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Case Studies in Epilepsy

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Learning Objectives

1. Recognize common and underrecognized epilepsy syndromes and etiologies
2. Understand work up for new onset seizures
3. Be able to counsel women with epilepsy regarding pregnancy, contraception, and birth considerations
4. Recognize autoimmune epilepsy

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Case 1

Case 1

- 23 year-old RH female presents with new onset seizure
  - GTC: bilateral tonic clonic during sleep, no clear lateralizing signs. +tongue biting.
  - No epilepsy risk factors and normal neuro exam

Case 1

- 23 year-old RH female presents with new onset seizure
  - One GTC: bilateral tonic clonic during sleep in the setting of viral illness
  - No clear lateralizing signs. Lasted 1 min, +tongue biting.
  - No epilepsy risk factors and normal neuro exam
- Additional testing? EEG? Medication?

Case 1

- Additional history
  - Additional spells of dizzy and tingling sensation in hands --> hot feeling, mouth tingling, --> feeling scared and worried --> nausea. Is able to speak, but prefers not to and prefers to be silent and "let it pass" does not lose awareness.
  - Duration: 30-60 s
  - frequency: varies, but typically multiple per week

Additional tests?

Additional Tests?

- MRI brain (outside): normal (report)
- EEG outside: right temporal slowing

Diagnosis and localization?

- 1 event of probable GTC, no localizing features
  - 1 min duration, description consistent with GTC, tongue biting, onset during sleep
- Other events are likely focal seizures (brief, stereotyped events)
  - Semiology suggestive of mesial temporal vs insula
  - Likely non-dominant, given preservation of speech

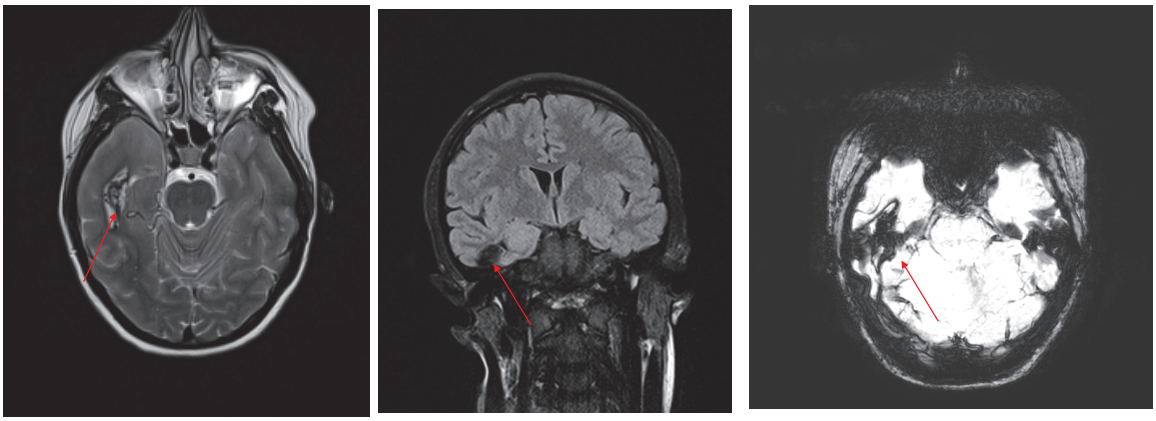
Additional Tests?

- MRI brain (outside): normal (report)
- EEG outside: right temporal slowing
- Spell classification
  - Type 1: GTC, cannot localize
  - Type 2: likely Focal aware seizures (prior simple partial seizures)
    - Recurrent, stereotyped, short duration (30-60 sec)
    - Preserved speech suggests non-dominant.
    - Alternatively, PNES vs panic attacks

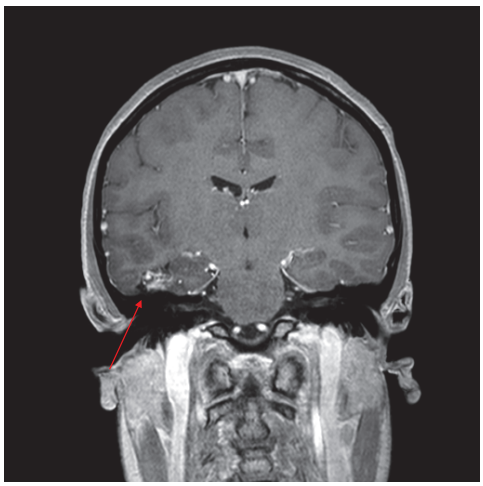
Next steps?

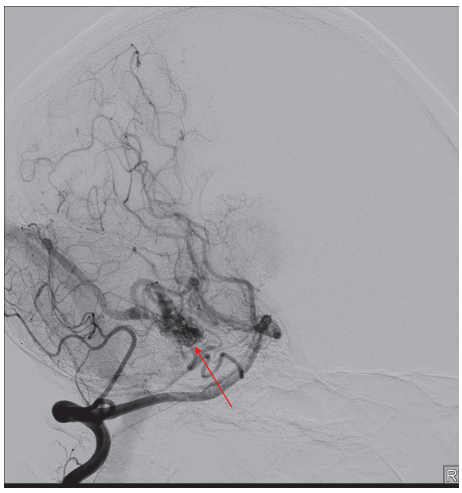
- EMU for spell classification?
  - Likely would not change management
  - Clinical history is compelling for focal seizures.
  - Brief focal seizures from deep focus may be "scalp-eeg negative" leading to false negative
- Imaging
  - Outside MRI report normal
- Medications
  - Initiate ASM (Keppra)

MRI



MRI





Treatment

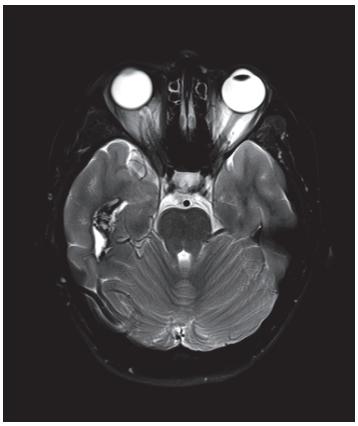
- Keppra, initial resolution of seizures
- Decision made to pursue radiation for AVM

Follow-up

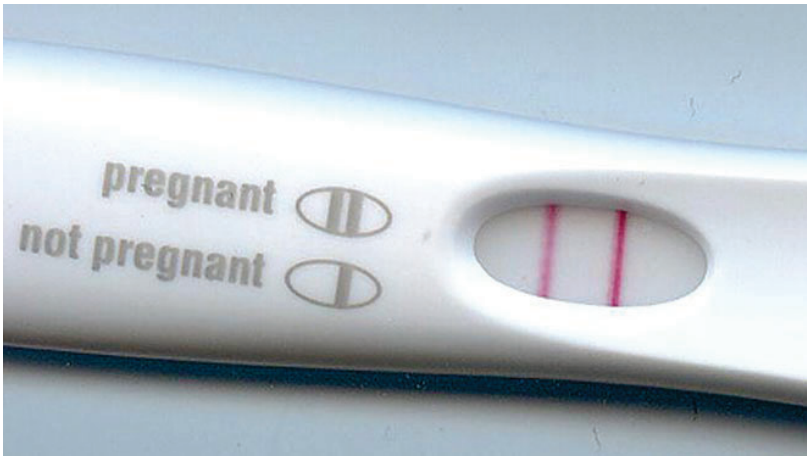
- Had recurrence of seizures prior to radiation
  - Initially, just focal aware seizures, but patient then had FIAS while driving, resulting in MVC
  - Had mood difficulties with Keppra
  - Tried Oxcarbazepine → diffuse whole body rash
  - Brivaracetam
    - Still has mood risk (1-10% vs Keppra 13-16%)
- Underwent Radiation therapy without complication
  - 2 goals: prevent hemorrhage, reduce/stop seizures

Subsequent follow up

- Seizures continued with Briv 100mg BID
- Added Lacosamide 100mg BID, seizure free



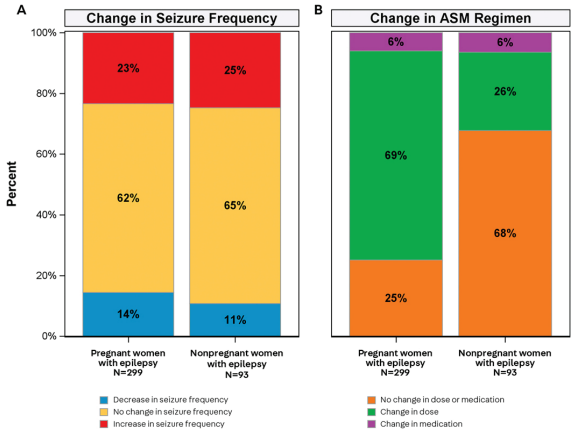
Surprise!



Epilepsy and Pregnancy

- 55-65% of pregnancy in WWE are unplanned (gen pop 45-51%)
- Spontaneous fetal loss is 2x more common in unplanned pregnancy
- Important to address contraception/family planning with patients in clinic
  - Patient had previously declined contraception and did not think she would become pregnant
  - Interactions with contraception and ASM
    - Enzyme inducing meds (e.g. PHT, PHB, CBZ, OXC, RUF, TPM, FYC, Xcopri, FEL) require higher dose OCP
    - IUDs are not affected by ASM
    - ***Lamotrigine levels are decreased 40-60% by ethinyl/estradiol/levonorgestrel***

Epilepsy and Pregnancy



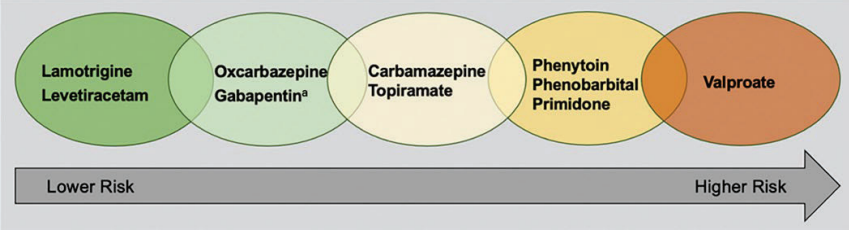
Pennell PB, et al, NEngl J Med, 2020

Preterm birth (<37 wks)

- Increased in WWE (7.6%)
- Exposure to ASM increases risk in both WWE and women w/o epilepsy on ASM for other reasons
- Uncontrolled seizures also increases risk

Congenital Malformations

- Increased risk in general in WWE
- Highest risk:
  - early ASM exposure
  - Total dose and type of ASM
    - Highest VPA (10.9%)
  - Low serum folate
  - Low maternal education



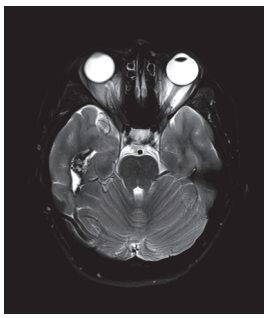
Weston et al. *Cochrane Database Syst Rev* 2016

Case 1

- Risk of BRIV and LCS
  - Highest risk has already occurred
  - Brivaracetam:
    - FDA category not assigned, insufficient data on developmental risk
  - Lacosamide
    - Also not assigned
    - Limited data has reported overall healthy live births in humans
    - case series of 65 pts reported bradycardia in 3 (Hoeltzenbein, *Seizure*, 2023)
    - Rodent studies have shown increased perinatal mortality and malformations
- North American Antiepileptic Drug (NAAED)

Case 1

- Checking ASM during pregnancy
  - Have baseline prior to conception
  - At least once per trimester (ideally monthly)
  - Remained seizure free throughout pregnancy
- Folic Acid (prescribed 1mg/d)
  - Patient previously was no taking, despite counseling
  - 47.6% of WWE not on folic acid prior to conception
  - AAN recommends 0.4 – 4 mg/d
- Repeat MRI/A
  - Stability of AVM
- Referral to high risk OB specialist
  - No contraindication to vaginal delivery with AVM



Case 1 Summary

- New onset focal seizures in adult require brain imaging
- Always look at the MRI yourself!
- Every WWE of childbearing age should be counselled regarding pregnancy, folic acid supplementation, and contraception
- Check ASM levels at least once per trimester and ideally baseline prior to conception

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Case 2

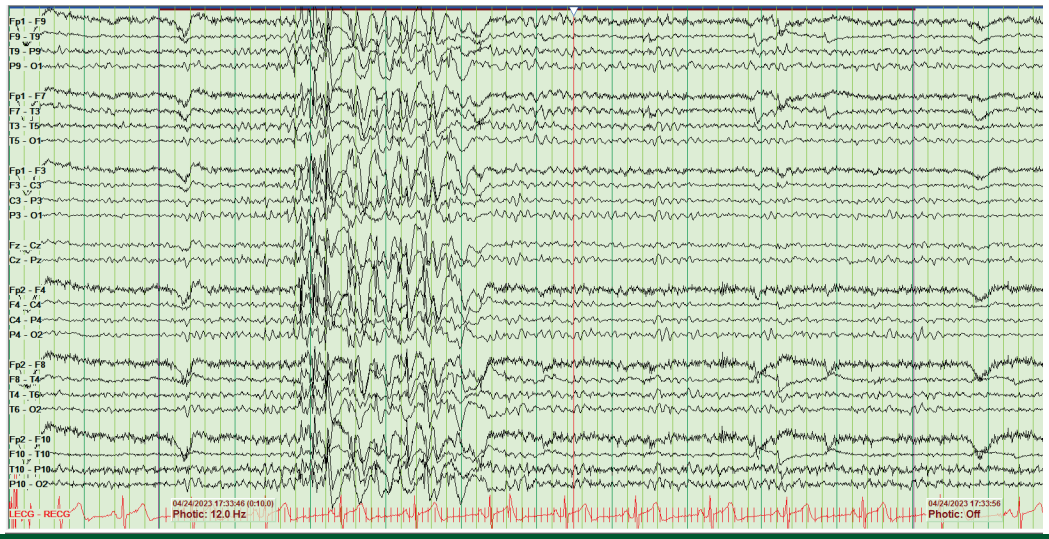
Case 2

- 41 year old right handed male presents with seizures since age 2
- Seizure types:
  - Tonic clonic seizures: ictal cry, thrashing and convulsion of bilateral upper and lower extr., cyanosis of lips, loss of awareness, possible head turn to left or right. ~ 1 min, often with post-ictal psychosis. Onset age 2.
  - Myoclonic jerks: whole body jerking with retained awareness, often in clusters, mostly during sleep but can happen during daytime sporadically.
- Prior meds: VPA, CBZ, PHT, LTG, LEV, CLB, GBP
- Current meds: ZON, FYC

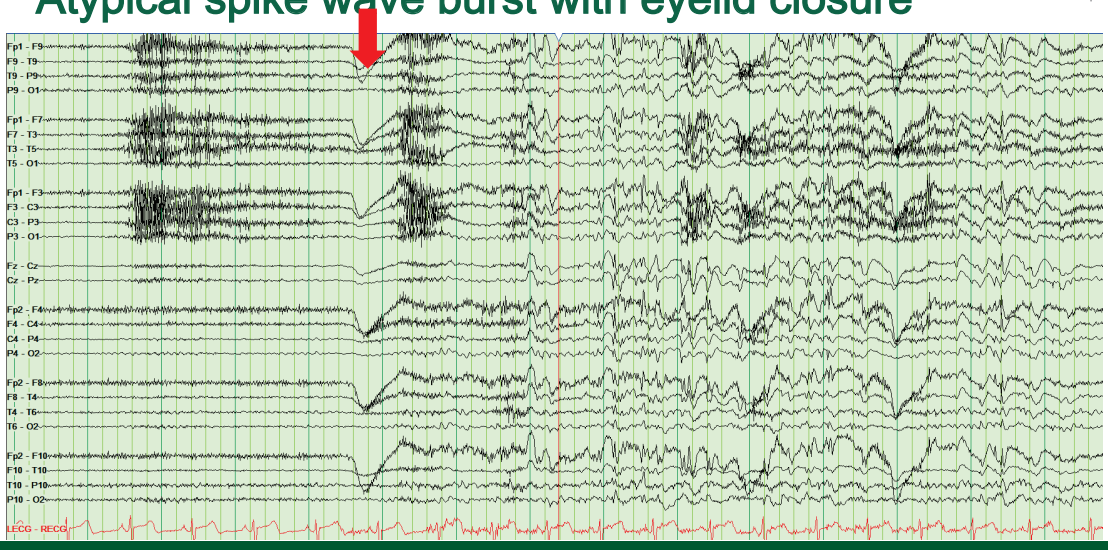
Case 2

- Family Hx: maternal great uncle with seizures, no other risk factors
- Prior Eval:
  - Outside EEG: "spike wave bifrontal but asymmetric, L > R, multiple brief seizures thought to be generalized vs frontal with rapid bisynchrony"
  - MRI: malrotation of right hippocampus, otherwise normal
  - MEG: spike sources identified right parietal lobe
  - SPECT: attempted but did not record seizure
- Admitted to EMU for seizure localization/pre-surgical evaluation

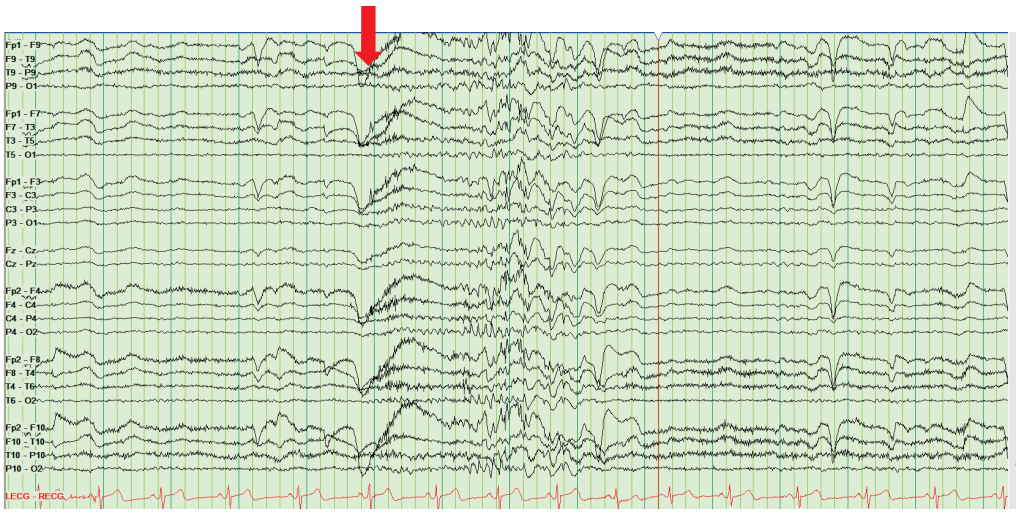
Photo Paroxysmal response



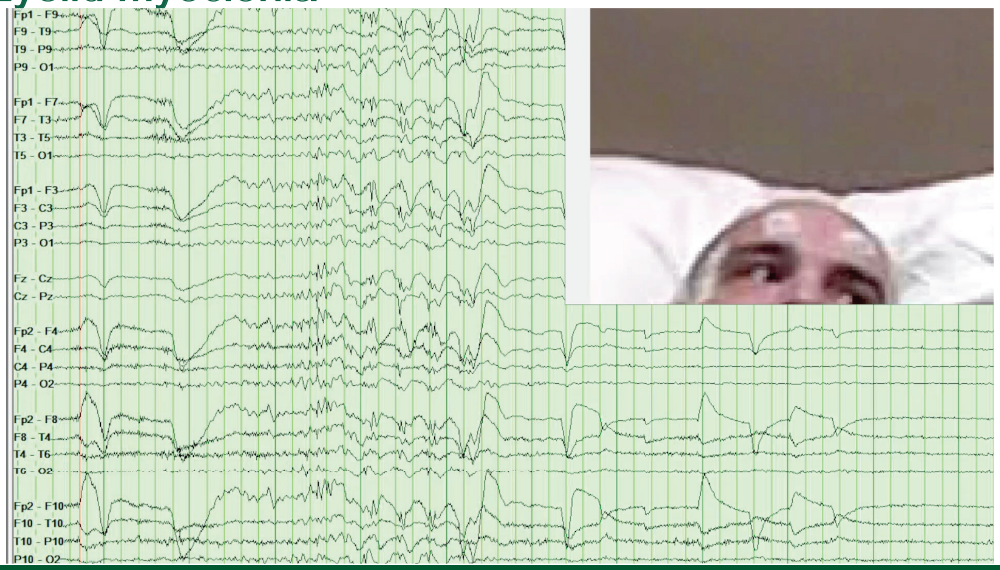
Atypical spike wave burst with eyelid closure



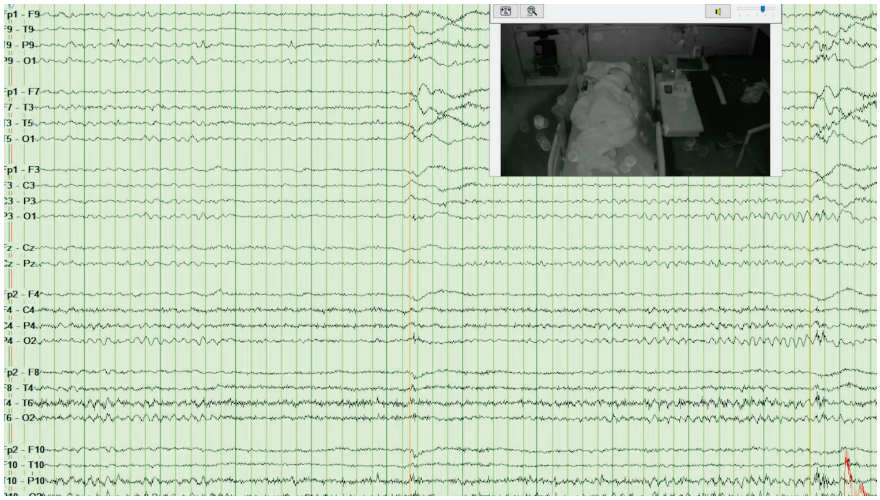
Paroxysm with eyelid closure



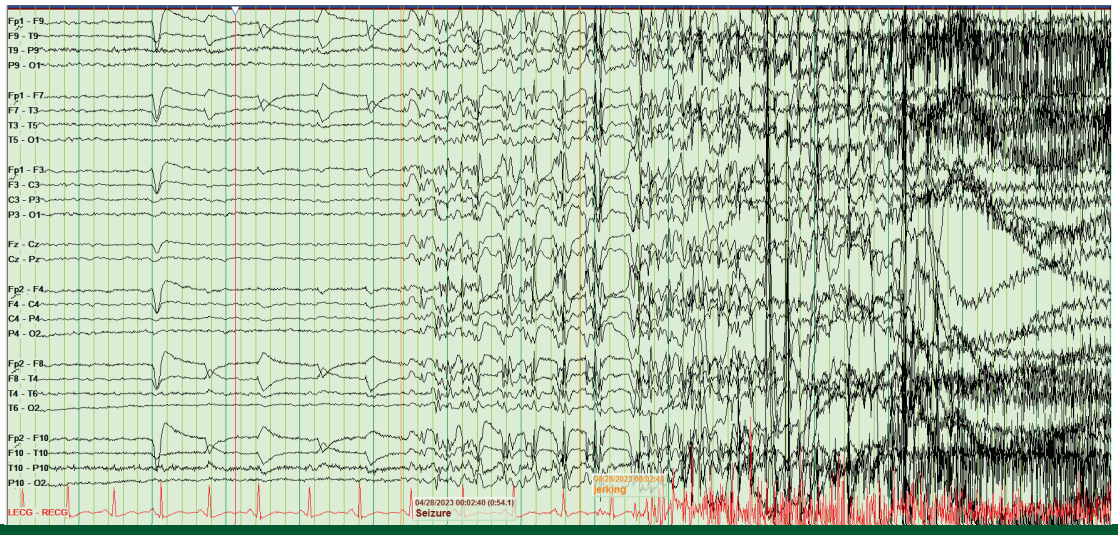
Eyelid Myoclonia



Myoclonic Jerks without EEG correlate



Generalized Tonic Clonic Seizure



Epilepsy with Eyelid Myoclonia (EEM, AKAJeavons Syndrome)

- First described in 1977 (Peter Jeavons, University of Birmingham – UK)
- Distinct subtype of photosensitive epilepsy
- Diagnostic criteria:
  - Eyelid myoclonia with or without absences
  - Eyelid closure induced seizures or paroxysms
  - Clinical or EEG photosensitivity

EEM

- Generally treated with broad spectrum ASM (VPA, LEV, LMT, and benzos)
- Average age of onset 6-8 years, but may be a late as late adolescence/young adult.
- Typically persists into adulthood
- Female to male 2:1
- Up to 50% medically refractory

Eyelid Myoclonia

- Jerking, flicker, or flutter of the eyelids, with jerking of the orbits up
- Can be associated with retropulsion of the head
- occurs after voluntary eye closure
- usually occurs frequently throughout the day
- May occur without EEG correlate
- Not specific to EEM

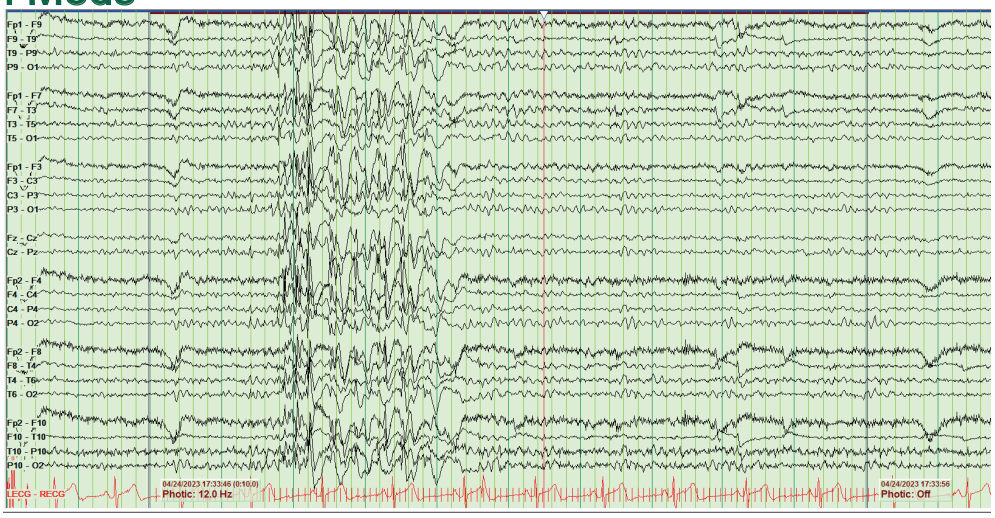
Eyelid closure-induced seizures and/or EEG paroxysmal

- Generalized atypical spike wave, 3-6 Hz, may have posterior lead in
- Best seen in bright light
- May accompany absence seizure
- Rare subtype of "sunflower syndrome"
  - Hand waving in front of eyes by bright light to induce seizures
  - Attraction to sunlight

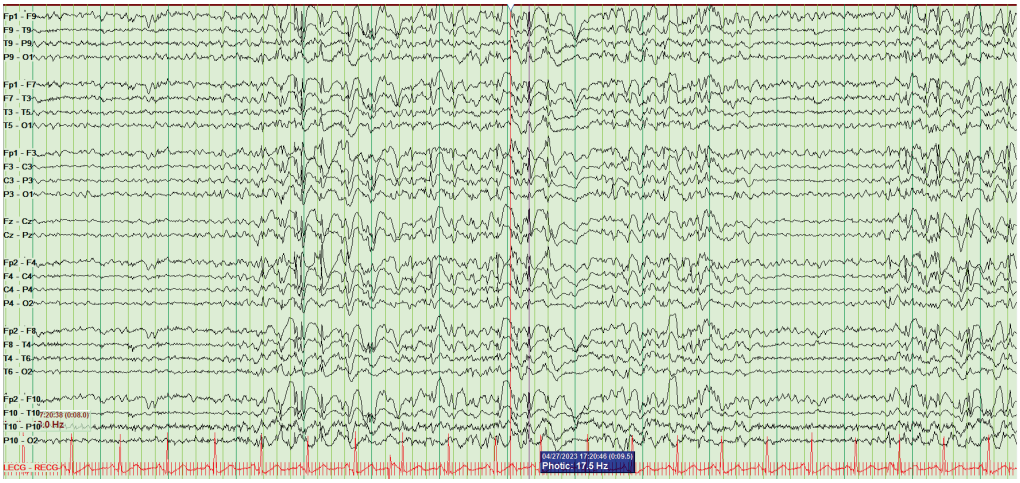
Photosensitivity

- Common, but may decrease with age or ASM
- May include GSW or occipital spikes
- May include seizures (absence, myoclonic, or GTC)

On Meds



Off Meds



Seizure types

- Most patients experience multiple
- 80% experience absence
- Seizure type may change with time
- Other sz types: GTC, myoclonic

Pathophysiology

- Recently, specific genetic mutations have been recognized in a minority patients, including in *SYNGAP1*, *NEXMIF*, *RORB*, and *CHD2* genes.
- fMRI Valdano et al. 2016:
  - EEM cases showed higher BOLD signal related to eye closure over the visual cortex, posterior thalamus, and network implicated in motor control of eye closure, saccades, and eye pursuit movements

Treatment

- Typically broad spectrum ASM (VPA, LEV, LMT, ZON, CLB, ETX, benzos)
- Eyelid myoclonia more difficult to treat, may be more responsive to benzos
- Prognostic implications:
  - Not expected to remit in adulthood
  - May be medially refractory
- Can consider genetic testing in cases with strong family history, although limited therapeutic implications at present.
- Blue lens Z1 may help with photosensitivity

Case 2 - outcome

- ZON and Fycompa largely controlled GTCs
- Clonazepam was added, which resolved myoclonic jerks and also improved eyelid myoclonia

Case 2 Summary

- Constellation of eyelid myoclonia, eye closure-induced discharges, and photosensitivity is suggestive of EEM or Jeavons syndrome
- Patients with EEM are much more likely to persist into adulthood and remain medically refractory
- Genetic testing can be considered for cases with strong family history, although no therapeutic implications at present

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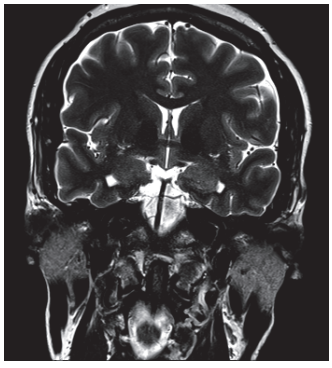
Case 3

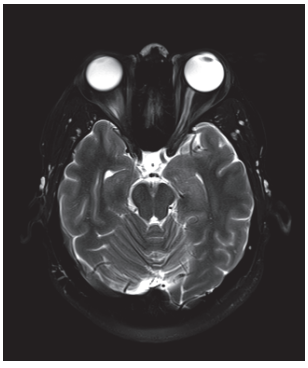
Case 3

- 46 year old RH AAF with prior hyperthyroidism (s/p radioablation), otherwise healthy, presents with 5 year history of seizures
- Semiology:
  - GTCs arising out of sleep. No clear lateralizing or localizing features, 30-60 sec, +TB. Every 3-8 weeks.
    - Daytime seizures may be preceded by an indescribable visual aura
  - FIAS:
    - Déjà vu, auditory sensation, stares with LOA, no other lateralizing signs
    - Lasts 3 minutes, post ictal grogginess up to 1 hour
    - 1x/week
- Medications: LMT, LEV, FYC
- Risk factors: son with febrile seizure, otherwise none.
- Comorbidities: has developed significant memory impairment since onset of seizures (resulted in job loss)

Prior work up

- Routine EEG 2 years prior: no epileptiform activity
- MRI: nonlesional
- CBC, CMP, TPO normal





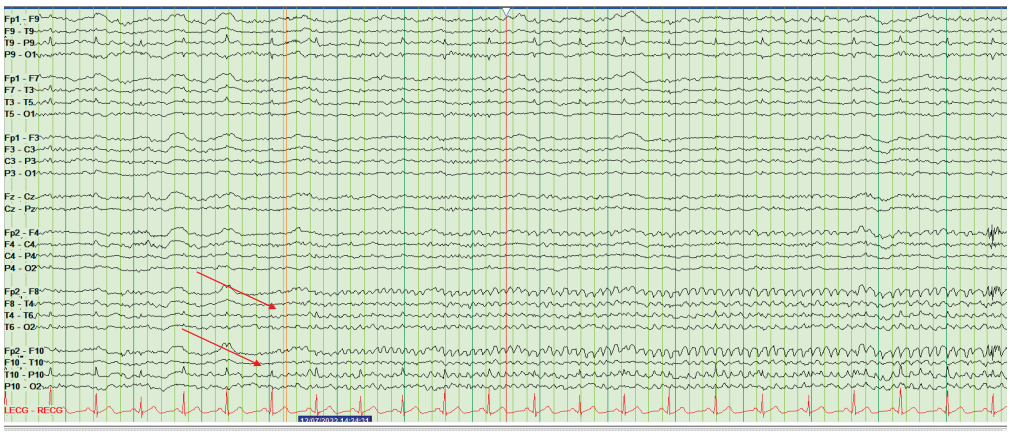
Exam

- Mental: patient alert and oriented to person, place, situation, and date. **Kokmen mental status test was 29/37 (-1 attention, -1 calc,-2 information, -2 construction, -2 recall)**
- CN: 2-12 intact (EOMI, facial movement symmetric bilaterally, tongue midline, visual fields full to confrontation bilaterally)
- Motor: full strength in upper and lower extremities without evidence of UMN or LMN pattern of weakness.
- Coordination: normal finger nose finger, heel shin, RAMs bilaterally
- Sensory: intact to light touch and proprioception bilaterally, Romberg negative
- Reflexes: 0 (mayo scale) in biceps, triceps, patellar, Achilles bilaterally. toesdowngoing
- Gait: normal gait, tandem, toe, heel walking

Diagnosis and localization

- Likely FIAS
  - Aura of déjà vu, auditory and visual hallucinations suggests temporal, likely neocortical.
  - Varying aura may suggest multifocal
- Unclear etiology of epilepsy
  - Unlikely presentation of IGE at age 41
  - No clear mass lesion
  - Son with febrile seizures may suggest genetic predisposition
  - Autoimmune etiology is an important consideration

EMU EEG (FIAS)



Autoimmune evaluation

- CSF:
  - Protein 65, lymphocytes 9
- APE score: 5
- Sent off autoimmune testing:
  - Mayo Clinic Autoimmune encephalitis panel (serum and CSF)

https://news.mayocliniclabs.com/antibody-prevalence-in-epilepsy-and-encephalopathy-ape2-score/

TABLE 2. ANTIBODY PREVALENCE IN EPILEPSY OF UNKNOWN ETIOLOGY SCORE (APE)	
Autonomic dysfunction: atrial bradycardia or sustained tachycardia, blood pressure labile, bradycardia, cardiac aystole, hyperhidrosis, orthostatic hypotension, ventricular tachycardia.	1
Brain MRI: consistent with limbic encephalitis (medial temporal T2/FLAIR signal changes)	2
Seizure or cognitive changes: rapidly progressive mental changes over 1-6 week period or new onset seizure (within 1 year of evaluation)	1
CSF findings consistent with inflammation: protein > 50 mg/dL and lymphocytic pleocytosis > 5 cells/dL, if total number of red blood cells is < 1,000 cells/dL	2
Facial dyskinesia or faciobrachial dystonia	2
Malignancy (excludes cutaneous basal cell carcinoma or squamous cell carcinoma)	2
Psychiatric symptoms (agitation, aggression, emotional lability)	1
Seizure refractory to medical treatment	2
Viral prodrome (low-grade fever, sore throat, rhinorrhea); scored only if there is no underlying malignancy	2
NOTE. An APE Score of ≥4 (max: 15) predicts detection of neural autoantibody in autoimmune epilepsy (sensitivity: 97.7%; specificity: 77.9%)[17] Abbreviations: CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery.	

Autoimmune testing

- Serum GAD65: 124nMol/L (ref <0.02)
- CSF GAD65: 0.83 nMol/L

GAD-65 associated neurologic disease

- Wide variety of clinical manifestations
  - Type 1 DM
  - Autoimmune thyroid disease
  - Pernicious anemia
  - Neurologic:
    - Limbic encephalitis
    - Psychosis/depression
    - Cerebellar ataxia
    - Stiff-person syndrome
    - Myelopathy
    - Large Fiber PN
    - Autonomic neuropathy
    - Epilepsy
- Common to have weak positive (0.02 – 2nMol/L) in gen population (8%)
- Lower range (<20 nMol/L) in pts with non-neurologic disease
- Patients with neurologic disease typically >100 nMol/L
- Some evidence of higher incidence in African-American populations (Pittock 2006)

McKeon et Tracy 2017

GAD-65 autoimmune epilepsy

- Tends to have predilection for temporal lobe seizures, often with neocortical semiology
  - May be unilateral, but often bilateral
  - Musicogenic epilepsy is a reported feature
  - Often more subacute and less severe than other autoimmune epilepsy (cf NMDAR)
- Patients often have other autoimmune conditions (e.g. thyroiditis)
- Rarely paraneoplastic (no routine recommendations for screening in these patients, compared to ANNA-1 abs, for example)

Treatment

- Steroids
- IVIG
- Rituximab
- ASM
- Often remain refractory despite immunotherapy (25% with sustained response)
  - Can consider epilepsy surgery (3/9 patients with resection Engel 1 or 2, Zhao-Flemming 2023)
  - Neuromodulation devices (Feyissa 2020)

Case 3

- Treated with oral prednisone resulted in 3 months seizure freedom, but developed hyperglycemia and weight gain
- IVIG was tried, but insurance repeatedly denied
- Pulse dose weekly steroid infusion have reduced side effects
- Optimization of ASM (FYC, LMT)

Case 3 Summary

- Know when to suspect autoimmune etiology for epilepsy
  - Utilize APE2 score
  - Explosive onset with frequent seizures
  - Prominent neurocognitive changes
  - History of autoimmune conditions in patient or family
- GAD-65 associated disease has a wide variety of neurologic and systemic disease
- Steroids and IVIG are the mainstay of therapy, in addition to ASM
- Despite autoimmune etiology, relatively low rates of seizure resolution with immunotherapy

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Questions?

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Thank you!