Disclosures: EBK has received funding from Seaside Therapeutics, Novartis, Roche, Alcobra, Neuren, Neurotrope, Marinus, Cydan, BioMarin, Fulcrum and Ovid Pharmaceuticals to consult on trial design or development strategies and/or conduct clinical trials in FXS, Rett syndrome, Angelman syndrome or Down syndrome, from Vtesse to conduct clinical trials in NP-C, and from Asuragen Inc to develop testing standards for FMR1 testing.
What is a Seizure? Epilepsy?

SEIZURE: a single event characterized by an abrupt change in behavior and accompanied by paroxysmal neuronal discharges...... either as a primary abnormal electrical excitability in an otherwise normal brain or secondary to another primary disorder.

Paroxysmal- come and go in a burst, not always there

EPILEPSY:

• Recurrent seizures
• Paroxysmal discharges from neurons (brain cells) are the primary disorder.
Causes of Seizures

• Acute response to an new condition (trauma, infection, stroke, toxin/drug, tumor, metabolic)
• Delayed effect due to a recent disease (trauma, infection, surgery)
• Permanent brain “scar” from an old disease (stroke, prenatal/perinatal insult, tumor, infection)
• Most common: Genetic brain hyperexcitability
  • Only hyperexcitability (seizures in otherwise normal person) – “idiopathic”
  • Other manifestations of brain dysfunction – eg. cognitive disorder, genetic syndrome, neurodegenerative disease, metabolic disease, neurocutaneous disorder, CNS malformation
Classification of Seizures:
International Classification of Epileptic Seizures

Seizure Classification

Partial (seizure activity originates in one part of the brain)
- Simple
- Myoclonic
- Absence
- Tonic clonic

Generalised (seizure activity involved entire brain)
- Complex
- Tonic
- Atonic
Partial Seizures

• Seizures in one area of brain - PARTIAL
  • Simple partial (patient awake – one localized seizure manifestation – eg. arm twitching)
  • Complex partial (alteration of consciousness plus localized movements, may be repetitive or odd movements like lip smacking)
    • simple at beginning, then alteration of consciousness (confusion to loss of consciousness)
    • impaired consciousness from beginning
    • with secondary generalization – as seizure progresses goes into generalized tonic-clonic seizure
Complex Partial Seizures

• AKA temporal lobe or psychomotor
• Impaired consciousness with complex symptoms, often partial seizure onset
• 20% of childhood epilepsy, old > young
• Focal brain problem can be present (eg. tumor, abnormal blood vessel)
• Partial seizures often part of genetic syndrome without specific area of brain abnormal
• Surgery can be treatment in severe cases
Generalized Seizures

• Seizures involving the whole brain at once - GENERALIZED
  • Absence (staring, eye blinking, old “petit mal”)
  • Generalized myoclonic (single or clusters of jerks)
  • Clonic (jerking)
  • Tonic (stiffening)
  • Tonic-clonic (stiffening followed by jerking, old “grand mal”)
  • Atonic (sudden loss of tone – head drops, falls)
Generalized Tonic Clonic Seizure

- most common seizure type in urgent care
- primary or secondarily generalized
- cause is found in about 25%
- 5-15% genetic factors
- 30-50% recurrence after one
Generalized Tonic Clonic Seizure

• Loss of consciousness + stiffening or clonic jerking
• Loud cry at onset, eyes roll up, noisy breathing, jaw clenched, oral secretions pool in mouth, incontinence, drowsiness after seizures
• Unwitnessed focal onset common
Status Epilepticus

• Single or repetitive seizure > 30 minutes

• Body changes
  • Poor breathing effort (shallow breathing)
  • Increased BP, pulse, and temperature
  • Increased blood measures: lactate, prolactin, and white blood cells

• Brain injury usually does not occur unless seizure is provoked by a brain damaging problem (like encephalitis)
Generalized and Partial Seizures
Febrile Seizures

• 2-5% of children will have at least one event
• Generalized
• Etiology: usually viral but any febrile illness possible
  • Genetic predisposition: family hx prognostic
• Criteria for diagnosis
  • Age: 6 months to 5 years
  • Fever present
  • <15 min
  • No evidence of CNS infection/other disease
  • No focal signs
  • Normal interictal EEG
Febrile Seizures – Prognosis and Treatment

• Most are “benign” and resolve by age 6
• 2-4% recur as non-febrile seizures in later life
  • The more febrile seizures a child has, the more likely he will develop epilepsy
• 20-40% will have recurrent febrile seizures
• Complexity of seizure important predictor for recurrence
• Control fever – Acetaminophen, Ibuprofen
• Treat infection (if present)
• Anticonvulsant treatment usually not needed, may use Diastat for longer episodes
Evaluation of Seizures

- Detailed **moment by moment** history of event (activity, body position, progression, duration, loss of sphincter tone, tongue biting, look for visual/auditory/olfactory auras)
- Note setting, last meal, provocative factors
- Birth and developmental status
- Head trauma and past CNS illness
- Family history
- Physical exam: Growth, optic fundi, skin (Wood’s lamp), dysmorphisms, asymmetries, organomegaly
Differential Diagnosis of Seizures
Non-Epileptic Spells

- Shuddering
- Neonatal Apnea
- Benign Nocturnal Myoclonus – when falling asleep
- Night terrors
- Migraine
- Panic Attacks
- Syncope (Fainting) – may end with brief convulsion
  - Breath-holding spells (kids<6y, start with cry/injury)
  - Hyperventilation
  - Neurocardiogenic Syncope
  - Prolonged QT (serious cause of fainting, may also have epilepsy)
- Can occur even in patient with syndrome known to be associated with seizures – need to be sure it’s a seizure to treat right
Work-up of Initial Seizure

• Always: glucose, electrolytes, calcium
• If partial seizure: MRI > infused CT
• If acute fever or persistent mental status change: L/P
• EEG 2 wks later
• If slow development or <age 2 yrs: metabolic and genetic evaluation
• If already known to have syndrome associated with seizures, may just blood tests and EEG
Neurologic Referral for Seizures

- Diagnostic dilemmas
- Poor response to single drug treatment
- Doctor uncomfortable with seizure treatment
- High family anxiety
- Patient with complex mix of problems – eg. behavior, ID, seizures – that may involved a specialized approach
EEG in Seizure Disorders

- For diagnosis of epilepsy type
- To determine if episodes are actually seizures
- For specific epilepsy syndrome
- To help guide treatment decision
- After a major seizure:
  - slowing
  - suppression of seizure foci
Ambulatory EEG for Diagnosis (Neurotech, Digitrace)
Seizures in X Chromosome Disorders

- All cases 1992-2002 University of Siena, N=43
- 16 Turner, 17 Klinefelter, 7 XXX, 3 other
- Klinefelter
  - 2/17 partial complex seizures
  - EEG abnormal in 4/17 occipital or parietotemporal paroxysmal discharges
- Turner – no seizures
- XXX
  - 5/7 partial complex seizures
  - All 5 abnormal EEG with paroxysmal activity in temporo-parieto-occipital areas – characteristic pattern
  - Seizures associated with subnormal IQ
- Clinically seizures easy to control and many grew out of them

Grosso et al. J Clin Neurophys, 2004
Seizures in X Chromosome Disorders

- **Klinefelters**
  - 5 patients referred to epilepsy clinic, 4 seizures = 2 complex partial, 1 single GTC, 1 febrile, 1 EEG abnormal no seizures
  - All good prognosis, grew out of seizures
  - EEG occipital paroxysms in 2
  - Suggest generally good seizure outcome

- **XXX**
  - Patients recruited nationally 2005-2014
  - Compare prenatal diagnosis vs post-natal diagnosis
  - 16.2% of 74 have seizures (2.3% of 44 prenatal, 36.7% of 30 postnatal)
  - Generalized tonic clonic and partial complex
  - 6 abnormal EEG with paroxysmal discharges

Wigby et al. AJMG, 2015
Treatment of Seizures
What to Do for Seizure Acutely

• Don’t panic
• Put on side
• Make sure breathing
• Do not put anything in mouth – they will not swallow the tongue
• Do not give food or drink
• Let them sleep after event if needed
• If turning blue, not breathing at all, or seizure lasts >15 minutes – call paramedics
• Diastat if has it
• If first seizure – bring in for testing for underlying cause
Status Epilepticus Treatment

• Seizure that goes on for 30 minutes without patient becoming alert/responsive
• Routine Airway, Breathing and Circulatory management
• Metabolic Studies on blood
• Anticonvulsants
  • Diazepam (Valium IV, or Diastat rectally)
  • Lorazepam (Ativan IV)
  • Phenytoin (Dilantin) or fosphenytoin IV
  • Phenobarbital
  • Valproic acid (Depacon IV)
  • Keppra IV
• Refractory status
  • Intubation (and ventilation)
  • Pentobarbital, benzodiazepam drip, propofal
Anti-epileptic Drug Selection

- Define the syndrome
- Select medicine for syndrome
- Match medicine to patient characteristics
Basic Principles: Anticonvulsants in Children

• 1. start after 2 or more seizures
• 2. stop 2 to 4 years after last seizure
• 3. single drug regimen is best
• 4. use lowest effective dose
• 5. dose guide is effectiveness and toxicity
• 6. blood levels are less important
• 7. EEG is adjunct for deciding which drug, how much, and how long
• 8. more drug is not necessarily more effective
Traditional Anticonvulsants – Not First Line Choices Any More

- Phenobarbital – not used much any more
- Phenytoin (Dilantin) – not used much in children now due to long term side effects (gum swelling, facial changes, acne)
- Carbamazepine (Tegretol Carbatrol) – in past was first line anticonvulsant for partial seizures
- Valproic acid (Depakene, Depakote) – in past was first line treatment for generalized seizures (atonic, myoclonic, absence, GTC)
New Anticonvulsants: 1992-2011

- Levetiracetam (Keppra) – now first line for most seizure types
- Oxcarbazepine (Trileptal) – partial seizures
- Felbamate (Felbatol)
- Lamotrigine (Lamictal)
- Gabapentin (Neurontin)
- Vigabatrin (Sabril)
- Tiagabine (Gabatril)
- Topirimate (Topamax)
- Zonisamide (Zonagran)
- Fosphenytoin
- Pregabalin (Lyrica)
- Rufinamide (Banzel)
- Lacosamide (Vimpat)
- Fycampa

(Blood monitoring not required except for Felbatol)
# New Anticonvulsants: 1992-2011

<table>
<thead>
<tr>
<th>New Drug</th>
<th>Main Treatment Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felbamate</td>
<td>partial; marrow &amp; liver toxic</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>partial, myoclonic, absence, LGS, may be used first for generalized seizures instead of valproic acid, slow to get on, watch for rash</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>partial; easy add on drug</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>partial, infantile spasms, watch vision</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>partial</td>
</tr>
<tr>
<td>Topirimate</td>
<td>partial, LGS, may be used instead of valproic acid, watch language and kidney stones</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>partial</td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>less toxic: phenytoin pro-drug, use for status</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>less toxic than Tegretol (no epoxide) – now may be used first line for partial seizures</td>
</tr>
<tr>
<td>Leviteracetam</td>
<td>first line for generalized and partial – no major body side effects or drug interactions, watch for 15% increase in behavioral issues</td>
</tr>
</tbody>
</table>
Ketogenic Diet

• Calorie restricted, high fat, low carb (very strict) – 90% calories from fat

• Causes ketosis, associated with seizure control

• About 20% good control rates in intractable patients

• Typically used when multiple anticonvulsants fail or when problems with anticonvulsant side effects

• Patient characteristics – works best under age 4, motivated older child, impaired older child

• Family characteristics – motivated, want to avoid meds if possible, capable with organized lifestyle

• Best for atonic and absence, but can work for all types
Vagal Nerve Stimulator

• Implanted by surgery at base of neck on vagal nerve
• Set to stimulate nerve at certain frequency
• Can adjust frequency to control
• About 10% rate of big improvement in control
• Work best for tonic seizures or when patient has aura and can activate device to abort full seizure
• Risks – hoarseness after surgery, infection
Epilepsy Surgery

• Types
  • Temporal Lobectomy
  • Other focal resection
  • Multiple sub-pial transection
  • Callosotomy

• Only for patients with partial epilepsy
• May be used in whole brain disorder if patient very intractable and appears to have dominant focus
Epilepsy: Seizure Recurrence Risks

- Non-compliance
- Too little sleep
- Intercurrent illness
- ? Stress
- Consider increasing, changing or adding medication
- Frequent recurrence with prolonged seizure or clusters – use rectal Diastat (valium) to stop at home
The Breadth of Epilepsy Care

- **SEIZURE CONTROL** -- Medication
- **SIDE EFFECTS** -- Lower or change drugs
- **PSYCHOSOCIAL** -- Support groups/ counseling
- **EDUCATION** -- IQ/LD testing; proper IEP
- **BEHAVIOR** -- Counseling, meds
- **ADULT INDEPENDENCE** -- Vocational counseling
When Can Seizure Medicines be Stopped?

- Consider stopping meds after 2 years seizure free, especially if EEG normal.
- May treat longer if patient has an underlying condition associated with significant seizure risk or if EEG still shows strong epileptic activity.
- If on multiple meds, may wean one after seizure free a year or two.
- Always some risk of recurrence no matter how long wait past 2 years.
- Can restart meds if recurrence.
Tremor - Definition

✓ Rhythmic, sinusoidal, oscillation of a body part

✓ Alternating contractions of opposing muscle groups
Types of Tremor

• Rest
  – Parkinsonian – at rest, “pill rolling”

• Action
  – Cerebellar – intention tremor can’t point directly to things, can have myoclonic tremor (jerky movements)
  – Kinetic – brought out by movement
  – Postural “Essential” – shaking when holding a posture
    • Most common type
    • “Benign”
      • More prominent in AM, after caffeine, when stressed
  – Enhanced physiological tremor – adrenalin release, can be side effect of medications
Distinguishing Tremor Types

Patient with tremor

Rest Tremor
- During voluntary Movement
  - Writing, eating, Finger-nose-finger

Action Tremor

Kinetic Tremor
- During specific Task
  - Primary Writing Tremor

Postural Tremor
- Maintains position against gravity
  - Hands outstretched, Holding a cup

Intention Tremor
- Crescendo tremor as Approach target
  - Finger-nose-finger, reaching

Isometric
- During muscle contraction against rigid object
  - Making a fist, Pushing against wall

Deuschl et al. 1998
Writing and Essential Tremor

**A** Spiral and line drawings by patient with essential tremor (case 1)

- Untreated
- Propranolol treatment
- Suppression with alcohol

**B** Handwriting samples from case patients

Patient with essential tremor (case 1)

This is a sample of my best handwriting

Patient with Parkinson disease (case 2)

These is my best handwriting.
Tremor in X Chromosome Disorders

• Many case reports of tremor in KS literature
• KS case-control questionnaire study—University of Iowa
  – All patients in hospital database
  – Recruit 44 KS and 94 controls
  – 63% KS report tremor, 13% controls
  – 10% KS previously diagnosed with ET, 0% controls
  – KS tremor patients have tremor at earlier age
  – Also KS reported gait/balance problems more than controls (?apraxia vs ataxia – needs more study)
  – ET characteristics based on questionnaire responses
  – Essential and kinetic tremors are very common in KS: XXY and XXYY

Harlow and Gonzalez-Alegre, Parkinsonism and Related Disorders, 2009
Tremor in X Chromosome Disorders

• XXX – few case reports
• XXX national study
  – Exam: 23.6% of 72 – intention tremor or ET
  – History: 16.8% of 74 have tremor (11.4% of 44 prenatal dx, 22.3% of 30 postnatal dx)

Wigby et al. AJMG, 2015
Essential/Kinetic Tremor Treatment

• Symptomatic – only when function is impaired
• Self medication with alcohol – makes tremor much less severe - diagnostic for ET in history
• Medications
  – Propranolol, other beta-blockers “olol”
  – Primidone
  – Less proven: gabapentin, leviteracetam, clonazepam and other benzodiazepines, topiramate, nimodipine
• Botox
• Deep brain stimulation
Treatment of X Aneuploidy-Associated Tremor

- ET and kinetic tremor – treatment same as general population
- A few reports of DBS with both positive and negative results
- Cases of KS with both alcohol-sensitive and -insensitive described