Characteristic phasic evolution of convulsive seizure in PCDH19-related epilepsy

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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 \textit{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

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

- 47 seizures in 5 patients detected on Video EEG
  \[\rightarrow\] 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
**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"

"Mild clonic"

Arhythmic

Asynchronous

"Post-ictal"

Oral automatisms

Time course
Patient 1 (A)
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
Febrile seizure (single)
• brother
• cousin (father’s side)

Patient 2 & father:  *PCDH19 missense*
Patient 2 (1)

Time course

“Jerks” Massive jerk
“Reactive” Get up
“Mild tonic”
“Fluttering” “Mild clonic”
“Post-ictal” Oral automatism

Eye deviation, Asymmetric tonic
Arhythmic Asynchronous
Patient 2 (2)

"Jerks" massive jerk

vocalization  "Reactive" turn up

"Mild tonic" eye and head turning

"Fluttering"

"Post-ictal"

Time course
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
- asymmetric tonic

“Mild tonic”
- less rhythmic
- less synchronous

“Fluttering”
- “Mild clonic”

“post-ictal”
- Oral automatism

Time course
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
- motionless
- ± 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**
These characteristic features may allow us to suspect PCDH19 disorder.

Note: significant phenotypic variability in epilepsy has been recognized.
Thank you
child-care specialists

Pediatric neurologists

Psychiatrists, Neurologists

Laboratory / EEG technicians

Neurosurgeons

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