Diagnosis & Treatment of Childhood Epilepsy

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Learning Objectives

• Seizure vs. epilepsy
• How to diagnose and classify epilepsy
• Epilepsy management:
  - Medical, surgical, dietary, neurostimulation
• Epilepsy prognosis
• Co-occurring developmental, cognitive/academic, and mental health difficulties
• When to refer to a Pediatric Epileptologist
• Seizure detection
• Transition from pediatric to adult care
• Resources for patients and families
Who Can Have “Seizures” Or “Epilepsy”? 

• Adults only?
• Children with developmental delay?

• **ALL** children at **ANY** age

• Kids are **NOT** merely little adults!
Seizure: Provoked vs. Unprovoked

Provoked/ “Acute Symptomatic”
- Fever – febrile seizure
- Head injury – acute post-concussion, contusion, hemorrhage
- Infection – meningitis, encephalitis
- Decreased sleep
- Anoxic – post-syncopal, breath holding spell
- Metabolic – electrolyte derangements, renal or liver failure
- Vascular – stroke, venous thrombosis
- Post-infectious/demyelinating – ADEM
- Toxic – alcohol withdrawal, drugs

Unprovoked/Spontaneous
- Single
- Recurrent

Beghi et al, Epilepsia 2010
Incidence Of Seizures vs. Epilepsy

- Pediatric epilepsy: incidence 0.5% to 1%
- The most frequent chronic neurologic problem in children
- Approximately 1 out of 150 children is diagnosed with epilepsy during the first 10 years
  - highest incidence rate during infancy

All Convulsive Disorders: 4%
Afebrile Seizures: 2%
Epilepsy: 1%

Figure 1. Age-related incidence and prevalence rates of epilepsy

Panyiotopoulos, 2006; Cloyd, 2006
How Do You Diagnose Epilepsy?

- **Old definition**: 2 unprovoked seizures occurring >24 hours apart
  - Why 2 seizures? Recurrence risk ~60% of another seizure within 5 years.

- **New definition (ILAE, 2014)**:
  1. Criteria above, or
  2. 1 unprovoked seizure with clinical, EEG, or radiographic evidence of >60% likelihood of having another unprovoked seizure, or
  3. Epilepsy Syndrome

- **When has it “resolved”?**
  1. Either in the setting of an age dependent epilepsy, now past age
  2. Or, after 10 years of seizure freedom and 5 years off of anticonvulsants

Hauser, NEJM 1998
Fisher et al., Epilepsia 2014
Under new definition, 1 seizure with these findings is epilepsy
Can EEG Alone Diagnose Epilepsy?
Is A Diagnosis Of “Epilepsy” Enough?

• Diagnosis is made with a good history and physical exam +/- EEG or MRI

• Epilepsy encompasses hundreds of sub-types, each with their own unique mechanism, prognosis, and treatment strategies

• Finding – or at least trying to find – the “etiology” or underlying cause of any epilepsy is **ESSENTIAL**
  • To refine treatments, investigate comorbidities, and better understand the future
What Causes Epilepsy?

• Old terms:
  • Seizures types – partial, complex partial, petit mal, grand mal
  • Epilepsy types – symptomatic, idiopathic, cryptogenic, unknown

• 2017 Classification (ILAE):
  • Seizure types – focal, generalized, unknown onset
  • Epilepsy types – focal, generalized, focal + generalized, unknown
  • Etiology –
    • Structural
    • Genetic
    • Infectious
    • Metabolic
    • Autoimmune
    • Unknown

Scheffer et al. ILAE Classification of the Epilepsies, Epilepsia, 2017
Scheffer et al. Operational Classification of the Seizure Types, Epilepsia, 2017
Etiology-specific Classification/Diagnosis - Examples

- **Structural** - focal cortical dysplasia, malformation of cortical development, stroke, hemorrhage, hippocampal malrotation
- **Genetic** - Tuberous Sclerosis (TSC1/2), Dravet Syndrome (SCN1A), CDKL5, KCNQ2, GRIN2A
- **Infectious** – viral or bacterial
- **Metabolic** – disorder of fuel breakdown (fat, protein, glucose); urea cycle disorders, amino acidopathies, lysosomal storage disorders, GLUT-1, mitochondrial disorders
- **Autoimmune** – autoantibody mediated; eg., NMDA, GAD
- **Unknown** - unknown
Epilepsy Of Unknown Cause

• Despite our best diagnostic efforts, the etiology remains unknown in 15-25% of pediatric epilepsy cases.

• This territory has been gradually shrinking largely due to advances in genetic diagnostic technology.
ILAE 2017 Classification of Seizure Types Expanded Version

Focal Onset
- Aware
- Impaired
  Awareness

Motor Onset
- automatisms
- atonic
- clonic
- epileptic spasms
- hyperkinetic
- myoclonic
- tonic

Nonmotor Onset
- autonomic
- behavior arrest
- cognitive
- emotional
- sensory

focal to bilateral tonic-clonic

Generalized Onset

Motor
- tonic-clonic
- clonic
- tonic
- myoclonic
- myoclonic-tonic-clonic
- myoclonic-atonic
- atonic
- epileptic spasms

Nonmotor (absence)
- typical
- atypical
- myoclonic
- eyelid myoclonia

Unknown Onset

Motor
- tonic-clonic
- epileptic spasms
Nonmotor
- behavior arrest
Unclassified

ILAE – glossary, definitions, videos: www.epilepsydiagnosis.org
Electro-clinical Epilepsy Syndromes

• Clinical entities reliably identified by a consistent cluster of features:
  • Clinical – age at seizure onset, seizure types, developmental antecedents/consequences, physical exam
  • EEG
  • Radiographic

• Similar epilepsy cause/etiology $\rightarrow$ similar treatment paradigms and prognoses
  • Refine our medical/surgical treatment, screen for co-morbid conditions, better anticipatory guidance for future
Diagnosis Relies (in part) On Evolution of / Advancements In Technology
Evolution Of Scalp EEG

Magneto-encephalography (MEG)
Intracranial EEG

Electrocorticography (ECoG)

Stereo EEG (SEEG)
Evolution Of Brain Imaging

CT

MRI

Positron Emission Tomography (PET)
Brain Imaging - Continued

**Interictal Sz focus**

**HYPOperfusion**

**Ictal Sz focus**

**HYPERperfusion**

Functional MRI

SPECT scan
The End Result - Coregistration
Evolution Of Laboratory Testing

- Most significant advances in recent years have been in –
  
  **Genetic:**
  - Karyotype/microarray – eg., Trisomy 21
  - Single gene testing – eg., SCN1A
  - Gene panels – eg., 40-200 most common causes of infantile onset epilepsy
  - Whole exome sequencing (WES)
  - Whole genome sequencing! (WGS)

**Autoimmune:** eg., NMDAR Ab, Potassium channel Abs

Rossignol et al. Epilepsia, 2014
Aspects of medical treatment

- **Goals:**
  - No seizures
  - No side effects

- **Medication Selection:**
  - Seizure type – focal vs. generalized vs. spasm
  - Side effect profile – eg., end-organ effects, fatigue, rash, behavior
  - Cross over effects –
    - Headache: topiramate, valproic acid
    - Dystonia: carbamazepine
    - Mood stabilization: lamotrigine, valproic acid
  - Drug-drug interactions

- **Symptom control vs. disease modification:**
  - “anticonvulsant,” “antiepileptic” vs. “antiepileptogenic”
### Focal vs. Generalized Seizures vs. Spasms

<table>
<thead>
<tr>
<th>Focal</th>
<th>Generalized</th>
<th>Spasms</th>
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<tbody>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td>Phenobarbital</td>
<td>Steroids/hormonal therapy – ACTH, prednisone, prednisolone</td>
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<tr>
<td>Oxcarbazepine (Trileptol)</td>
<td>Phenytoin (Dilantin)</td>
<td>Vigabatrin</td>
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<td>Lacosamide (Vimpat)</td>
<td>Valproic Acid (Depakote)</td>
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<td>Gabapentin (Neurontin)</td>
<td>Ethosuximide (Zarontin)</td>
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<tr>
<td>Vigabatrin (Sabril)</td>
<td>Topiramate (Topamax)</td>
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<td>Eslicarbazepine (Aptiom)</td>
<td>Zonisamide (Zonegran)</td>
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<td>Lamotrigine (Lamictal)</td>
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<td>Felbamate (Felbatol)</td>
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<td></td>
<td>Levetiracetam (Keppra)</td>
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<td>Clobazam (Onfi)</td>
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<td>Rufinamide (Banzel)</td>
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<td>Perampanel (Fycompa)</td>
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<td></td>
<td>Brivaracetam (Briviact)</td>
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Disease Modification – Preventing Epilepsy?

• Goal is not simply antiepileptic, but antiepileptogenic properties
• To modify signaling pathways BEFORE they begin to generate epileptic seizures

• Tuberous Sclerosis Complex:
  • mTOR inhibitors – Everolimus, Sirolimus
    • Limit the functional disruption caused by TSC1/2 genetic changes
    • Initially used to suppress growth of SEGAs and kidney tumors
    • Discovered anti-seizure AND anti-epilepsy results
    • Many unknowns:
      • Timing and duration of therapy?
      • Side effects - generally well-tolerated, but significant adverse effects may occur: opportunistic infections, hyperlipidemia, thrombocytopenia, and apthous ulcers.

• Other types of epilepsy?

Galanopoulou, Epilepsia, 2012
The Future - Precision Medicine?

• NIH: “an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.”

• Would allow doctors/researchers to predict more accurately which treatment/prevention strategies for a particular disease will work in which groups of people or a person.
  • If you need glasses, you aren't assigned a generic pair. You get a prescription customized for you.
  • If you have an allergy, you get tested to determine exactly what you're allergic to.
  • If you need a blood transfusion, it has to match your precise blood type.

• Unfortunately, we are still far way from tailoring medication therapy to genetic profiles of patients with epilepsy – but, there is a lot of exciting work in the basic science research pipeline!
When Medications Don’t Work, Ask/Think About Surgery

Medically Refractory Epilepsy

EMU - Phase 1 vEEG (Sz) & MRI

Functional Neuroimaging: PET/SPECT

Eloquent Cortex Evals: Neuropsych, WADA, MEG, fMRI, Ophtho (VF)

Phase 2 vEEG: Extra-operative (EMU)

Nonsurgical

AEDs
VNS
Keto Diet

ECOG

SURGERY
• Resection > disconnection:
  • craniotomy +/- brain surface recording (ECoG)
    • Next generation → SEEG prior to craniotomy

• Laser ablation: Visualase
  • Thermal ablation
  • Minimally invasive
  • Best circumstances – discrete lesion(s) on MRI, regularly shaped

• Rationale For Early Surgery
  ↓ Seizure frequency
  ↓ Rates development/behavior issues
  ↓ Early morbid/mortality
  Stabilize/↑ DQ/IQ
  • IS & Early Surgery ↑↑↑
  Lower Complication Rates
  ↑ Plasticity
  Eloquent Cortex
  Transfer of function

Loddenkemper et al, Pediatrics 2007
Vendrame et al, Epilepsy & Behavior 2009
Dietary Therapies

- Principal dates back to observations made in the old testament and ancient Greece!
  - Erasistratus – “One inclining to epilepsy should be made to fast without mercy and be put on short rations.”
- First used by Dr. Russel Wilder in 1921 at the Mayo Clinic

- Range of restrictiveness:
  1. **Ketogenic Diet** – (most restrictive) high fat, low carbohydrate, adequate protein; typical ratio 3-4:1
  2. **Modified Atkins Diet** – 10g carbs per day; no limit on calories or protein
  3. **Low Glycemic Index Treatment** – (least restrictive) 40-60g carbs per day

- Particularly helpful in: infantile/epileptic spasms, GLUT-1 deficiency, Pyruvate Dehydrogenase (PDH) deficiency, Dravet Syndrome, Myoclonic Astatic Epilepsy (MAE), other refractory epilepsies

- For some, a more favorable side effect profile

Baranano, Curr Treat Options Neurol. 2008
Can Children Outgrow Their Seizures/Epilepsy?

- It depends on the underlying cause/etiology

- Reflex/Triggered Seizures  Yes
- Acute Symptomatic Seizures  Yes
- Genetic generalized or Benign
  - Childhood Focal Epilepsies  Very Possible
- Symptomatic Epilepsy  Less likely
- Unknown Cause  Difficult to predict
Treatment Response

New Onset Epilepsy

Electro-clinical Syndrome

No Electro-clinical Syndrome

Self-limited 20-30%

Pharmacosensitive 30%

Pharmacodependent 20%

Pharmacoresistant / Intractable 13-17%

30% period of seizure freedom > 12 months

70% seizures recur

Rosati et al, CNS Drugs 2015
What Is Intractable Epilepsy?

• Persistent seizures after 2 appropriate medications at appropriate doses
  • No consensus on how frequently those seizures need to occur (1 per month vs. 1 per year?)

• Risk factors for intractable epilepsy?
  • Having many seizures prior to starting medical therapy, e.g., delay to diagnosis or therapy
  • No response to first appropriately selected medication
  • Having “symptomatic” epilepsy – identified fixed structural, genetic, metabolic, mitochondrial, infectious, or autoimmune cause
  • Focal slowing on EEG
  • History of neonatal seizures (apart from benign familial epilepsy syndromes)

Kwan, Epilepsia 2010
Brodie, NEJM 2000
Dlugos, Neurology 2001
Berg, Neurology 2001
Why Refer To A Pediatric Epileptologist?

• **Time:**
  - The longer seizures persist – untreated or on medication – the harder full control becomes
  - Ongoing seizures impact learning and development

• **Diagnosis:**
  - Etiologically specific

• **Medication choice:**
  - Selection of the wrong medication first can make things worse
  - Chances of seizure freedom decline after first 2 medications
  - Limit episodes of status epilepticus - morbidity and mortality

• **Options beyond traditional anticonvulsants:**
  - Medical, surgical, dietary, neurostimulation

• **More than just seizures:**
  - Effects on developmental, learning, mood, behavior, social, family

Brodie, NEJM 2000
Brodie, Neurology 2012
Berg, Epilepsia 2010
When To Refer?

• At any time
• When 1st medication hasn’t worked
• When you don’t know which medication to choose
• When you can’t readily identify an epilepsy etiology/diagnose more than just “seizures”
• When you identify an etiology highly associated with intractable epilepsy
• When there is a structural brain lesion/surgery is a possibility
• When there are multiple other health issues
• At any time
Who Is On Our – And Your! – Team?

- Neurologists
- Epileptologists
- Advanced Practice Providers: NP / PA
- Nurses
- Program Coordinators
- Dietician
- Social Worker
- Child Life Specialists
- Pediatric EEG technologists
- Other specialists
Other Subspecialists Involved

- Radiologists
- Nuclear Medicine
- Neurosurgeons / Epilepsy Surgeon
- Psychologists
- Psychiatrists
- Ophthalmologists
- Neurodevelopmental Specialists
- Physiatrists/PM&R
- PT/OT/ST/Audiology
- Primary Care Providers: Pediatrician, Family Doctor
Other Considerations

• **Developmental** – before and after seizure onset
  • Speech/language
  • Gross Motor
  • Fine Motor
    • Referral for Early On, Developmental Pediatrician, or PT/OT/ST as appropriate

• **Cognitive/academic** – before and after seizure onset
  • Learning difficulties
  • ADD/ADHD
    • IEP: “Individualized Education Plan”; >3 yo; upon request if not already offered
    • 504: any medical condition
    • Referral to Neuropsychologist or Pediatric Psychiatrist

• **Mental health**
  • Depression
  • Anxiety
    • Referral to Pediatric Psychiatrist; peer-to-peer support groups

• **Sleep Difficulties**
  • Discuss with Neurologist/Epileptologist; referrals possible to Pediatric Sleep Medicine Specialist

• **Compliance**
  • Text alerts/electronic reminders; promoting independence with pill bottles/refills
Seizure Alert Devices

- **Theoretical utility:**
  - Detect repeated shaking/“clonic” movements during a seizure.
  - Notify nearby family/caregivers when a seizure occurs via alarms, phone calls or text alerts.

- **Practical limitations:**
  - Do not alert caregivers of breathing problems or changes in heart rate.
  - Seizures lacking clonic or significant movement not detected.
  - Devices currently available are not FDA approved.
  - Supporting evidence from studies performed in hospital epilepsy monitoring units and in some home situations – not systematic
Seizure Alert Devices - Details

• **Mattress sensors** – Mattress devices are usually placed under a mattress. When seizure-like movements are detected an alarm will sound. EmFit, MedPage

• **Watches** – Embrace; Smart Watch; EpiLert
  - Embrace also uses autonomic data (galvanic skin response/electrodermal activity); open clinical trial to collect and validate biometric data

• **Camera** – Records A/V information from infrared video camera. Info relayed to smart phone where an app records/analyzes the video for seizure like activity. Alarms sounds when event detected; SAMi

• **Dogs** – specially trained service animal. No rigorous data supports dog’s accuracy in seizure prediction. In theory, dogs can:
  - Get help - find a person or activate a medical alert after a seizure begins.
  - Pull potentially dangerous objects away a person’s body.
  - Help keep a person safe, eg., keep them from walking into dangerous areas.
  - Try to arouse an unconscious person during/after a seizure.
  - Carry emergency medication and/or hander’s health info.

• None prevent SUDEP – PAME Webinar “Preventing SUDEP: Current Thinking and Strategies”
• Financial support: some insurance companies; Danny Did Foundation, Chelsea Hutchinson Foundation.
Transitioning to Adult Care

2016 AAN Consensus Statement:

1. Discussions starting no later than age 13; annually thereafter
2. Annual assessments of self-management skills starting age 12
3. Discussions regarding legal competency no later than age 14; review annually as needed
4. Create a multidisciplinary transition plan addressing, in addition to health care: legal and financial matters, housing, employment, etc. Ideally, PCP acts as medical home and lead coordinator.
5. Collaborate with parents in identification of adult Neurologist before expected time of transfer.
6. Communicate directly with adult Neurologist to ensure transition has been made and care established.

Resources for Patients, Families, and Pediatricians

- Epilepsy Foundation (Michigan) www.epilepsymichigan.org
- Epilepsy Foundation (National) www.epilepsyfoundation.org
  ➢ “Epilepsy and My Child Toolkit”
- American Epilepsy Society www.aesnet.org
- International League Against Epilepsy www.ilae.org
- Children’s Special Health Care Services www.michigan.gov/CSHCS
- Beaumont Children’s Hospital www.beaumontchildrens.org/PediatricEpilepsy
Thank you