Clinical phenotypes of mutations causing catastrophic epilepsies in infancy

9 December 2013

Ingrid E Scheffer MBBS PhD FRACP
University of Melbourne & Florey Institute
Austin Health & Royal Children’s Hospital
Melbourne, Australia
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Genetic infantile epileptic encephalopathies
Recognition of phenotypes
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## Disclosure

<table>
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<tr>
<th>Name of Commercial Interest</th>
<th>Type of Financial Relationship</th>
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<td>UCB, Athena, Transgenomic, GSK</td>
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<td>Grants</td>
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Learning Objectives

• Recognition of specific infantile-onset genetic epileptic encephalopathies

• Delineate clinical and radiological features of these entities
Frequent epileptic activity contributes to severe cognitive and behavioral impairment and can worsen over time.
Cause of Epileptic Encephalopathies

• Until recently regarded as acquired disorders
• 2001 - Dravet syndrome: 80% SCN1A mutations
• *De novo* mutations of genes in many cases
• More we know, more complicated it gets!
  – Several genes for an epilepsy syndrome
  – Several syndromes for a gene
K^+ channel
Epileptic Encephalopathies

Neonatal
Infantile

Kobertz et al Biochemistry
2000;39:10347-10352
Benign Familial Neonatal Epilepsy

- Well neonates until seizures begin on day 2 or 3
- Onset by 3 months
- Premature infants delayed onset until term
- Seizures – tonic, apnoea, clonic, focal, autonomic
- EEG – normal or multifocal
- Autosomal dominant, 85% penetrance
- 5% febrile seizures
- 11% later epilepsy
M-Current Potassium Channels

*KCNQ2, KCNQ3*

Mutations in Benign Familial Neonatal Epilepsy

Singh et al. *Brain*, 2003
Daughter with *KCNQ2* encephalopathy
Father with Benign Familial Neonatal Epilepsy

- **34 year old father**
  - BFNS phenotype
  - Seizures 4d – 11w
  - 6 seizures between 4 - 32 yrs

- **2.7 year old girl**
  - Severe global delay
  - Seizures 2d – 14m
  - Generalised spasticity

**☆ KCNQ2  c.638G>A (p.R213Q)**

- Mosaic wt / 30%☆
- BFNE  with  Epilepsy
- Neonatal Epileptic Encephalopathy

Sarah Heron, John Mulley
KCNO2 Encephalopathy: Emerging Phenotype of a Neonatal Epileptic Encephalopathy

Sarah Weckhuysen, MD,1,2,3 Simone Mandelstam, MB ChB,4,5 Arvid Suls, PhD1,2 Dominique Audenaert, PhD1,2,6 Tine Deconinck, MSc1,2 Lieve R.F. Claes, PhD1,2 Liesbet Deprez, PhD1,2 Katrien Smets, MD1,2,7 Dimitrina Hristova, MD8 Iglika Yordanova, MSc9 Albena Jordanova, PhD1,2 Berten Ceulemans, MD, PhD2,10 An Jansen, MD, PhD11,12 Danièle Hasaerts, MD11 Filip Roelens, MD13 Lieven Lagae, MD, PhD14 Simone Yendle, BSc (Hons)15 Thorsten Stanley, MD16 Sarah E. Heron, PhD17 John C. Mulley, PhD18,19 Samuel F. Berkovic, MD, FRS,15 Ingrid E. Scheffer, MBBS, PhD4,15,20 and Peter de Jonghe, MD, PhD1,2,7

ANN NEUROL 2012;71:15–25
**KCNQ2 encephalopathy**

- Tonic seizures < 1 week, bradycardia
- Seizures resolve by 4 years, carbamazepine responsive
- EEG at onset: burst suppression, multifocal
- Motor features - spasticity
- Profound – moderate intellectual disability
- Early MRI characteristic abnormalities
  - Hyperintensities in basal ganglia and thalamus resolve
- 10% neonatal epileptic encephalopathies including Ohtahara syndrome

*Weckhuysen et al, Ann Neurol 2012; Neurol 2013*
- Increased T1 signal in lentiform nuclei at 14 days - Normalized by 2 yrs 7 mths
- Small frontal lobes, increased CSF spaces
- Thin splenium of corpus callosum
Patient 5, 3 yrs 5 mths
- Small frontal lobes
- Under opercularized sylvian fissures

Patient 2, 6 yrs 7 mths
- Marked thinning CC
- Increased frontal interhemispheric spaces
**KCNQ2** mutants show functional correlation

\[ W = BFNS, \ Q = EE \]

Destabilize open state
Decrease channel voltage sensitivity \( \rightarrow \) loss function

Retigabine, K channel activator, reverses defect

*Micelli et al* PNAS 2013
Seizure remission often by 4 yrs

KCNQ2 Encephalopathy

Onset in first week

Seizure remission often by 4 yrs

Tonic seizures

Focal, tonic-clonic spasms

Severe to profound intellectual disability

MRI abnormalities resolving BG hyperintensities

Burst-suppression

Multifocal

Spasticity
• Epilepsy of infancy with migrating focal seizures
• Rare epileptic encephalopathy
  • Onset < 6 months
  • Focal seizures migrating between hemispheres
  • Poor developmental outcome
• 6/12 patients had de novo KCNT1 mutations
Rat *Kcnt1* in *Xenopus oocytes*

2 electrode voltage clamp recordings

Mutants show 2-3 fold increase in currents

*Barcia et al Nat Genet 2012*
Kcnt1 mutants mimic PKC activation

- PKC (protein kinase C) activation increases KCNT1 currents 2-3 fold
- TPA, a PKC activator, increases current in WT
- Mutations affect PKC phosphorylation sites on KCNT1
- Mutants show no change as locked into state similar to PKC activation

Barcia et al Nat Genet 2012
**KCNT1** mutations in Epilepsy of Infancy with Migrating Focal Seizures

- Gain of function: hyperactivation of channel
- **KCNT1** also mutated in Severe Autosomal Dominant Nocturnal Frontal Lobe Epilepsy
- Channel may also have non-conducting function
  - Alter developmental signaling pathways coupled to C terminus of channel
- Both epilepsy and impaired signalling contribute to severe developmental outcome

*Barcia et al Nat Genet 2012; Heron et al Nat Genet 2012*
Recently recognised Infantile-onset Genetic Epileptic Encephalopathies

STXBP1
CHD2
SYNGAP1

Others emerging but not covered
SCN2A, SCN8A, GABRB3, ALG13
EEG: Burst-Suppression

Ohtahara Syndrome
Early Infantile Epileptic Encephalopathy With Suppression-Burst

Onset <2-3 mths (often by 10 days)

Tonic spasms

75% evolve to West syndrome

Abnormal examination
Early mortality

Profound intellectual disability
Burst-Suppression pattern

High voltage generalized bursts with spikes and polyspikes alternating with 1-20 seconds of flattening
Ohtahara Syndrome

- Early Infantile Epileptic Encephalopathy With Suppression-Burst
- EEG: Burst-Suppression
- Onset <2-3 mths (often by 10 days)
- Abnormal examination
- Early mortality
- Tonic spasms
- Profound intellectual disability

75% evolve to West syndrome
**STXBP1**

- Encodes syntaxin binding protein 1, *MUNC18-1*
- Neuron-specific protein and member of SEC1 family of membrane-trafficking proteins
- Expressed throughout brain
- Key component of calcium dependent neurotransmitter release
- Inhibits contact of synaptic vesicle with synaptic membrane
- At GABAergic and glutamatergic synapses
Ohtahara syndrome
Early infantile epileptic encephalopathy with suppression burst

- \textit{STXBP1} mutations in 20/100 (20%)
- 75% evolve to West syndrome
- Variable outcome
  - 12 poor outcome, 3 good (Saitsu 2008, 2010)
  - Seizures resolve (5/5), 4 by 1 yr, EEG normalized (Milh 2011)
- Non epileptic movement disorders prominent
- MRI – frontal atrophy, thin CC, delayed myelination
- Profound impairment
Ohtahara syndrome

STXBP1 encephalopathy
**STXBP1 encephalopathy**

**Disease presentation**

- Onset < 6 months
- Seizures: tonic, spasms, focal, myoclonic
- EEG: Burst suppression or lateralized or bilaterally synchronous epileptiform activity
- Movement disorders: stereotypies
- Profound impairment

- Expect 10-20% mutation rate in EIEE & EOEE
- Few % infantile spasms

Movement disorder in *STXBP1* encephalopathy

- May be more prominent than seizures
- Onset in early infancy
- Choreiform axial movements
- Dyskinetic/dystonic/ballismus
- Trembling episodes lasting few minutes
- Axial contractions (1 second) in series mistaken for epileptic spasms
- No EEG correlate
- Persist into childhood and adolescence
Head and hand stereotypies in STXBP1 encephalopathy

Kim et al, DMCN 2013
EIEE (Ohtahara) and EOEE

**STXBP1 encephalopathy**

- Onset typically < 6 mths
- Tonic Spasms
- Myoclonic
- Focal seizures
- Tonic
- Profound impairment
- *Movement disorders*

- Burst-suppression, lateraled bilaterally synchronous
CHD2 encephalopathy (6/500, 1.2%)

- Chromodomain helicase DNA-binding protein 2
- Selected from 15q.26.1 microdeletion
- Alters access to the transcriptional apparatus of DNA and therefore gene expression (modifies chromatin structure)

Carvill et al Nat Genet 2013
**CHD2 encephalopathy (6/500, 1.2%)**

- Seizure onset: median 18 mths (12 mths - 3 yrs)
- All had myoclonic seizures, 3 photosensitive
- Intellectual disability: 2 moderate - 4 severe, 2 ASD
- Epilepsy syndromes
  - 2 Epilepsy with Myoclonic Atonic Seizures
  - 1 Lennox-Gastaut Syndrome
  - 3 non-specific epileptic encephalopathy
- *De novo* mutations reported in
  - Patient with ID, absence seizures (Rauch *et al.*, 2012)
  - Patient with ASD (Neale *et al.*, 2012)

*Carvill *et al* Nat Genet 2013
CHD2 Encephalopathy
De Novo Loss-of-Function Mutations in CHD2 Cause a Fever-Sensitive Myoclonic Epileptic Encephalopathy Sharing Features with Dravet Syndrome

AJHG 2013

- 3 patients
- Seizure onset: median 14 mths – 3.5 yrs
- Presented with febrile seizures, simple or clusters
- All had myoclonic seizures
- Other seizure types: GTCS, atypical absence, atonic
- All generalized polyspike wave
- 2 normal, 1 mild delay prior to seizure onset
- Mild intellectual disability, 1 ASD, 2 ataxia
*chd2* knockdown zebrafish larvae

pericardial edema, microcephaly, body curvature, absent swim bladder, stunted growth

*Suls et al, AJHG 2013*
**chd2 knockdown 4 day old zebrafish larvae**

Abnormal movements – whirlpool-like, twitching, trembling

Electrographic activity

A – Uninjected larva

B – Knockdown ictal discharges

C – Control MO injected larva

*Suls et al, AJHG 2013*
**SYNGAP1 (5/500, 1%)**

- Synaptic RAS GTPase-activating protein 1
- Brain specific protein that is part of the NMDA receptor complex of post-synaptic density
- Associated with AD mental retardation

*Carvill et al Nat Genet 2013*
SYNGAP1 encephalopathy (5/500, 1%)  

- Seizure onset median 14 mths (6 mths - 3 yrs)
- Multiple seizure types
- All delayed then regressed
- Intellectual disability: 2 moderate - 3 severe, 4 ASD
- EEG: slow spike wave, multifocal discharges
- Previously associated with ID and epilepsy but not epileptic encephalopathy

Carvill et al Nat Genet 2013
Whole new world in infantile epileptic encephalopathies

- Unravelling the genetic architecture
- Many due to *de novo* mutations
- Rapidly increasing number of genes responsible
- Distinctive electroclinical syndromes emerging
e.g. *STXB1*, *CDKL5*, *KCNQ2*, *CHD2*, *SCN1A*
Impact on Clinical Care and Practice

• Huge impact for patients and families
• Definitive diagnosis
• Cohort studies
  • inform selection of optimal anti-epileptic therapy
  • long term outcome
  • co-morbidities – intellectual disability, psychiatric
Genetic counseling
Parent and community support groups
Development of targeted therapies

HETEROZYGOATS

Just allele uneven.