Pediatric Epilepsy: State of the Art Seizure Management

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Disclosures

- Dr. Brenton has received personal compensation for consulting and serving on a scientific advisory board with Novartis.
Pediatric Epilepsy – Learning Objectives

• Learn the recent changes to diagnostic definitions of epilepsy

• Evaluate the role of medication and non-pharmacologic treatments in epilepsy and drug-resistant epilepsy

• Recognize the role of autoimmunity in a subset of epilepsy cases and the need to think differently about treatment approaches
Poll Question

Which of these children meets current criteria for a diagnosis of epilepsy?

A. A 10 year old girl with two unprovoked seizures, 1 year apart.
B. A 16 year old girl who has a first seizure 1 month following a stroke involving her left temporal lobe. On EEG, there are frequent left temporal spikes.
C. A 6 year old boy that has 3 provoked seizures over the past month in the setting of playing video games. EEG shows an epileptiform response (e.g. photoparoxysmal response) when exposed to photic stimulation.
D. An 8 year old boy with a single nocturnal convulsion. EEG later that week demonstrates evidence supporting a diagnosis of benign rolandic epilepsy (aka benign epilepsy with centrotemporal spikes)
E. A & C
F. All scenarios except B
G. All of the above
Introduction

• **Epilepsy** – a heterogenous neurologic disorder that is characterized by a chronic predisposition to seizures.

• Traditionally diagnosed by history of 2 or more unprovoked seizures >24 hours apart

• **ILAE 2014** – Redefining and expanded definition of epilepsy:
  • Epilepsy is a disease of the brain defined by any of the following:
    • At least 2 unprovoked (or reflex) seizures occurring more than 24 hours apart
    • Single unprovoked seizure but a >60% chance of additional seizures occurring over the next 10 years
      • This may be based upon the presence of lesional epilepsy or a highly epileptogenic EEG
    • Diagnosis of an epilepsy syndrome (e.g. BECTS)
Introduction
Introduction

According to the Epilepsy Foundation, the goal of all epilepsy treatment is to:

• Prevent further seizures
• Avoid side effects
• Make it possible for people to lead active lives

Individual treatment goals may include:

• Ability to regain/retain your driving privileges
• Job stability
• Academic success
Medication Therapy – Basic Principles

• **Use a single drug whenever possible**
  - Only around 60% of patients are controlled on one medication

• **Start low and go slow**
  - Increase the dose of that medication to either seizure control or toxicity (decreasing the dose if toxicity occurs)
  - If a medication does not control seizures without toxicity, switch to another appropriate medication used alone, and again increase the dose until seizure control occurs or toxicity intervenes
Medication Therapy – Basic Principles

• The chance of seizure freedom after starting one medication is about 60%
• If you fail an adequate trial of one medication, the likelihood you will be seizure free on the second medication is about 10%
• If you fail the second medication, the likelihood you will be seizure free on the third medication is about 1 to 3 %
# Medication Therapy

## Older Medications

### (1st Generation)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Year Introduced</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromides</td>
<td>1857</td>
<td>—</td>
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<tr>
<td>Phenobarbital</td>
<td>1912</td>
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<td>1956</td>
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<td>Ethosuximide</td>
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<td>Diazepam</td>
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<tr>
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<td>1968</td>
<td>Tegretol®</td>
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<td>Lorazepam</td>
<td>1977</td>
<td>Ativan®</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>1978</td>
<td>Depakene®</td>
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<tr>
<td>Divalproex sodium</td>
<td>1983</td>
<td>Depakote®</td>
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<tr>
<td>Carbamazepine</td>
<td>1986</td>
<td>Epitol®</td>
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<tr>
<td>Diazepam</td>
<td>1997</td>
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<tr>
<td>Carbamazepine</td>
<td>1997</td>
<td>Carbatrol®</td>
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<tr>
<td>Phenytoin Sodium</td>
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<td>Phenytek®</td>
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## Newer Medications

### (2nd & 3rd Generation)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>FDA Approval</th>
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<tr>
<td>Felbamate</td>
<td>1993</td>
<td>Felbatol®</td>
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<td>Gabapentin</td>
<td>1993</td>
<td>Neurontin®</td>
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<tr>
<td>Lamotrigine</td>
<td>1994</td>
<td>Lamictal®</td>
</tr>
<tr>
<td>Topiramate</td>
<td>1996</td>
<td>Topamax®</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>1997</td>
<td>Gabitril®</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1999</td>
<td>Keppra®</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>2000</td>
<td>Trileptal®</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>2000</td>
<td>Zonegran®</td>
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<tr>
<td>Pregabalin</td>
<td>2005</td>
<td>Lyrica®</td>
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<tr>
<td>Rufinamide</td>
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<td>Banzel®</td>
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<td>Lacosamide</td>
<td>2008</td>
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<td>Vigabatrin</td>
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<tr>
<td>Clobazam</td>
<td>2011</td>
<td>Onfi®</td>
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<td>Perampanel</td>
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<td>Fycompa®</td>
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<td>Esticarbazepine</td>
<td>2013</td>
<td>Aptiom®</td>
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<tr>
<td>Brivaracetam</td>
<td>2016</td>
<td>Briviact®</td>
</tr>
<tr>
<td>Cannabidiol</td>
<td>2018</td>
<td>Epidiolex®</td>
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</table>
Newer Anti-Seizure Medications

• **Brivaracetam (Briviact)**
  - 15-30 fold higher affinity to synaptic vesicle protein than levetiracetam and inhibits neuronal voltage-gated sodium channels
  - Effective as add on treatment for those 16 years or older with focal seizures
  - Most common adverse effects are drowsiness, decreased appetite, nausea

• **Perampanel (Fycompa)**
  - Highly selective antagonist of the AMPA receptor; therefore, reduces excessive excitatory signaling in the brain
  - FDA approved for treatment in adults and children as young as 4 years with focal seizures. Also approved for treatment of GTCs.
  - Most common adverse effects are dizziness, fatigue and drowsiness
  - Controlled Substance category III and it has a black box regarding “serious psychiatric and behavioral reactions”
Newer Anti-Seizure Medications

• Cannabidiol (Epidiolex®)
  • 98% CBD and <0.1% THC
  • 3, large randomized placebo-controlled trials assessed safety and benefits of Epidiolex in Lennox Gastaut syndrome and Dravet syndrome
    • Studies showed a significant improvement in generalized seizures (with focus on convulsions and drop seizures) compared to placebo.
  • June 2018 - FDA approved for the treatment of seizures in LGS and Dravet
  • Adverse effects appear mild with somnolence, decreased appetite, diarrhea, and transaminitis
  • The addition of Epidiolex to the anti-seizure armamentarium is exciting, but the complete spectrum of cannabis-derived products is still highly questionable

Poll Question

7 year old girl with global hypoxic-ischemic injury and significant neurologic sequelae s/p cardiac arrest. She has > 50 seizures per day – mostly consisting of atonic, tonic, and tonic-clonic seizures. Her EEG and clinical presentation are consistent with Lennox-Gastaut syndrome. She is currently on 2 anti-seizure medications at maximal doses and continues to have frequent seizures. What is the best next step?

A) Attempt a third seizure medication
B) Ketogenic diet trial
C) Evaluation for epilepsy surgery
D) Vagal nerve stimulator
E) B & D
F) All of the above
Non-Pharmacologic Treatments for Epilepsy

• Approximately one-third of patients have seizures that are unresponsive to pharmacologic therapy
• Safety and tolerability issues associated with both the acute and chronic side effects and toxicity complications further diminish the effectiveness of AEDs
• Nonadherence to AEDs, which is highly prevalent in populations with epilepsy, can also diminish treatment effectiveness and further increase mortality as well as significantly increase healthcare utilization
Dietary Therapy

• Ketogenic Diets
  • Well-established, nonpharmacologic treatments for children and adults with medically-refractory epilepsy
  • These diets are low-carbohydrate, high-fat diets that mimic a fasting state
    • Classic ketogenic diet
    • Modified Atkins diet
    • Medium chain triglyceride diet
    • Low glycemic index diet
  • There have been 4 randomized, controlled trials to-date focusing on efficacy of KDs compared to continued medications or a placebo arm
    • ½ of all children with medically-refractory epilepsy have a >50% reduction in seizures on the ketogenic diet

Dietary Therapy

• Patient Selection
  • Can effectively treat epilepsy in individuals from infancy through adulthood
  • Should be first line for several genetic epilepsy conditions – including glucose transporter 1 deficiency syndrome and pyruvate dehydrogenase deficiency.
  • These diets are contraindicated in specific disorders where patients may have an issue with fat metabolism
    • Fatty acid transport and oxidation disorders

• Side effects
  • Hyperlipidemia
  • Reduced vertical growth
  • Osteopenia
  • Nephrocalcinosis
  • Nausea/vomiting, constipation
  • Hypoglycemia
Dietary Therapy

• Start and Discontinuation
  • Most children are started on classic ketogenic diet in the hospital
  • We recommend at least 3-6 months trial to determine an assessment of efficacy
  • In children with a >50% seizure reduction, KDs are often discontinued after 2 years; however, in children where seizure control is greater and side effects are low, these diets can be used for several years.
Vagal Nerve Stimulator

• VNS therapy is approved for the treatment of epilepsy without age or seizure type restrictions (in most countries)
  • Also approved for treatment-resistant depression

• Works much like a pacemaker for the brain
  • Prevents seizures by sending regular, mild pulses of electrical energy to the brain via the vagus nerve
  • Extra stimulation can be provided by parents, with use of a magnet, to abort a seizure once it starts

• Response to VNS is independent of age, seizure type, or epilepsy syndrome.
  • Studies show that when used in children with treatment-resistant epilepsy, seizure frequency can be significantly reduced by 50-60% over 1-3 years

• Side effects
  • Surgical-related are the most common (incisional infections, vocal cord paralysis)
  • Voice alteration when firing, cough, headache

Poll Question

You have a 6 year old boy with a history of febrile status epilepticus at the age of 8 months and subsequent epilepsy. His seizures are stereotyped and MRI shows evidence of left-sided hippocampal sclerosis within the temporal lobe. He has failed 2 anti-seizure medications at maximal doses. What is the next best step for his epilepsy care?

A. Epidiolex
B. Dietary therapy
C. Vagal nerve stimulator
D. Evaluation for left anterior temporal lobectomy
Pediatric Epilepsy Surgery

- Children with pharmacologically-resistant epilepsy are potential candidates for epilepsy surgery.
- In children, earlier surgery may provide a prolonged window of developmental plasticity after epilepsy resolution.
- Seizure freedom after resection ranges from 60-70%:
  - Mesial temporal resections with better outcomes (58-78%) than those with lateral temporal (59-70%) or extratemporal resections (54-66%).
- Evaluation for surgical candidacy begins with a Phase I evaluation:
  - Continuous EEG monitoring
  - Imaging studies to help localize ictal zone (SPECT, PET)
  - Detailed neuropsychologic testing
- Surgical conference
- +/- Phase II evaluation
- Surgery
• Young boy with febrile status epilepticus at the age of 8 months
  • Found in his crib seizing - >
  • EMS was called and gave him 2 doses of IV Versed en route to the ER.
  • Once reaching the ER, he was still seizing and was given a 3rd dose of Versed.
  • Duration of the seizure from start to finish was reported as 30-40 minutes.
  • He admitted where an infectious work-up and an MRI, EEG were completed. EEG was “normal” however, MRI showed small signal abnormality within the left hippocampus.
  • At the age of 4, he began having seizures with head/eye deviation to the left with clonic movements of that side and postictal aphasia
  • Began Trileptal. Eventually this was maximized without full seizure control, so Zonisamide was started.
  • Repeat MRI
Case

- He was admitted for Phase 1 monitoring and medications were weaned. During this admission, several focal seizures were captured arising from the left temporal lobe.
- He had a left anterior temporal lobectomy with amygdalohippocampetcomy without complications.
- Mom did not note any deficits after the surgery.
- Pathology report from his surgery came back revealing hippocampal sclerosis associated with focal cortical dysplasia.
A 10 year old girl (previously-healthy) presents with new-onset intermittent expressive aphasia, psychosis, and focal seizures. She has been given Ativan x 1 and Fosphenytoin in the ER to abort her seizure clusters. She is admitted to the general pediatrics team. She continues to have further seizures on the floor, despite repeat Ativan dosing and valproic acid load. You suspect an autoimmune encephalitis based on her clinical presentation, CSF studies, and imaging studies. What is the next appropriate step in the treatment of her seizures?

A. High dose intravenous solumedrol  
B. Plasma exchange  
C. Intravenous load of Keppra  
D. Emergent ketogenic diet start
The Immune System in Pediatric Epilepsy

- The risk of new-onset seizures is particularly high in childhood
- More than 60% of seizure disorders remain without an identifiable cause
- The hypothesis that inflammation plays a role in epileptogenesis has long been suggested
  - Role of fever in triggering febrile-related epilepsies
  - Anticonvulsant effect of steroids in some forms of pediatric epilepsy
  - Higher frequency of epilepsy in systemic autoimmune disease
- Children with autoimmune disease are 5x more at risk for epilepsy compared to age-matched controls
- Maternal history of autoimmunity increases the risk of childhood epilepsy
  - Having clinical RA at the time of pregnancy generated a higher risk of childhood epilepsy compared to controls
  - Consider the influence of fetal environmental factors on risk of future epilepsy in childhood

Ong MS et al. JAMA Neurol 2014; Rom AL et al. Neurology 2016
The Immune System & Seizures

• Identifying Seizures with an Autoimmune Basis
  • Unusually high seizure frequency at onset
  • Early refractoriness to classic anti-seizure medications
  • Acute/subacute signs/symptoms of CNS involvement
  • Personal or family history of autoimmune disease
  • Exclusion of other causes (e.g. identifiable epilepsy syndromes, structural, or toxic/metabolic)
  • Signs and/or symptoms consistent with a well-defined auto-antibody-mediated disease

### The Immune System & Seizures

**Clinical Characteristics of Individual Antibody-Associated Encephalitides in Childhood**

<table>
<thead>
<tr>
<th>Autoimmune Encephalitis</th>
<th>Ages Described</th>
<th>Clinical Manifestations</th>
<th>Associated Tumor</th>
<th>Risk of Relapse</th>
<th>Long-Term Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDAR</td>
<td>20 mo-17 yr</td>
<td>Seizures, behavioral disturbance, aphasia, psychosis, orofacial dyskinesias, catatonia</td>
<td>30% of females with ovarian teratoma</td>
<td>Up to 25% when causative tumor is not identified and removed</td>
<td>80% or greater have full recovery</td>
</tr>
<tr>
<td>VGKC</td>
<td>10 mo-17 yr</td>
<td>Seizures, behavioral disturbance, movement disorders, dysarthria, developmental regression</td>
<td>Neuroblastoma in one case (patient with multiple autoantibodies)</td>
<td>Unknown: reported in single case series as 25% relapse rate in childhood</td>
<td>Unknown, but most reported patients show marked to full recovery</td>
</tr>
<tr>
<td>GlyR</td>
<td>1-14 yr</td>
<td>PERM, seizures, ADEM with ON</td>
<td>None currently reported in childhood</td>
<td>Unknown: reported in single case series as 25% relapse rate in childhood</td>
<td>Unknown; generally considered to have good outcomes</td>
</tr>
<tr>
<td>GABA_A</td>
<td>2-17 yr</td>
<td>Seizures, cognitive and memory alterations, movement abnormalities</td>
<td>Hodgkin’s lymphoma</td>
<td>Unknown, but reported in a single pediatric case</td>
<td>Unknown: most have good recovery but residual seizures</td>
</tr>
<tr>
<td>GABA_B</td>
<td>3-18 yr</td>
<td>Seizures, movement disorders, memory loss, delirium, psychosis</td>
<td>None currently reported in childhood</td>
<td>Unknown in childhood</td>
<td>Unknown: majority reported show full recovery</td>
</tr>
<tr>
<td>AMPA</td>
<td>7-8 yr</td>
<td>Seizures, memory loss, behavioral changes</td>
<td>None currently reported in childhood</td>
<td>Unknown in childhood</td>
<td>Unknown</td>
</tr>
<tr>
<td>D2R</td>
<td>4 mo-15 yr</td>
<td>Seizures, lethargy, psychiatric symptoms, dystonia, parkinsonism, chorea, ataxia</td>
<td>None currently reported in childhood</td>
<td>Unknown: reported in case series as 25% relapse rate in childhood</td>
<td>Unknown: a single case series reports full recovery in 40%</td>
</tr>
<tr>
<td>mGluR5 (Ophelia syndrome)</td>
<td>Adolescence</td>
<td>Memory loss, depression, hallucinations, behavior abnormalities</td>
<td>Hodgkin’s lymphoma</td>
<td>Uncommon if treated appropriately</td>
<td>Full recovery with appropriate treatment</td>
</tr>
<tr>
<td>Hu</td>
<td>1-15 yr</td>
<td>Behavioral changes, seizures, posterior cord syndrome, ataxia</td>
<td>Estimated 25% associated with neuroblastoma</td>
<td>Unknown in childhood</td>
<td>Reported patients with continued seizures despite treatment</td>
</tr>
<tr>
<td>Mo1 and Mo2</td>
<td>2-14 yr</td>
<td>Seizures, behavioral changes, memory loss, speech changes</td>
<td>None currently reported in childhood</td>
<td>Unknown in childhood</td>
<td>Reported patients with poor outcomes</td>
</tr>
<tr>
<td>GAD</td>
<td>2-17 yr</td>
<td>Seizures, cognitive decline, psychosis, memory loss, stiff-person syndrome, progressive developmental delay</td>
<td>None currently reported in childhood</td>
<td>Unknown in childhood</td>
<td>Variable outcome potentially related to rapidity of treatment</td>
</tr>
</tbody>
</table>

Brenton JN et al. Pediatric Neurology 2016;
Conclusions

• The definitions of “epilepsy” are changing in attempts to keep up with the practical applications in the clinic.
  • A single seizure with a greater than 60% risk of future seizures is now a basis for diagnosis.

• Anti-seizure medications remain first-line for majority of epilepsy diagnoses and the majority of the population will be controlled on a single medication.

• When 2 anti-seizure medications fail, consideration should be given towards non-pharmacologic treatments.
  • Dietary Therapy
  • Surgical devices (VNS)
  • Epilepsy surgery

• Autoimmunity has been strongly linked with some presentations of epilepsy and needs to be considered in the context of a child who demonstrates a lack of response to early anti-seizure medications with high seizure frequency at onset.
Questions?
References