Boston Children's Hospital
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Harvard Medical School

WHEN TO REFER TO AN EPILEPTOLOGIST

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When To Refer

- No disclosures or conflicts of interest

Epilepsy: Epidemiology

- A disorder more prevalent at the extremes of age
- Overall incidence from birth to 16yrs of age is 40 cases out of 100,000 children per year.
- In childhood, the incidence is highest in children less than 12 months of age – up to 120 out of 100,000
- School aged children (1-10yrs) have incidence around 40-50/100,000
- In teenagers the incidence is closer to adults at 20/100,000
- Estimated to affect 750,000 children ages 0-17 in the USA

When to refer: Introduction

- Possible reasons for referral
  - One time consult to see if on right track (diagnosis/treatment)
  - Medically Refractory
    - Surgical candidacy
    - Ketogenic diet trial
    - VNS
  - Epileptic encephalopathy
  - Epilepsy genetics
- Reasons not to be discussed
  - Parents are lawyers
  - Annoying family

When to refer: Introduction

- What makes a Pediatric Epileptologist
  - Training
    - At least 2 years pediatric residency
    - 3 year child neurology residency
    - 1-2 years of fellowship –Either clinical neurophysiology with focus in EEG or the more recent Epilepsy
  - Board certified in Neurology with special focus in Child Neurology
  - Board certified in Clincial Neurophysiology or newer Epilepsy board
  - Access to inpatient EMU (epilepsy monitoring unit)
  - May be associated with epilepsy surgery center and/or ketogenic diet program

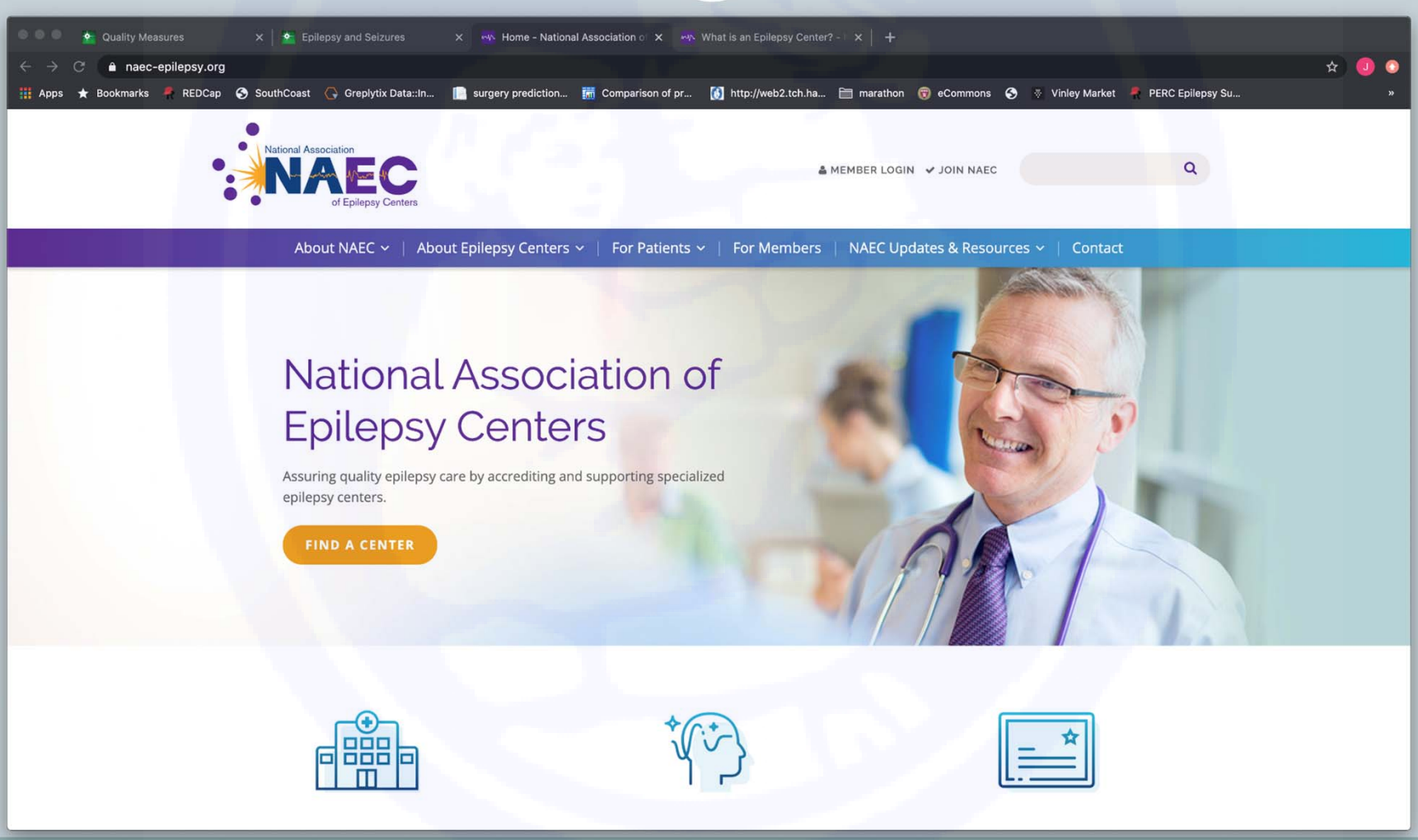
NAEC

NAEC is a non-profit association with a membership of more than 230 specialized epilepsy centers in the United States. NAEC published its first iteration of its *Guidelines for Essential Services, Personnel, and Facilities in Specialized Epilepsy Centers* in 1990.

Mission

- NAEC supports epilepsy centers in delivering quality comprehensive care to people with epilepsy, by setting standards of care, advocating for access to high quality epilepsy center services, and providing knowledge and resources to its member centers.

Epilepsy Centers - NAEC



NAEC Level 3 and 4 Centers

- Level 3: provides the basic range of medical, neuropsychological, and psychosocial services needed to treat patients with refractory epilepsy. Level 3 epilepsy centers provide basic neurodiagnostic evaluations, as well as basic medical, neuropsychological, and psychosocial services. Some level 3 centers offer noninvasive evaluation for epilepsy surgery, straight-forward resective epilepsy surgery, and implantation of the vagus nerve stimulator. These centers do not perform intracranial evaluations or other more complex epilepsy surgery.

- Level 4: provides the more complex forms of intensive neurodiagnostic monitoring, as well as more extensive medical, neuropsychological, and psychosocial treatment. Level 4 centers also offer a complete evaluation for epilepsy surgery, including intracranial electrodes and a broad range of surgical procedures for epilepsy.

NAEC

- video

When to refer: Introduction

- Referral options:
  - One time consult to provide additional treatment or diagnostic options
  - Transfer of care for exceptionally complex patients
  - Joint care for specialized treatment such as pre-surgical evaluation or ketogenic diet

When to refer: Example case

- 11yo previously healthy girl presents to clinic with episodes of staring. Having up to 3-4 per day
- She will stop an activity, eyes deviate up and to the side and she may have lip smacking and picking with her hands. When episode is over patient returns to baseline
- In office had patient hyperventilate for 2.5min with no spells
- Concern for focal dyscognitive seizure, though also considered possibility of IGE
- Routine EEG ordered.....

EEG Report

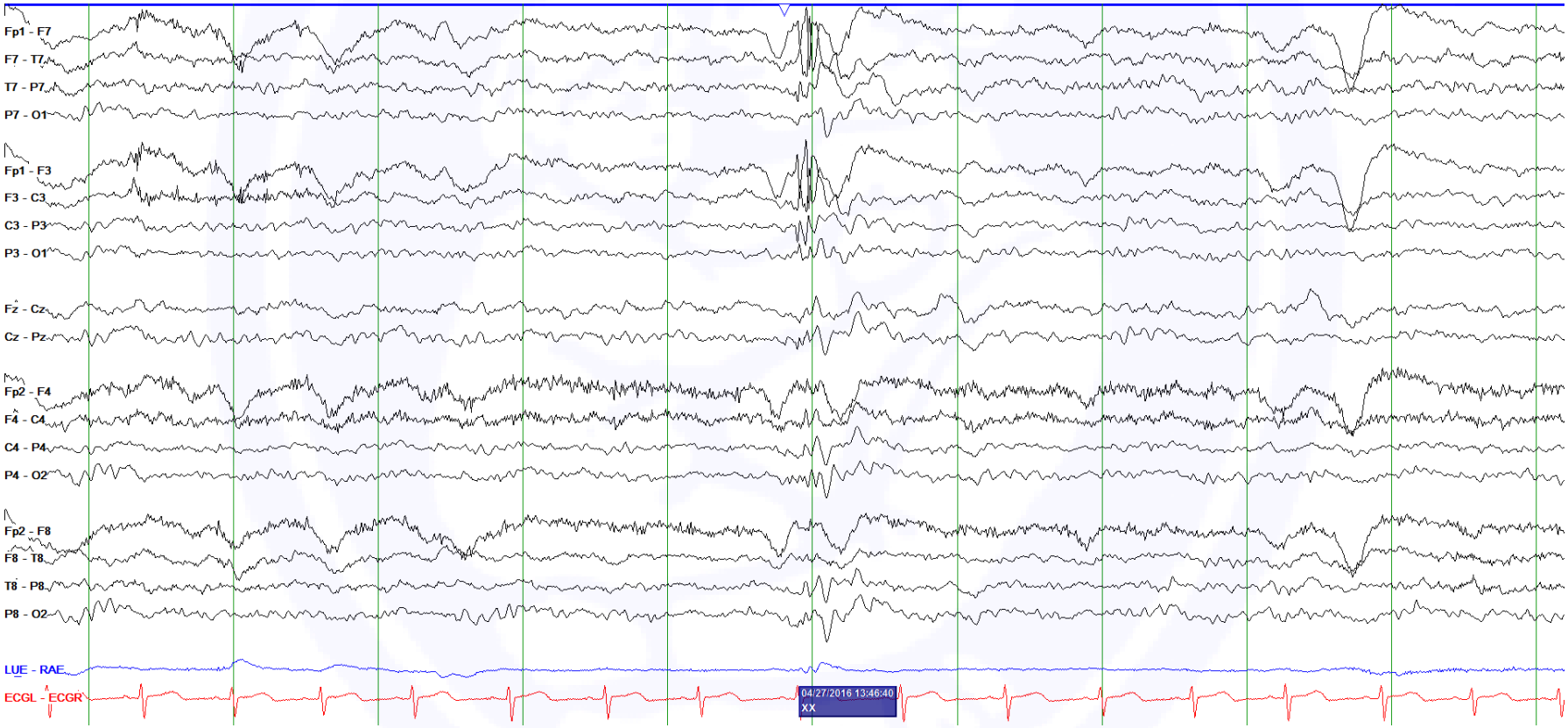
INTERPRETATION

- This EEG in the awake and drowsy states is abnormal due to:
- Focal left frontotemporal spikes
- Left midtemporal slowing

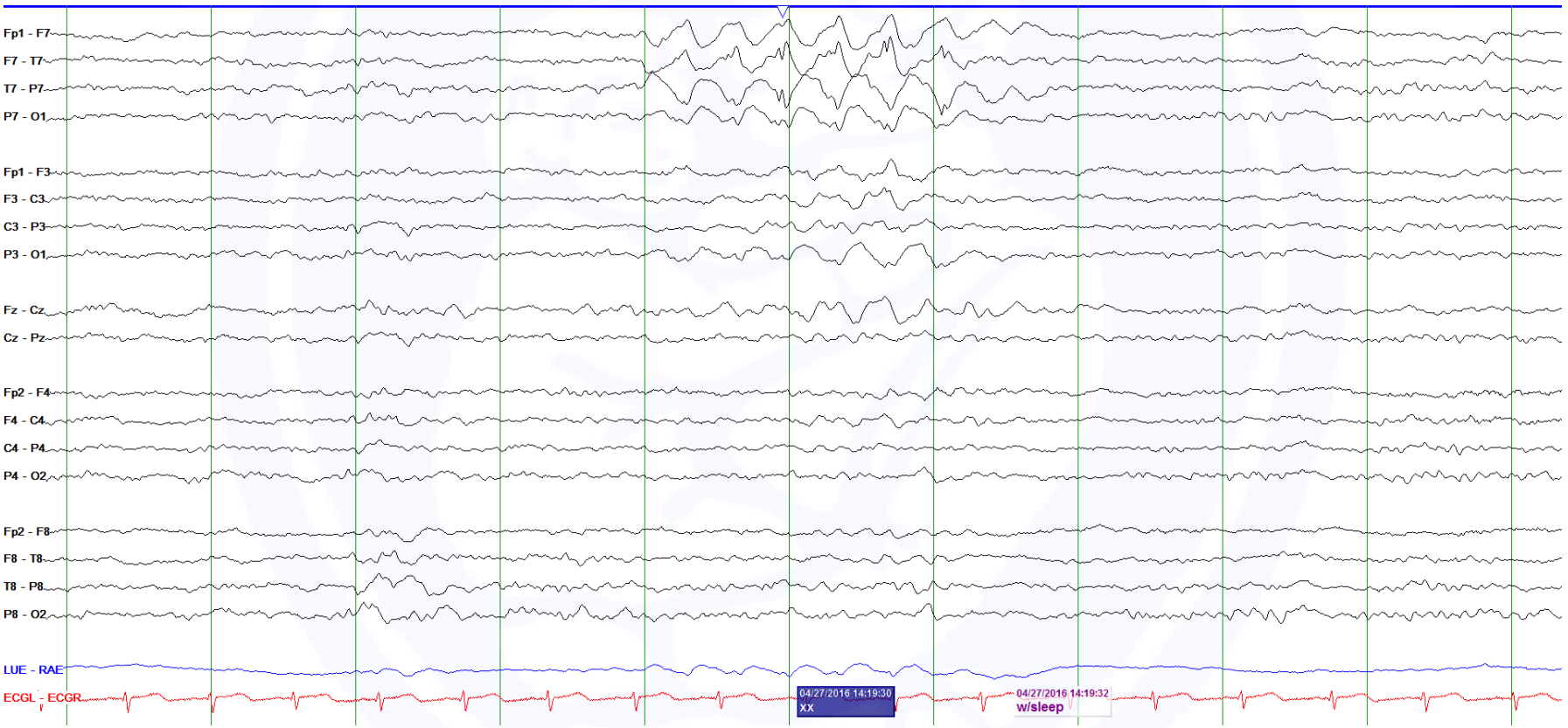
CLINICAL CORRELATION

- This EEG indicates a decreased seizure threshold with focal onset in the left frontotemporal region. Focal slowing indicates cortical dysfunction in the same region.

Routine EEG



Routine EEG



Clinical Course

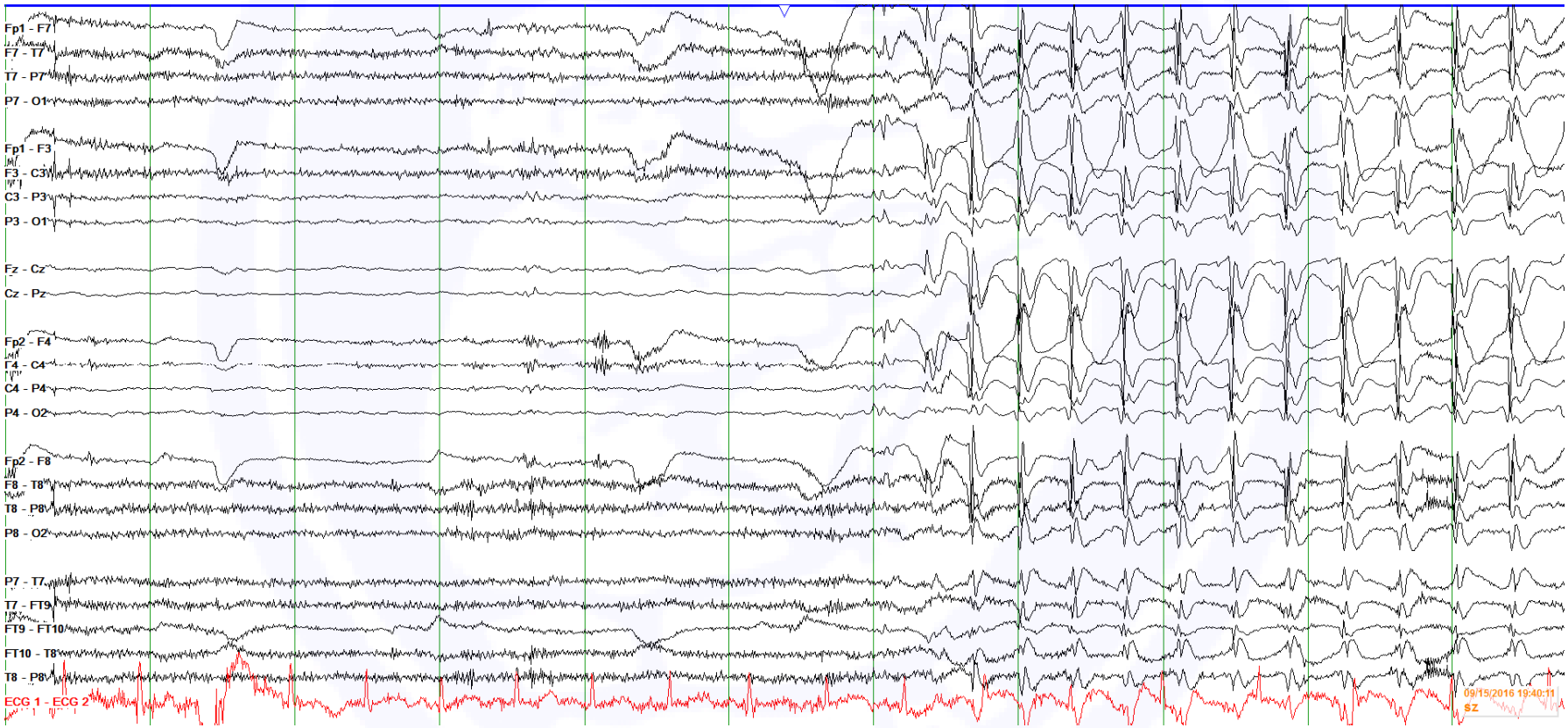
- After EEG results, diagnosed with left temporal lobe epilepsy and started on OXC
- MRI ordered – WNL
- 6-8 weeks later family reports continued seizures, possibly more frequent, up to 10/day
- LEV added and seizures subside for 2-3 weeks but then returned
- LEV increased however parents note behavioral side effects
- Seen back in clinic (3mo follow-up) – plan to start LAC and wean off LEV
- Seizures worsen as LEV is weaned
- Referral to Epilepsy!

Epilepsy Clinic

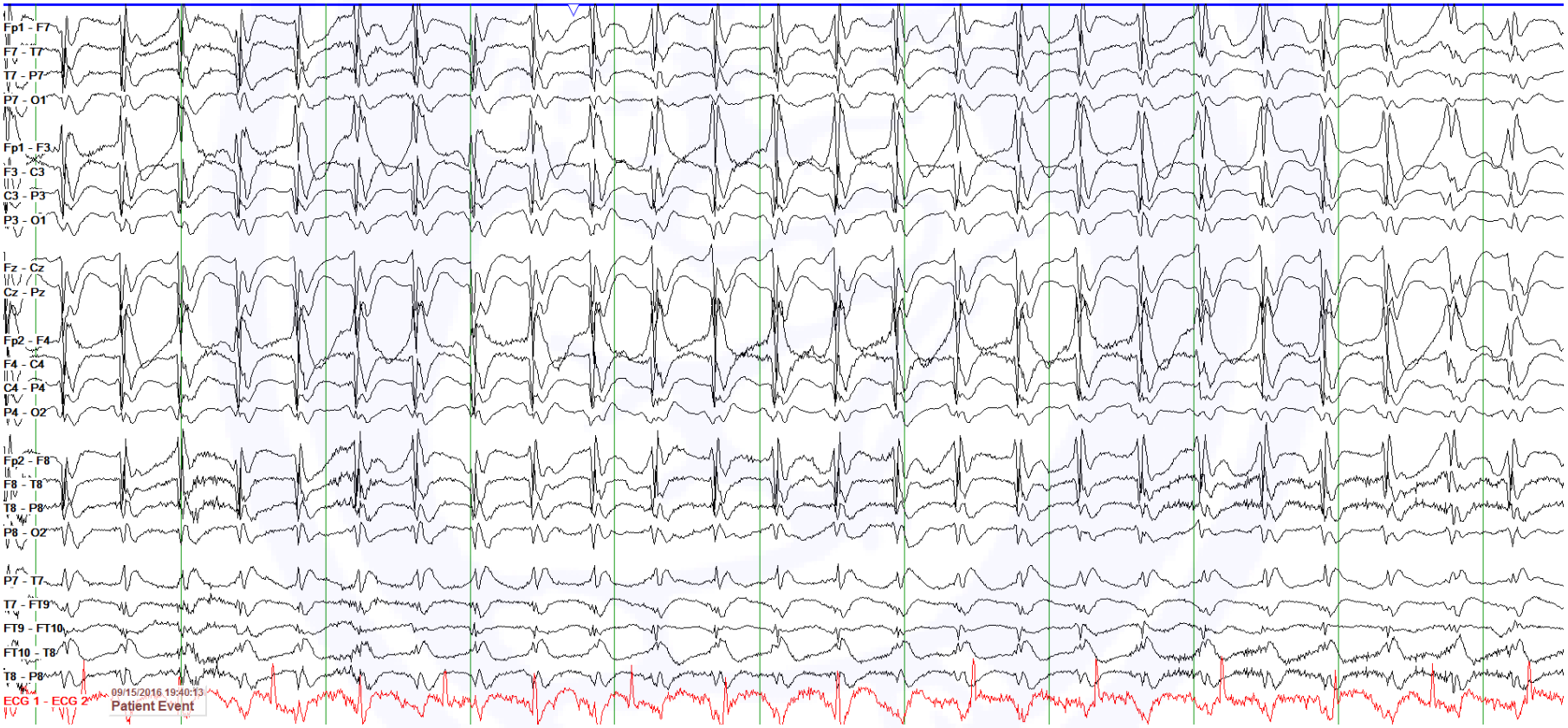
- History and EEG reviewed and felt to be consistent with TLE
- Plan urgent 24hr EEG to better characterize seizures
- Likely proceed to pre-surgical evaluation

- Later that week presented to ED with fall at school, possibly related to seizure – admitted urgently to EMU for better characterization of seizures

EMU EEG



EMU EEG



Case conclusion

- Several seizures captured, all with 3Hz generalized spike and wave correlate
- Diagnosis is Absence Epilepsy, childhood v. juvenile
- OXC stopped immediately as could be causing "pseudointractability" and ETX initiated

Psychogenic Non-Epileptic Seizures

- Events which may look like a clinical seizure but are not epileptic and instead caused by psychological factors
- Up to 20% of patients presenting with sz-like events receive the diagnosis (Kostopoulos et al., 2003)
- Most common in patients 15-30yrs of age with female predominance (Reuber, 2008)
- Not uncommon to occur in patients with known epilepsy
- vEEG and video recordings are important in diagnosis

Intractable Epilepsy

WHEN TO REFER

When to Refer: Refractory Epilepsy

- Roughly 30% of all patients with epilepsy will not respond completely to AEDs
  - Symptomatic epilepsies have a higher failure rate
  - Close to 50% of patients with focal cortical dysplasia are refractory to AEDs
- Medically Refractory is defined as failing trials of two appropriate AEDs
  - Debate about duration before calling refractory. In adults some will argue for waiting 2yrs however given the dramatic effect epilepsy has on development, pediatric epileptologist argue for much shorter duration ??6mo

Kwan and Brodie NEJM 2000

AAN Epilepsy Quality Measure

Referral or discussion of referral to a comprehensive epilepsy care center for patients with intractable (treatment-resistant) epilepsy

Despite the strong evidence of superior outcomes among those who receive epilepsy surgery and other specialized services at comprehensive epilepsy centers, only a small fraction of patients are referred within 2 years of developing intractable epilepsy (treatment-resistant epilepsy), with years of delay occurring before referral for epilepsy surgery.[20,–,22] Contributors to the delay in referral include improper identification of medication treatment resistance (intractability) and gaps in knowledge related to epilepsy surgery guidelines.[23] Evaluation and treatment at comprehensive epilepsy centers can also lead to appropriate diagnosis for patients without epilepsy, but with nonepileptic spells, in addition to the utilization of specialized treatments including, for example, dietary therapy, neurostimulation, medical research trials, and psychosocial supports for those with intractable epilepsy.

Quality improvement in neurology
Epilepsy Quality Measurement Set 2017 update
Anup D. Patel, Christine Baca, Gary Franklin, Susan T. Herman, Inna Hughes, Lisa Meunier, Lidia M.V.R. Moura, Heidi Munger Clary, Brandy Parker-McFadden, Mary Jo Pugh, Rebecca J. Schultz, Marianna V. Spanaki, Amy Bennett, S. Andrew Josephson
Neurology Oct 2018, 91 (18) 829-836;

https://www.aan.com/practice/quality-measures/

When to Refer: Refractory Epilepsy

- Options for refractory epilepsy
  - Epilepsy Surgery
  - VNS, RNS, DBS
  - Ketogenic or modified Atkins diet
  - Additional medication trials

  - Non-invasive stimulation (TMS/TCDS)*

Refractory Epilepsy: VNS

- Approved for adjunctive treatment of medically refractory focal epilepsy in 1997
- May be beneficial for either focal or generalized epilepsy
- Benefits increase over time, taking up to 2 years to see full effect
- Around 60% of patients will have >50% reduction in seizure frequency
- Around 5-8% will become seizure free
- Requires regular visits for adjustment of settings

Refractory Epilepsy: VNS

- Implanted as day procedure by neurosurgeon
- Has baseline stimulation parameters plus option to stimulate via magnet swipe across chest to abort seizure
- Newer model has HR detection feature to provide stimulus in response to tachycardia (sign of seizure)

- Downsides:
  - Battery life around 6-8yrs
  - Must be turned off for MRI
  - May cause change in voice or sensation in throat
  - May worsen OSA

Refractory Epilepsy: Ketogenic Diet

- High fat, adequate protein, low carbohydrate diet
- Indicated for medically refractory epilepsy
  - Glucose transport deficiency
  - Pyruvate Dehydrogenase deficiency
- Contraindicated in:
  - Disorders of fatty acid transport or beta-oxidation
  - Some inborn errors of metabolism such as organic acidurias and pyruvate carboxylase deficiency
- Must be initiated and managed under close supervision of a knowledgeable dietician

Refractory Epilepsy: Ketogenic Diet

	Number of children
Generalised epilepsy	
Lennox–Gastaut syndrome	14
West syndrome (with continued spasms)	11
Myoclonic absence epilepsy	7
Unspecified myoclonic epilepsy	8
Myoclonic astatic epilepsy	8
Atypical absence seizures	3
Continuous spike wave of slow sleep	2
Childhood absence epilepsy	2
Myoclonic encephalopathy	1
No specific syndrome diagnosis	22
Focal epilepsy	
Structural brain abnormalities	27
Presumed focal	16
Multifocal	14

Table 2: **Number of children in each epilepsy syndrome category**

	Diet group (n=54)	Control group (n=49)
Mean percentage of baseline seizures after 3 months (95% CI)	62·0% (50–74%)	136·9% (105–169%)
Median percentage of baseline seizures after 3 months (SD, IQR)	47·7% (43, 0–200%)	106·3% (111, 28–575%)

Table 3: **Comparison of seizures as a percentage of baseline after 3 months**

	Patients who achieved cut-off points		p value
	Diet group (n=73)	Control group (n=72)	
>90% reduction in seizures	5 (7%)	0 (0%)	0·0582
>50% reduction in seizures*	28 (38%)	4 (6%)	<0·0001
<50% reduction in seizures†	45 (62%)	68 (94%)	<0·0001

Percentages based on numbers allocated to each intervention. *Includes patients who reported >90% reduction. †Includes 71 patients with data and 42 unknown (16 did not recieve treatment, 10 discontinued treatment, 16 with no data).

Table 4: **Number of children in each group who achieved 50% and 90% seizure reduction at 3 months**

	Patients who reported side-effect*
Vomiting	13 (24%)
Diarrhoea	7 (13%)
Abdominal pain	5 (9%)
Constipation	18 (33%)
Medication for constipation needed	13 (24%)
Lack of energy	13 (24%)
Hunger	12 (22%)

*Data are number (%) of the 55 children who continued on the diet for 3 months.

Table 5: **Side-effects reported after 3 months on the ketogenic diet.**

Neal et al. Lancet Neurology 2008

Intractable Epilepsy

EPILEPSY SURGERY

Epilepsy Surgery: When to refer

Criteria for candidacy

- Pharmacoresistance
- Lack of known epilepsy syndrome which may subside with time
- Ability to delineate epileptogenic zone
- Absence of prohibitive consequences from the suggested surgery

When to Refer: Epilepsy Surgery

- ILAE recommends surgical evaluation performed with a multidisciplinary team including epileptologists, neurosurgeons, neuroradiologist and neuropsychiatrists
- Pre-surgical data should be presented at a multidisciplinary case conference for consensus plan

Epilepsy Surgery

ORIGINAL ARTICLE

Surgery for Drug-Resistant Epilepsy in Children

Rekha Dwivedi, Ph.D., Bhargavi Ramanujam, M.D., D.M., P. Sarat Chandra, M.Ch., Savita Sapra, Ph.D., Sheffali Gulati, M.D., D.M., Mani Kalaivani, Ph.D., Ajay Garg, M.D., Chandra S. Bal, M.D., Madhavi Tripathi, M.D., Sada N. Dwivedi, Ph.D., Rajesh Sagar, M.D., Chitra Sarkar, M.D., and Manjari Tripathi, M.D., D.M.

N ENGL J MED 377;17 NEJM.ORG OCTOBER 26, 2017

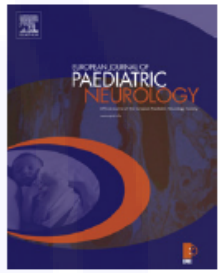
Epilepsy Surgery

- Single center trial of pediatric population with medically refractory epilepsy and deemed good surgical candidates (n=116)
- Randomized into surgical group vs. continued medication (wait listed for surgery)
- Primary outcome was seizure freedom at 12mo
- 77% of surgical cohort seizure free at 12mo vs. 7% in medical therapy group ($p<0.001$)

Epilepsy Surgery

ELSEVIER

Official Journal of the European Paediatric Neurology Society



Original article

Seizure and cognitive outcomes of epilepsy surgery in infancy and early childhood

Georgia Ramantani [a,*], *Navah Ester Kadish* [b], *Karl Strobl* [c], *Armin Brandt* [a], *Angeliki Stathi* [a], *Hans Mayer* [c], *Susanne Schubert-Bast* [b], *Gert Wiegand* [d], *Rudolf Korinthenberg* [e], *Ulrich Stephani* [d], *Vera van Velthoven* [f], *Josef Zentner* [f], *Andreas Schulze-Bonhage* [a], *Thomas Bast* [b,c]

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[f] *Department of Neurosurgery, University Hospital Freiburg, Germany*

Epilepsy Surgery: Classic Candidates

- Focal Cortical dysplasia (FCD)
- Mesial temporal sclerosis (MTS)
- Tumors
- Tuberous sclerosis
- Heterotopias
- Remote/Perinatal infarcts
- Sturge-Weber Syndrome
- Hemimegencephaly
- Rasmussen's Encephalitis

Epilepsy Surgery: Options

Current Surgical Options

- Small focal resection
  - With or without invasive monitoring
- Single lobectomy
- Multi-lobectomy
- Hemispherectomy
  - Functional v. anatomic
- Corpus callosotomy
- LITT (Laser interstitial thermal therapy)
- RNS/Neuropace*

Epilepsy Surgery: Outcomes

- Temporal lobe lesions – 60-70's%
- Hemispherectomy – 70-90's%
- Extra-temporal lesion -40%

Less favorable outcomes

- Incomplete resections
- FCD type 1 v. 2
- Acute post-operative seizure
- Seizure onset >5yrs prior to surgery
- Contralateral PET abnormalities

Cost Effective?

- Studies looking at cost effectiveness of epilepsy surgery in pediatric population
  - All three found epilepsy surgery was advantageous compared to continued medical management

Bowen JM, Snead OC, Chandra K, et al. Epilepsy care in Ontario: an economic analysis of increasing access to epilepsy surgery. Ont Health Technol Assess Ser 2012;12:1–41. 41.

Widjaja E, Li B, Schinkel CD, et al. Cost-effectiveness of pediatric epilepsy surgery compared to medical treatment in children with intractable epilepsy. Epilepsy Res 2011;94:61–68. 42.

Oldham MS, Horn PS, Tsevat J, et al. Costs and clinical outcomes of epilepsy surgery in children with drug-resistant epilepsy. Pediatr Neurol 2015;53:216–220

Epilepsy Surgery: Presurgical Evaluation

- Goal is to define the epileptogenic zone and hopefully differentiate from the functional/eloquent zone
- Starts with a good history including seizure semiology, epilepsy risk factors and developmental progression
- Detailed neurologic exam
- Good skin exam

Epilepsy Surgery: Presurgical Evaluation

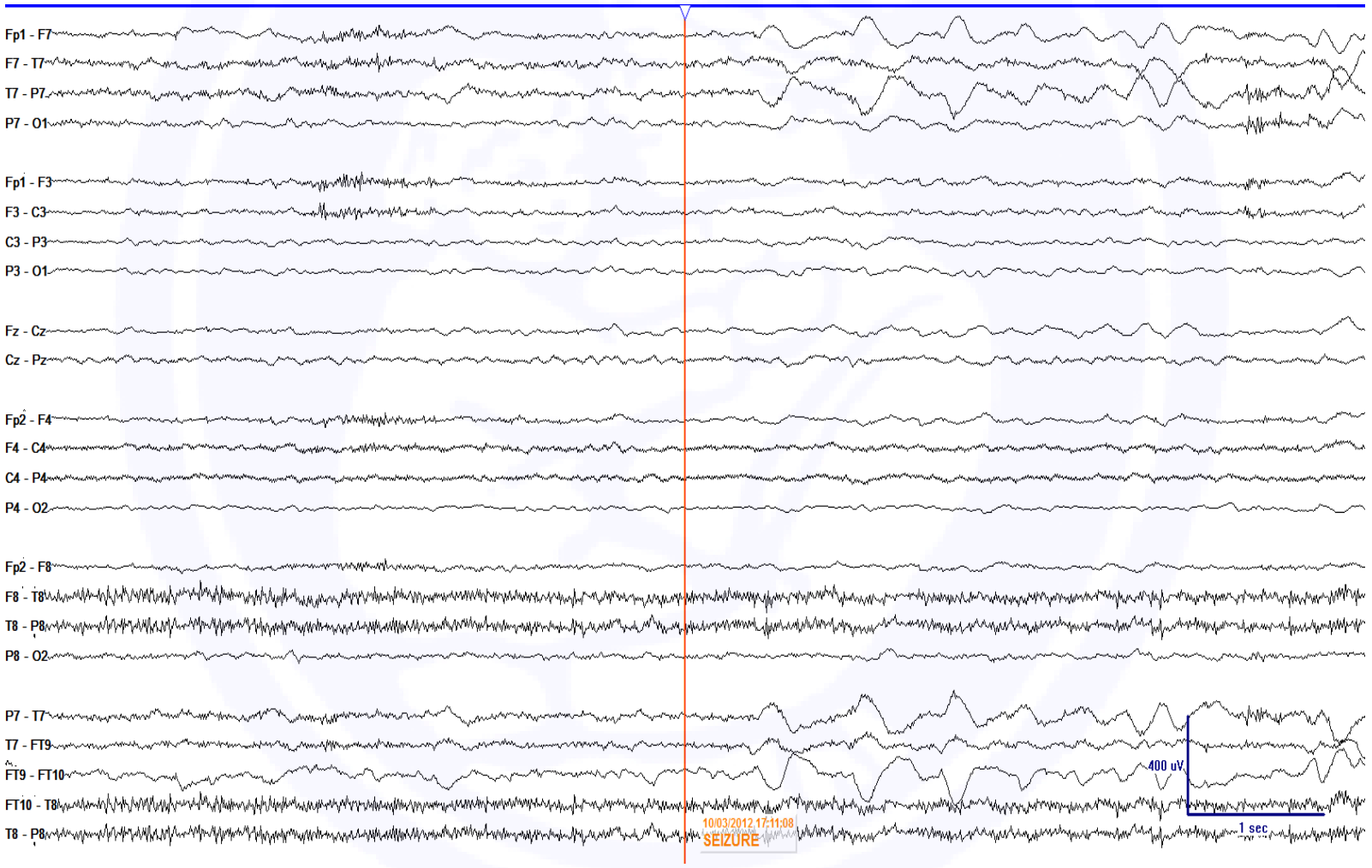
- Wide array of technologies available to help identify epileptogenic and functional zones
- Not all testing may be indicated for every case (just because we can, doesn't mean we need to)
- Recent set of recommendations published by the Pediatric Epilepsy Surgery task force in Epilepsia
- Evaluations should be done at skilled centers using multidisciplinary surgical conference

Jayakar et al Epilepsia 2014

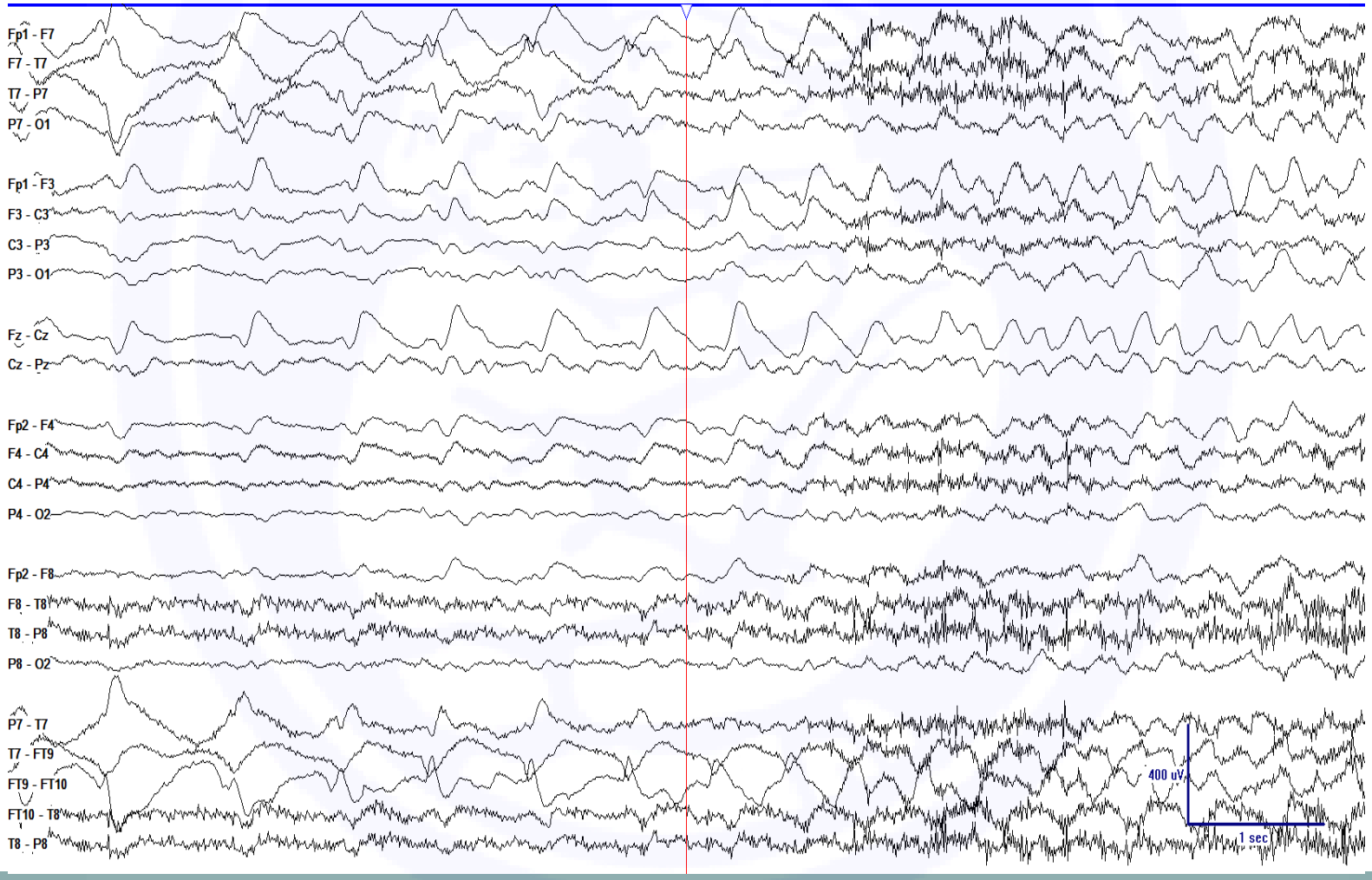
Presurgical Evaluation: Video EEG

- In all cases, video EEG with ictal recordings is strongly recommended
- First step in identifying the ictal onset zone
- Limitations:
  - Poor spatial resolution
  - Less sensitive for deep foci
  - May be falsely lateralizing in certain cases

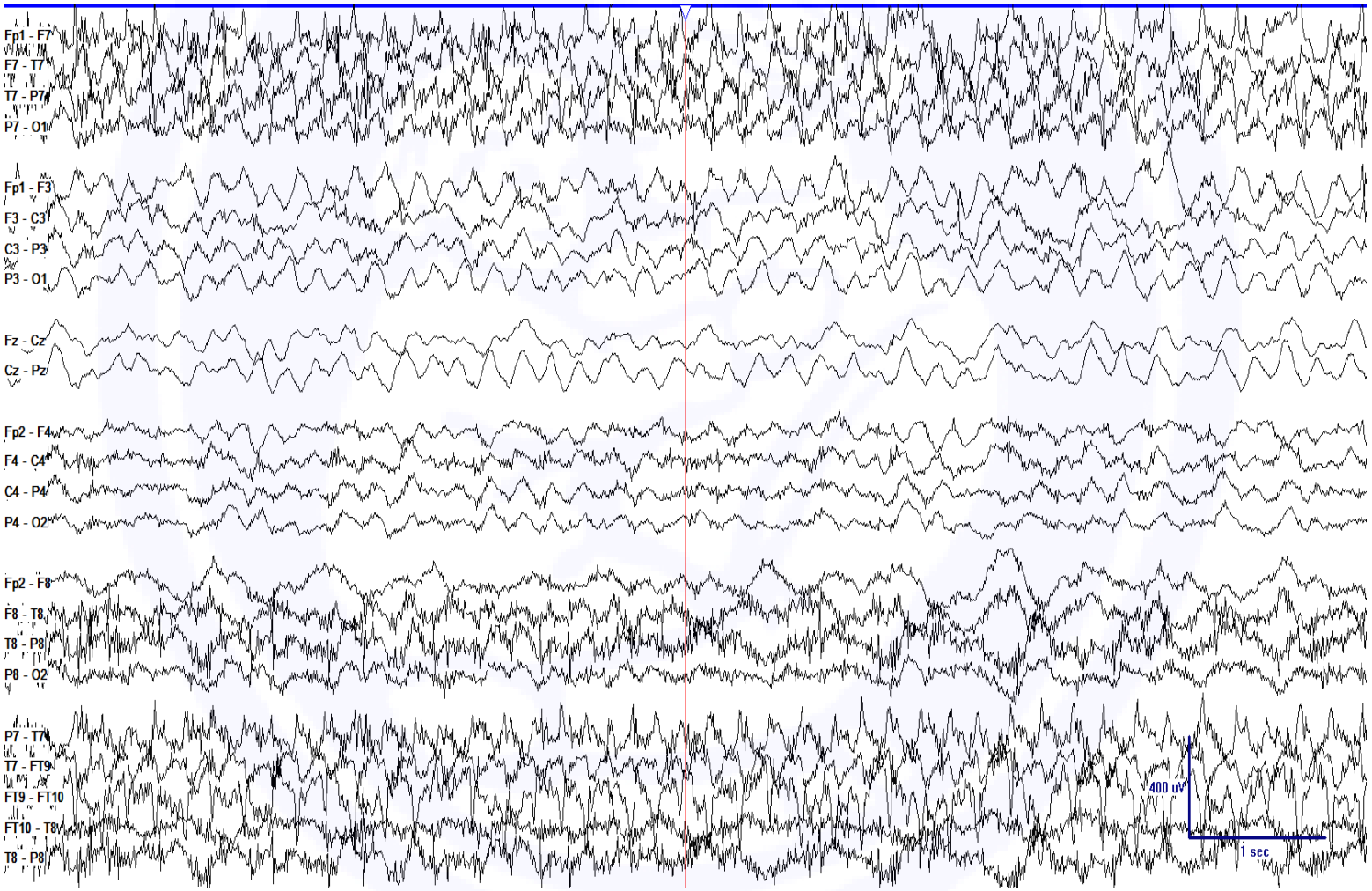
Ictal EEG



Ictal EEG



Ictal EEG



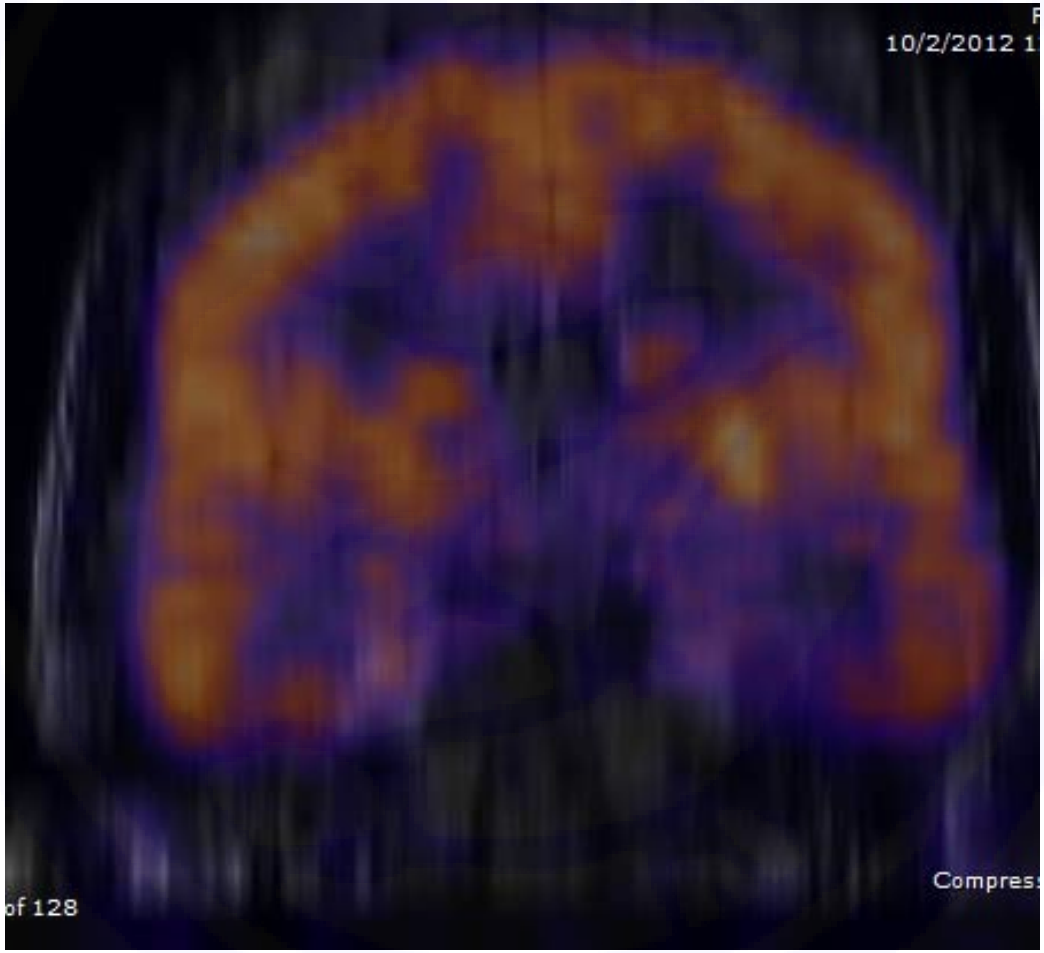
Presurgical Evaluation: Anatomic Imaging

- High resolution 3T MRI
- Epilepsy protocol with coronal slices through the temporal lobes
- Should be re-reviewed with skilled neuroradiologist after electrophysiologic data is available; look for subtle areas of cortical malformation
- Studies done before 2yrs of age may miss subtle FCD
- 7T MRI is available in limited centers on a research basis. Can provide even better detail of grey/white boarder

Presurgical Evaluations: PET and SPECT

- FDG-PET – Interictal study assessing areas of hypometabolism which may correspond to epileptogenic zone
- AMT-PET – Research based study useful in identifying the most epileptiform tuber in patients with TSC
- SPECT – SISCOM (subtraction ictal SPECT coregistered to MRI) – Assess areas of mismatched perfusion during seizures

PET



Presurgical Evaluation: Functional Testing

- fMRI – Able to define functional cortex for motor, language, memory and visual tasks. Provides some spatial relationship to theoretic epileptogenic zone
- WADA –Useful for lateralization of language, less well validated for memory function
- TMS – Non-invasive method for direct stimulation of cortex. Most useful for motor mapping, newer protocols for expressive language mapping as well.

Presurgical Evaluation: Functional Testing

Neuropsychology or neurodevelopmental testing is required for all patients pre-op

- Provides baseline level of functioning
- May provide further localization of poorly functioning brain regions
- Estimate risks of post-operative cognitive deficits

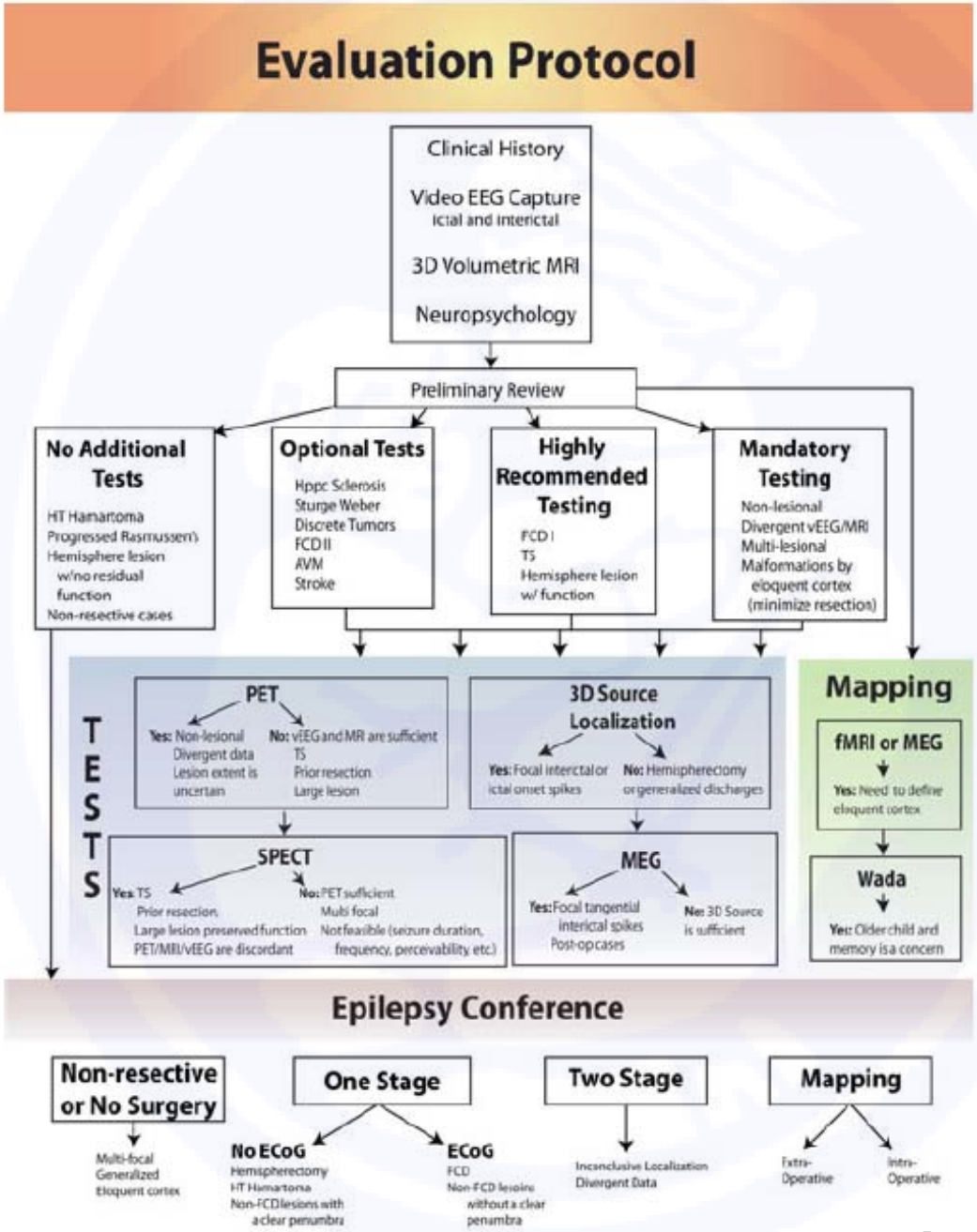


Figure 1.
Evaluation protocol.
Epilepsia © ILAE

Jayakar et al Epilepsia 2014

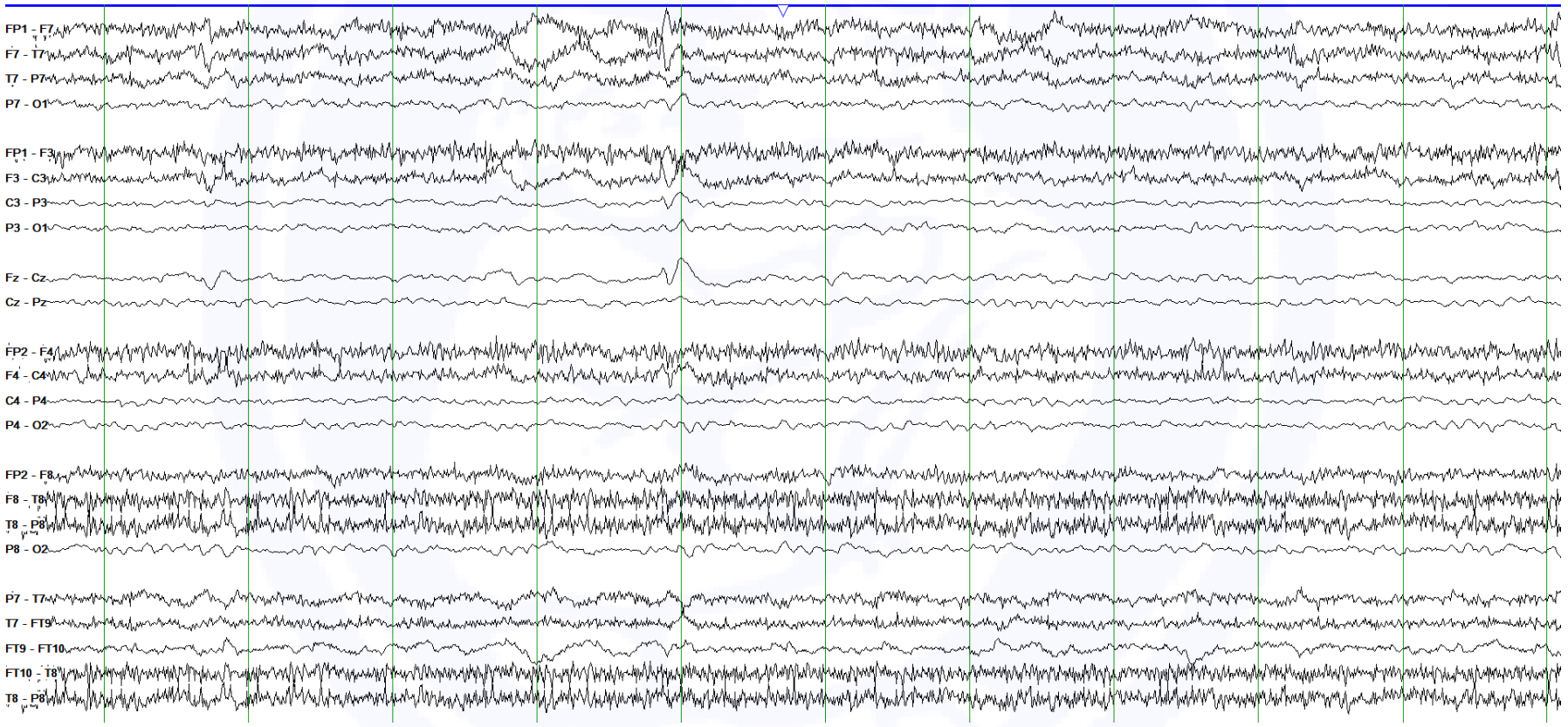
Epilepsy Surgery: Conclusions

- In medically refractory epilepsy, surgery may provide a significant chance at seizure freedom
- Patients require intensive testing with results discussed in a multidisciplinary surgical conference
- Surgery must be tailored to patients underlying pathology, level of function and predicted deficits

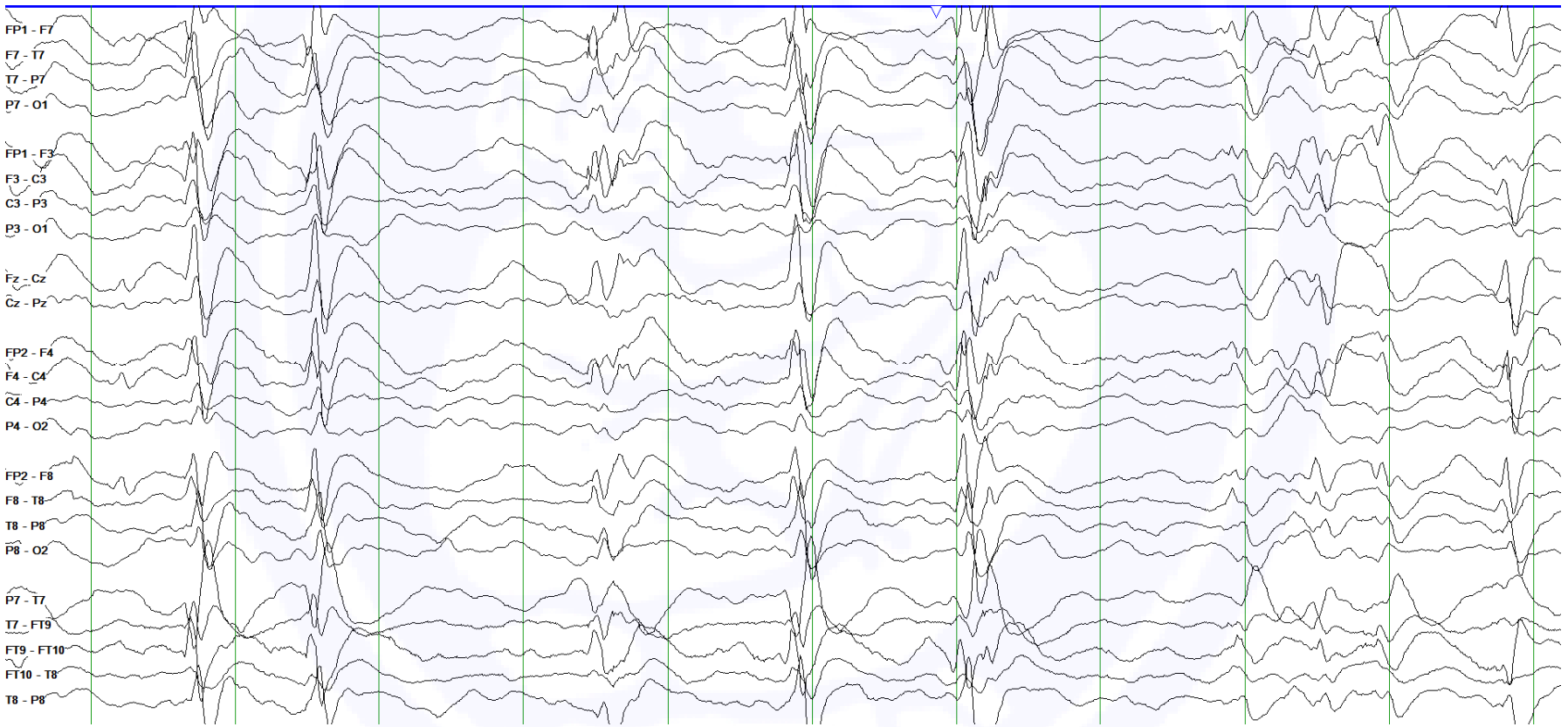
When to Refer: Epileptic Encephalopathy

- Epileptic encephalopathy embodies the notion that the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g., cortical malformation), and that these can worsen over time.
- These impairments may be global or more selective and they may occur along a spectrum of severity.
- May have early life onset with static encephalopathy or experience regression later in childhood with onset of epilepsy

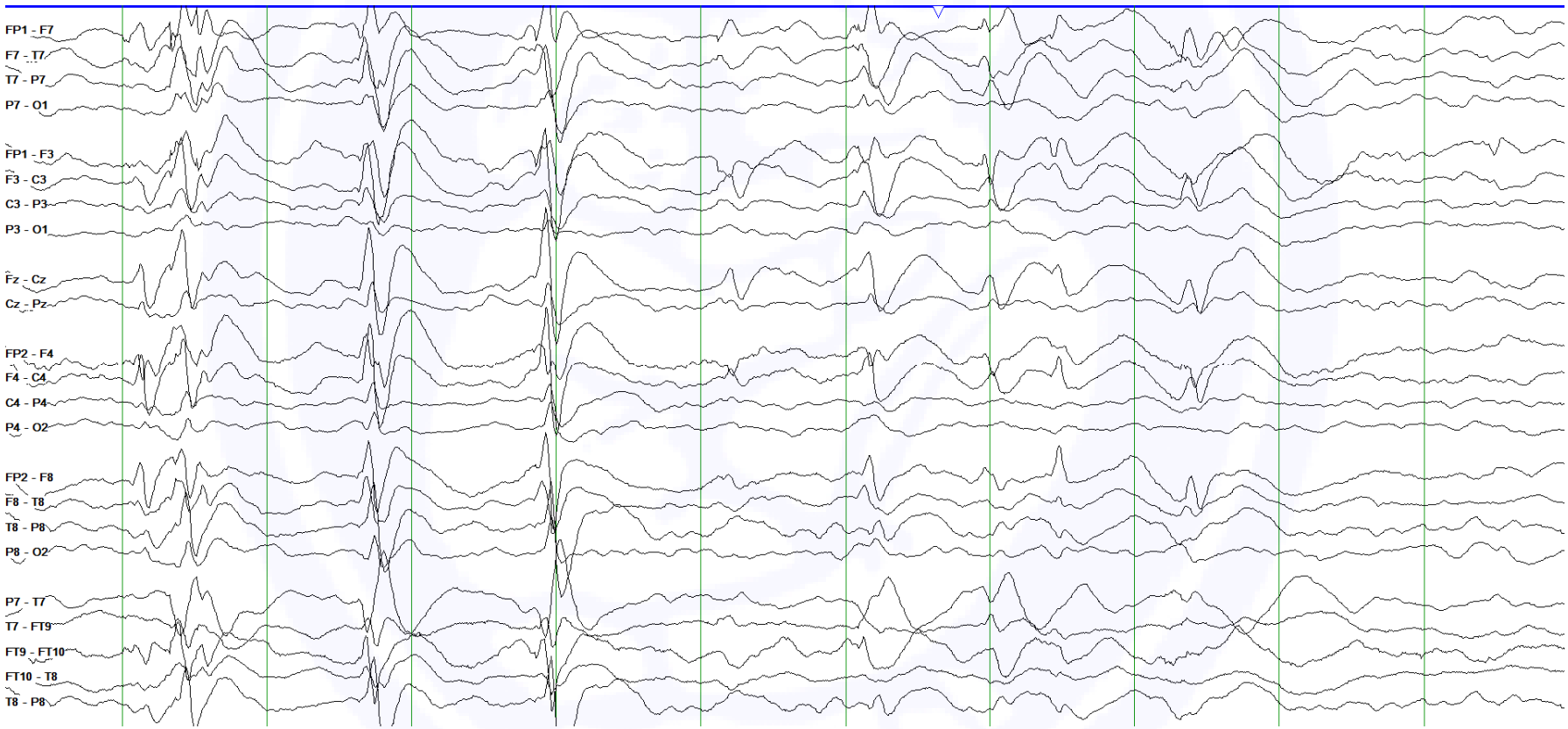
Epileptic Encephalopathy: ESES



Epileptic Encephalopathy: ESES



Epileptic Encephalopathy: ESES



When to Refer: Epileptic Encephalopathy

- Early myoclonic encephalopathy
- Ohtahara syndrome
- West syndrome
- Dravet syndrome
- Myoclonic status in nonprogressive encephalopathies
- Lennox-Gastaut syndrome
- Landau-Kleffner syndrome
- Epilepsy with continuous spike waves during slow-wave sleep
- Other genetic etiologies
  - CDKL5
  - KCNQ2

When to Refer: Conclusions

- Referral can take several forms
  - One time consultation
  - Co-management for surgery evaluation, keto diet, etc…
  - Transfer of care
- May provide insight into additional treatment options and/or diagnostic testing
- Should consider after failing two appropriate medications
- If lesional and refractory or with significant medication side effects, strongly suggest referral for surgical evaluation

When to refer

- Questions?