Seizures in Neonates and Infants

Cleveland Clinic Epilepsy Review Course
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• Nothing to disclose

Outline
• Neonatal age group
  – Neonatal seizures
  – Neonatal Epileptic Encephalopathy
• Infant age group
  – Febrile Seizures
  – West syndrome or Infantile Spasms
Epidemiology

- Neonatal seizures occur in 1.5–3.5 per 1000 live term births (Eriksson and Zetterstrom, 1979; Lanska et al., 1995; Ronen et al., 1999).

Etiology of Neonatal Seizures

- Acute metabolic
- Hypoglycemia
- Hypocalcemia
- Hypomagnesia
- Hypoxic-ischemic encephalopathy
- Infections (e.g., sepsis, meningitis)
- Structural brain abnormalities (e.g., hypoxic ischemic encephalopathy)
- Genetic disorders (e.g., tuberous sclerosis, neurodevelopmental disorders)
- Inborn errors of metabolism (e.g., tyrosinemia, galactosemia)
- Prematurity
- Intraventricular hemorrhage
- Intracranial mass lesions
- Intracranial infections
- Cerebral palsy
- Hypoxic-ischemic encephalopathy
- Myoclonic seizures
- Status epilepticus

Neonatal seizures

- Neonates have a high seizure burden (~7 seizures per hour)
- Seizures can involve a single electrode
- Often the seizures are multifocal and can be simultaneous multifocal
- Often seizures are surface positive
- Minimal duration of the seizures is 10 seconds
  - Mean duration of seizures is around 90 seconds
  - Minimal duration between 2 seizure patterns has to be ≥10 seconds to be considered independent seizures
- Background pattern can be present during the seizure and is often abnormal

Neonatal EEG seizures

- Seizures can be detected by EEG
- EEG can show multifocal activity

Seizure burden in neonates

Seizures can involve a single electrode

Often the seizures are multifocal

Often the seizures are simultaneous multifocal

C3 seizure, no clinical signs

78% of neonatal seizures appeared in the C3 -> C4 channel. Shellhaas R et al. Clin Neurophysiology 2007; 118:2156-2167

Sz with independent rhythms
Clinical symptoms

- Subtle seizures (50%)
  - Ocular movements
  - Oro-buccal-lingual movements
  - Progression movements (pedaling, bicycling, etc)
  - Autonomic symptoms
- Complex purposeless movements (pneumopsic, crying, hyperactivity)
- Tonic seizures (5%)
- Clonic seizures (25%)
- Myoclonic seizures (20%)
- Non-paroxysmal repetitive behaviors
- Spasms

Pathophysiology

Volpe Mizhari
Treatment

• First line
  – phenobarbital (doses ranging from 20–40 mg/kg),
  – phenytoin (20 mg/kg), or fosphenytoin, and/or
• Second-line adjuvant
  – benzodiazepines such as lorazepam (0.05–0.1 mg/kg)
  – midazolam
• Other:
  – Lidocaine
  – Topiramate
  – Levetiracetam

HIE = hypothermia


NEONATAL EPILEPTIC ENCEPHALOPATHIES

Neonatal Epileptic Encephalopathy

• Ohtahara syndrome or Early Infantile Epileptic Encephalopathy (EIEE)
• Early Myoclonic Epileptic Encephalopathy (EME)
• KCNQ-related epilepsy
  – Benign familial neonatal seizures (BFNS)
  – Benign familial neonatal-infantile seizures (BFNIS)
  – KCNQ severe encephalopathy
Clinical features

**Ohtahara or EIEE with BS**
- Tonic seizures
- Onset in the first week of life
- Grossly abnormal brain MRI

**Early Myoclonic Epileptic Encephalopathy (EMEE)**
- Myoclonic seizures
- Onset in the first week of life or prenatal
- Normal brain MRI

Etiology

- Brain structural abnormalities
  - hemimegalencephaly, magancephaly, lissencephaly, polymicrogyria, focal or multifocal cortical dysplasia, porencephaly, agenesis of the corpus callosum or the mamillary bodies, posterior fossa abnormalities, etc
  - HIE
- Genetic metabolic
  - ARX, CDKL5, SLC25A22 and STXBP1, KCNQ2, SCN2A and ALDH7A1, mitochondrial diseases, inborn error of the metabolism such as non-ketotic hyperglycinemia or glycine encephalopathy, propionic or methylmalonic acidemia, molybdenum cofactor deficiency, and other more rare inborn errors of the metabolism
Treatment: the evidence

• Evidence class C; Poorly effective; Weak recommendation
  – Topiramate
  – Conventional AEDs
  – ACTH, prednisone
  – pyridoxine

Epilepsia 2015; 56(8): 11-85–1197

FEBRILE SEIZURES

Definition of febrile seizures

• Seizures associated with a fever
• 6 months - 6 years of age
• No acute central nervous system infection
• No acute systemic metabolic abnormality that can produce seizures
• No previous afebrile seizures
Complex seizure

- Recurrent (> 1 in 24 hours)
- Focal
- Prolonged (>15 minutes)
  - Strong correlation between focality and long duration (2/3rds of long seizures are partial)

Risk of recurrence: 1/3 of patients

- Half of recurrences within 6 months
- 75% within 1st yr
- 98% within 4 yrs

Age of onset most important predictor of recurrence

- If 1st seizure occurred at
  - < 12 months of age, 50% recurred and 30% had >1 recurrences
  - >12 months of age, 28% recurred and 11% had >1 recurrences
- Probably due to longer period of being at risk rather than increased tendency to have seizures
Risk of developing epilepsy in child had a febrile seizure

Nelson and Ellenberg
Through age 7

<table>
<thead>
<tr>
<th>Number of complicating features</th>
<th>% of group</th>
<th>Risk of epilepsy (%)</th>
<th>Risk of atypical seizures (%)</th>
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</thead>
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<td>No febrile seizures</td>
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<td>0.5</td>
<td>0.9</td>
</tr>
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<td>34</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>10</td>
<td>13</td>
</tr>
</tbody>
</table>

*PH atypical seizures, pre-existing neurological abnormality, complex seizures

Risk of developing epilepsy if child had a febrile seizure
NCPP multivariate analysis

• Significant
  – Family history of afebrile seizures
  – Prior neurologic status
  – First seizure type
• Not significant
  – Age of onset
  – Race
  – Sex
  – Family history of febrile seizures
  – Number of febrile seizures

Risk of epilepsy after prolonged febrile seizures
NCPP study

• Prolonged (>30 minutes) in 4% of children
• 4% epilepsy, 5% afebrile seizures
• 91% of children who developed epilepsy after a febrile seizure never had a prolonged febrile seizure
• Risk of “atypical absence” seizures (complex partial seizures??) increased to the same degree as epilepsy as a whole
Risk of epilepsy after complex febrile seizures
Rochester Epidemiology Project

- Overall cumulative risk of unprovoked seizures in patients with febrile seizures
  - 2% by age 5
  - 4.5% by age 10
  - 5.5% by age 15
  - 7% by age 25
  - Still low but much higher than NCPP 3% where followed until age 7

Management points

- Acute recurrence at the time of simple febrile seizure does not alter the subsequent risk for epilepsy (Class I evidence)
- Antipyretic intervention does not affect the recurrence rate of subsequent febrile seizures (Class I evidence)
- There is not indication for the initiation of chronic AEDs for simple febrile seizures (Class I evidence)

Management points (cont.)

- In the acute treatment of febrile seizures it is important to treat seizures lasting 10 min or longer (expert opinion)
- There should be a low threshold for referral of infants with febrile seizures for further management and exclusion of underlying etiologies (level of evidence U, expert opinion)
WEST SYNDROME

Infantile Spasms or West Syndrome
- Most common epileptic encephalopathy
- Incidence 1: 1900 to 1:3900
- Age on onset: 4-7 months
- Boys more than girls
- Clinical triad = West Syndrome:
  - Infantile spasms
  - Arrest of development
  - EEG: hypsarrhythmia

Etiological Classification of IS
- Cryptogenic
  - 20% of IS
  - Onset 4-9 months
  - Spasms symmetric
  - EEG:
    - Symmetric hypsarrhythmia
    - Multifocal sharp waves have similar frequencies left and right hemispheres
- Symptomatic
  - > 200 etiologies
  - Variable age on onset, frequently earlier
  - Atypical spasms, asymmetric, asynchronous, focal, subtle or combined with other partial seizures
  - EEG:
    - Asymmetric hypsarrhythmia
    - Asymmetric multifocality

Additional studies: YES
...but work up is targeted to uncover the most common etiologies first
Treatment: the evidence

- Class B evidence, probably effective, Strong recommendation
  - Low dose ACTH
  - High dose ACTH

- Class C evidence, Possibly effective, Weak recommendation
  - Prednisone
  - Vigabatrin (except for tuberous sclerosis)

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Choosing Antiepileptic Drugs

Infantile spasms or West Syndrome

start treatment EARLY!!!

- Depends on the etiology
  - Tuberous Sclerosis: Vigabatrin
  - Other etiologies:
    - Steroids
      - ACTH …..VERY EXPENSIVE ($100,000)
        - response rate 70-74%
        - 58% when data was pooled from 7 studies
      - Prednisone, less evidence
    - Vigabatrin
      - Response rate 48-54%
        - 47% when data was pooled from 7 studies
        - Visual field loss in ~30% if treated >3 months.


Other treatment alternatives of IS

- Other antiepileptics:
  - Topiramate
  - Valproate
  - Zonisamide
  - Clonazepam
  - Nitrazepam
  - Pyridoxine
- Ketogenic diet
- Surgical treatment

IS response to treatment

- Complete cessation of spasms confirmed by video-EEG
- Abolition of hypsarrhythmia on prolonged EEG

AAN and CNS Practice Parameters
Mackay MT et al. Neurology 2004; 62: 1168-81
Prognosis

• Favorable prognostic factors
  – Short treatment lag
  – Cryptogenic etiology
  – Age at onset > than 4 months
  – Absence of atypical spasms and partial seizures
  – Absence of asymmetrical EEG abnormalities
  – Early and sustained response to treatment


Outcome

• Prognosis for infantile spasms is poor
• High risk for developing other types of epilepsy, including severe Lennox-Gastaut syndrome (~20%)
• Diagnosed with mental retardation (nearly 90%).
• At increased risk for cerebral palsy and early death
• In symptomatic patients, the prognosis is often dominated by the underlying diagnosis
• Cryptogenic patients do better
  – best predictor for a good outcome is a normal neurodevelopmental exam at the time of syndrome onset

Long Term Outcome of IS
(Cohort, N=214, 100% f/u x 20-35 years, Finland)

RX was ACTH

• Seizure outcome
  – 1/3 seizure free
  – 1/3 daily seizures
  – The rest, less frequent seizures
• Death
  – 1/3 died (1/3 before age 3 years)
• EEG:
  – 60% normal if good outcome
• Intelligence
  – ¼ normal or mildly abnormal
• Co-morbidities
  – ¼ psychiatric disorders, hyperactivity and autism

Questions ???