Pediatric Epilepsy Syndromes:

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Project ECHO Epilepsy Education Day
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Faculty/Presenter Disclosure

• Faculty/Speaker: Dr. Robyn Whitney
• March 26, 2019
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  – Consulting Fee: None
  – Other: None
Disclosure of Commercial Support

• Potential for conflict(s) of interest:
  – Dr. Whitney has no conflict(s) of interest
Objectives:

• Review the concept of an epilepsy syndrome
• Review the ILAE classification of pediatric epilepsy syndromes
• To review some pediatric epilepsy syndromes throughout the lifespan
• To review the concept of epileptic encephalopathies
Pediatric Epilepsy:

• Most common neurologic disorder of childhood
• Incidence of 60 per 100,000 persons per year in childhood, 100-233 per 100,000 in infancy
• Highest in first year of life becoming lower in later childhood and adolescence
• Approximately 25-30% of cases are pharmaco-resistant
• The impact of intractable seizures on development is most profound early in life
Definition of Epilepsy:

- *Epilepsy* is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the cognitive, psychological and social consequences of this condition.
Definition of Epilepsy:

Table 2. Operational (practical) clinical definition of epilepsy

Epilepsy is a disease of the brain defined by any of the following conditions:

1. At least two unprovoked (or reflex) seizures occurring >24 h apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
3. Diagnosis of an epilepsy syndrome

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.
ILAE Classification:

• Epilepsy classification system needs to be relevant and reflect changes in our thinking over time
• The classification system needs be robust and universal
• The primary purpose of the classification system is for diagnosis
• However, the classification system also aids in epilepsy research and in the development of new therapies

Three levels/stages of classification:

– 1) Seizure type
– 2) Epilepsy type
– 3) Epilepsy syndrome

*Etiology is incorporated at each of the 3 stages
ILAE Classification:

• Seizures types are classified into
  – Generalized onset
  – Focal onset
  – Unknown onset

• Epilepsy Type is classified as:
  – Generalized Epilepsy
  – Focal Epilepsy
  – Combined Generalized and Focal Epilepsy
  – Unknown
ILAE 2017 Classification of Seizure Types Expanded Version

**Focal Onset**
- **Aware**
- **Impaired Awareness**
  - Motor Onset
    - automatisms
    - atonic
    - clonic
    - epileptic spasms
    - hyperkinetic
    - myoclonic
    - tonic
  - Non-Motor 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
- **Non-Motor (absence)**
  - typical
  - atypical
  - myoclonic
  - eyelid myclonnia

**Unknown Onset**
- **Motor**
  - tonic-clonic
  - epileptic spasms
- **Non-Motor**
  - behavior arrest

**Unclassified**

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1 Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms

2 Degree of awareness usually is not specified

3 Due to inadequate information or inability to place in other categories
Seizure Mimics:

- Breath-holding spells: precipitated by trauma, anger, frustration, emotional stress
- Nightmares/night terrors
- Benign myoclonus of infancy
- Migraine
- Syncope
- Shuddering attacks
- Spasmus nutans
- Gastroesophageal reflux/Sandifer’s syndrome
- Paroxysmal tonic upgaze of childhood
- Non-epileptic events
- Reflex anoxic seizures
- Hereditary hyperekplexia
- Self-stimulation/stereotypies
Pediatric Epilepsy Syndromes:

• The term epilepsy syndrome refers to:
  – “A complex of signs and symptoms that define a unique epileptic condition”
  – “Epilepsy syndromes denote specific constellations of clinical seizure types, EEG findings & other characteristic clinical features”
ILAE Proposal for Revised Terminology for Organization of Seizures and Epilepsies 2010

Electroclinical Syndromes and Other Epilepsies Grouped by Specificity of Diagnosis

Electroclinical syndromes

One example of how syndromes can be organized: Arranged by typical age at onset

Neonatal period
- Benign neonatal seizures
- Benign familial neonatal epilepsy (BFNE)
- Ohtahara syndrome
- Early Myoclonic encephalopathy (EME)

Infancy
- Febrile seizures, Febrile seizures plus (FS+)
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- West syndrome
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- Epilepsy of infancy with migrating focal seizures

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Adolescence – Adult
- Juvenile absence epilepsy (JAE)
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Variable age at onset
- Familial focal epilepsy with variable foci (childhood to adult)
- Progressive myoclonus epilepsies (PME)
- Reflex epilepsies

Distinctive constellations/surgical syndromes

Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
Rasmussen syndrome
Gelastic seizures with hypothalamic hamartoma
Hemiconvulsion-hemiplegia-epilepsy

Epilepsies attributed to and organized by structural-metabolic causes
- Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
- Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)
- Tumor, infection, trauma, angioma, antenatal and perinatal insults, stroke, etc.

Epilepsies of unknown cause

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Epileptic Encephalopathy:

• Epileptic activity including seizures & EEG spike discharges contributes to:
  – Cognitive deterioration/stagnation
  – Behavioral disorders

• Beyond that expected from the underlying pathology and can worsen over time

• Proposed that epileptic activity occurring at a critical time contributes to progressive disturbance in cerebral function

Developmental Encephalopathy:

• Developmental component independent of the epileptic encephalopathy
• The developmental delay may precede seizure onset
• Outcome is poor even though seizures stop
• Developmental encephalopathy may begin in utero or occur after birth
• Epileptic encephalopathy may occur at any age
Drug Resistant Epilepsy:

- Drug resistant epilepsy is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.
Drug Resistant Epilepsy:

• What percent of patients respond to the first AED, second AED and third AED?
Drug Resistant Epilepsy:

- What percent of patients respond to the first AED, second AED and third AED?
  - 47%, 13%, <5%
Pediatric Epilepsy Syndromes: Across the Lifespan
ILAE Proposal for Revised Terminology for Organization of Seizures and Epilepsies 2010

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Case Presentation:

• A 1 month old infant presents with a history of repetitive tonic spasms, as well as focal seizures
• The seizures are medically refractory
• EEG shows the following in wake and sleep
Case Presentation:

• Burst suppression pattern
  – EME
  – Ohtahara Syndrome
  – Propofol
  – Anoxic brain injury
  – Hypothermia
  – Anesthesia

• Diagnosis: Ohtahara Syndrome
Ohtahara Syndrome:

- Begins in the first months (before 3 months) of life
- Seizure type(s):
  - Frequent brief tonic seizures
  - Tonic spasms occur in clusters, both in awake and sleep states
- EEG:
  - Suppression-burst (waking and sleeping states), but with longer bursts than in EME
  - EEG transition from SB to hypsarrhythmia
  - SB disappears at around age 6 months
Ohtahara Syndrome:

• Etiology:
  – Brain malformations
  – Genetic epileptic encephalopathy
  – Inborn errors of metabolism

• Severe psychomotor retardation

• Often evolution to West syndrome at age 4-6 months
Early Myoclonic Encephalopathy:

- **Prevalence:** Rare (<1% of all childhood epilepsy)
- **Age of onset:** Neonatal period, before 3 months of age
- **Seizure type(s):**
  - Myoclonus is the essential feature
  - Fragmentary (segmental, erratic: isolated twitching of distal extremities, eyelids, corners of mouth) myoclonic, generalized myoclonic and partial motor, evolving after several months into infantile spasms
  - Tonic spasms typically occur later
Early Myoclonic Encephalopathy:

• EEG-interictal and ictal:
  – Suppression-burst enhanced by or seen exclusively during sleep
  – Suppression-burst pattern can persist up to 4 year
  – No specific EEG evolution
Early Myoclonic Encephalopathy:

- **Etiology:**
  - Metabolic disorders, including non-ketotic hyperglycinemia, propionic aciduria, methylmalonic acidemia, sulfatide and xanthine oxidase deficiency, Menkes disease, Zellweger syndrome

- **Treatment:**
  - AEDS, corticosteroids, but usually no effective therapy

- **Prognosis:**
  - Poor
Ohtahara syndrome versus early myoclonic encephalopathy

<table>
<thead>
<tr>
<th></th>
<th>Ohtahara syndrome</th>
<th>Early myoclonic encephalopathy</th>
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</thead>
<tbody>
<tr>
<td><strong>Main seizures</strong></td>
<td>Tonic spasms</td>
<td>Erratic myoclonias, focal seizures, clusters of spasms</td>
</tr>
<tr>
<td><strong>Main aetiology</strong></td>
<td>Malformations of cerebral development</td>
<td>Genetic and metabolic</td>
</tr>
<tr>
<td><strong>Burst-suppression</strong></td>
<td>Pseudo-rhythmic and continuous in sleep and awake – starts earlier and is of shorter duration</td>
<td>Probably accentuated by sleep and may not occur in wakefulness – starts later and lasts longer</td>
</tr>
<tr>
<td><strong>Paroxysmal bursts</strong></td>
<td>Longer</td>
<td>Shorter</td>
</tr>
<tr>
<td><strong>Suppression</strong></td>
<td>Shorter</td>
<td>Longer</td>
</tr>
<tr>
<td><strong>Transformation to West syndrome</strong></td>
<td>As a rule</td>
<td>Common but transient</td>
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* The arrangement of electroclinical syndromes does not reflect etiology.
* Not traditionally diagnosed as epilepsy
* Sometimes referred to as Electrical Status Epilepticus during Slow Sleep (ESSE)
** Forms of epilepsies not meeting criteria for specific syndromes or constellations
Case Presentation:

• A developmentally delayed 6 month old female presents with a 2 week history of sudden jerky body movements

• Mostly head and neck with arms tensing

• The events are worse upon wakening and often occur in clusters, each lasting about 1 minute

• Her birth/pregnancy history is unremarkable

• The family history is non-contributory

• EEG shows the following
Infantile Spasms:

• 2% of childhood epilepsies; 25% of epilepsy with onset <1yr
• M:F = 1.5:1, all ethnic groups
• Initial onset between 3 to 7 months of life (50%) 
• >90% begin before 12 months of life
• West syndrome
  – Infantile Spasms
  – Hypsarrythmia
  – Developmental delay/MR/psychomotor arrest or regression
Infantile Spasms:

- Different types:
  - Flexor (most characteristic)
  - Extensor (least common)
  - Mixed (most common)
- Symmetric or asymmetric
- Appear temporally related to sleep
- Type of spasms does not seem to be affected by etiology nor the prognosis
- Presence of asymmetry - may indicate cortical brain pathology
Infantile Spasms:

• 1/3 of cases, development is normal prior to onset of spasms

• Development regression
  – Axial hypotonia
  – Loss of hand grasp
  – Visual inattention - has negative prognostic significance
Infantile Spasms:

• Name 3 mimics of Infantile Spasms?
Infantile Spasms Mimics:

• Benign myoclonus of infancy
• Benign myoclonic epilepsy of infancy
• Sandifers/GERD
• Shuttering
• Self-stimulatory behavior
• Stereotypies
Etiology:

- **Symptomatic**
  - Structural brain abnormality or metabolic cause present in a child with preexisting neurologic abnormality

- **Cryptogenic**
  - No apparent cause identified but is suspected because child is delayed or has neurological impairment prior to onset of spasms

- **Idiopathic**
  - No identifiable cause
  - Normal neurological exam and normal development prior to onset of spasms
## Etiology:

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical dysgenesis</td>
<td>Cortical dysplasia, Laminar heterotropia, Lissencephaly, Hemimegalencephaly, Septal dysplasia, Schizencephaly, Pachygyria, Porencephaly, Microgyria, Agenesis of corpus callosum</td>
</tr>
<tr>
<td>Chromosomal aberrations and genetic syndromes</td>
<td>Tuberous sclerosis, Incontinentia pigmenti, Neurofibromatosis, Sturge Weber syndrome, Aicardi’s syndrome, Down’s syndrome</td>
</tr>
<tr>
<td>Infections</td>
<td>CMV, Toxoplasma, Herpes encephalitis, Bacterial meningitis, Brain abscess</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Inborn errors of metabolism: phenylketonuria, amino acid and organic acidopathies, nonketotic hyperglycinemia, Pyridoxine deficiency/dependency, Mitochondrial disorders, Neonatal hypoglycemia</td>
</tr>
<tr>
<td>Vascular</td>
<td>Hypoxic-ischemic insult, Hemorrhagic insult</td>
</tr>
<tr>
<td>Tumors</td>
<td>Ependymomas, Gliomas, Gangliogliomas, Choroids plexus papillomas</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
</tr>
</tbody>
</table>
Inter-ictal EEG:

• Hypsarrythmia
  – Continuous, chaotic, non-rhythmic, asynchronous, disorganized, high voltage spike and slow wave activity
  – Most common in non-REM sleep, followed by awake state
  – Does not occur or is greatly reduced during REM
  – Classic pattern usually seen in early stages, pt <1yr
  – *EEG must capture non-REM sleep
Imaging:

- **MRI**
  - 40-50% show clear migrational abnormalities
  - 20% show nonspecific abnormalities (i.e. atrophy)
  - MRS may identify inborn errors of metabolism
  - Repeat may be necessary after myelination complete (~24-30mo) to see full changes

- **PET**
  - May be warranted when focality is suggested, but MRI is normal (surgical candidate)
Labs:

• Blood tests
  – CBC, electrolytes, pH, lactate, BUN, creatinine, glucose, CPK, AST, ALT, total bilirubin, alkaline phosphatase, thyroid function, serum amino acid,
  – CMV IgG & IgM, Toxoplasma IgG & IgM, and/or PCR studies
  – Chromosomal/genetic testing

• Urine
  – Urinalysis, amino acid screen, organic acid screen, CMV culture or PCR

• Ophthalmology, cardiology, genetics consultation as needed
Treatment:

IS

Vigabatrin

2 weeks

Response by cessation of spasms and disappearance of hypsarhythmia

YES

Continue for total of 6 months

NO

Consider ACTH or prednisolone

Response by cessation of spasms and disappearance of hypsarhythmia

YES

Finish course of ACTH or prednisolone

NO

Consider other AEDs or the ketogenic diet
Infantile Spasms:

- What are the side effects of vigabatrin?
Vigabatrin: Side effects

• Retinal Toxicity
  – Electroretinogram
    • Most sensitive measure of VGB toxicity
    • Reduction of 30 Hz flicker-cone b-wave amplitude in full-field ERG
  – Kinetic perimetry
    • Concentric visual-field defects
  – Electro-oculogram studies also suggest effect on outer retinal function

• Sedation, hypotonia, movement disorder
Images courtesy of Dr. E. Widjaja
Vigabatrin: Side effects

- Pearl, 2009
  - Identified 32% of infants treated with VGB for IS
  - T2 weighted hyperintense and restricted diffusion thalami, GP, dentate, brainstem or corpus callosum

- VGB and MRI
  - Appears dose dependent
  - Reversible most following VGB discontinuation
  - Peak incidence 3-6 months of VGB
  - Not related to movement disorder
Hormonal Therapy – Side effects

• Occurs in about 37% of cases
• Hypertension, irritability, susceptibility to infections, increased body weight, hypotonia, drowsiness, electrolyte imbalance, reversible cerebral atrophy
AAN 2012 IS Practice Parameter Update

• Short-term
  – ACTH & VGB useful
    • ACTH preferred
  – Consider low-dose ACTH
  – Other agents, including other forms of corticosteroids: insufficient evidence

• Long-term
  – Shorter lag time to treatment (hormonal therapy or VGB) improves developmental outcomes
  – ACTH better than VGB in CIS for long-term developmental outcomes
Consensus

• Most studies reported that neurodevelopment prognosis is better in CIS

• Shorter time treatment lag possibly improves the intermediate to long-term prognosis for cognitive and seizure-free outcomes especially in CIS
Outcomes

- Spasms often resolve by 3-5y, replaced by other seizures
- 95% have epilepsy at 10y, 40% evolve to LGS by 11y
- Cognitive impairment 80%
- Regardless of treatment, spasms & EEG pattern resolve in 50% by 2y, 100% by 5y
- Spontaneous remission in untreated patients reported in 25% by 1y
Case Presentation:

• 12 month old female presents with a history recurrent prolonged (>40 minutes) episodes of seizure (GTCs) with fever

• The first episode occurred after her immunizations at 4 months and she has had 7 admissions to hospital since for prolonged febrile seizures

• Her development is slightly delayed (at a 10 month old) and past medical history is unremarkable.

• There is a family history of febrile seizures. Her examination is normal.
Red Flags: Febrile Seizures

• Hemiclonic seizures
• Prolonged seizures
• Family history of seizures
• Afebrile seizures
SCN1A Mutations

Febrile seizures persist for longer
Seizures are pharmacoresistant
Multiple prolonged seizures are frequent
Hemiclonic seizures are characteristic
Significant developmental impairment is seen
Dravet Syndrome:

- Dravet Syndrome now preferred terminology rather than “severe myoclonic epilepsy of infancy”
- Characterized by early unilateral clonic seizures precipitated by fever
- Subsequent appearance of myoclonic seizures, atypical absence & focal seizures
- Presents between 2-12 months of age with peak onset at age 5 months
Clinical Presentation:

- Starts with prolonged (10-90 minute) unilateral clonic febrile seizures or febrile GTCs
- Subsequent development of seizures in a febrile context occur in the next few months
- Hemiclonic seizures on alternate side of body or GTCs with frequent episodes of febrile SE
- Lateralization often changes during the same attack
- Afebrile seizures may be triggered by vaccination, mild infection or hot baths
Clinical Presentation:

- Seizure sensitivity to photic stimulation in 40%
- Development remains normal in first year of life with psychomotor slowing noted thereafter
- Second & third year of life are marked by emergence of other seizure types:
  - Myoclonic seizures (massive or erratic)
  - GTCS or clonic seizures
  - Atypical absence
  - Focal seizures
  - Tonic seizures are exceedingly rare
Clinical Presentation:

- Development is normal in the first year of life.
- During the second or third year of life, developmental progression deteriorates.
- Gait becomes unsteady, ataxia and pyramidal signs are common.
- Language progresses slowly.
- Behavior deteriorates; ADHD is common.
- Almost all continue to present with seizures, period of active epilepsy up to age 12-13 years.
Genetics:

• Dravet syndrome is associated with a family history of seizures in at least 50%

• Associated with mutations in the SCN1A gene encoding the alpha-1 subunit of the sodium channel

• Familial SCN1A mutations have been reported to be inherited from mildly affected parents

• Most SCN1A mutations are de novo (95%) & give rise to truncations

• Approximately 80% of classic Dravet cases have mutations in SCN1A
Genetics:

• Familial mutations involving the GABRG2 have been reported rarely in individuals
• Rare mutations in SCN1B have been reported
• Other genes:
  – STXBP1, GABRA1, SCN9A, PCDH19
• Etiology remains unknown in 20% of cases of Dravet
EEG:

- Normal during first months
- Background varies from normal to slow; slows over time theta/delta
- Theta rhythm of 5-6 Hz is present over central & vertex regions
- Appearance of generalized, focal & multifocal abnormalities
- In approximately 25% diffuse spike-waves elicited by intermittent photic stimulation
Interictal EEG:

Figure 1.
B.C. is a 17-month-old patient. At awakening, there are brief bursts of SWs induced by opening and closing of the eyes while crying. During sleep, there is a recurrence of brief discharges of diffuse SWs. Note the predominance of the fast polyspike component on the frontocentral regions and vertex.

Epilepsia © ILAE
Ictal EEG:

Figure 6.
Two bursts of generalized SWs accompanied by myoclonic jerks, followed by a discharge of slow waves. On the left a 14-month-old boy with benign myoclonic epilepsy of infancy and on the right a 5-year-old girl with a DS. Recording: 15 μV/mm, 15 mm/s.

Epilepsia © ILAE
Treatment & Prognosis:

• Classically seizures are very difficult to treat

• Preventative measures include
  – Avoiding hot bats in young children
  – Sunglasses to reduce photo/pattern sensitivity
  – Treatment of febrile disease is recommended

• AEDS that have shown to have therapeutic value:
  – Valproate
  – Levetiracetam
  – Topiramate
  – Zonisamide
Treatment & Prognosis:

• AEDS that have shown to have therapeutic value:
  – Stiripentol in conjunction with clobazam & valproate for refractory GTCs
  – When administered as an “add-on” demonstrates positive effect on reducing frequency of seizures

• AEDS that can worsen seizures:
  – Vigabatrin
  – Lamotrigine
  – Carbamazepine/Oxcarbazepine
  – Phenytoin
Treatment & Prognosis:

• Alternative therapies:
  – Ketogenic diet
  – Vagal nerve stimulator
  – Anecdotal cases of steroid use

• Outcome is generally poor

• Seizures are extremely difficult to control, developmental delay present in all

• Ataxia & pyramidal signs are frequent, motor symptoms persist

• High mortality (i.e. SUDEP)
SUDEP:

- Defined as a sudden, unexpected death in a person with epilepsy
- Death may be witnessed or unwitnessed
- With or without evidence of a preceding seizure.
- SUDEP excludes deaths due to trauma, drowning and documented status epilepticus, in which post-mortem examination does not reveal a toxicologic or anatomic cause of death
SUDEP:

• What is the single most important risk factor for SUDEP?
SUDEP:

• What is the single most important risk factor for SUDEP?

Established Risk Factors for SUDEP:

- The presence of generalized tonic-clonic seizures (OR: 10)
- The frequency of generalized tonic-clonic seizures; 3 or more generalized tonic-clonic seizures per year (OR: 15.46)
- Failure to add an additional anti-epileptic medication when patients are refractory (OR: 6)
- Not being seizure free for 1-5 years (OR: 4.7)

SUDEP Risk Reduction:

- The use of nocturnal listening devices (OR 0.1)
- The presence of nocturnal supervision (OR 0.4)
ILAE Proposal for Revised Terminology for Organization of Seizures and Epilepsies 2010

Electroclinical Syndromes and Other Epilepsies Grouped by Specificity of Diagnosis

- Neonatal period
  - Benign neonatal seizures
  - Benign familial neonatal epilepsy (BFNE)
  - Ohtahara syndrome
  - Early Myoclonic encephalopathy (EME)

- Infancy
  - Febrile seizures
  - Febrile seizures plus (FS+)
  - Benign infantile epilepsy
  - Benign familial infantile epilepsy (BFIE)
  - West syndrome
  - Dravet syndrome
  - Myoclonic epilepsy in infancy (MEI)
  - Myoclonic encephalopathy in nonprogressive disorders
  - Epilepsy of infancy with migrating focal seizures

- Childhood
  - Febrile seizures
  - Febrile seizures plus (FS+)
  - Early onset childhood occipital epilepsy (Panayiotopoulos syndrome)
  - Epilepsy with myoclonic atonic (previously astatic) seizures
  - Childhood absence epilepsy (CAE)
  - Benign epilepsy with centrotemporal spikes (BECTS)
  - Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)
  - Late onset childhood occipital epilepsy (Gastaut type)
  - Epilepsy with myoclonic absences
  - Lennox-Gastaut syndrome (LGS)
  - Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)
  - Landau-Kleffner syndrome (LKS)

- Adolescence – Adult
  - Juvenile absence epilepsy (JAE)
  - Juvenile myoclonic epilepsy (JME)
  - Epilepsy with generalized tonic-clonic seizures alone
  - Autosomal dominant epilepsy with auditory features (ADEF)
  - Other familial temporal lobe epilepsies

- Variable age at onset
  - Familial focal epilepsy with variable foci (childhood to adult)
  - Progressive myoclonus epilepsies (PME)
  - Reflex epilepsies

Distinctive constellations/surgical syndromes

- Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
- Rasmussen syndrome
- Gelastic seizures with hypothalamic hamartoma
- Hemiconvulsion-hemiplegia-epilepsy

Nonsyndromic epilepsies**

- Epilepsies attributed to and organized by structural-metabolic causes
  - Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
  - Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)
  - Tumor, infection, trauma, angioma, antenatal and perinatal insults, stroke, etc.

Epilepsies of unknown cause

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We welcome your thoughts on this proposal. Please visit our Classification & Terminology Discussion Group at: http://community.ilae-epilepsy.org/home/ to login and register your comments.
Case Presentation:

• 2 year old presents with episodes of GTCs, myoclonics and episodes of dropping to the ground
• His development and examination is normal
• History is remarkable for febrile seizures
• Family history is negative
Epilepsy:

• Two possible epilepsy syndromes?
Doose Syndrome vs. LGS

**Myoclonic-Atonic/Astatic**
- +FHx epilepsy
- Normal development prior to onset
- Interictal EEG: 2-3 Hz generalized spike-wave with 4-7 Hz centropatietetal rhythms

**Lennox-Gastaut Syndrome**
- -FHx of epilepsy
- Past history of neurodevelopmental delay
- Tonic seizures
- Interictal EEG: <2.5 Hz generalized spike-wave and fast anterior rhythms (GPFA)
Doose Syndrome:

- Onset between 7 months-6 years, peaks at 3-4 years
- Previously developmentally normal children
- Constitutes 1-2% of childhood onset epilepsies
- Males more affected than females (2:1)
- Family history of epilepsy in 1/3
- Only few cases carry mutations in GEFS+ genes, including SCN1A, SCN1B, GABARG2
- Present with febrile GTCs in 1/3, afebrile GTCs in remainder
Clinical Presentation:

- Myoclonic-astatic, myoclonic, atonic, atypical absence & GTCs
- Myoclonic-astatic seizures are required for diagnosis
- Begin with sudden myoclonic extension of both arms with neck flexion, followed by axial tonic contraction
- Subtle myoclonic-atonic seizures may cause head nod with or without myoclonic jerk of extremities
- NCSE may occur in 1/3 of patients
- Focal seizures & tonic seizures are rarely seen
EEG:

- **Interictal EEG**
  - Background is generally normal & sleep
  - Paroxysmal rhythmic 4-7 Hz biparietal theta activity
  - Generalized 2-3 or 4-6 Hz spike-wave & polyspike wave
  - Photosensitivity with 4-7 Hz spike complexes

- **Ictal EEG:**
  - Myoclonic & atonic seizures correspond with generalized irregular spike-wave or polyspike wave at 2.5-3 Hz or more
  - Atonia corresponds with slow wave of a single or multiple spike-wave complex and EMG paucity
Treatment & Prognosis:

• 50% of patients manifest regression later in disease course
• Overall prognosis is variable with respect to cognitive outcome & often depends on seizure control
• Approximately 50% of patients have a good response to AEDs
• While the others continue to have seizures with cognitive impairment & behavioral abnormalities
Treatment & Prognosis:

• Treatment with valproate is advocated by many
• Other AEDs can be used in conjunction
• Ketogenic diet:
  – May be the most efficacious therapy
  – Some advocate the ketogenic diet as first line therapy; others after 1-2 AEDs have failed
• Some children have fairly frequent seizures of multiple seizure types and still have spontaneous remission usually after 3 years
• Up to 60% will experience a remission of seizures
Lennox Gastaut Syndrome:

- Rare 6-7% of children with intractable epilepsy
- M>F
- 1/3 West syndrome, 2/3 pre-existent brain abnormalities

Clinical Features:

- Triad of symptoms
  - Multiple generalized seizure types (tonic, atonic, atypical absence, GTC, focal)
  - Interictal EEG pattern of diffuse spike-wave complexes and
  - Cognitive dysfunction

- Nonconvulsice status epilepticus common
Epilepsy:

• Three EEG findings seen in LGS?
EEG:

- Interictal 1.5-2.5 Hz generalized slow spike and wave
- Multifocal polyspike and spike-wave discharges (MISF)
- Slow background
- Low-voltage frontally predominant > 10 Hz generalized paroxysmal fast activity
- Abnormalities increase in sleep
Treatment:

• Pharmacoresistant

• AED:
  – VPA, clobazam, lamotrigine, topiramate, rufinamide, felbamate

• Ketogenic diet early in the course

• Epilepsy surgery if lesional

• Corpus callosotomy is a possible treatment for intractable drop seizures

• VNS
Treatment & Prognosis:

- Significant morbidity/mortality associated with seizures (i.e. head injuries, accidents, SUDEP)
- Mortality rate 3-7%
- Seizures persist into adulthood
- Goal is to reduce severity of seizures and to improve quality of life
Case Presentation:

- 5 year old girl with unremarkable birth and pregnancy history and normal development

- Nocturnal events occurring in the last year
  - Paresthesia around the mouth and tongue, followed by right or left facial spasm/twitching, guttural noises/drooling and aphasia.
  - Total of 5 seizures
  - Each seizure lasts between 30 seconds to 2 minutes and afterwards the child goes back to sleep.
  - There are no post-ictal deficits

- There is no family history of epilepsy, delay or neurological disorder

- EEG shows the following:
Focal Epilepsy Syndromes:

- Benign childhood focal seizures and related epilepsy syndromes are very common
- They affect 25% of children with non-febrile seizures
- They are age limited epilepsy syndromes
- At least one-third have only a single seizure
- Overall prognosis is felt to be better
- Although not so benign as may have cognitive/behavioral comorbidities (i.e. BECTS)
Focal Epilepsy Syndromes:

• Two common idiopathic focal epilepsy syndromes:
  – Benign Childhood Epilepsy with Occipital Paroxysms (BECOP)
  – Benign Rolandic Epilepsy/Childhood Epilepsy with Centrotemporal Spikes (BECTS)
Benign Rolandic Epilepsy:

• Most frequent focal epilepsy syndrome in childhood
• 15% of children with epilepsy
• Incidence 10-20/100,000 children 0-15 years
• M:F = 3:2
• Atypical presentation is rare, 1 case per 130 cases of rolandic epilepsy
Benign Rolandic Epilepsy:

• Age of onset 3-14 years, peaks at 8-9 years
• Normal development and cognition prior to the onset
• 10-20% have a history of febrile seizures
• Present with infrequent focal seizures
• Seizures typically occur in NREM sleep in 75%
• 30% have seizures during wakefulness, 15% during wake and sleep
Benign Rolandic Epilepsy:

- Typically they have brief seizures < 2 minutes
- Awareness is generally preserved in up to 60%
- Focal seizures with unilateral facial sensorimotor symptoms, oro-pharyngeal-laryngeal manifestations, speech arrest and hyper salivation/drooling
- 30% have hemi-motor seizures, frequently with unilateral clonic, but also tonic-clonic
- 50% can progress to GTCs
Benign Rolandic Epilepsy:

• Number of seizures is usually limited
  – 13% have single seizure
  – 66% infrequent seizures (2-10 total)
  – 21% will have frequent seizures
Benign Rolandic Epilepsy:

- 50% have neuro-psychiatric manifestations:
  - Behavioural
  - Language Delay
  - Memory problems
  - ADHD
  - Learning disability
  - *? More frequent/severe in pt with more frequent spikes and with bilateral discharges?*
Etiology:

• Polygenic & multifactorial causation is suspected
• Linkage to a locus on Ch 15q14 has been described
• Mode of inheritance is not fully known
• AD inheritance with age dependent penetrance refers to EEG central temporal spikes and not syndrome
• Recently GRIN2A gene (encoding N-methyl-D-aspartate (NMDA) glutamate receptor alpha 2 subunit GluNA) has been implicated
Differential Diagnosis:

• Focal epilepsy due to structural brain lesion
• CSWS/LKS may occur in 1-4% of BECTS
• Atypical benign partial epilepsy
  – BECTS with frequent refractory seizures
  – Status epilepticus
  – Transient oromotor dysfunction/acquired opercular syndrome
  – Atonic seizures, negative myoclonus
EEG:

- Background is normal
- Interictal high amplitude diphasic spikes with predominant after going slow wave
- Typically C3/C4, T3/T4
- Spikes are unilateral or bilateral (in 40%)
- When unilateral, are distributed equally in both hemispheres
- Bihemispheric spikes can vary in synchrony and symmetry
- Activated in NREM sleep
Awake
Asleep
Neuroimaging:

- Children with typical features do not require neuroimaging
- Suggest imaging if:
  - Atypical clinical presentation
  - Focal deficits on exam
  - EEG suggestive of focal pathology
Treatment:

• Indications for treatment:
  – Frequent daytime seizures
  – Frequent GTCs
  – Prolonged seizures
  – Status Epilepticus
  – Seizure onset <4y
  – Parental anxiety
Treatment:

Table 1  NICE recommendations for management of RE/PS (rolandic epilepsy/Panayiotopoulos Syndrome)

<table>
<thead>
<tr>
<th>First-line AEDs</th>
<th>Adjunctive AEDs</th>
<th>Other AEDs considered in tertiary care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Carbamazepine</td>
<td>Eslicarbazepine acetate</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Clobazam</td>
<td>Lacosamide</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Gabapentin</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Lamotrigine</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>Levetiracetam</td>
<td>Pregabalin</td>
</tr>
<tr>
<td></td>
<td>Oxcarbazepine</td>
<td>Tiagabine</td>
</tr>
<tr>
<td></td>
<td>Sodium valproate</td>
<td>Vigabatrin</td>
</tr>
<tr>
<td></td>
<td>Topiramate</td>
<td>Zonisamide</td>
</tr>
</tbody>
</table>

AEDs, antiepileptic drugs; BECTS, Benign Epilepsy with CentroTemporal Spikes; NICE, National Institute of Health and Care Excellence.
Prognosis:

• Characterized as a self-limited disorder by the ILAE
• Remission 2-4 years after onset, 100% remit by 16
• Majority of patients have less than 10 seizures
• 10-20% frequent seizures, 10-20% single seizure
• <2% have a risk of developing infrequent generalized seizures in adult life, absence more common than GTCs
• May have ongoing behavioral & learning difficulties
Case Presentation:

- 7 year old female referred for staring spells
- History of Presenting Illness:
  - Staring spells occurring multiple times per day
  - Lasting approximately 5-7 seconds
  - Associated with fumbling of the clothes
  - No postictal state & returns to baseline
- Developmental/past medical history is normal, no family history
- Neurological exam is normal
Case Presentation:

• What would you do next with regard to investigations?
Case Presentation:

• What is the most likely diagnosis?
Childhood Absence Epilepsy:

- Accounts for approximately 10% of childhood epilepsies between 2-10 years of age
- Occurs in developmentally normal children
- Females > males
- Onset is between age 4-10 years
- Peaks between age 5-7 years
Typical Absences:

• Frequent and most last between 4-20 seconds
• Many attacks per day, may be > 100
• Abrupt & severe impairment of consciousness with cessation of voluntary activity
• Eyes stare/move slowly, random eye blinking
• Automatisms are frequent, occur in 2/3 of patients
• Occasional autonomic phenomenon
Typical Absences:

• May have myoclonic or clonic components
• Mild myoclonic elements of the eyes, eyebrows/eyelids may occur
• Myoclonic elements more common at start of seizure (first 3 seconds)
• Attack ends abruptly with resumption of the pre-absence activity as if it had not been interrupted
• EEG > 2.5 Hz generalized spike and wave activity
Atypical Absences:

- Usually occur before the age of 4-5 years
- Associated with developmental difficulties
- Tend to be longer & may have a postictal state
- Brief loss or lapse of consciousness, but in some they may be partially responsive
- Changes in tone, drooling, myoclonic activity
- Onset/ end is more gradual
- EEG < 2.5 Hz irregular generalized spike wave
Differential Diagnosis:

<table>
<thead>
<tr>
<th>Generalized Absence</th>
<th>Focal Impaired Awareness Seizure</th>
<th>Behavioural Staring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple daily</td>
<td>Rarely &gt; 1-2 per day</td>
<td>Situational</td>
</tr>
<tr>
<td>4-20 seconds</td>
<td>Prolonged, &gt;1 minute</td>
<td>Seconds to minutes</td>
</tr>
<tr>
<td>No aura</td>
<td>Aura common</td>
<td>No aura</td>
</tr>
<tr>
<td>No post-ictal</td>
<td>Post-ictal state</td>
<td>No post-ictal</td>
</tr>
<tr>
<td>Hyperventilation provokes</td>
<td>Hyperventilation rarely activates</td>
<td>HV doesn’t activate</td>
</tr>
<tr>
<td>EEG: Gen 3 HZ SW</td>
<td>Focal epileptiform</td>
<td>Normal EEG</td>
</tr>
<tr>
<td>Simple Automatisms</td>
<td>Complex Automatisms</td>
<td>Stereotypies</td>
</tr>
<tr>
<td>Treatment: VPA/ETX/LMG</td>
<td>Treatment: CBZ, OXC</td>
<td>No AED</td>
</tr>
</tbody>
</table>

Childhood Absence Epilepsy

- What are the typical EEG findings?
EEG Findings:

- Normal background
- OIRDA which may be a good prognostic sign
- Generalized high amplitude regular & spike and wave complexes at 3-4 Hz
- Can have focal discharges (i.e. frontal, central temporal, multi-focal spikes), which are fragments of generalized discharges
- Hyperventilation nearly invariably provokes absences in 90%
Treatment:

• Usually seizures remit before the age of 12
• Infrequent GTCs can occur in 10% of patients in adolescence
• Later age of onset = higher risk for GTCs
• Worse prognosis:
  – GTCs
  – Multiple spike-wave complexes
  – Fragmented discharges
Treatment:

- Up to 15% of patients with CAE can evolve into JME
- May also evolve into JAE
- Children with CAE may have subtle cognitive deficits, linguistic difficulties & attentional difficulties
- Poor social adjustment has been reported
Treatment:

• Treatment with ethosuximide, valproic acid or lamotrigine has proven to be efficacious
• Monotherapy first, may require combination therapy
• First medication may be unsuccessful
• Approximately only 60% respond to first AED
• Medication wean generally considered at 2 years, if seizure free
• Predictive value of EEG is not absolute
Treatment:

• What medications are contraindicated with absence epilepsy?
Treatment:

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  - Carbamazepine
  - Oxcarbazepine
  - Gabapentin
  - Phenytoin
  - Vigabatrin
  - Phenobarbital
ILAE Proposal for Revised Terminology for Organization of Seizures and Epilepsies 2010

Electroclinical Syndromes and Other Epilepsies Grouped by Specificity of Diagnosis

**Electroclinical syndromes**

One example of how syndromes can be organized:
Arranged by typical age at onset

- **Neonatal period**
  - Benign neonatal seizures
  - Benign familial neonatal epilepsy (BFNE)
  - Ohtahara syndrome
  - Early Myoclonic encephalopathy (EME)

- **Infancy**
  - Febrile seizures*, Febrile seizures plus (FS+)
  - Benign infantile epilepsy
  - Benign familial infantile epilepsy (BFIE)
  - West syndrome
  - Dravet syndrome
  - Myoclonic epilepsy in infancy (MEI)
  - Myoclonic encephalopathy in nonprogressive disorders
  - Epilepsy of infancy with migrating focal seizures

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  - Febrile seizures*, Febrile seizures plus (FS+)
  - Early onset childhood occipital epilepsy
  - Panayiotopoulos syndrome
  - Epilepsy with myoclonic atonic (previously astatic) seizures
  - Childhood absence epilepsy (CAE)
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  - Epilepsy with myoclonic absences
  - Lennox-Gastaut syndrome (LGS)
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  - Landau-Kleffner syndrome (LKS)

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  - Juvenile absence epilepsy (JAE)
  - Juvenile myoclonic epilepsy (JME)
  - Epilepsy with generalized tonic-clonic seizures alone
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  - Other familial temporal lobe epilepsies

- **Variable age at onset**
  - Familial focal epilepsy with variable foci (childhood to adult)
  - Progressive myoclonus epilepsies (PME)
  - Reflex epilepsies

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- Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
- Rasmussen syndrome
- Gelastic seizures with hypothalamic hamartoma
- Hemiconvulsion-hemiplegia-epilepsy

**Nonsyndromic epilepsies****

- Epilepsies attributed to and organized by structural-metabolic causes
  - Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
  - Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)
  - Tumor, infection, trauma, angioma, antenatal and perinatal insults, stroke, etc.

**Epilepsies of unknown cause**

* The arrangement of electroclinical syndromes does not reflect etiology.
* Not traditionally diagnosed as epilepsy
* Sometimes referred to as Electrical Status Epilepticus during Slow Sleep (ESSE)
** Forms of epilepsies not meeting criteria for specific syndromes or constellations

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Case Presentation:

- 11 year old right handed female had a generalized seizure after staying up late at night & complains of dropping things easily
- Past medical history unremarkable, normal cognition
- Family history is non-contributory
- Neurological exam is normal
- What investigation would you order next?
Case Presentation:

• What epilepsy syndrome(s) would you consider based on the history and EEG?
Case Presentation:

- Juvenile myoclonic epilepsy
- Juvenile absence epilepsy
- Jeavon’s syndrome
- Epilepsy with GTCs upon awakening
- Progressive myoclonic epilepsies (if cognitive/behavioral regression)
Juvenile Myoclonic Epilepsy:

- Most common Idiopathic Generalized Epilepsy (IGE)
- Accounts for 5-10% of all epilepsies
- Onset is between 8-36 years
- Peaks at 12-18 years
- Males and females are equally affected
Juvenile Myoclonic Epilepsy:

- Seizures often triggered by sleep deprivation, alcohol use, fatigue or photosensitivity in 30%
- Characterized by isolated myoclonic seizures that generally occur upon wakening
- Bilateral, single or repetitive, arrhythmic irregular jerks that involve upper extremities
- GTCs in 80-90% often 1-2 times per year, often occur after a series of myoclonic jerks
JME- Seizure Types

• 1/3 of GTCs may have focal features
• Typical absences are seen in 1/5
• Absences are often mild, infrequent, inconspicuous
Etiology:

- 40-50% have positive family history
- Genetic heterogeneity is common
- Probably complex and polygenic inheritance
- Susceptibility loci on Chromosome 6p11-12 (EJM1) and Chromosome 15q14 (EJM2)
- Other implicated genes in rare cases: CACNB4, GABRA1, CLCN2
EEG Findings:

- Normal background
- Generalized discharges or irregular 3-6Hz generalized spike/polyspike-slow wave
- Intradischarge fragmentations
- 1/3 have focal abnormalities
- 1/3 have photoparoxysmal response
- 50% may have normalization of EEG with AED
Treatment:

- Valproic Acid is regarded as the first line AED
- In women of childbearing age due to risk of teratogenicity, alternatives are suggested:
  - Lamotrigine
  - Levetiracetam
  - Topiramate
  - Benzodiazepines (i.e. clonazepam)
Treatment:

• Which AEDs are contraindicated in JME?
Treatment:

• Which AEDs are contraindicated in JME?
  – Carbamazepine
  – Oxcarbazepine
  – Phenytoin
  – Gabapentin
  – Pregabalin
  – Tiagabine
  – Vigabatrin
Prognosis:

• Seizure severity varies from mild myoclonic jerks to frequent and severe falls and GTCs
• ~80% patients respond well to medication
• If all 3 seizure types present, more likely to be resistant to treatment
• Many patients require life long therapy
Prognosis:

• About 1/3 may be able to wean off medications
• More likely with fewer GTCs
• Long-term psychosocial difficulties not uncommon
• Impulsiveness, depression, social isolation, unemployment have been reported
Conclusion:

• Epilepsy is the most common neurologic disorder of childhood
• Pediatric epilepsy syndromes are heterogeneous
• They vary by their age of onset, seizure types, clinical features and EEG findings
• Recognition of epilepsy syndromes is essential for management as well as prognostication