The neonatal presentation of genetic epilepsies

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I have nothing to disclose
Objectives

- Provide an apileptological approach to seizures in the neonate
- Improve the early recognition of neonates with genetic epilepsies
- Discuss personalized treatment of these disorders
Challenges and tools

- The challenge of recognition: neonates are in the NICU
  - Collaboration with neonatologists and nurses is key
- The challenge of treatments: does one size fits all?
- Increased availability of genetic testing
- Increasing use of video-EEG in the NICU
- Implementation of brain-oriented neonatal intensive care units
The electroclinical presentation in the neonatal period of neonatal-onset epilepsies is not yet well defined.

Many patients are diagnosed later in life, and clinical and EEG findings related to the neonatal period may be scarce.
The forgotten neonatal phenotype

Does it matter?
Benign Familial Neonatal Epilepsy

- Age-dependent genetic epilepsy of the newborn
- Autosomal dominant, penetrance 85%
- Healthy neonates
- Seizure onset in the first days of life
- Seizure semiology: tonic phase with focal features and autonomic component often followed by a clonic phase
- Brief frequent seizures lasting 1 to 2 minutes
- Interictal EEG background is normal - may have interictal epileptiform abnormalities
- Mean duration of clusters varies from 2 hours to 3 days
- Favorable outcome in regard to seizures and neurological development
- Two genes: KCNQ2 and KCNQ3

Clinical Observations

Exacerbation of Benign Familial Neonatal Epilepsy Induced by Massive Doses of Phenobarbital and Midazolam

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ABSTRACT

BACKGROUND: Barbiturates and benzodiazepines are the first-line anticonvulsants for neonatal seizures. However, in immature brains, those drugs may lead to paradoxical neuronal excitation. PATIENT: A patient with benign familial neonatal epilepsy developed epileptic encephalopathy after massive doses of phenobarbital that were followed by a continuous infusion of midazolam on postnatal day 3. Electroencephalography revealed rhythmic delta activity in clusters with migrating epileptic foci. After discontinuation of both drugs, the patient’s consciousness promptly improved and her electroencephalography normalized on postnatal day 5. RESULTS: This baby developed persistent electroencephalographic seizures due to massive doses of phenobarbital and midazolam. CONCLUSION: Clinicians should be aware of this anticonvulant-induced paradoxical neuronal excitation and the uncoupling phenomenon, especially in individuals with benign familial neonatal epilepsy, who have low seizure thresholds.

Keywords: benign familial neonatal epilepsy, phenobarbital, midazolam, paradoxical exacerbation, uncoupling phenomenon, amplitude-integrated electroencephalography

Pediatr Neurol 2014; 51: 259-261
Seizures Involving the Supplementary Sensorimotor Area in Children: A Video-EEG Analysis

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All 12 patients described by Vigevano and Fusco (19) and many of the patients described by Scheffer et al. (23) responded to carbamazepine (CBZ) therapy. Of the 6 patients in our study who are seizure-free, 3 are receiving CBZ, 2 developed a rash while receiving CBZ and are seizure-free with phenobarbital and clobazam (CLB) treatment, and 1 child has never received CBZ and is seizure-free with CLB treatment. Therefore, CBZ monotherapy was effective in all patients whose seizures were controlled and who received an adequate trial of CBZ. Seizure control was achieved in the other 3 patients after the addition of CLB.
Rapid and safe response to low-dose carbamazepine of benign neonatal epilepsy

Sands, et al. Epilepsia, in press
Neurology, 2013

KCNQ2 Encephalopathy: Emerging Phenotype of a Neonatal Epileptic Encephalopathy

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Extending the KCNQ2 encephalopathy spectrum
Clinical and neuroimaging findings in 17 patients

doi:10.1111/epi.12200

Clinical spectrum of early onset epileptic encephalopathies caused by KCNQ2 mutation

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The neonatal phenotype
The response to carbamazepine

KCNQ2 ENCEPHALOPATHY: DELINEATION OF THE ELECTROCLINICAL PHENOTYPE AND TREATMENT RESPONSE

Neonatal-onset epilepsies are rare conditions, mostly genetically determined, that can have a benign or severe phenotype. There is recent recognition of de novo KCNQ2 mutations in patients with severe neonatal-onset epilepsy with intractable seizures and severe psychomotor impairment, termed KCNQ2 encephalopathy. This disorder has been associated with frequent

Semiology was characterized by tonic head, conjugate eye, and mouth deviation, associated with unilateral tonic abduction of the limbs, apnea, and desaturation requiring oxygen administration (videos 1 and 2, video legend). Ictal and interictal EEGs are shown in figures e-1 and e-2.

After several treatments had failed, oxcarbazine/carbamazepine was initiated at 3 months, 13 months, and 4 months of life in cases 1, 2, and 3, respectively. Patients 1 and 2 experienced a dramatic reduction of

The response to carbamazepine and phenytoin

FULL-LENGTH ORIGINAL RESEARCH

Early and effective treatment of KCNQ2 encephalopathy

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Epilepsia, **(*)1–7, 2015
doi: 10.1111/epi.12984
SCN2A-related epilepsies: Benign Familial Neonatal-Infantile Epilepsy

- BFNIS is a benign autosomal dominant epilepsy
- Family syndrome
- Intermediate phenotype between benign familial neonatal seizures (BFNS) and benign familial infantile seizures (BFIS).
- Age of onset in these BFNIS families varied from 2 days to 6 months, with spontaneous resolution in most cases before the age of 12 months.
- Seizures are focal and generally occur in clusters over one or a few days with often a posterior focal seizure autosomal dominant.
Clinical spectrum of SCN2A mutations expanding to Ohtahara syndrome

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ABSTRACT

Objective: We aimed to investigate the possible association between SCN2A mutations and early-onset epileptic encephalopathies (EOEEs).

Methods: We recruited a total of 328 patients with EOEE, including 67 patients with Ohtahara syndrome (OS) and 150 with West syndrome. SCN2A mutations were examined using high resolution melt analysis or whole exome sequencing.

SCN2A encephalopathy

A major cause of epilepsy of infancy with migrating focal seizures

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Jacinta M. McMahon, BSc (Hons)
Gemma L. Carrill, PhD

ABSTRACT

Objective: De novo SCN2A mutations have recently been associated with severe infantile-onset epilepsies. Herein, we define the phenotypic spectrum of SCN2A encephalopathy.

Methods: Twelve patients with an SCN2A epileptic encephalopathy underwent electroclinical phenotyping.
SCN2A encephalopathy

- Mutations are *de novo*
- Neonatal onset
- Infantile onset
- Developmental delay
- EEG shows a pattern of epileptic encephalopathy with multifocal epileptiform discharges
- Brief, very frequent tonic seizures shifting laterality
- Response to sodium channel blockers

Howell et al, Neurology 2015
Epilepsy of Infancy with Migrating Focal Seizures

- Multifocal intractable seizures arising independently and sequentially from both hemispheres
- Severe developmental delay
- Decline of head circumference percentile
- Seizures do not respond to sodium-channel blockers nor other conventional AEDs
- Some seizure control reported with potassium bromide and levetiracetam

De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy


doi:10.1038/ng.2441
Received 12 April 2012 Accepted 17 September 2012 Published online 21 October 2012
The first epilepsy-associated gene identified by exome sequencing in sporadic cases

Preliminary phenotyping for the identification of homogeneous cohorts

A powerful approach for unraveling the genetic mechanisms underlying rare epilepsies

Table 1  *KCNT1* mutations identified in individuals with MMPSI

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Ancestry</th>
<th>Genomic position (bp)</th>
<th>Mutation</th>
<th>Protein alteration</th>
<th>Polyphen-2 prediction</th>
<th>SIFT prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>European (France)</td>
<td>138671275</td>
<td>c.2800G&gt;A</td>
<td>p.Ala934Thr</td>
<td>Possibly damaging</td>
<td>Deleterious</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>European (France)</td>
<td>138657552</td>
<td>c.1283G&gt;A</td>
<td>p.Arg428Gln</td>
<td>Probably damaging</td>
<td>Deleterious</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>European (France)</td>
<td>138657552</td>
<td>c.1283G&gt;A</td>
<td>p.Arg428Gln</td>
<td>Probably damaging</td>
<td>Deleterious</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>European (France)</td>
<td>138657552</td>
<td>c.1283G&gt;A</td>
<td>p.Arg428Gln</td>
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<td>Deleterious</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>European (France)</td>
<td>138660694</td>
<td>c.1421G&gt;A</td>
<td>p.Arg474His</td>
<td>Probably damaging</td>
<td>Deleterious</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>European (Ukraine)</td>
<td>138667192</td>
<td>c.2280C&gt;G</td>
<td>p.Ile760Met</td>
<td>Probably damaging</td>
<td>Deleterious</td>
</tr>
</tbody>
</table>

M, male; F, female.

Barcia et al., Nature Genetics 2012
Electrophysiological studies of MPSI-associated mutations

- Gain-of-function
- Activation of the channel
- Enhanced $K^+$ current

- Its C terminal region is involved in protein-protein interaction with several partners including FMRP (Fragile-X Mental Retardation Protein)
  - Seizures due to the impairment of channel function
  - Motor and cognitive delay due to the impairment of the ability to interact with developmentally relevant proteins

KCNT1 Gain of Function in 2 Epilepsy Phenotypes is Reversed by Quinidine

Carol J. Milligan, PhD, Melody Li, BSc, Elena V. Gazina, PhD, Sarah E. Heron, PhD, Umesh Nair, BSc, Chantel Trager, BSc, Christopher A. Reid, PhD, Anu Venkat, MD, Donald P. Younkin, MD, Dennis J. Dlugos, MD, Slavé Petrovski, PhD, David B. Goldstein, PhD, Leanne M. Dibbens, PhD, Ingrid E. Scheffer, MBBS, PhD, Samuel F. Berkovic, MD, and Steven Petrou, PhD

- KCNT1 gain-of-function is not affected by any conventional AEDs
- It is target of several cardiac drugs
- Antiarrhythmic drug quinidine operates as a pore blocker

Annals of Neurology, 2014

Targeted Treatment of Migrating Partial Seizures of Infancy with Quinidine

Bearden et al.
Quinidine as targeted treatment for KCNT1-associated epilepsies

Exposure to Quinidine, a drug approved for the treatment of cardiac arrhythmias, significantly reduced the gain of function in all mutations studied.

Milligan et al,
Annals of Neurology 2014
Genetic neonatal-onset epilepsies

- Phenotype does matter
- One size does not fit all!
- Video-EEG as a diagnostic tool
- Collaboration is key
- Early diagnosis is essential for early treatment and prognosis
- Goal is seizure control
- Targeted treatment may change prognosis of severe neonatal-onset epilepsies
- Phenotype does matter
- Early diagnosis is essential for early treatment
- Determining mutation pathogenicity and mechanisms of disease
- Early treatment of seizures may lead to better outcome by reducing the effects of frequent seizures in the neonatal brain
- Targeted treatment may drastically change prognosis
EGI has created a data repository of clinical exome and genome sequences.

Data is being reanalyzed every 6 months for novel genetic changes.

New results will be communicated back to patients via their doctor.

Data will also be made available to advance epilepsy research.

www.CUREepilepsy.org/EGI
“To improve is to change, to be perfect is to change often”

Winston Churchill

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