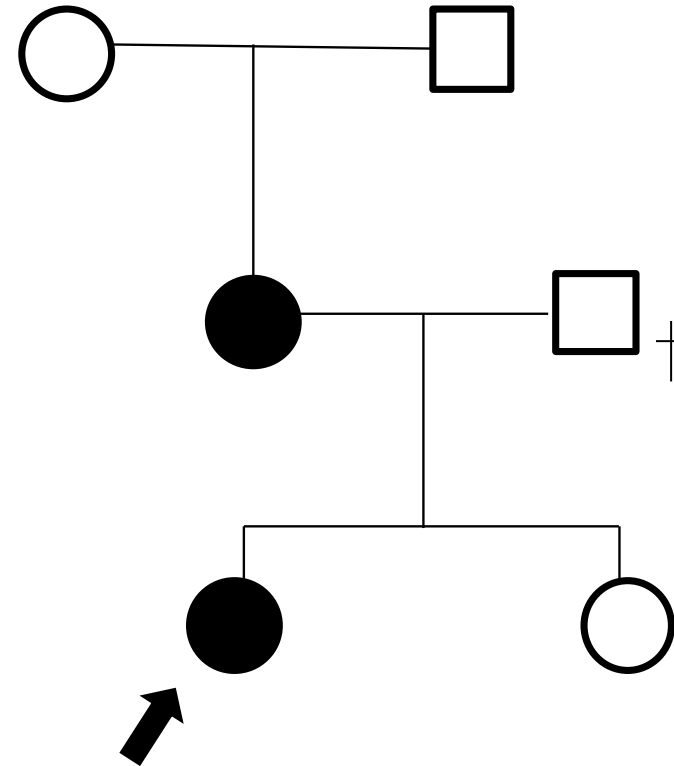
Onset: 5 months

Fever precipitation

Sz type: similar to Patient 1

Last seizure: 31y

VPA discontinuation: 45 y



Patient 1 & mother: *PCDH19* missense mutation
SCN1A testing : negative

Patient 1 (1)

Jerks

Axial jerks with cough-like sounds

“Mild tonic”

Legs prominent

“fluttering”

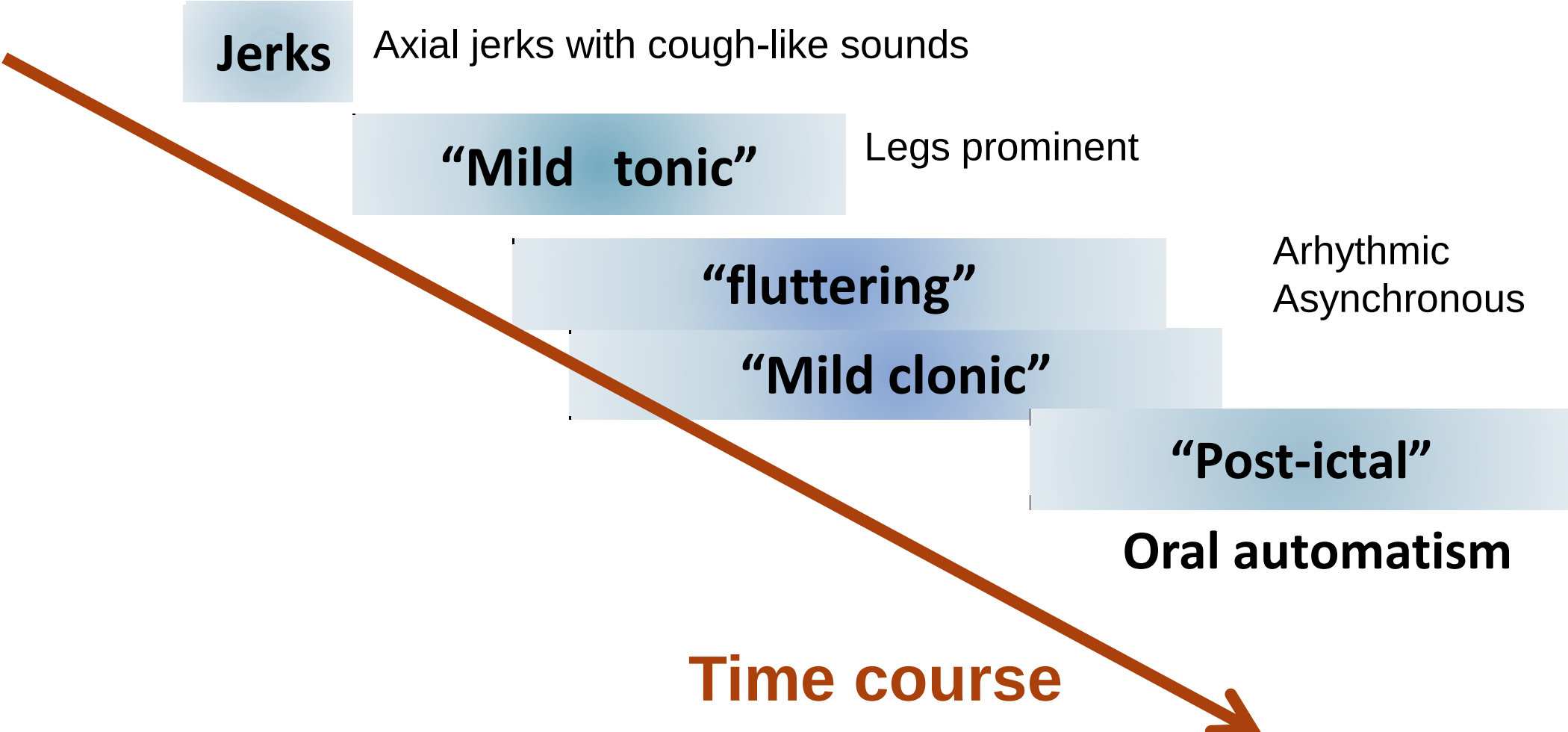
Arhythmic
Asynchronous

“Mild clonic”

“Post-ictal”

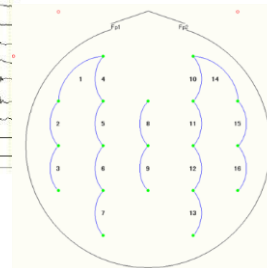
Oral automatism

Time course



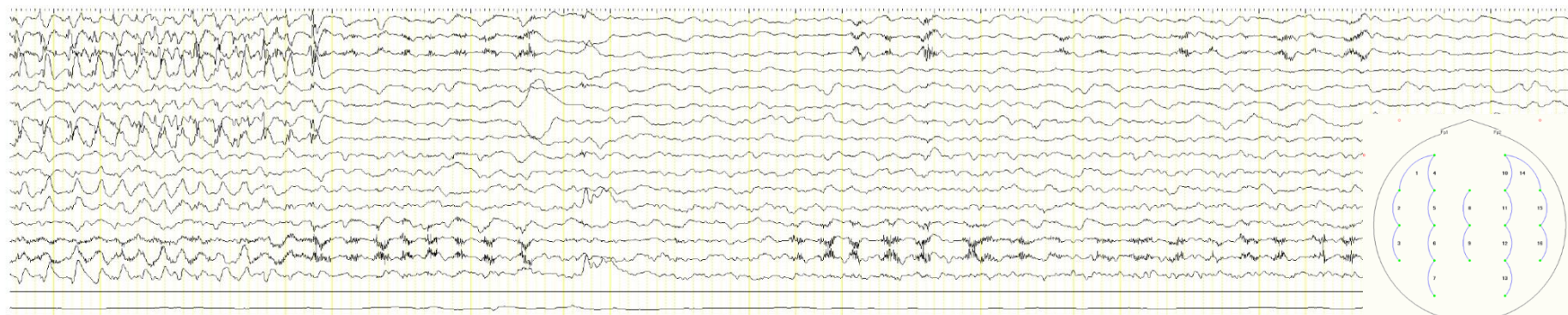
Patient 1 (A)

Ictal EEG



Patient 1 (B)

Ictal EEG



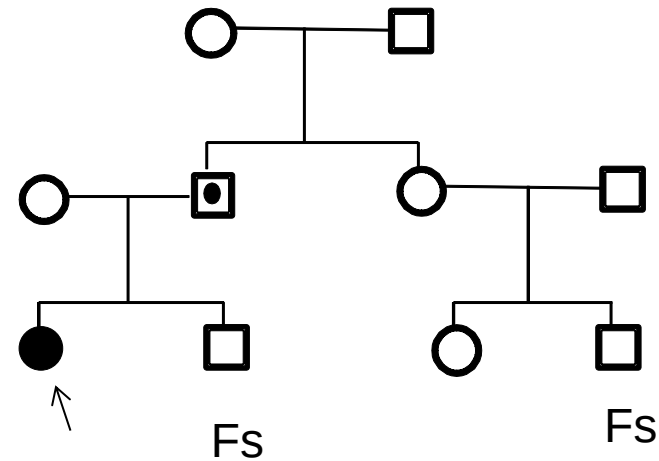
Patient 2

- 6-year-old female
- Perinatal; unremarkable
- Past history; unremarkable
- Development
 - Normal before, Delayed after epilepsy onset (6 m)
 - Intellectual disability and motor development delay; FSIQ 49
 - Autism
- MRI/CT; slight diffuse brain atrophy

Family history

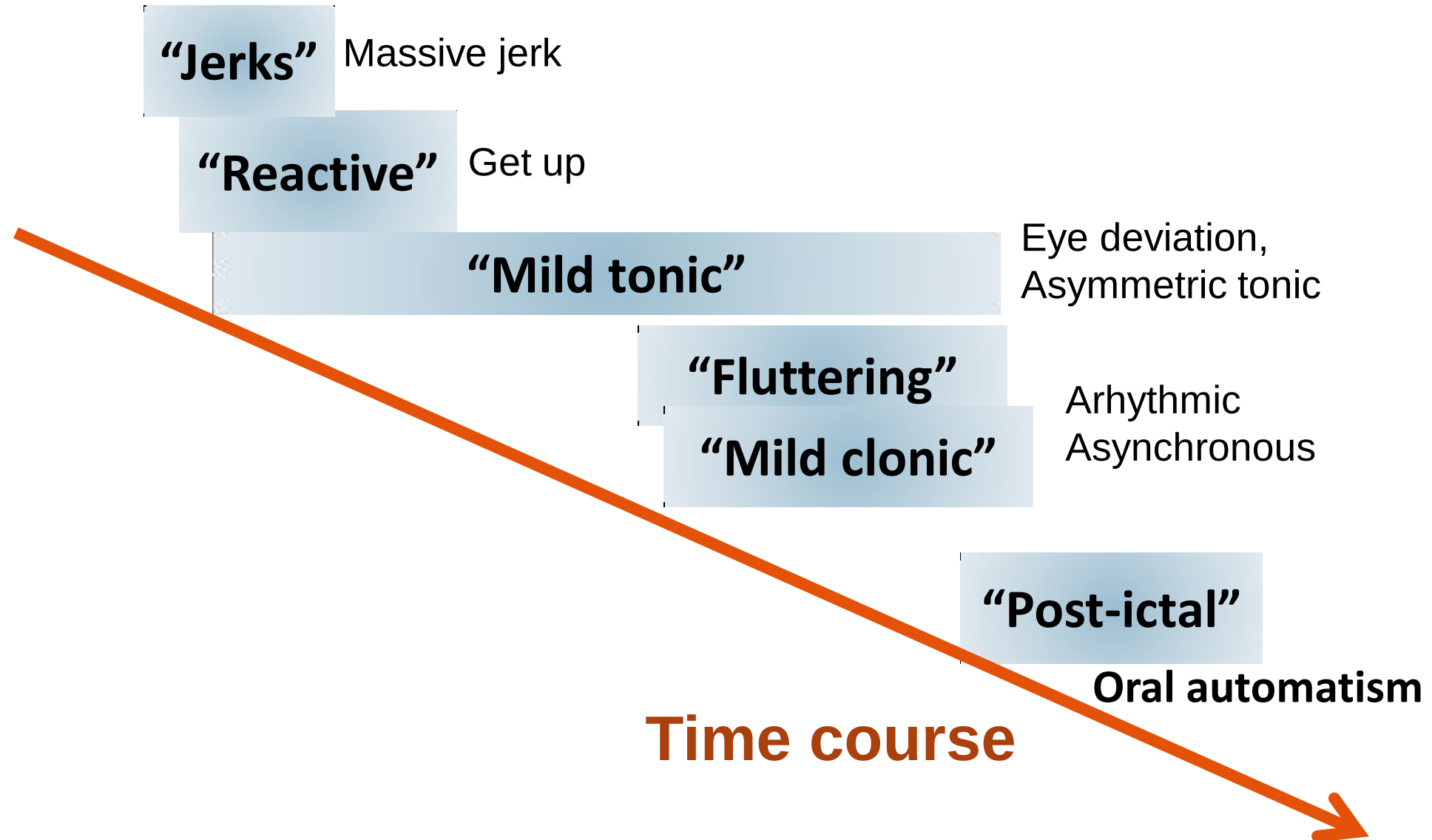
Febrile seizure (single)

- brother
- cousin (father's side)



Patient 2 & father : *PCDH19* missense

Patient 2 (1)

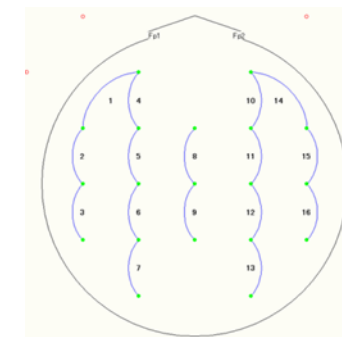
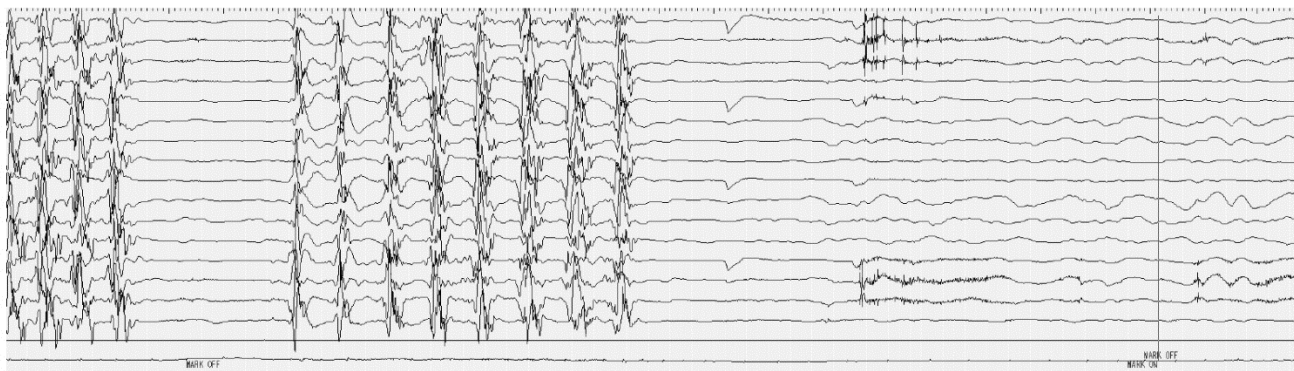
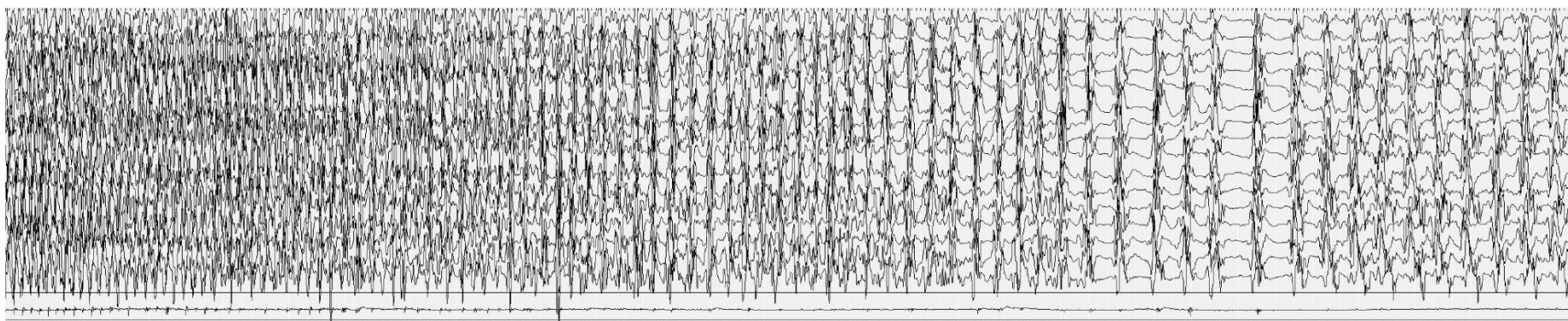
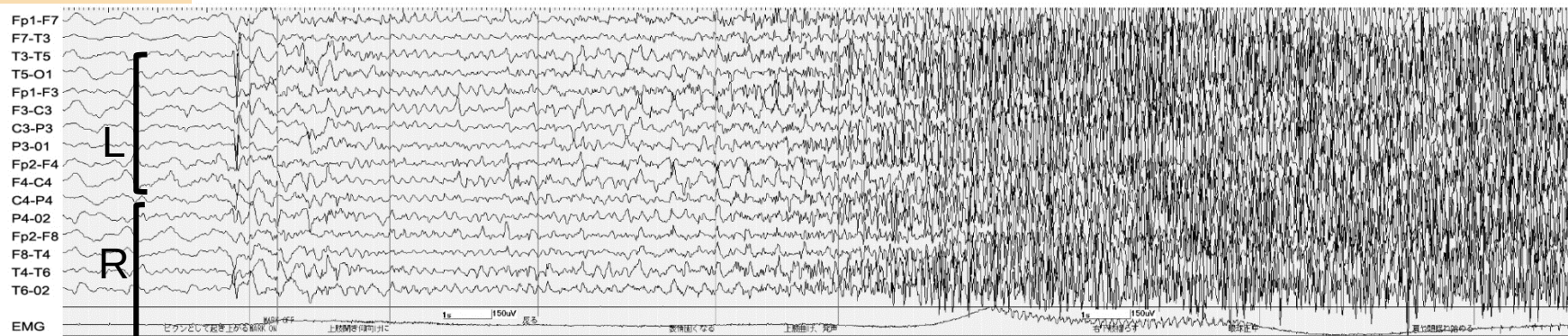


Patient 2 (1) *1

*2

*3

Ictal EEG



Patient 2 (2)

“Jerks”

massive jerk

vocalization

“Reactive”

turn up

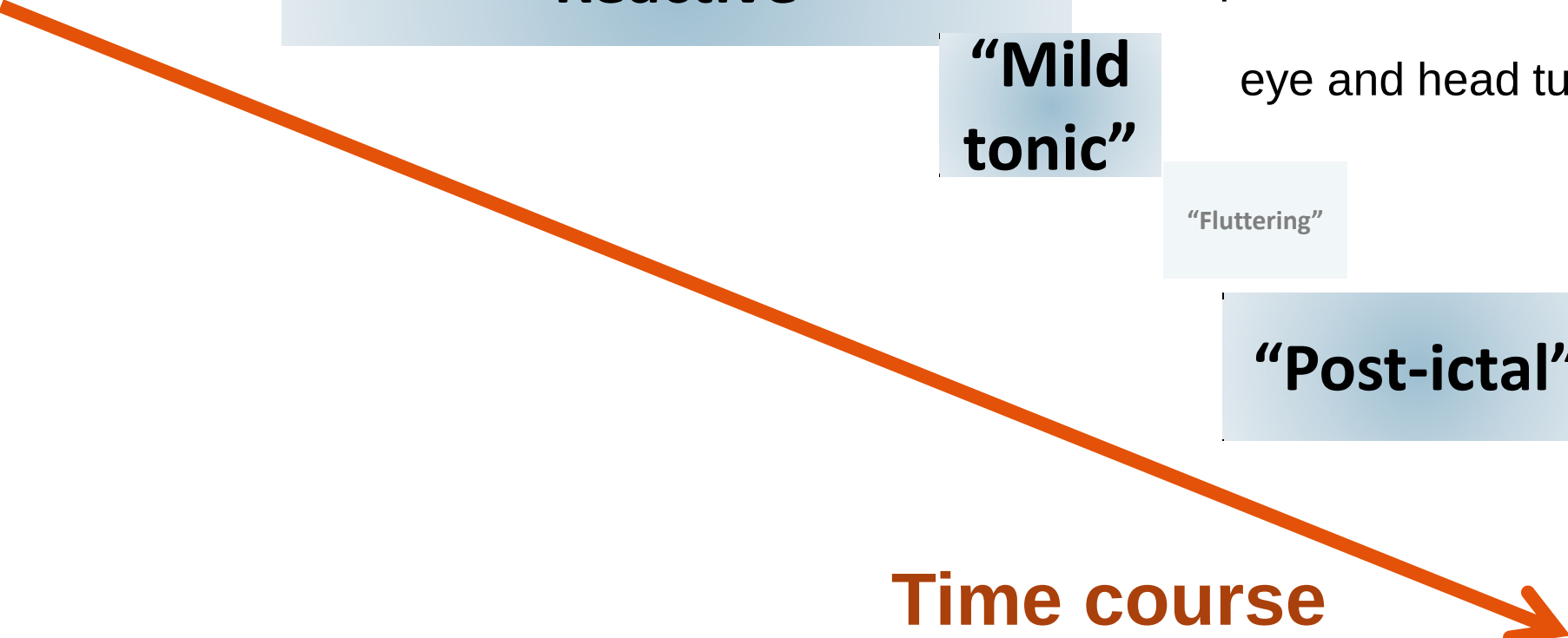
**“Mild
tonic”**

eye and head turning

“Fluttering”

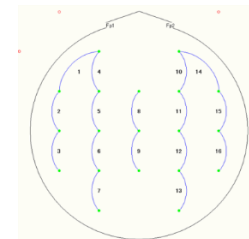
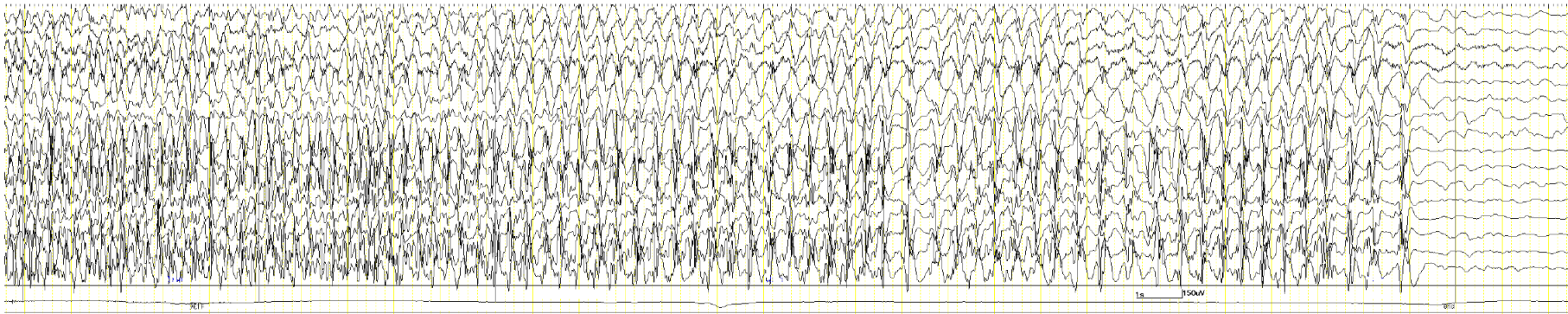
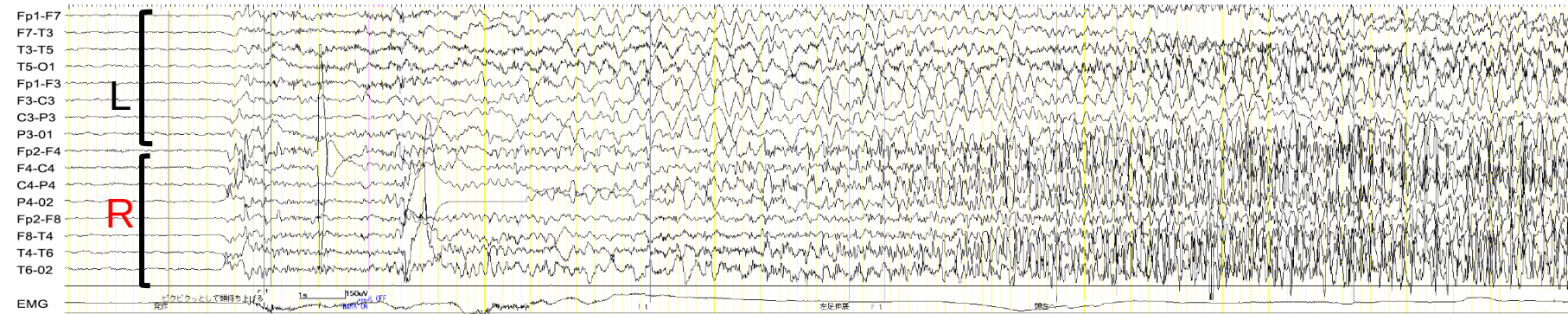
“Post-ictal”

Time course



Ictal EEG

Patient 2 (2)



Patient 3

- 3-year-old female
- Perinatal; unremarkable
- Past history; unremarkable
- Development

Normal before, Delayed after sz onset (9 m)

Intellectual disability and motor development delay

FSIQ 49

- Autism

Family history

Febrile seizure (single): Aunt (mother's side)

Patient 3 : *PCDH19 heterozygous whole-gene deletion*

Patient 3

“Jerks”

multiple jerks

“ Reactive ”

Turns onto her side

“Mild tonic”

asymmetric tonic

“Fluttering”

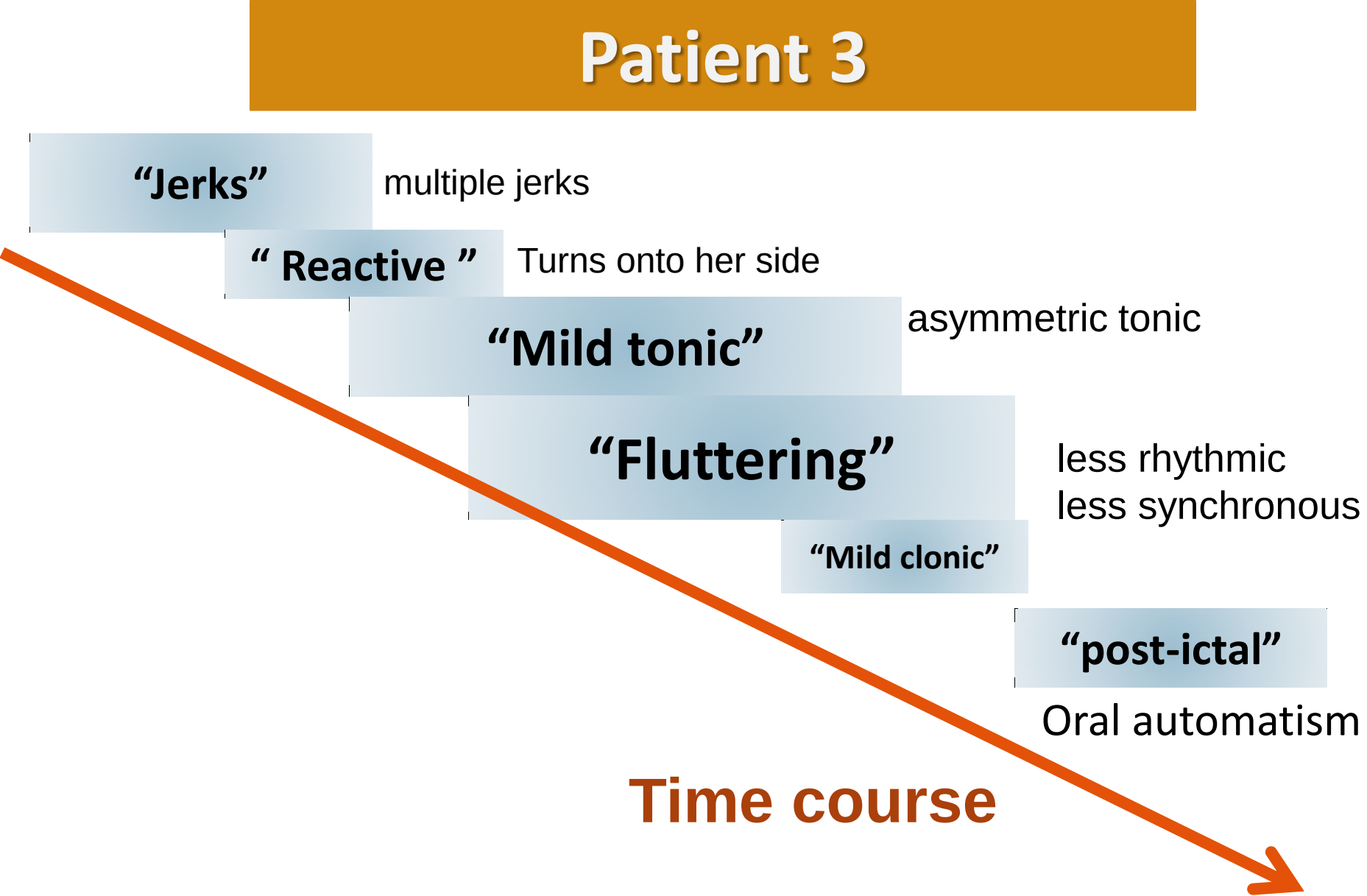
less rhythmic
less synchronous

“Mild clonic”

“post-ictal”

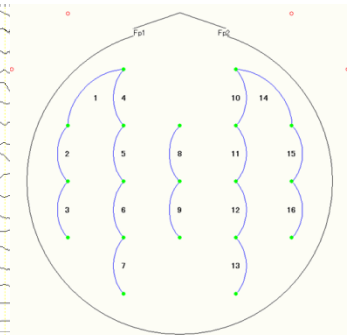
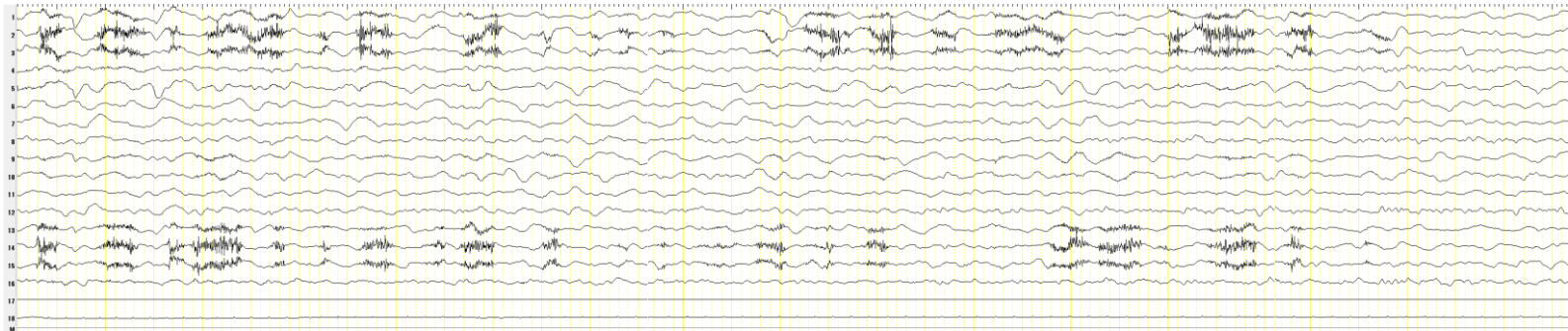
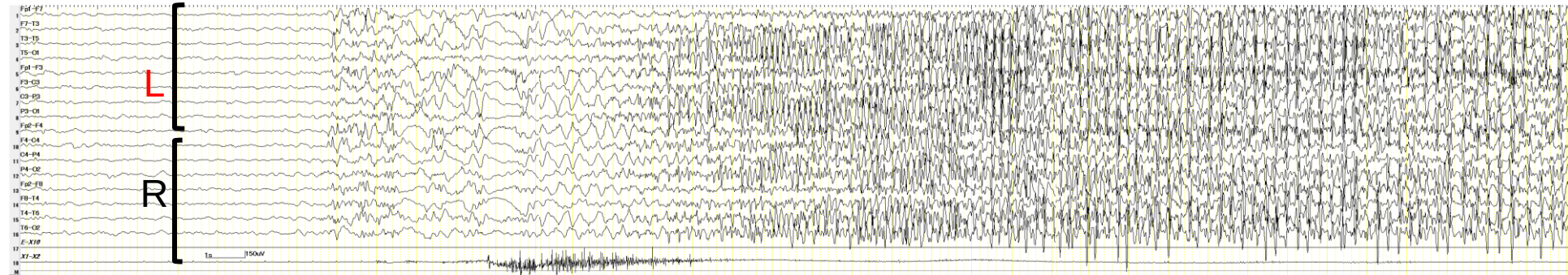
Oral automatism

Time course



Patient 3

Ictal EEG



Discussion



Six phases of sequence of seizures

"Jerks"

"Reactive"

"Mild tonic"

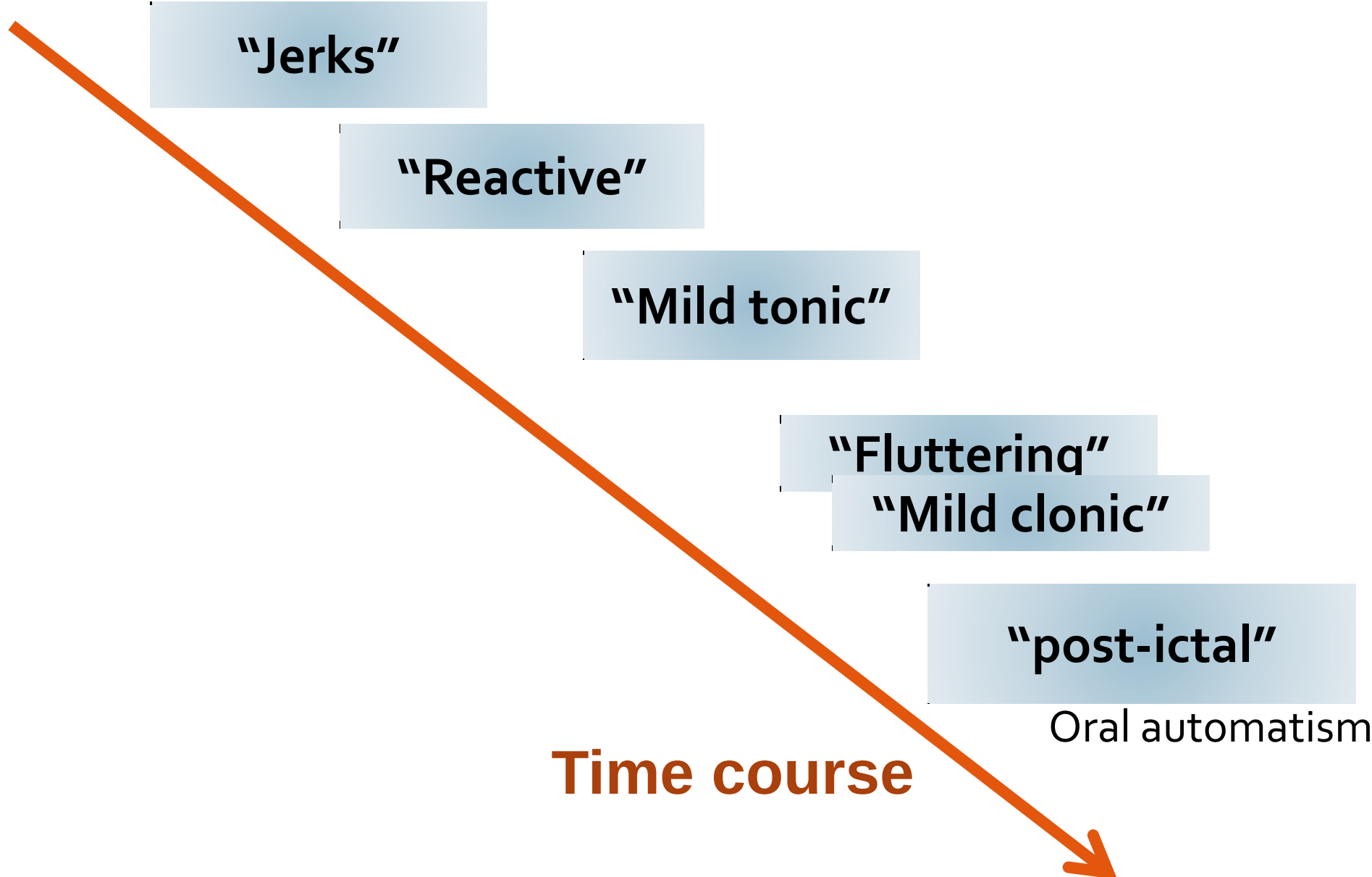
"Fluttering"

"Mild clonic"

"post-ictal"

Oral automatism

Time course



“Jerks”

- axial ~ limbs
 - cough/gurgling sound (axial jerks)
- singly or repeated irregularly
 - without spikes and waves on EEG

“Reactive”

- “panic” , fearful state
- turn over / sit up
- affective symptoms
- complex gestural automatisms

“Mild tonic”

- less intense
 - reduced involvement of the deltoid muscles
 - Asymmetric
- EEG
 - recruiting fast rhythm
 - from unclear or different foci

“Fluttering” → “Mild clonic”

- Extremities
 - distal prominent
(fingers, hands)
 - trembles and jerks
 - asymmetric
 - less rhythmic
 - less synchronous
- Later phase = “Mild clonic”
 - more synchronous (nearly clonic)
 - less intense clonic

“Post-ictal ”

- motionless
- $\pm$ oral automatism
- EEG:
 - slow waves
 - bil. diffuse / continuous

- all 6 phases; 19/26 seizures
 - Patient 1 : 4 out of 6 seizures
 - Patient 2 : all 6 seizures
 - Patient 3 : 9 out of 14 seizures

- some phases can be:
 - shorter or lacking
 - longer or more pronounced



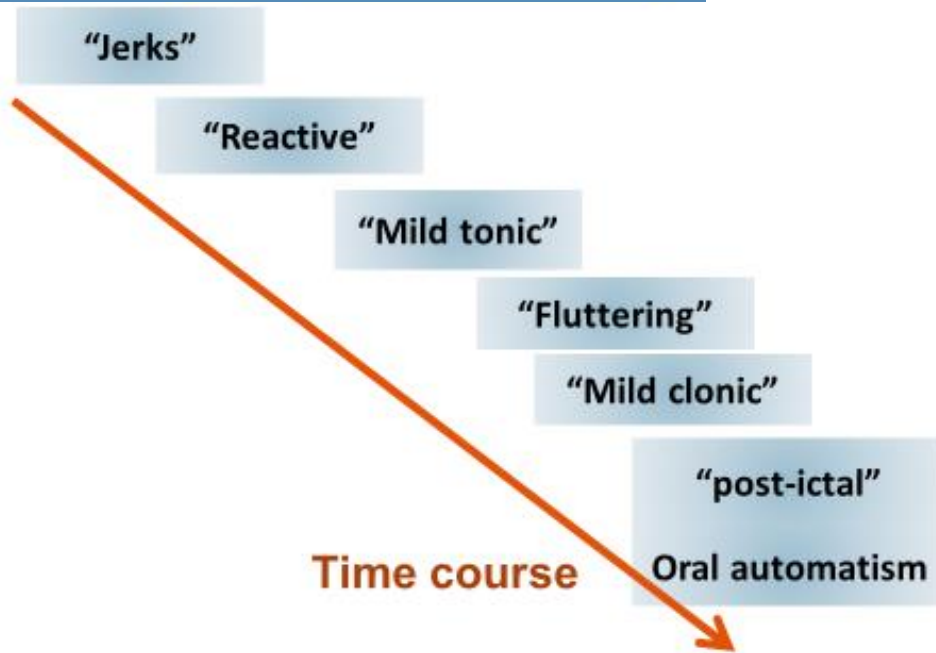
“diversity of seizure manifestations” in literature

- focal-onset seizures
- secondary generalization
- originate from either side

Hyperexcitability of the brain
widespread and **unstable**

➡ the seizures **easily propagate**

Seizure sequence



Cluster (monthly-yearly)
during sleep

Onset < early childhood
Fever sensitivity
Intellectual disability
/Autism

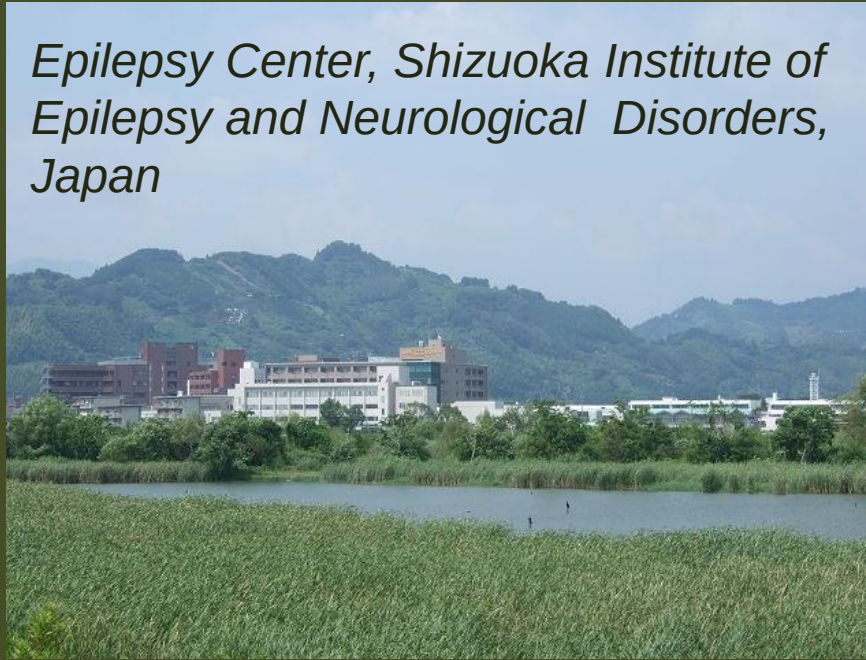
**These characteristic features may allow us
to suspect PCDH19 disorder.**

Note; significant phenotypic variability in epilepsy has been recognized

*Epilepsy Center, Shizuoka Institute of
Epilepsy and Neurological Disorders,
Japan*

Pediatric neurologists

child-care specialists



Psychiatrists, Neurologists

pediatric clinical psychologists

Laboratory / EEG technicians

Neurosurgeons

Thank you