New-Onset Epilepsy in Children

December 6, 2013

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Disclosure

• Cyberonics Speaker Bureau
• Lundbeck Speaker Bureau
Learning Objectives

1. Seizures versus non-epilepsy paroxysms.

2. Pairing childhood Epilepsy Syndromes and constellations with the correct Anti-Epileptic Medications.
The Chronicles of the life of a Patient with “ Spells”

• 7 year old who is on the honor roll in school going into 2nd grade.

• At 3-1/2 years of age he began having atypical events
  — tongue and facial twitching, usually to the left, with occasional articulation difficulties
  — He has never a secondarily generalized tonic-clonic event.

• Most of his events occur early in the morning (1/3 months).

• Levetiracetam, Topiramate, Lamotrigine, Oxcarbazepine
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• Does he have Epilepsy?

• Does he have a defined Epilepsy Syndrome?

• What is the evidence for effective treatment in this or any other Epilepsy Syndrome?
Scope of the problem

• **Methods:** 127 children seen in a tertiary care First Seizure Clinic. (1 month -17 years)

• **Results:**
  – *Non-epileptic* in 31 (24%) and unclassifiable in two (2%).
  – Pediatricians were more likely to refer true epileptic events (92%) than ED physicians (76%) or family physicians (65%).
  – 15% - developmentally delayed; abnormal neurological exam - 11%.

• **Conclusions:** One quarter of children were incorrectly diagnosed as having a seizure while the diagnosis of epilepsy was missed in over one-third of children.

Diagnostic Inaccuracy in Children Referred with “First Seizure”: Role for a First Seizure Clinic (L. D. Hamiwka et al., 2006)
### Non-epileptic mimics

#### Generalized seizures

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>Mimics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized tonic-clonic seizure</td>
<td>Convulsive syncope, * pseudoseizure, * concussive convulsion, hyperekplexia*, Confused arousals</td>
</tr>
<tr>
<td>Absence seizure</td>
<td>Daydreaming, pseudoseizure*, <strong>Hypersomnia</strong></td>
</tr>
<tr>
<td>Myoclonic seizure</td>
<td>Myoclonus syncope,* benign sleep myoclonus, * other forms of non-epileptic myoclonus*</td>
</tr>
<tr>
<td>Atonic seizure</td>
<td>Syncope,* cataplexy*</td>
</tr>
<tr>
<td>Tonic Seizure</td>
<td>Paroxysmal dykinesia,* hyperekplexia,* breath-holding attack, paroxysmal extreme pain disorder* confused arousals, self stimulatory type behavior</td>
</tr>
<tr>
<td>Epileptic spasms</td>
<td>Benign sleep myoclonus,* infantile colic</td>
</tr>
</tbody>
</table>

#### Partial-onset seizures

<table>
<thead>
<tr>
<th>Lobe</th>
<th>Mimics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal lobe</td>
<td>Migraine,* panic attack, trasient ischemic attack (with aphasia), physiological déjà vu, narcolepsy with automatisms,* non-itcal confusional states, sleep –related auditory hallucination</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>Migrainous visual aura,* Charles-Bonnet phenomenon, <strong>hypnagogic hallucinations</strong></td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>Parasomnia* (when from sleep), panic attack, pseudoseizure,* syncope,* paroxysmal dyskinesia*</td>
</tr>
</tbody>
</table>

*Disorders explored further in this Review

Common epileptic seizure types and some non-epileptic mimics

Crompton DE, Berkovic SF. Lancet Neurol 2009;8:370-381
Myoclonic/ataxic
Sleep pathology
Self Stimulatory behavior
Tonic Seizure
Electroclinical Syndrome: Rolandic Epilepsy with Centrotemporal Spikes

- 3-13 years
- A typical attack involves twitching, numbness, or tingling of the child's face or tongue which often interferes with speech and may cause drooling. Secondarily generalized seizures are common.
AED’s and Abbreviations

CBZ – Carbamazepine
CLB - Clobazam
CZP – Clonazapam
DZP- Diazepam
ESM - Ethosuximide
FBM - Felbamate
GBP – Gabapentin
PB – Phenobarbital
Piracetam
PGB - Pregabalin
NTZ – Nitrazepam
ACTH - Adrenocorticotropic hormone
STM – Sulthiame
STP – Stiropental
\*Orphan drug status in US
  # not available in the US
OXC – Oxcarbazepine
LCS - Lacosamide
LEV – Levetiracetam
LEV – Levetiracetam
LTG – Lamotrigine
PHT - Phenytoin
RFM - Rufinamide
Corticosteroids
TGB - Tiagabine
TPM - Topiramate
VPA - Valproate
VGB – Vigabatrin
ZNS - Zonisamide
How do we choose the correct AED?

1. Randomized Clinical Trials:
   – Variation in study design and number of subjects
   – Hypothesis: Superiority, equivalence, non-superiority
   – Outcome: Efficacy versus effectiveness

2. AAN/AES Efficacy and tolerability of the new antiepileptic drugs\(^1\) - class I evidence: prospective, random, controlled trial (I,II,III,IV)

3. ILAE classification Criteria\(^2\) - class I: Randomized controlled trial, Outcome, Treatment duration, Design, superiority, study exit, Appropriate statistical analysis. (Class I-IV)
   – Level of evidence: Level A = Class I criteria or 2 class II (A,B,C,U)

References:
2. Glauser T et al. Epilepsia 2013; Mar;54(3):551-63
1. Food and Drug Administration approval
   1. Evidence Superiority
   2. Benefit out weight risk
   3. Product quality etc.

2. National Institute of Health and Clinical Excellence

3. Scottish Intercollegiate Guidelines Network

4. Expert Consensus

5. Clinical relevance

References:
How do we choose the Correct AED?
Initial treatment of epilepsy  Sankar R et al Neurology 2004;63(Suppl 4): S30-S39

Choices:
Seizure type and Epilepsy Syndrome  (Wheless JW, Clarke DF et al. 2007)
Age specific toxicity – VPA hepatotoxicity in children under 2 years
Overall Health – Decrease appetite with topiramate
Learning and Behavior
    Phenobarbital and neurocognitive performance  (Park J, Yum MS et al. Epilepsy and Behavior, 2013)
Comorbidities  (Dunn DW et al. Psychiatry et al. 1999;53(suppl 2):S17-23)
    Depression
    Hyperactivity or inattentiveness
    Migraine
    Symptoms of ASD  (Tuchman R et al. Brain Dev. 2010 Oct;32(9):709-18.)
Sleepiness
Other Considerations (Child specific)

Formulation (Age, Developmental/Neurocognitive status, taste):
- Tablet, Chewable or Wafer, Capsule, Liquid/Suspension, Sprinkles, Injection (ACTH), PR (Rectal diazepam)

Route of Administration:
- Oral
- G-tube

Is the patient on the Ketogenic Diet: Low carbohydrate formulations – crushed tablet

Compliance: Dosing times (Around parent’s jobs, school, sleep/wake schedule)
Common Seizure types, Epilepsy Syndromes and or Constellations

Neonatal seizures
Infantile spasms
Focal (Partial seizures)
  BECTS (rolandic epilepsy)
Generalized tonic-clonic
  Lennox-Gastaut syndrome
  Absence epilepsy (CAE, JAE)
  Juvenile myoclonic epilepsy
Atypical, Syndrome Specific Management
  Dravets Syndrome and other Progressive Myoclonic Epilepsies, LKS, ESES,
Febrile convulsions
Enhanced network excitability/
Lack of maturation of cortical circuits
  a)  Focal seizures
  b)  Migrating or multi-focal seizures
  c)  GTC are rare in neonates

Epilepsy after neonatal seizures.
  a)  22% within 12 months
  b)  33.8% within 48 months

(Garcias Da Silva LF, Nunes ML, Da Costa JC.
Pediatr Neurol. 2004 Apr;30(4):271-7.)

Phenobarbital and Phenytoin the
Traditional AED’s of choice.
Both less than 50% efficacy.
Other AED’s used in Neonatal Seizures

Animal studies suggest Topiramate may be anticonvulsant and neuro-protective\(^1\)

Anecdotal evidence for its use in humans - No suspension or IV preparation

Case series: Levetiracetam, Clonazepam, Midazolam, Lidocaine, Paraldehyde, Carbamazepine, Valproic Acid, Primidone, Vigabatrin

Expert concensus: PHT, PB, IV benzodiazepine\(^2\)

2. Wheless J, Clarke D, Carpenter D Child Neurol. 2005 Dec;20 Suppl 1:S1-56; quiz S59-60
Variability in Treatment: type and number of anticonvulsants among five neonatal intensive care units 2000-2003 (N=480)\textsuperscript{1}.

Initially treatment:
- phenobarbital (82%)
- lorazepam (9%)
- phenytoin (2%)
- other anticonvulsants (1%)

55 Pediatric Neurologist at the 2007 CNS meeting-Neonatal Epilepsy\textsuperscript{2}:
- 73% levetiracetam and topiramate
- 47% (26/55) recommended levetiracetam
- 55% (30/55) recommended topiramate

West Syndrome (infantile spasms)

- clusters of repetitive flexor spasms (salams) > extensor spasms, head nods

- 15% to 30% unknown etiology (cryptogenic) Tuberous Sclerosis or any brain abnormality

- EEG: Hypsarrhythmia, high voltage slowing with chaotic multifocal spike wave, electodecremental seizures
Infantile Spasms

• AAN Practice Guidelines¹
  – ACTH probably effective for short term treatment
  – Vigabatrin was found to be possibly effective for short term therapy
  – Superiority of Vigabatrin in Tuberous Sclerosis could not be substantiated

Infantile Spasms Working Group²:
  – ACTH is effective as first-line therapy for IS.
    • insufficient evidence to define precisely the optimum ACTH dose and duration of treatment for IS
  – VGB as a first-line treatment option (6-9 months because of constriction of visual fields)

Infantile Spasms

• The United Kingdom Infantile Spasms Study (UKISS)$^1$ – outcome to 14 months: A multicenter RCT (VGB vs. Hormonal therapy):
  – Better efficacy with hormonal therapy initially but no difference at 14 months
  – neurocognitive outcome better.

• Other agents: VPA, Nitrazepam, Topiramate, Zonisamide, Pyridoxine

• Ketogenic Diet: Few cases of initial therapy but possibly effective$^2$

• FDA approval: ACTH, Vigabatrin

1) Lux AL, Edwards SW. The Lancet, 2004; 364 (9447), 13–19 1773-1778
Focal Seizures

• 25 RCT’s and 1 meta-analysis\(^1\)
  – 2 (OXC, PHT) had class 1 evidence, 1 study demonstrated differential effectiveness (OXC)

• Level A, B: Oxcarbazepine; Level C: CBZ, PB, PHT, TPM, VPA

• AAN/AES Efficacy and tolerability of the new antiepileptic drugs\(^2\): Monotherapy - GBP, LTG, TPM, OXC

• SIGN\(^3\) & NICE\(^4\): In addition to the agents above - LEV, VGB, CLB, LCS, TGB, ZNS

# Recommendation for Focal Seizures

## USA\(^1\)

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<thead>
<tr>
<th>Clinical presentation</th>
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<th>Sometimes appropriate*</th>
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<td><strong>Oxcarbazepine</strong></td>
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<td>after initial</td>
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Rolandic Epilepsy with Centrotemporal Spikes

- ILAE treatment guidelines
  - Level A,B – None
  - Level C: CBZ, VPA

- RCT: Sulthiame, Gabapentin

- NICE: CBZ, LTG, LEV, VPA, OXC, CLB, GBP, TPM

2. Oguni H. Brain Dev. 2011;33:207-212
Medication recommendation for Benign Rolandic Epilepsy

Expert consensus in the US\textsuperscript{1}:
OCZ and CBZ usually appropriate
LTG, LEV, GBP sometimes appropriate

Expert Consensus in Europe\textsuperscript{2}:
VPA usually appropriate
CBZ sometimes appropriate

Is treatment Necessary?\textsuperscript{3} – 43 treated and 36 not treated patients had the same seizure outcome.

Generalized Epilepsy Syndromes
Absence - Childhood (CAE) and/or Juvenile (JAE)

1. ILAE treatment guidelines
   — Level A: ESM, VPA, LTG
2. SIGN, NICE: VPA, ESM, LTG
3. Expert Consensus Europe and USA: VPA, ESM, LTG

• PHT, CBZ, GBP, VGB, TGB, ?OCB – may exacerbate the condition

Juvenile Myoclonic Epilepsy (myoclonic Epilepsy of Janz Impulsive petit mal, jerk Epilepsy)

- Most cases occur between 12 and 18 years

- Seizure types:
  - Myoclonic seizures (100%)
  - GTC (approx. 90%)
  - Absence (10-30%)

- Triggers: Lack of Sleep, Fatigue, Alcohol

- VPA historical drug of choice\(^1\) (side effect profile my negate its use)
Juvenile Myoclonic Epilepsy
(Epilepsy with Grand Mal on Awakening)

1. ILAE treatment guidelines\(^1\)
   - No level A, B or C evidence
   - Class 4 studies: Clonazepam, LTG, LEV, TPM, VPA, ZNS

2. SIGN\(^2\): VPA, LTG, TPM

3. NICE\(^3\): VPA, LTG, TPM, LTG

4. Expert Consensus Europe and US\(^4\): VPA (male), LTG (female), LEV (Europe) – TPM, ZNS, CLB usually appropriate.

5. PHT, CBZ, GBP, VGB, TGB, OXC – may exacerbate the condition

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Lennox-Gastaut Syndrome

- EEG: Slow spike and wave
- 1-4% of patients with childhood epilepsy but 10% of epilepsy when younger than 5 years.

- Seizures often pharmacoresistant: tonic, atonic, myoclonic, GTC, atypical absence

- VPA historical drug of choice.

Lennox-Gastaut Syndrome

1. ILAE treatment guidelines - Not reviewed
2. Felbamate was the first to show efficacy\(^1\)
   1. Side effects and organ toxicity negates or limits its use.
3. SIGN\(^2\): VPA, LTG, TPM, CLB, FBM, RFM
4. NICE\(^3\): VPA, LTG, RFM, TPM
5. US Expert Concenssus - usually appropriate: VPA, TPM, LTG; Sometimes appropriate ZNS
6. Europe Usually Appropriate – VPA; Sometimes LTG, TPM, CLB, ETM

Syndromes associated with neurocognitive deficits, language impairment and continuous epileptiform activity during sleep:

1. Landau-Kleffner Syndrome
2. Syndrome of Continuous Spike and Wave Activity in Sleep
3. Malignant Rolandic Epilepsy

Diagnosis:

1. History
2. Prolonged EEG capturing NREM sleep is required for the diagnosis

Initial medications of choice - High Dose Diazepam (1mg/kg), VPA, Corticosteroids, ACTH, IVIG

1. ILAE treatment guidelines, NICE, SIGN, Expert Opinion - **Not reviewed**

2. Case reports: VPA, diazepam, ETH, CLB, CZP.

- **Treatment of epilepsy with electrical status epilepticus during slow sleep and its related disorders** *(Inutsuka M, Kobayashi K et al. Brain and Dev. 2006, Pages 281–286)*
  - **High-dose valproate therapy**
  - **Combination therapy of VPA and ethosuximide**;
  - Short cycles of high-dose diazepam (oral or PR DZP, 0.5–1 mg/kg per day for 6–7 days)
  - Intramuscular synthetic ACTH-Z therapy (0.01–0.04 mg/kg per day for 11–43 days).
Dravet Syndrome and other Progressive Epilepsy Syndromes associated with myoclonic, atonic and other generalized or mixed seizure types

• Dravet Syndrome (Severe Myoclonic Epilepsy of Infancy):
  – Prolong febrile seizure
  – Triggers – photic stimulation, exogenous body heat, eye closure and fixation on patterns.
  – Multiple seizure types – Myoclonus is often prominent.

• Progressive Myoclonic Epilepsy:
  – Severe Myoclonus
  – Generalized Seizure types predominate but focal seizures may be seen
  – Progressive Course including Neurocognitive regression and cerebellar manifestations +/- visual and hearing impairment
• Dravet Syndrome\(^1\): Valproate, benzodiazepine is used as an abortive agent
  – Topiramate, levetiracetam, bromide, and the ketogenic diet
• Stiripentol (modulator of GABA A receptor) – proved efficacy in two independent randomized placebo-controlled trials, when combined with valproate (71% > 50% reduction versus 5% in placebo group) and clobazam

• PMEs\(^2\): ZNS, Piracetam, LEV, CZP, VPA.
• Historically, both alcohol and N-acetylcysteine have been helpful in some patients with PMEs.

Common Seizure types, Epilepsy Syndromes and or Constellations

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>Medication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Seizures</td>
<td>Phenobarbital (LEV, TPM)</td>
</tr>
<tr>
<td>Infantile spasms</td>
<td>ACTH, Vigabatrin</td>
</tr>
<tr>
<td>Focal (Partial seizures)</td>
<td>Oxcarbazepine, Carbamazepine</td>
</tr>
<tr>
<td>Rolandic Epilepsy</td>
<td>Oxcarbazepine, Carbamazepine,</td>
</tr>
<tr>
<td></td>
<td>GBP, STM</td>
</tr>
<tr>
<td>Absence epilepsy (CAE, JAE)</td>
<td>Ethosuximide, Valproic Acid,</td>
</tr>
<tr>
<td></td>
<td>LTG</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>Lamotrigine (F), Valproic Acid (M)</td>
</tr>
<tr>
<td>Lennox-Gastaut syndrome</td>
<td>Valproic Acid, Lamotrigine, TPM, FLB</td>
</tr>
<tr>
<td>Atypical, syndrome Specific Management</td>
<td></td>
</tr>
<tr>
<td>Dravets syndrome and other Progressive Myoclonic Epilepsies</td>
<td>Stiropental (D), Valproic Acid</td>
</tr>
<tr>
<td>LKS, ESES</td>
<td>High dose diazepam, Valproic Acid, Corticosteroids</td>
</tr>
</tbody>
</table>
**Conclusion**

- Many Pediatric Epilepsy Syndromes were not covered and have not been adequately studied (more studies are required).

<table>
<thead>
<tr>
<th>Neuronal Ceroid Lipofuscinosis</th>
<th>PPT1, TPP1, CTSF.....</th>
<th>Large occipital spikes to low frequency photic (Green, 1971)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpers Syndrome</td>
<td>POLG-related disorders</td>
<td>1-3/sec spike and wave with focal motor activity (Brick, 1984)</td>
</tr>
<tr>
<td>Sialidosis Type 1</td>
<td>NEU1</td>
<td>Posterior spikes over vertex (Engel, 1977)</td>
</tr>
<tr>
<td>Retts Syndrome</td>
<td>MECP2, CDKL5</td>
<td>Central spike with contralateral touch (Robertson 1978)</td>
</tr>
<tr>
<td>Lissencephaly</td>
<td>ARX, LIS1..................</td>
<td>High voltage alpha and theta frequency with admixed delta (Niedermeyer, 1986)</td>
</tr>
</tbody>
</table>

- Future Hope – We may be able to (based on Genetics, EEG, Signs and symptoms) choose case or Epilepsy Syndrome specific management.