Disclosures

- No industry disclosures
- will discuss off-label treatments
Malignant Epilepsies
Catastrophic Epilepsies

- severe and refractory seizures
- usually onset in first year of life
- typically poor cognitive outcome
Malignant Epilepsies
Catastrophic Epilepsies

- EME
- EIEE (Ohtahara)
- West Syndrome
- SMEI \approx Dravet Syndrome
- Myoclonic-Astatic Epilepsy (Doose Syndrome)
- Lennox-Gastaut Syndrome
- Sturge-Weber Syndrome
- Tuberous Sclerosis
- Cortical Dysplasias
- Hemimegalencephaly
- Landau-Kleffner Syndrome
- Continuous Spike-wave during slow wave sleep
- Rasmussen’s Syndrome
- Refractory lesional epilepsy
Full term 7 lb, 3½ oz baby born to a healthy mother, good Apgar scores. He did well first few hours, but then began to feed sluggishly. Mother unwrapped baby and saw repetitive myoclonic jerks “he’s done that before!” Evolves through days to massive myoclonia. Baby Rx’d with PHB, PHT, and LZP. Metabolic studies, LP, and MRI all normal. EEG showed invariant burst-suppression pattern.

Baby has 5-20 seizure episodes daily despite therapy with all marketed AEDs. Seizures become multifocal clonic, tonic, and complex partial. No psychomotor development. Burst-suppression pattern last years…
EME in Newborn

The Malignant Epilepsies of Infancy and Childhood

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Early Myoclonic Encephalopathy (EME)

- fetal seizures in some
- fragmentary or massive myoclonia, partial seizures, occasional tonic seizures
- seizures start in first month, often first days
- burst-suppression pattern (more dramatic in sleep)
- acquired microcephaly
- lack of psychomotor development
Early Myoclonic Encephalopathy

- treatment-resistant
- approximately half caused by IEMs:
  - non-ketotic hyperglycinemia
  - propionic acidemia
  - Sulfite oxidase/molybdenum cofactor deficiency
  - methylmalonic acidemia
  - pyridoxine dependency, etc.
- MRI normal (vs. ACC)
- some familial cases
burst-suppression in EME
A full term, 6 lb, 12 oz baby girl was born with Apgar scores of 8¹ and 8⁵ with a history of borderline polyhydramnios and decreased fetal movement just before delivery. On the second day of life she began to have tonic seizures with whole body stiffening, eyes to the left, a shrill cry, and cyanosis. The EEG showed a persistent burst-suppression pattern with superimposed electrographic seizures coming from the right hemisphere. There was no response to infusion of vitamin B6.

Metabolic testing was normal. The initial MRI was normal; subsequent scans showed thinning of the corpus callosum and delayed myelination.
Early Infantile Epileptic Encephalopathy (EIEE): 
Ohtahara Syndrome

- early tonic seizures, also mixed seizures
- starts first days/weeks of life
- burst-suppression pattern on EEG (invariant)
- poor psychomotor development
- poor response to treatment
Early Infantile Epileptic Encephalopathy (EIEE): Ohtahara Syndrome

- “age-dependent epileptic encephalopathy”
  - may evolve to West S. or Lennox-Gastaut S.
- minority with anatomic abnormalities:
  - dysgenesis/dysplasia
  - Aicardi S.
  - porencephaly
  - hemimegalencephaly
18 m/o with EIEE

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EME vs. EIEE

- erratic fragmentary myoclonus of slightly earlier onset
- burst-suppression EEG
- Aicardi and Goutières 1978
- absent OB/perinatal complications
- first MRI normal (rare dysgenesis)

- intractable tonic spasms, single or in clusters, early onset
- burst-suppression EEG
- Ohtahara 1976
- perinatal injury, dysgenesis most common causes
EME vs. EIEE

- half die by one year, others persist in a "vegetative state"
- higher incidence of familial cases
- indistinguishable from NKH
- frequent evolution to West Syndrome
- "atypical infantile spasms" in the newborn
- half evolve to hypsarrhythmia
- other half evolve to "focal spike patterns"
Early Infantile Epileptic Encephalopathy (EIEE): Ohtahara Syndrome

- STXBP1 (9q34.1—syntaxin-binding protein—impaired synaptic vesicle release)
- ARX (Xp21.3—boys with liss/hydranencephl, IS, abnl genitalia, MR)
- CDKL5 (Xp22.13, girls with Rett or Angelman-like presentation)
Early Infantile Epileptic Encephalopathy (EIEE): Ohtahara Syndrome

- KCNQ2 (best known for benign neonatal seizures)
- PCDH19 (protocadherin 19: EFMR—epilepsy in females with mental retardation, and other phenotypes)
- and over a dozen others...
A previously well 6 month-old boy had 3 prolonged febrile seizures over four months, followed by an afebrile GT-C seizure at one year. Seizure frequency and duration increased. GT-C and frequent focal seizures appeared. Fevers frequently triggered seizures. He lost the few words he had acquired and lost other cognitive skills.
Severe Myoclonic Epilepsy in Infancy (SMEI): Dravet Syndrome

- hallmark prolonged febrile (and afebrile) seizures in first year in normal infant
- later myoclonus, atypical absence, and partial seizures (worse with fever)
- all resistant to AEDs
- 25% or more with FHx of epilepsy
- may be part of GEFS+ spectrum
- de novo SCN1A defect in many (~70%)
Severe Myoclonic Epilepsy in Infancy (SMEI): Dravet Syndrome

- initial neuroimaging normal
- sporadic myoclonic seizures (mild to massive) follow FS—“optional”
- later GT-C, alternating unilateral “unstable” clonic seizures, atypical absence, partial and CPS, rare tonic seizures
Severe Myoclonic Epilepsy in Infancy (SMEI): Dravet Syndrome

- EEG findings non-specific:
  - generalized, focal, multifocal
- Intermittent photosensitivity
- Poor long-term outcome
I beg to call the attention of the medical profession to a very rare and singular species of convulsion particular to young children...
A 3 month-old boy presents with episodes of apparent GI pain; a barium enema to rule out intussusception was negative. An EEG showed a high voltage, hypsarrhythmic pattern. Seizure episodes consisted of clusters of brief shoulder abduction and forearm pronation with hip flexion. He was treated with a course of ACTH.
West Syndrome
(Infantile Spasms)

- incidence: 2 to 5 per 10,000 live births
- West Syndrome triad:
  - infantile spasms
  - hypsarrhythmia
  - developmental failure
- typical onset: 4-8 months
- Spasms
  - 1-2 seconds of phasic contraction
  - +/- 2-10 seconds of tonic contraction
  - occur in clusters, often after awakening
West Syndrome  
(Infantile Spasms)

- may proceed to Lennox-Gastaut S.
- 90% with spasms have later developmental delay
- focal vs. generalized pathogenesis?
- 70-80% symptomatic; 10-15% cryptogenic
- hypsarrhythmia pattern:
  - high voltage, disorganized, chaotic, multifocal
  - accentuated in slow-wave sleep
West Syndrome: Etiologies

- no specific cause in 40%
- tuberous sclerosis, Aicardi S., cortical dysplasias, porencephaly, HIE, tumor, Sturge-Weber, PVL, congenital CNS infections, AVM, Down syndrome
- B6-dependency, PKU, glucose transporter defect, biotinidase deficiency, NKH, urea cycle disorders, Menke’s D., MSUD
West Syndrome: Therapy

- Success = elimination of spasms and hypsarrhythmia
- Natural history: eventual clearance
- Developmental outcome good when seizures clear and poor when seizures (focal or LGS) persist
- **ACTH**: multiple dosing regimens (many start at 40 IU per day “natural” ACTH)
- Complications: cardiomyopathy, GI bleeding, hypertension, hyperglycemia, cushingoid response, intense irritability, immunosuppression
West Syndrome: Therapy

- **Vigabatrin**: may have advantages in tuberous sclerosis (and Down S.?)
  - recently FDA-approved with strict limitations
  - visual field constriction (15-50% of patients)
    may be irreversible
- **Benzodiazepines, valproate, ZNS, TPM, KGD, IVIg, surgical resection**
16 m/o awake
16 m/o asleep
16 m/o asleep
12 m/o with hyps pattern
Modified Hypsarrhythmias

- with increased synchrony
- asymmetrical (“hemihypsarrhythmia”)
- with a consistent focal discharge
- with episodes of attenuation
- primarily high voltage slow activity
- with clearance during wakefulness
A 3-year-old girl considered normal except for slow speech development develops drop seizures. Tonic seizures also occur during sleep. There is mild regression in motor milestones. Slow-spike wave discharges are seen on EEG.
Lennox-Gastaut Syndrome

- **Triad:**
  - mixed seizures
  - diffuse slow-spike wave complexes
  - cognitive dysfunction
10 y/o with L-GS
Lennox-Gastaut Syndrome

- seizures are refractory
- onset 1-8 years (peak 3-5 years)
- 25% normal at baseline
- 30-40% with previous history of West S.
- causes: dysplasia, TS, HIE, past CNS infection, genetic abn’s (including GEFS+, Aicardi S., lissencephaly)
Lennox-Gastaut Syndrome

- A “symptomatic generalized epilepsy”
- Multiple generalized seizure types:
  - Tonic
  - Atonic
  - Myoclonic
  - Atypical absence
  - Less common: GTC, clonic, partial
- EEG: slow spike-wave complexes
- Cognitive dysfunction (in most)
Lennox-Gastaut Syndrome

- therapy:
  - valproic acid
  - clonazepam, clobazam
  - felbamate, lamotrigine, topiramate, rufinamide
  - ethosuximide (active against absence)
  - vigabatrin
  - carbamazepine may worsen atypical absence
  - IVIg
  - corpus callosotomy
Age-dependent Epileptic Encephalopathies

- EIEE
- West Syndrome
- Lennox-Gastaut Syndrome
A 3-year-old boy with normal development presents with a drop attack accompanied by a “goofy look on his face.” The event was followed by rhythmic twitching of all extremities. GT-C seizures occurred at night. Behavior deteriorated over the next months and seizures persisted.
Myoclonic-Astatic Epilepsy: Doose Syndrome

- absence of tonic seizures
- onset 1-5 years, 50% normal at baseline
- strong genetic component (GEFS+ phenotype)
- SSW not common, rather GSW ≥ 3 Hz
- VPA, BZPs, LTG often used
- KGD, ACTH, ESX may be most effective
A previously normal 3-year-old boy begins to have 2-3 seizures per day in the left face, arm, or leg. The seizures increase in frequency to 20 per day. He fails multiples medications and his left side becomes weak.
A previously normal 3-year-old boy begins to have 2-3 seizures per day in the left face, arm, or leg. The seizures increase in frequency to 20 per day. He fails multiples medications and his left side becomes weak.

By age 6 years he walks dragging his left leg. On the left he has little hand function and mild facial weakness, some dysarthria, and a high activity level.
Rasmussen’s Encephalitis
(Chronic Focal Encephalitis)

- progressive disorder of childhood
  - focal hemispheric atrophy
  - severe focal epilepsy
  - intellectual decline
  - hemiparesis
- onset 1-13 years (mean 6½ years)
- starts with partial seizures ± generalization, many semiologies, usually motor component
Rasmussen’s Encephalitis
(Chronic Focal Encephalitis)

- focal motor seizures → EPC (refractory)
  - stage 1: seizures before fixed hemiparesis
  - stage 2: fixed hemiparesis to completion of neurologic deterioration
  - stage 3: stabilization w/o further progression, mild improvement of seizures

- two patterns:
  - earlier, more severe pattern onset 1-6 years
  - adolescent/adult onset, milder and more protracted course
Rasmussen’s Encephalitis (Chronic Focal Encephalitis)

- atypical variants: onset < 2 years, *bilateral* involvement, adult onset, focal variant, “double pathology” (tumor, angioma, etc.)

- EEG:
  - abnormal background, slower in diseased hemisphere
  - IEA: multifocal over one hemisphere or bilateral, but unilateral preponderance
  - clinical or subclinical seizures, focal, multifocal or generalized, EPC
Rasmussen’s Encephalitis (Chronic Focal Encephalitis)

- MRI: progressive, lateralized atrophy
- Loss of gray and white matter volume, including deep gray nuclei
- Abnormal signal in gray and white matter (T2 and FLAIR), swelling, non-enhancing
- Decreased perfusion on PET and SPECT
Rasmussen’s Encephalitis (Chronic Focal Encephalitis)

**Pathology:**
- perivascular lymphocytic cuffing
- proliferation of microglial nodules
- neuronal loss and gliosis
- lesions are confluent rather than multifocal
- inflammatory changes decrease with time ("burn-out")
What causes Rasmussen’s Encephalitis?

- direct viral infection?
- viral-triggered autoimmune process?
- primary autoimmune response?
- (inflammation as a response to injury?)
  - no seasonal, geographical, or clustering effect
  - often no antecedent infectious illness
  - no consistent demonstration of virus
  - anti-GluR3 Ab in some patients
  - anti-GluR3 Ab causes RE-like illness in rabbits
  - but Ab present in other catastrophic epilepsies
What causes Rasmussen’s Encephalitis?

Theory:
- initial focal event (trauma, infection, seizures)
- Ag presentation and immune reaction
- cytotoxic T-cells enter across disrupted BBB
- T-cells attack neurons, cytokines spread inflammation and recruit more T-cells
- presentation of further Ag (e.g., GluR3) leads to “second wave attack”
Rasmussen’s Encephalitis

Criteria for (Early) Diagnosis:

- refractory partial motor seizures, EPC, progressive hemiparesis, cognitive deterioration
- EEG: focal/regional slowing, multifocal (usually lateralized) ictal and interictal discharges, progressive background slowing
- MRI: focal cortical swelling, white and gray hyperintensity, followed by progressive atrophy
Rasmussen’s Encephalitis

- Rx: interferon alpha, steroids, IVIg, plasmapheresis, cyclophosphamide, SURGERY
A 3½-year-old boy presented with speech delay. Speech development seemed normal until 2 years of age after which he lost ground. He had echolalia. Staring seizures and nocturnal G-TC seizures appeared. Comprehension was particularly poor. The EEG showed left centrotemporal spikes, nearly continuous in sleep.
The Landau-Kleffner Syndrome and Continuous Spike Wave of Slow Sleep (CSWSS)

- *Epileptic Encephalopathies*: disturbed cognitive/behavioral/motor activity from seizures or epileptiform activity
- LKS may be a subset of CSWSS
- ESES is the EEG abnormality
- CSWSS is the clinical syndrome
CSWSS Definition (Tassinari)

- global or selective neuropsychological regression
- motor impairment (e.g., ataxia, dyspraxia, dystonia, hemiparesis)
- Epilepsy with any seizure type (tonic rare)
- ESES >85% of slow sleep on 3 EEGs for more than one month (usually diffuse)
CSWSS

- **subgroups:**
  - (1) no neuropsych deterioration, severe epilepsy $\rightarrow$ rolandic localization
  - (2) language deterioration/LKS $\rightarrow$ temporal lobe prominence
  - (3) neuropsych deterioration (but not language) $\rightarrow$ frontal prominence
  - (4) lesional cases at presentation $\rightarrow$ frontal prominence
CSWSS

- Seizures:
  - often not prominent
  - a few seizures between 3 and 5 years of age (before diagnosis)
  - focal or generalized motor seizures (nocturnal)
  - absence, atypical absence, drop attacks
CSWSS

- **Etiologies:**
  - single report of affected monozygotic twins
  - MRI abnormal in 33%:
    - diffuse unilateral/bilateral atrophy
    - some cases with perisylvian polymicrogyria
    - LKS MRIs often normal
- **ESES pattern tends to burn out in teenage years**
- **50% in normal range, live independently**
- **relationship of outcome to early Rx unknown**
LKS (Acquired Epileptic Aphasia): Clinical Presentation

- normal language development for at least first two years of life
- onset between 3-7 years (range: 2-14 years)
- impaired *comprehension* with centrotemporal epilepsy
- no seizures by presentation in 20-30%
- may have sx of ADD, motor organization problems, ASD, or global regression
LKS: Acquired Epileptic Aphasias

- postictal (Todd’s) hemiparesis/aphasia
  common
- progressive language impairment:
  verbal auditory agnosia → mutism
- mixture of aphasias seen (not predicted by EEG localization)
LKS: Acquired Epileptic Aphasia

- EEG: centrotemporoparietal regions
- frontal in one third
- discharges bilateral, independent, or synchronous, may fluctuate L vs. R
- superior temporal gyrus and perisylvian area most common
- 20% fulfill CSWSS EEG definition
- better recoveries with shorter durations
LKS: Acquired Epileptic Aphasia

- Etiology unknown:
  - inflammatory?
  - genetic (given relationship to BRE)
  - sometimes temporal hypometabolism on SPECT and PET
LKS: Acquired Epileptic Aphasia

- Treatment targets:
  - seizures, encephalopathy, behavior, communication support
- attempts at spike suppression:
  - steroids/ACTH, BZPs (e.g., CLB), IVIg, cycles of high dose DZP
  - possible worsening with CBZ
  - multiple subpial transections (MST)
“All classifications in all sciences make distinctions more exact and abrupt than any that exist in nature.”

Hughlings Jackson, 1874