Seizures in the neonate: differential diagnosis and treatment

Maria Roberta Cilio, MD, PhD
Professor of Neurology and Pediatrics
University of California San Francisco
Seizures in the neonate: different diagnoses and different treatments

NEONATAL SEIZURES SHOULD NOT BE CONSIDERED AS A WHOLE

Early distinction between acute seizures and neonatal onset epilepsies has important therapeutic and prognostic implications
Objectives

- Diagnose seizures in the neonate
- Differentiate acute seizures from neonatal-onset epilepsies
- Understand the implications of diagnostic accuracy for patient management in terms of work-up and treatment
The challenges of diagnosing seizures in the neonate

- Recognition
- Correct terminology
- Correct diagnosis
- Appropriate treatment
- Protocol versus tailored treatment
The majority of seizures in the neonate are occasional seizures, occurring as reactive events to acute insults.

A significant percentage are the first symptoms of a neonatal-onset epilepsy requiring a targeted treatment.
THE CHALLENGE OF SEIZURE RECOGNITION
6 minutes later
MRI
Acute ischemic stroke

T2

DWI

ADC
Classic presentation of stroke in a term infant

- Focal clonic seizures
- Seen clinically, and on EEG
- EEG helped reassure this was a limited insult
- Clinical, EEG and MRI findings were all consistent
Recognition of seizures remains the foremost challenge to overcome

- Immaturity of the central nervous system in the neonate
- Limited accessibility to the sick infant in the NICU due to environmental restrictions
- Technical challenges, limited availability and need of expertise in performing and interpreting EEG in the neonatal period
**Benign Neonatal Sleep Myoclonus**

- Healthy newborns, familial occurrence
- Onset within 15 days of life
- Repetitive myoclonic jerks of the extremities exclusively during quiet sleep
- Normal interictal and ictal EEG
- Myoclonus stops as infant wakes up or sleep phase changes
- Spontaneous disappearance within 3-4 months of life
Benign Neonatal Sleep Myoclonus Mimicking Status Epilepticus

ABSTRACT

Benign neonatal sleep myoclonus is a self-limited movement disorder characterized by neonatal-onset myoclonic jerks only during sleep, abrupt and consistent cessation with arousal, and absence of concomitant electrographic changes suggestive of seizures. It has a good outcome and was included in the differential diagnosis of neonatal seizures. A presumed transient serotonin imbalance and genetic factors may play a role in the pathogenesis of this disorder. We report a case of benign neonatal sleep myoclonus mimicking status epilepticus in an infant with a family history of nocturnal myoclonus, tic disorder, and sleep disturbance. We suggest that this benign entity should be included in the differential diagnosis of status epilepticus during the newborn period. (*J Child Neurol* 2004;19:62–63).
20 video clips (11 seizure, 9 non seizure) were evaluated by 91 doctors and 46 nurses.

The average number of correctly identified events was 10/20

Discussion: It is often impossible to accurately differentiate between seizure-related and nonseizure movements in infants using clinical evaluation alone. In addition, doctors do not have a higher capacity for discriminating between neonatal paroxysmal events than other health care professionals. Until reliable continuous neurologic monitoring of newborn babies is available, it is likely that some babies with seizures will remain undetected and others with nonseizure movements will continue to be treated with potentially harmful anticonvulsants.
Current clinical practice

- Neonates at risk are visually monitored for clinical manifestations of seizures
- Clinical suspicion of seizures $\rightarrow$ routine EEG or empiric treatment
- This approach presumes that most seizures give rise to visually observable clinical manifestations
Seizures without clinical correlate

- Infants with severe diffuse encephalopathies
- Infants who had received AEDs
- Infants who received neuro-muscular blocking drugs
41 newborns with HIE treated with hypothermia
Continuous video-EEG monitoring
Seizures were diagnosed in 34% (14/41)

Nash et al, Neurology 2011
Majority of Seizures During Hypothermia are Subclinical

Electro-clinical dissociation was common

- 6/14 infants (43%) never had clinical correlate
- 51 of 76 EEG seizures (67%) without clinical correlate
- 3 of 4 infants with status epilepticus never had a clinical correlate
- Status epilepticus was only seen in newborns with moderate/severe MRI injury ($p = 0.01$)

Nash et al, Neurology 2011
Baby girl

- 35 week baby transferred for apnea
- C-section for known vasa previa.
- Fetal monitoring reassuring
- Required CPAP at birth with resolution of respiratory distress after 4 min. Cord and baby gasses normal.
Baby girl

- Within 6 hrs had multiple episodes of apnea with desaturation, some with spontaneous resolution but most required vigorous stimulation. No bradycardia. No abnormal movements.
- Rule out sepsis initiated; HUS normal
- Labs - metabolic panel, CBC, LP normal
- Neuro exam - appropriate for GA, no asymmetry
CFM monitoring is started

- Apnea associated with changes on CFM consistent with seizure
- Continuous EEG monitoring is started
Ictal apnea

- Rhythmic epileptic discharge
- Usually accompanied by other clinical manifestations (eye deviation, eye opening)
- Rarely associated with bradycardia

- Mesial temporal lesions (Deepa Sirsi et al., 2007; Hoogstraate et al, 2009)
- Occipital lesions (Castro Conde et al, 2012)
STROKE IN THE NEWBORN

- 1/4000 newborn at term
- The FIRST cause of hemiplegia
- The most common clinical presentation of stroke in children is acute hemiparesis
- The most common clinical presentation of stroke in newborn are focal seizures
- Most are delayed diagnosis
**OBG guidelines for seizure treatment in neonates with HIE**

**Suspected seizures**

- Labs: glucose and calcium
- Rx: **midazolam** 0.1 mg/kg i.v.

**0-5 min**

- If the patient has already received **phenobarbital** or a benzodiazepine before the transfer
- **No further seizures**
  - Video-EEG monitoring

**Start video-EEG ASAP**
**Consult Neurology**

**Persistence of seizures**

**5-10 min**

- Rx: **phenobarbital** 20 mg/Kg i.v.

**No further seizures**

**30 min**

- Video-EEG monitoring
- Rx: **Maintenance phenobarbital** 5mg/kg/day divided BID

- **Persistence of seizures**
Persistence of seizures

50 min
Rx: phenytoin 20 mg/kg i.v.
Repeat 10 mg/kg i.v. if persistence of seizures until a maximal loading dose of 30 mg/kg i.v.

70 min
Persistence of seizures

No further seizures

Video-EEG monitoring
Rx: Maintenance
phenobarbital 5mg/kg/day divided BID
phenytoin or phenytoin
5 mg/kg/day divided BID
Reassess after 48-72 hours
Labs: trough drug levels daily

Bolus and maintenance dosing of 2nd and 3rd line medications may need individual tailoring

90 min
Rx: add levetiracetam 60 mg/kg i.v.
(consider a trial with pyridoxine)

Video-EEG monitoring
Rx: Maintenance
phenobarbital 5mg/kg/day
levetiracetam 40 mg/Kg/day
phenytoin 5 mg/kg/day divided BID
Reassess after 48-72 hours
Labs: check phenobarbital and/or phenytoin levels daily
THE NEW CHAPTER OF NEONATAL EPILEPSIES AND THE IMPORTANCE OF SEIZURE SEMEIOLOGY
Age at onset

Developmental course

Other seizure types

Initial seizure type

Diagnosis

Examination findings

MRI findings

Genes
Fp2-T4
T4-O2
Fp2-C4
C4-O2
Fp1-C3
C3-O1
Fp1-T3
T3-O1
T4-C4
C4-Cz
Cz-C3
C3-T3
Fz-Cz
Cz-Pz
Chest Resp
Nasal Resp
Right Hand
Left Hand
EARLY MYOCLONIC ENCEPHALOPATHY

- Onset in the neonatal period
- Burst-suppression EEG pattern
- Segmental and erratic myoclonus, sometimes massive, affecting the face and limbs
- Focal seizures
- Absence of neurological development
- Extremely treatment resistant
- Etiologies: Glycine encephalopathy, Methylmalonic or propionic acidemia, Pyridoxine deficiency
- Familial recurrence
OHTAHARA SYNDROME

- Onset often within the first 10 days of life
- Main seizure pattern: tonic spasms
- Suppression-burst EEG pattern during both waking and sleep states
- Severe psychomotor retardation
- Poor prognosis
- Vigabatrin may improve the condition
- Progression to West syndrome
OHTAHARA SYNDROME

- Hemimegalencephaly
- Focal cortical dysgenesis
- Early surgery can be considered
- Genetics:
  - STXBP1 gene mutations (Synaptin binding protein 1)
  - ARX gene mutations
More important is the type of seizure (myoclonic versus tonic spasm) because this will influence the work-up and treatment.
BURST-SUPPRESSION PATTERN

- Burst of high voltage (75-200 µV) activity lasting 1 to 10 s, mixed features (spikes, sharp waves, theta, delta) but no age-appropriate activity
- Periods of marked background attenuation (voltage < 10 µV) lasting 2 to 45 s
- Persistent throughout awake and asleep states, unreactive and unaltered by exogenous stimuli

- Barbiturate anesthesia
- Hypoxic-ischemic encephalopathy
- Deep brain tumors
- Severe congenital metabolic disorders
- Extensive brain malformations

- Bad prognosis
BURST-SUPPRESSION PATHOPHYSIOLOGY

- Alteration of the normal organization of cortical connections
- Intrinsic pacemaking properties of thalamic neurons
- 30-40% of thalamic cells continue firing while the cortex is silent
- Volleys from these thalamocortical neurons cyclic wave bursts over a cortical background depressed or totally inactive
Extreme discontinuity can be due to immaturity: discontinuous EEG of the premature infant

The term burst-suppression should not be used when describing neonatal EEG prior to 35 weeks
DOUBLE TROUBLE: SEIZURES IN TWINS
Seizures were stereotyped and quite similar in each twin.

The twins were having more than 20 episodes per day.

Neurological examination in between attacks was normal in both infants.
DOUBLE TROUBLE: SEIZURES IN TWINS

- Very frequent seizures occurred despite PB levels > 40 µg/mL, clonazepam, and intermittent diazepam therapy.

- Oral CBZ was added and there was a total cessation of seizures.
Benign Familial Neonatal Epilepsy

- Age-dependent genetic epilepsy of the newborn
- Autosomal dominant, penetrance 85%
- Healthy neonates
- Seizure onset on day 2 or 3
- Mixed features: tonic phase with focal features and autonomic component followed by a clonic phase
- Brief frequent seizures lasting 1 to 2 minutes
- Interictal EEG background is normal
- 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

Ronen et al, 1993; Singh, 1998; Charlier 1998; Cilio 2004
Molecular correlates of KCNQ2 and KCNQ3 potassium channel subunits

Loss-of-function

Reduced $K^+$ currents

Neuronal hyperexcitability

Seizures
Neurobiology of Disease

Atypical Gating Of M-Type Potassium Channels Conferred by Mutations in Uncharged Residues in the \( S_4 \) Region of KCNQ2 Causing Benign Familial Neonatal Convulsions

Maria Virginia Soldovieri,1 Maria Roberta Cilio,2 Francesco Miceli,1 Giulia Bellini,1 Emanuele Mira goia del Giudice,4 Pasqualina Castaldo,1 Gricia C. Hernandez,9 Mark S. Shapiro,9 Antonio Pascotto,9 Lucio Annunziato,1 and Maurizio Tagliatela1,6

Seizures on DOL 2, CT scan, LP (nl), diagnosed with meningitis PB and PHT for 6 years

Seizures on DOL 2, MRI, LP, extensive metabolic screening, 15 days hospitalization, PB load then PB for 1 year

Seizures on DOL 2, US, hospitalized for 24 hours, low-dose oral CBZ for 1 year
KCNQ2 Encephalopathy: Emerging Phenotype of a Neonatal Epileptic Encephalopathy

Sarah Weckhuysen, MD,1,2,3 Simone Mandelstam, MB ChB,4,5 Arvid Suls, PhD,1,2 Dominique Audenaert, PhD,1,2,6 Tine Deconinck, MSc,1,2 Lieve R.F. Claes, PhD,1,2 Liesbet Deprez, PhD,1,2 Katrien Smets, MD,1,2,7 Dimitrina Hristova, MD,8 Iglika Yordanova, MSc,9 Albena Jordanova, PhD,1,2 Berten Ceulemans, MD, PhD,2,10 An Jansen, MD, PhD,11,12 Danièle Hasaerts, MD,11 Filip Roelens, MD,13 Lieven Lagae, MD, PhD,14 Simone Yendle, BSc (Hons),15 Thorsten Stanley, MD,16 Sarah E. Heron, PhD,17 John C. Mulley, PhD,18,19 Samuel F. Berkovic, MD, FRS,15 Ingrid E. Scheffer, MBBS, PhD,4,15,20 and Peter de Jonghe, MD, PhD1,2,7

Objective: KCNQ2 and KCNQ3 mutations are known to be responsible for benign familial neonatal seizures (BFNS). A few reports on patients with a KCNQ2 mutation with a more severe outcome exist, but a definite relationship has not been established. In this study we investigated whether KCNQ2/3 mutations are a frequent cause of epileptic encephalopathies with an early onset and whether a recognizable phenotype exists.

Methods: We analyzed 80 patients with unexplained neonatal or early-infantile seizures and associated psychomotor retardation for KCNQ2 and KCNQ3 mutations. Clinical and imaging data were reviewed in detail.

Results: We found 7 different heterozygous KCNQ2 mutations in 8 patients (8/80; 10%); 6 mutations arose de novo. One parent with a milder phenotype was mosaic for the mutation. No KCNQ3 mutations were found. The 8 patients had onset of intractable seizures in the first week of life with a prominent tonic component. Seizures generally resolved by age 3 years but the children had profound, or less frequently severe, intellectual disability with motor impairment. Electroencephalography (EEG) at onset showed a burst-suppression pattern or multifocal epileptiform activity. Early magnetic resonance imaging (MRI) of the brain showed characteristic hyperintensities in the basal ganglia and thalamus that later resolved.

Interpretation: KCNQ2 mutations are found in a substantial proportion of patients with a neonatal epileptic encephalopathy with a potentially recognizable electroclinical and radiological phenotype. This suggests that KCNQ2 screening should be included in the diagnostic workup of refractory neonatal seizures of unknown origin.

ANN NEUROL 2012;71:15-25

Weckhuysen et al, Ann Neurol 2012
KNCQ2 encephalopathy: delineation of the electroclinical phenotype and treatment response

1. Seizures are focal tonic, alternating, with apnea and desaturation
2. Low voltage fast activity followed by recruiting spikes mainly from the central regions followed by marked and prolonged post-ictal attenuation
3. Lack of organization and physiological features with multifocal epileptiform abnormalities and random attenuations
4. Resistant to PB, Benzodiazepines, Levetiracetam, Topiramate, ketogenic diet, Vigabatrin,…
5. Response to Carbamazepine

Numis et al. Neurology 2014
Benign Familial Neonatal Seizures

- Tonic seizures accompanied by motor and autonomic features
- Mutations in KCNQ2 gene
- Normal interictal EEG
- Favorable seizure outcome
- Normal developmental outcome

KCNQ2 Encephalopathy

- Similar type of seizure as BFNS at onset
- Mutations in KCNQ2 gene
- EEG: multifocal
- Development of treatment resistant epilepsy
- Poor developmental outcome

In patients with KCNQ2 mutations the EEG pattern correlates better with prognosis than the molecular genetic findings
EEG
Neonatal seizures
Diagnosis
Genes

- Same pattern EEG but different seizure type
- Same seizure type but different pattern EEG
- Mutations in one gene may be linked to severe and benign epilepsies

The assumption that gene is equal to disease is absolutely false.
EXPLORING NEW THERAPIES

BEDSIDE TO BENCH

Opening up the potassium door in neonatal seizures

Rod C Scott & Gregory L Holmes

Scott and Holmes, Nature Medicine, 2012
RETIGABINE (EZOGABINE) - a potassium channels opener

- Approved in 2011 as a treatment for refractory focal seizures in adults

---

**Drug Safety Communications**

**FDA Drug Safety Communication: Anti-seizure drug Potiga (ezogabine) linked to retinal abnormalities and blue skin discoloration**

**Safety Announcement**

[04-26-2013] The U.S. Food and Drug Administration (FDA) is warning the public that the anti-seizure medication Potiga (ezogabine) can cause blue skin discoloration (See photos in Appendix 1) and eye abnormalities characterized by pigment changes in the retina. FDA does not currently know if these changes are reversible. All patients taking Potiga should have a baseline eye exam, followed by periodic eye exams. FDA is working with the manufacturer to gather and evaluate all available information to better understand these events. FDA will update the public when more information is available.
Key points

- Seizures recognition remains the foremost challenge to overcome
- Continuous Video-EEG monitoring helps to detect seizures in high-risk infants
- Correct interpretation of the clinical manifestation is the first step toward the right diagnosis and appropriate treatment
- Seizures should be considered in their overall context
- Treatment should be tailored (drug and duration)
- Use protocols ONLY in defined subgroups of newborns
Acknowledgements

Federico Vigevano
Martina Balestri
Maurizio Taglialatela
Donna Ferriero
David Rowitch
Jim Barkovich
Adam Numis
The EEG techs