Management of Neonatal Seizures
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Disclosures

- I have none!
Objectives

- Recognition and appropriate testing of neonate for seizures
- Long-term monitoring
- Pathophysiology of neonatal seizures
- Multicenter variability in management protocols: current treatment practices
- Management: drugs
- Etiologies: how does this play a role in the drugs you use and what is most effective
- Summary

Neonates-diagnostics

- Sick babies often have unusual movements
  - Most of these are not seizures

- >50% of all neonatal seizures are subclinical
  - Only detectable with EEG monitoring

- Electroclinical dissociation / uncoupling:
  - With treatment, clinical signs may vanish while subclinical electrographic seizures continue.

Historical factors to know in order to interpret neonatal EEG

- Post Conceptional Age: Gestational age at birth (weeks) + chronological age
- Behavioral State of the infant
- Medications
- Location (isolette versus open bed)
- Recent medical procedure
- Topographic - Caput or cephalhematoma

Clinical vs. electrographic seizures

Video-EEG monitoring of high-risk infants

- 9% of electrographic seizures (48/526) had clinical signs recognized and documented by NICU staff

- 27% of seizures which did have clinical signs (48/179) were recognized and recorded

- 73% of “seizures” documented by NICU staff had no electrographic correlate (129/177)

Neonates at risk for seizures

<table>
<thead>
<tr>
<th>High risk of acute brain injury</th>
<th>Demonstrated acute acquired brain injury</th>
<th>Clinically suspected seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged circulatory arrest</td>
<td>Arterial ischemic stroke</td>
<td>Focal clonic or tonic movements</td>
</tr>
<tr>
<td>Hypoxic-ischemic encephalopathy</td>
<td>Cerebral sinovenous thrombosis</td>
<td>Eye blinking, gaze-deviation</td>
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<tr>
<td>Infants with sustained hypoxia</td>
<td>Intracranial hemorrhage</td>
<td>Unexplained apnea</td>
</tr>
<tr>
<td>Pharmacologically-induced paralysis</td>
<td>Encephalitis</td>
<td>Myoclonus</td>
</tr>
<tr>
<td>Head trauma with altered mental status</td>
<td>Cerebral edema due to inborn errors of metabolism</td>
<td>Bicycling</td>
</tr>
</tbody>
</table>

Neonates are tricky!

- Most abnormal neonatal movements have no electrographic correlate
- Neonates don’t have generalized tonic-clonic seizures!
- Heart rate changes during seizures are not consistent
- Isolated changes in vital signs are rarely due to seizures
Seizures are associated with poor outcomes?

- Gluckman et al: Cool Cap Trial 2005

Data demonstrates that seizures themselves are independently associated with biomarkers of brain injury.

- Miller et al.: Neurology 2002; 58-542
Clinical neonatal seizures are also associated with adverse neurodevelopmental outcomes, adjusted for MRI abnormalities.

Table III. WPPSI-R FSIQ score at age 4 years by seizure severity in 77 children at risk for perinatal hypoxic-ischemic brain injury.

<table>
<thead>
<tr>
<th>FSIQ score, mean (95% CI)</th>
<th>Severe seizures (n = 11)</th>
<th>Mild/moderate seizures (n = 14)</th>
<th>No seizures (n = 52)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>64.7 (52.6 to 76.9)</td>
<td>83.1 (72.4 to 93.9)</td>
<td>100.2 (94.6 to &lt; 105.8)</td>
<td>.0001</td>
</tr>
<tr>
<td>Adjusted†</td>
<td>67.2 (54.6 to 79.8)</td>
<td>82.7 (72.7 to 92.7)</td>
<td>96.9 (90.7 to 103.1)</td>
<td>.001</td>
</tr>
</tbody>
</table>

+ F-test.

Glass et al., J Peds; 155: 318-23

Effect of treatment of subclinical neonatal seizures detected with aEEG: Randomized, controlled trial.

Pediatrics 2010

Treatment of clinical sz management vs. aEEG
Baby receptors are not like adult receptors....

Babies have GABA immature neurons NKCC1→KCC2 in older patients.

Epileptogenesis in the immature brain: emerging mechanisms.

N Saxone, J Jensen.
Management of Status Epilepticus

First line drug of choice for neonatal status epilepticus is phenobarbital (yes, still....)

**Phenobarbital**
- Penetrates BBB within minutes, safe at serum levels exceeding 40 mg/L, peak CSF 60 minutes
- Estimated that 40 mg/kg IV load total serum level of 40 mg/L
- PHB binding is variable in neonates (ranges 8-43%)
- IV loading dose 20 mg/kg IV vs. 40 mg/kg?
- Total amount in 24 hour period-40 mg/kg vs. 50 mg/kg?
- Goal level 40 mg/l or 50 mg/l?

**Phenobarbital?**
- Maintenance dosing 3-5 mg/kg/day (start 12-24 hours after load)
- Be aware of pharmacokinetics!
- Elimination occurs in liver> kidney, so should dose adjust in patient with liver and renal dysfunction (especially in HIE neonates)
- Preterm infants have greater ½ life of PHB than term neonates
- Monitoring serum levels important to be done to avoid toxicity and prove therapeutic range, but do not have to check daily
2\textsuperscript{nd} line Aeds? Refractory status epilepticus

- Fosphenytoin, Keppra, Lidocaine, Versed
- Other drugs? Lacosamide, topiramate

Refractory neonatal status epilepticus

**Fosphenytoin**
- Typically given 20 mg (PE)/kg IV load followed by maintenance dose 12 hours after load 5 mg (PE)/kg divided BID
- When converting to PO, phenytoin has variable pharmacokinetics and hepatic metabolism, poor oral bioavailability in neonates
- When can take PO, can use oxcarbazepine
  - 10 mg/kg/day, divided BID, round to nearest 0.5 ml (30 mg) for 3 days
  - 20 mg/kg/day, divided BID, round to nearest 0.5 ml (30 mg) for 3 days
  - 30 mg/kg/day, divided BID, round to nearest 0.5 ml (30 mg) to continue
Refractory neonatal status epilepticus

Levetiracetam
- Not an evidence based first line medication
- May be good option in patients with liver and kidney disease
- Load dose of at least 40 mg/kg IV, followed by maintenance dose of 40-60 mg/kg/day, divided BID IV
- Converts easily to oral

Midazolam
- Good safety profile with minimal cardiovascular effects, may be preferred in patients who will be or who are already intubated
- Efficacious in stopping seizures in neonates refractory to phenobarbital and fosphenytoin
- Dosing: IV bolus of 0.15 mg/kg followed by continuous infusion of 0.12-0.15 mg/kg/hr
- Can increase to effect by 0.05 mg/g/hr every 2 minutes to max of 1.1 mg/kg/hr
- Bolus dose can be repeated 15-30 minutes after initial bolus if seizures persist (0.15 mg/kg IV)
Refractory neonatal status epilepticus

Lidocaine

- Bolus of 2 mg/kg then continuous infusion 6 mg/kg/hr
- Dose may need adjustment for patients on hypothermia protocols
- Major concern is arrhythmia-contraindicated in patients with CHD or that have received fosphenytoin previously

Acute Neonatal Encephalopathy (ANE)

- My preference is fosphenytoin and versed drip if hemodynamics stable
- Most of these patients are intubated
- Prefer to use only fosphenytoin OR phenobarbital, not both because you are playing with fire if use both-phenobarbital and phenytoin interact-both enzyme induce one another (fosphenytoin decreases phenobarbital levels and phenobarbital reduces phenobarbital levels)
- Can use levetiracetam as adjunct, but if need more than one drug, likely to need IV drip (midazolam preferred)
- If super-refractory, can do pentobarbital drip to induce burst suppression-suppression to effect of 6-7 seconds
Refractory neonatal status epilepticus

Lacosamide
- Load IV with 10 mg/kg dose and look for effect
- Particularly good in patients with SCN2A mutations or malignant migrating focal seizure of infancy phenotype (MMFSI) or Ohtahara syndrome
- Benefit is can be given IV, available in liquid forms
- Should not give with patients with Qtc interval prolongation, fhx of QTC or early sudden death, and may want to speak with cardiology to clear with other patients with heart problems
- Maintenance dose 5-15 mg/kg/day divided BID
- Babies usually need more-at least 10 mg/kg/day

Refractory neonatal status epilepticus

Pyridoxine (vitamin B6)
- Should be given to any neonate refractory to conventional AEDs
- Pyridoxine and PLP (pyridoxyl-5’-phosphate) the active form of pyridoxine
- Pyridoxine-dependent make up small portion of neonatal seizures, but B6 easy to administer and non-toxic-treatable!!!
- Dose is 100 mg IV x 1, can repeat
- Side effects: apnea and depression of cerebral activity
- Need close observation with administration
Refractory neonatal status epilepticus

Topiramate
  ➢ Through NG tube - 5 mg/kg

Valproic acid
  ➢ Only if POLG testing done and negative for hepatic failure risk - POLG genetic test usually only takes 2 weeks (genetic epilepsy panel 2-3 months)
  ➢ 20 mg/kg/dose

Other treatable neonatal epilepsies

Biotinidase deficiency
  ➢ Neurosensory hearing loss, visual pathway defects, ataxia and mental retardation
  ➢ Dose 20 mg/day

Folinic acid deficiency
  ➢ Treatment with 2-3 mg/kg/day
  ➢ Other metabolic diseases
  ➢ Be suspicious when EEG read says background is burst-suppression, migrating seizures, refractory seizures

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Treatable metabolic causes of early onset epilepsy</th>
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<tbody>
<tr>
<td>Vitamin-responsive epilepsies</td>
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<tr>
<td>Pyridoxine-dependent epilepsy</td>
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<tr>
<td>Pyridox(am)ine phosphate oxidase deficiency</td>
<td></td>
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<tr>
<td>(pyridoxal phosphate-responsive epilepsy)</td>
<td></td>
</tr>
<tr>
<td>Folinic acid-responsive seizures</td>
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<tr>
<td>Biotinidase deficiency</td>
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<tr>
<td>Other metabolic epilepsies</td>
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<tr>
<td>Glucose transporter 1 deficiency</td>
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<td>Serine deficiency syndromes</td>
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<tr>
<td>Creatine deficiency syndromes</td>
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<td>Untreated phenylketonuria</td>
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</tbody>
</table>
Genetic epilepsies—Early Infantile Epileptic Encephalopathies

OMIM 2014: 19 genes

- Main message is do genetic testing on any babies with refractory seizures, hypotonia, microcephaly, dysmorphic features, hypertonia, multi-system problems, prematurity, etc.!!!
- Do not hesitate, this can make a difference for the diagnosis, prognosis, and management of your patients!
- Insurance usually not an issue for genetic epilepsy panels especially if ordered from the hospital and/or patient has medication-resistant epilepsy in infancy.

Genetic Testing Results For Newborns With Neonatal Epilepsy Syndromes*

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Total, N=79</th>
<th>Any genetic testing</th>
<th>Tested with a putative genetic etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal epileptic encephalopathy</td>
<td>35 (44%)</td>
<td>29 (83%)</td>
<td>24 (83%)</td>
</tr>
<tr>
<td>Brain malformation</td>
<td>32 (40%)</td>
<td>23 (72%)</td>
<td>6 (26%)</td>
</tr>
<tr>
<td>Benign neonatal seizures</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Benign familial neonatal epilepsy</td>
<td>11 (14%)</td>
<td>6 (55%)</td>
<td>4 (67%)</td>
</tr>
</tbody>
</table>

*In a cohort of consecutive patients from US neonatal intensive care units. Values are n (%) includes exome, copy number variation, targeted, single gene tests, gene panels, and whole exome sequencing. For details of the abnormal test results, see table 9-5.

- Pathogenic or likely pathogenic KCNQ2 variants (n=10) were the most commonly identified etiology of epileptic encephalopathy.
- Genetic testing is now warranted for newborns with epilepsy in order to guide management and inform discussions of prognosis.
Malignant migrating focal seizures of infancy

- 2 cases, lacosamide most effective, oxcarbazepine some efficacy
- SCN2A mutations-lesson learned from the first, then I recognized pattern in second and tried lacosamide to see if same efficacy
- For both patients, lacosamide 10 mg/kg/day kept them out of the hospital!
- Etiology is important! Being able to recognize what you are dealing with matters!
Neonatal seizures and Multicenter Variability in Current Treatment Practices


**Neonatal seizures: multicenter variability in current treatment practices.**

Bartha A1, Shen J, Katz KH, Mistal RE, Yao KG, Ivancic JA, Andrews EM, Farriero DM, Mend LR, Silverstein FS.

**Author Information**

**Abstract**

Standardized approaches to the treatment of neonatal seizures remain undeveloped. We assessed the type and number of anticonvulsants selected, blood levels attained, and postdischarge anticonvulsant treatment of neonatal seizures among five neonatal intensive care units in the United States between 2000-2003. Almost all of the 480 neonates (94%) with seizures were treated, initially with phenobarbital (82%), lorazepam (9%), phenytoin (2%), other anticonvulsants (1%), or a combination of the first two drugs (6%). While the majority of neonates were treated with one drug (59%), the number of anticonvulsants varied (P<0.0001), as did the peak serum phenobarbital levels (P<0.0001). The majority (75%) of survivors received anticonvulsant treatment after discharge. These neonates were more likely to have had abnormal electroencephalography or brain imaging, or to have needed a second anticonvulsant, compared with neonates whose drug therapy was discontinued. Anticonvulsant therapy is used in the majority of neonates with seizures, mostly with phenobarbital, and treatment is continued beyond discharge. The observed wide therapeutic variability may reflect a lack of standardized diagnostic and treatment approaches, particularly for seizures refractory to initial phenobarbital therapy. Trials of anticonvulsants with long-term neurodevelopmental follow-up are needed to develop evidence-based treatment guidelines.
My training at Children’s Hospital of Pittsburgh with Mike Painter (a legend in neonatal seizures)
UPMC/CHP (where I trained with Painter....)

Have I changed what I do?

- Absolutely!
- I am rarely the one treating, though!
- Neurologists vs. epileptologists vs. neonatologists
Summary

- Neonatal seizures are often subclinical and of widely variable etiologies
- Neonatal seizures impact neurodevelopmental outcomes
- Recognition of possible etiology may greatly impact treatment course
- One treatment protocol may not work, but at least can have some sort of initial treatment, then tailor to patient
- If refractory neonatal seizures and no HIE, genetic workup and unconventional therapies may be appropriate
- We did not talk about surgery, but some patients may be candidates for focal resection (TS)