Epilepsies and Electroclinical Syndromes: Neonatal and Infantile

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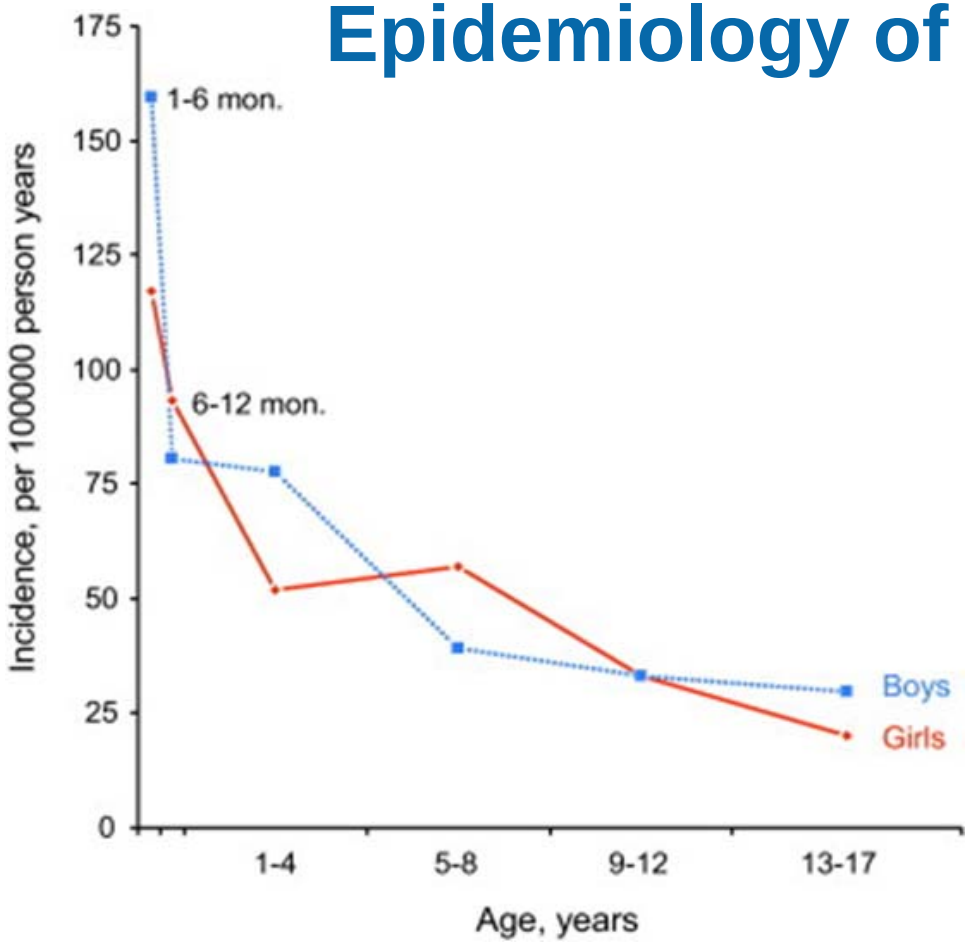
Objectives

- Overview of early-life epilepsy syndromes:
  - Self-limited
  - Developmental and Epileptic Encephalopathies
- Clinical and EEG features, treatment and prognosis

Epidemiology of Early Life Epilepsies



Wirrell et al. 2011

Many early-life epilepsies are considered DEEs

- **Developmental encephalopathy**
  - Due to underlying etiology
  - Not improved with better seizure control but may be helped with precision therapies
- **Epileptic encephalopathy**
  - Epileptic activity itself contributes to profound neurological and cognitive impairment, thus improved with better seizure control

Identifying *syndrome* and/or *etiology* may help to select the optimal therapy

- **SCN1A (Dravet)**
  - Use STP, CBD, FFA, avoid Na channel agents
- **TSC** –VGB
- **KCNQ2** and ezogabine
- **KCNT1** and quinidine
- **GRIN2A/2D** and memantine
- **SCN2A and SCN8A** and phenytoin

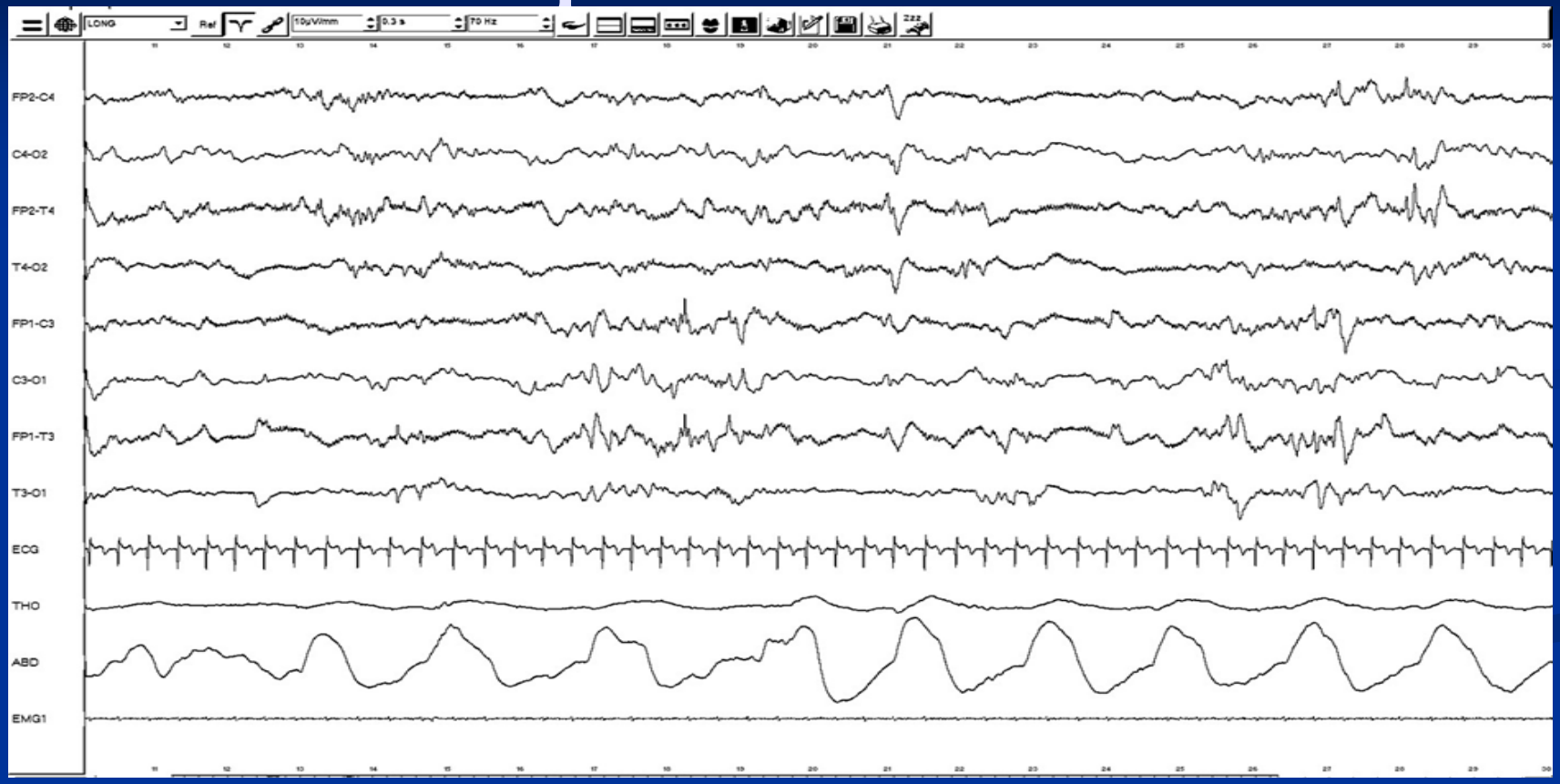
Chiron 2000, Ceulemans 2012, Curatolo 2016, Millichap 2016, Bearden 2014, Mikati 2015, Fukuoko 2017, Pierson 2014, Li 2016, Howell 2015, Boerma 2016

Self-Limited Syndromes

Self-limited Neonatal Epilepsy (familial and non-familial)

- Usual onset 2-7 days of age, otherwise well baby
- Focal clonic or focal tonic seizures, often with apnea/cyanosis, changing lateralization
- EEG:
  - normal, focal or multifocal discharges
  - ***Theta pointu alternant*** interictal pattern in 50% - runs of nonreactive theta, often intermixed with sharp waves, frequently with interhemispheric asynchrony

Theta pointu alternant



Self-limited Neonatal Epilepsy (familial and non-familial)

- Imaging normal
- Genetics: AD with incomplete penetrance. KCNQ2, KCNQ3 or SCN2A
- Usually resolves by 6 mos. Approx 10% may have seizures in later life

Self-limited Infantile Epilepsy (familial and nonfamilial)

- Onset between 3-20 months in neurologically normal infants
- Seizures are often frequent, focal (typically posterior onset), occur in clusters over several days and may secondarily generalize

Self Limited Infantile Epilepsy

- Interictal EEG: normal or posterior EDs
- Imaging is normal
- Genetic studies often positive – PRRT2 (90%), SCN2A, KCNQ2, KCNQ3
- Pharmacoresponsive and remit within 6-24 months
- Difficult to diagnose with certainty if genetics are negative, need careful follow-up to ensure epilepsy course is consistent with this diagnosis

Myoclonic Epilepsy of Infancy

- Rare compared to IS - ≈ 2% of epilepsies with onset before age 3 years
- Massive myoclonic jerks occurring singly or in brief cluster, in neurologically normal child between 4 mos and 3 yrs, often at sleep transitions
- Subgroup with reflex-induced seizures
- Positive family history for epilepsy or febrile convulsions in 30%

Myoclonic Epilepsy of Infancy

- EEG:
  - GSW maximal in sleep; photosensitivity may be seen
- Treatment:
  - Pharmacoresponsive (benzos, LEV or VPA)
  - AEDs can be weaned after 1-2 years
- DDx:
  - Benign myoclonus of infancy (normal EEG)
  - Infantile spasms
  - Other myoclonic epilepsy syndromes (Dravet, MAE)
  - Metabolic disorders

Genetic Epilepsy with Febrile Seizures Plus

- AD with incomplete penetrance, 2 or more family members affected
- Semiology varies:
  - FS and FS+ (persist beyond 6 yrs of age)
  - Focal or generalized afebrile seizures
  - Epileptic encephalopathies (Dravet, MAE)
  - Most are self-limited and pharmacoresponsive

Genetic Epilepsy with Febrile Seizures Plus

- EEG – nonspecific, may show GSW
- Neuroimaging normal if done
- Treatment: based on seizure semiology/frequency/syndrome

Developmental and Epileptic Encephalopathies

Early Infantile DEE

- Encompasses former Early Myoclonic Encephalopathy and Ohtahara syndrome
- Onset in first 3 months of life
- Abnormal neurological exam – tone, movement disorders, cortical visual impairment
- Moderate to severe ID with time

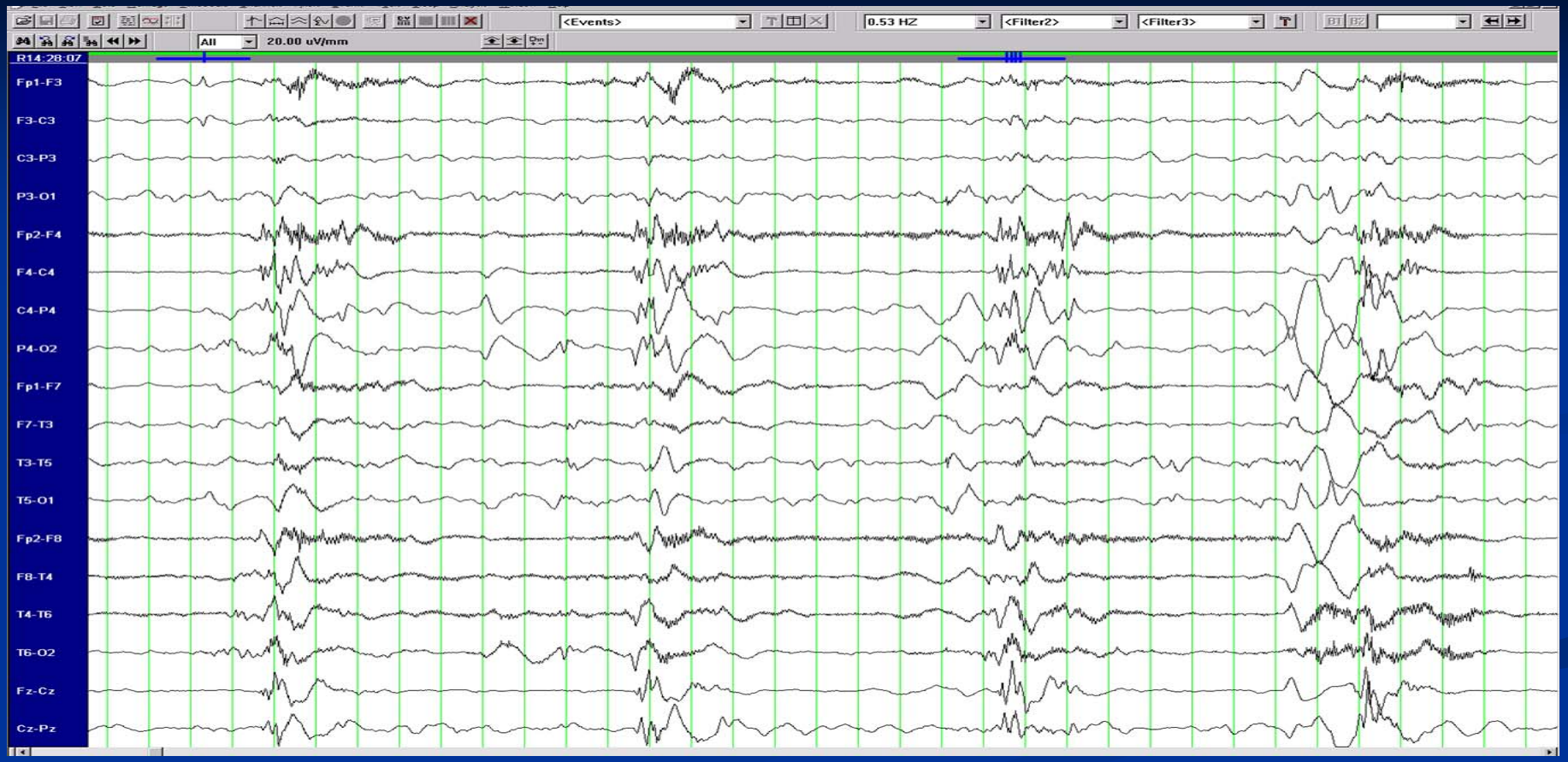
EIDEE – Seizures

- Very frequent, drug-resistant
- Seizure types vary – often several types:
  - Focal or generalized tonic – often in clusters
  - Myoclonic – erratic or massive bilateral
  - Spasms
  - *Sequential* seizures – progress in a sequential manner with tonic, clonic, myoclonic or spasms following each other, without a single predominant feature
  - Focal clonic

EIDEE

- EEG very abnormal and typically deteriorates shortly after seizure onset
  - Burst suppression or diffuse slowing with multifocal discharge
- Imaging – **structural** brain abnormalities are important and frequent causes

3 month old boy with focal spasms and focal clonic seizures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C4-P4
P4-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F8
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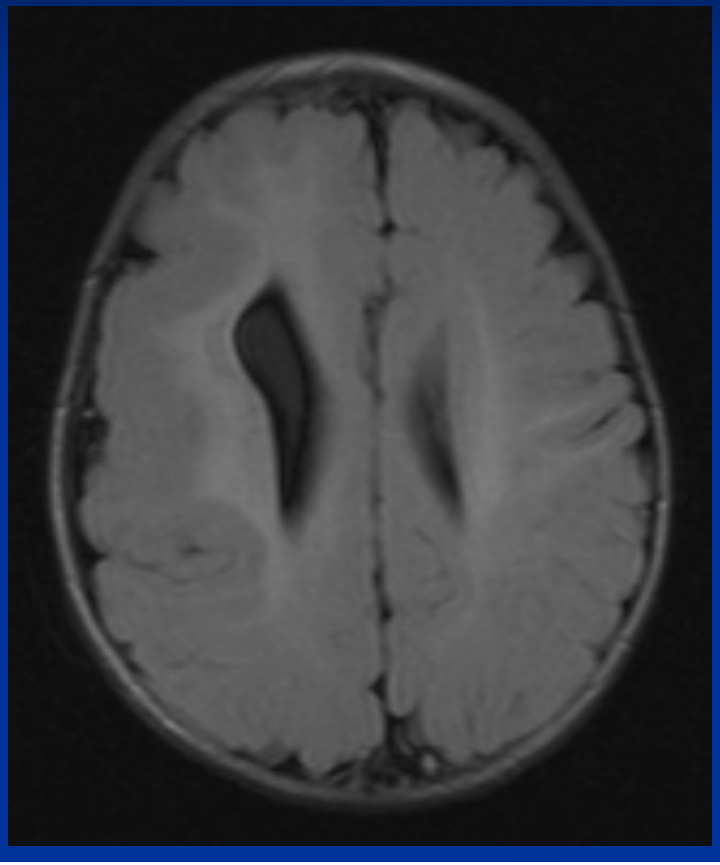
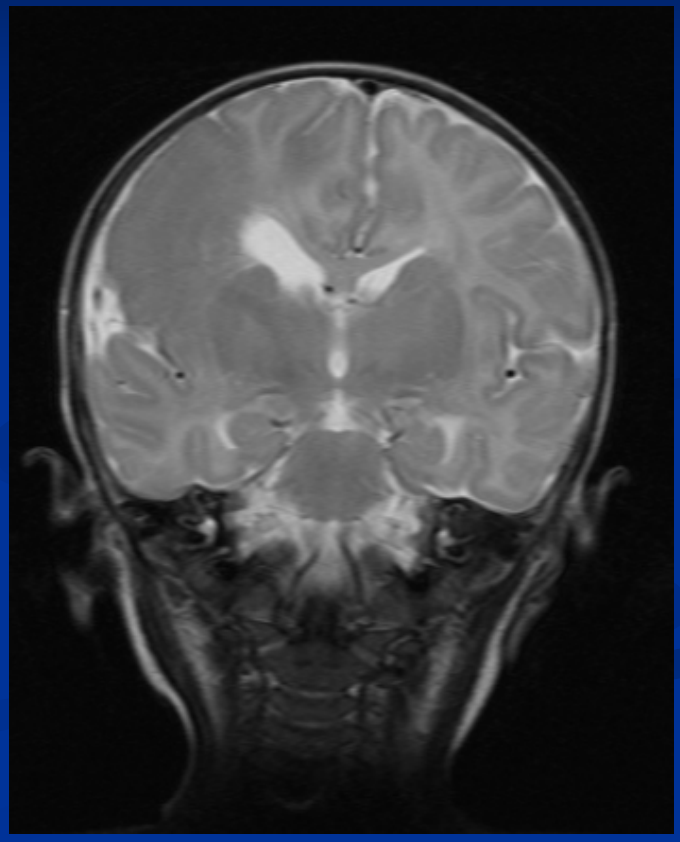
T4-T6
T6-O2
Fz-Cz
Cz-Pz

Right Hemimegalencephaly





EIDEE

- **Genetic** etiologies are found in >50% and may co-exist with abnormal neuroimaging
- **Metabolic** studies should be considered, particularly if MRI is normal

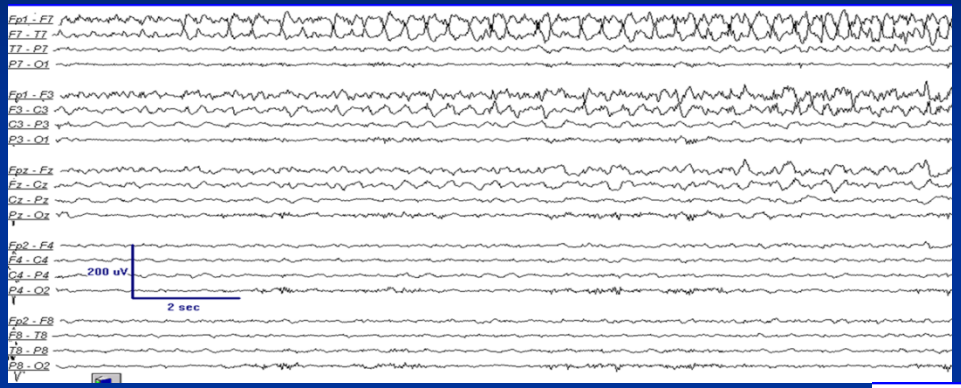
CDKL5 Hypermotor-tonic-spasm

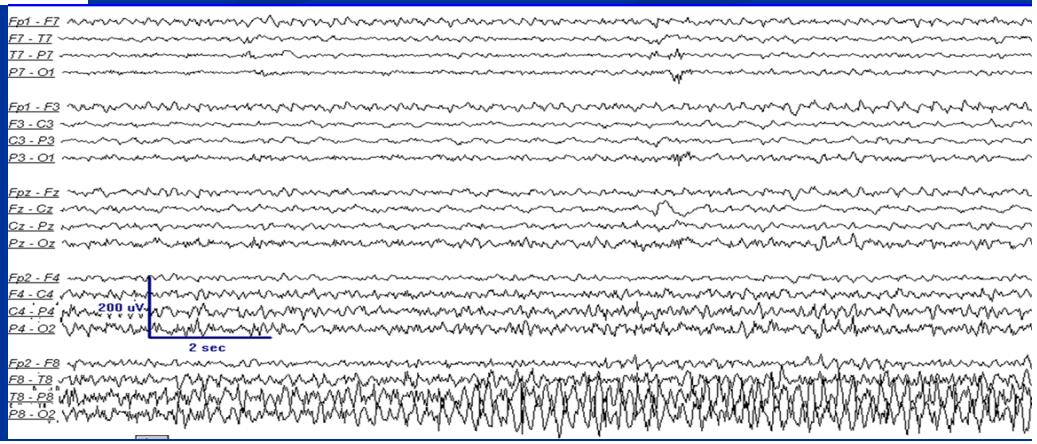
Klein et al. Neurology 2011

Epilepsy in Infancy with Migrating Focal Seizures

- Very frequent, multifocal seizures, often with autonomic features, onset <6 months
- Developmental plateau/regression
- Etiology:
  - often unknown
  - genetic mutations in a minority (KCNT1, SCN1A, SCN2A, SCN8A, and PLCB1)
  - MRI may be normal at onset but shows atrophy with time

EIMFS: Seizures show a migration pattern clinically or on EEG





EIMFS

- Treatment dictated by genetic mutation:
  - SCN2A and SCN8A –high dose phenytoin
  - KCNT1 - quinidine
  - Other options: levetiracetam, clobazam, rufinamide, ketogenic diet, stiripentol, bromides
- Long term prognosis for development and seizure control is poor

West (Infantile Spasms) Syndrome

- Most common severe epilepsy in first year of life (1 in 5000)
- Peak onset 3-9 months
- Seizures:
  - Clusters of spasms, characteristically shortly after waking
- Development:
  - Delay often precedes spasms
  - Often regress after spasm onset

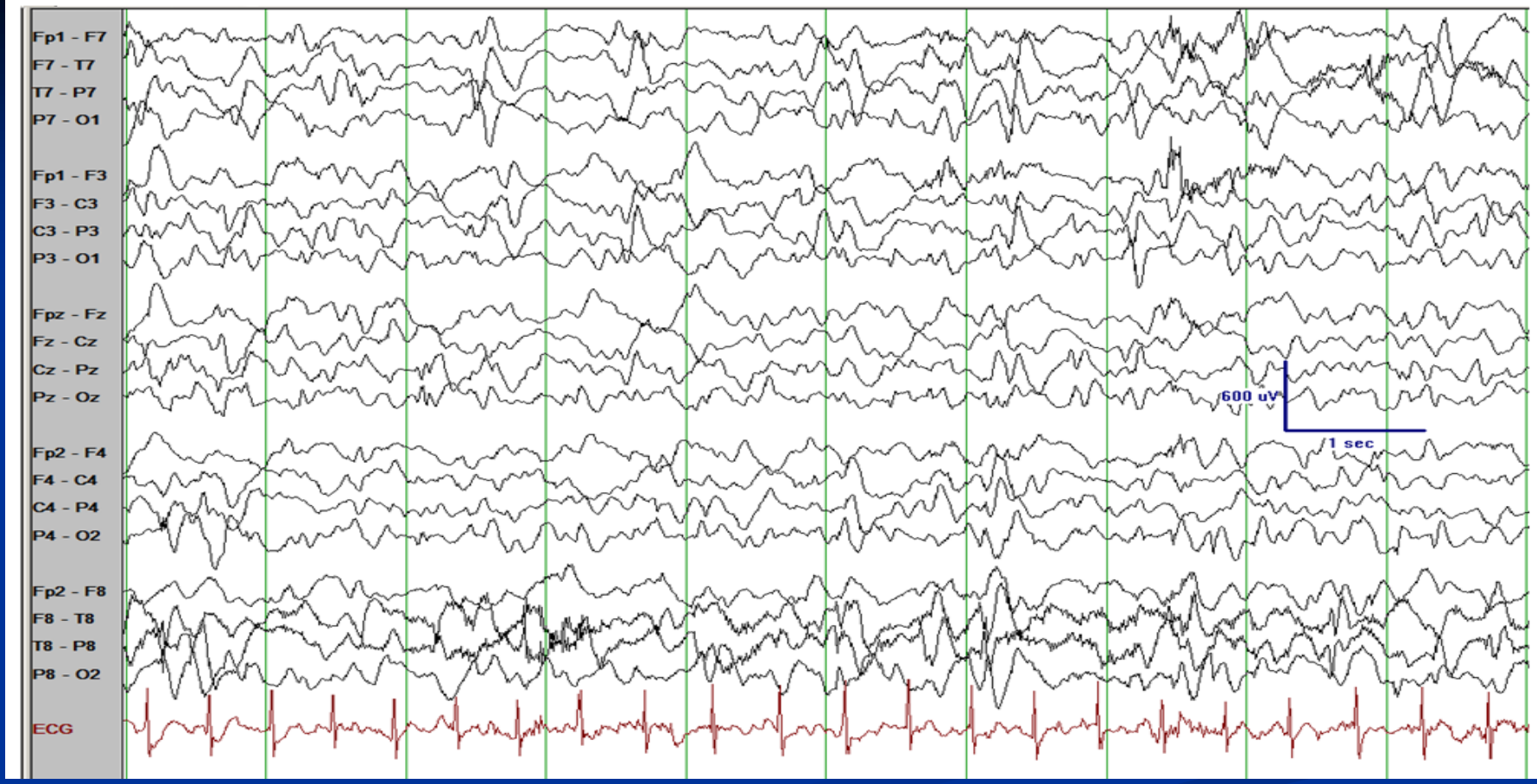
West Syndrome

- EEG
  - 90% have hypsarrhythmia interictally (should record nREM sleep)
    - High amplitude, slow background with multifocal discharge (*Mytinger et al. 2015*)
    - BUT lack of hypsarrhythmia should not change your treatment plan! (*Demarest et al. 2017*)
  - Ictal: slow wave preceded or followed by electrodecrement

Improving inter-rater reliability of hypsarrhythmia – BASED score

BASED score	Description
NA	When using five minute epochs, EEG grade 0 (normal) and 1 (any definite nonepileptiform abnormality) cannot be used
≤2	<3 spike foci **AND** no common background slow waves ≥200 μv[b,c]
3	MFS <50% of one second bins[a] and no common background slow waves ≥200 μv[b,c], **OR** no MFS but common background slow waves ≥200 μv[b,c]
4 Hypsarrhythmia[e]	MFS <50% of one second bins[a] **AND** common background slow waves ≥200 μv[b,c]
5 Hypsarrhythmia[e]	MFS ≥50% of one second bins[a], **OR** common background slow waves ≥300 μv[b,d] in two or more bilateral head regions

Mytinger et al. 2015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T7 - P7
P7 - O1
Fp1 - F3
F3 - C3
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P3 - O1
Fpz - Fz
Fz - Cz
Cz - Pz
Pz - Oz
Fp2 - F4
F4 - C4
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P4 - O2
Fp2 - F8
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P8 - O2
ECG
600 uV
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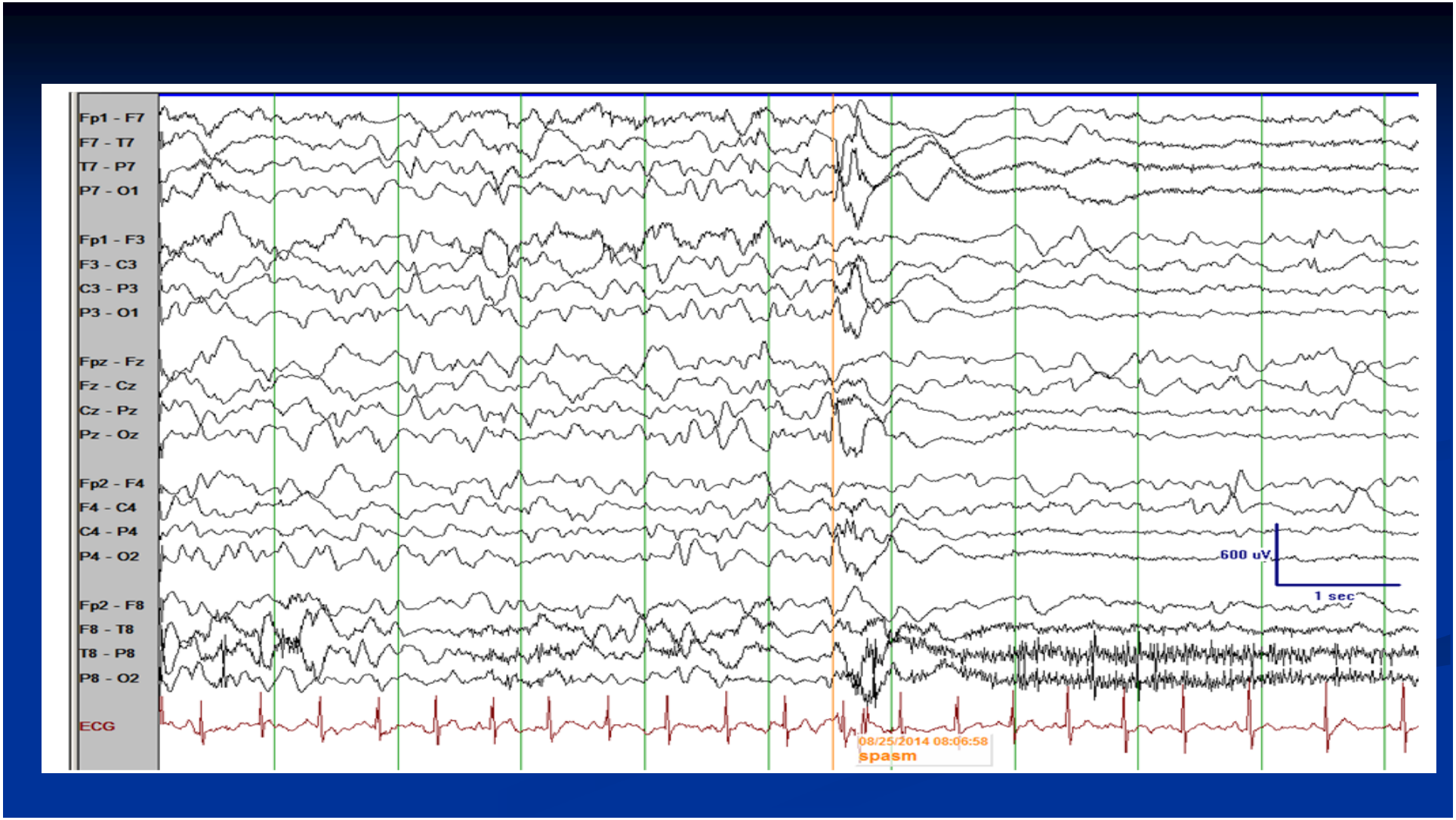
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P4 - O2
Fp2 - F8
F8 - T8
T8 - P8
P8 - O2
ECG
600 uV
1 sec
08/25/2014 08:06:58
spasm

West Syndrome
Etiology

- 20-30% - unknown
- 70-80% - known cause:
  - Structural – malformation or acquired
  - Genetic
  - Less commonly metabolic, infectious

West Syndrome: Treatment

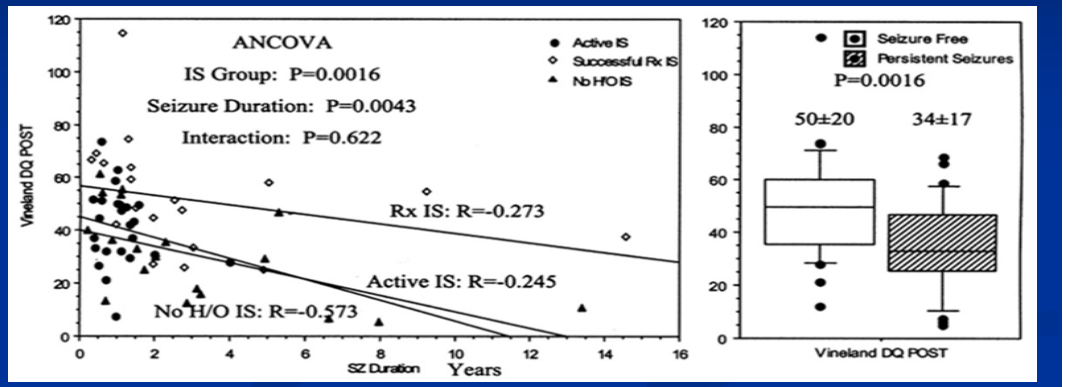
- First line agents:
  - Vigabatrin (150 mg/kg/d) – best if TSC or FCD
  - ACTH (150 U/m2) or high dose oral prednisolone (4-8 mg/kg/d, max 60 mg) – likely are similarly efficacious (*Grinspan et al. in press*)
  - Combination therapy most efficacious to stop spasms but did not alter longterm outcome (*O'Callaghan et al. 2017*)
- Pyridoxine trial if no clear underlying cause (100 mg/d x 1-2 wks) – should not delay first-line treatment
- TPM, VPA, CLN, ketogenic diet are other options but **not** first line

West Syndrome: Surgery

- Consider surgical evaluation if first line therapies fail and in whom a focal lesion is known or suspected
- Lack of classic hypsarrhythmia is more common in TSC or FCD
- Resections can be more localized or extensive (multilobar or hemispheric)
- Detection of FCD on MRI can be challenging in infants – other imaging modalities may be needed

West Syndrome: Surgery

- Outcomes:
  - 58-71% Engel Class 1
  - Better cognitive outcomes with shorter duration of epilepsy and presence of MRI lesion



Jonas et al. 2005, Chugani et al. 2015, Kwon et al. 2016

West Syndrome Prognosis

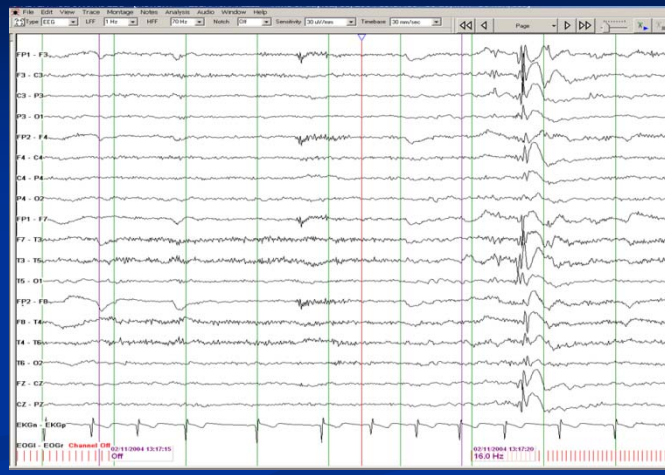
- Etiology matters:
  - Unknown cause - 40-50% good outcome
  - Known cause - >95% ID
- Risk of ASD longer term
- Spasms typically resolve by 1 year of age but are often replaced by other seizure types
- Longer the lag to effective treatment = poorer prognosis

Dravet Syndrome

- 5% of all early onset epilepsy
- Seizure types:
  - Recurrent, prolonged, hemiconvulsive seizures with fever in first year
  - Other seizure types onset between 1-6 years of age (myoclonus, atypical absences, focal seizures)
- Development:
  - normal prior to seizure onset
  - plateaus and rarely regresses in preschool years
- Most develop ataxia, pyramidal signs and crouch gait

Dravet Syndrome

- EEG
  - Abnormal by age 2 years
  - Slow background
  - Focal, multifocal or generalized d/c
  - Some show early photosensitivity



- Imaging and metabolic studies are normal
- 80% have SCN1A mutation (often truncated protein) – but not all SCN1A mutations lead to Dravet syndrome
- Treatment:
  - VERY resistant to ASMs
  - Older standards: clobazam, valproic acid, topiramate, ketogenic diet,

Dravet Syndrome: New Treatment Options

Study	>50% reduction in seizures	>75% reduction in seizures
Fenfluramine vs Placebo	70% vs 7.5%	45% vs 2.5%
Cannabidiol vs Placebo	43% vs 27%	
Stiripentol vs Placebo	71% vs 5%	

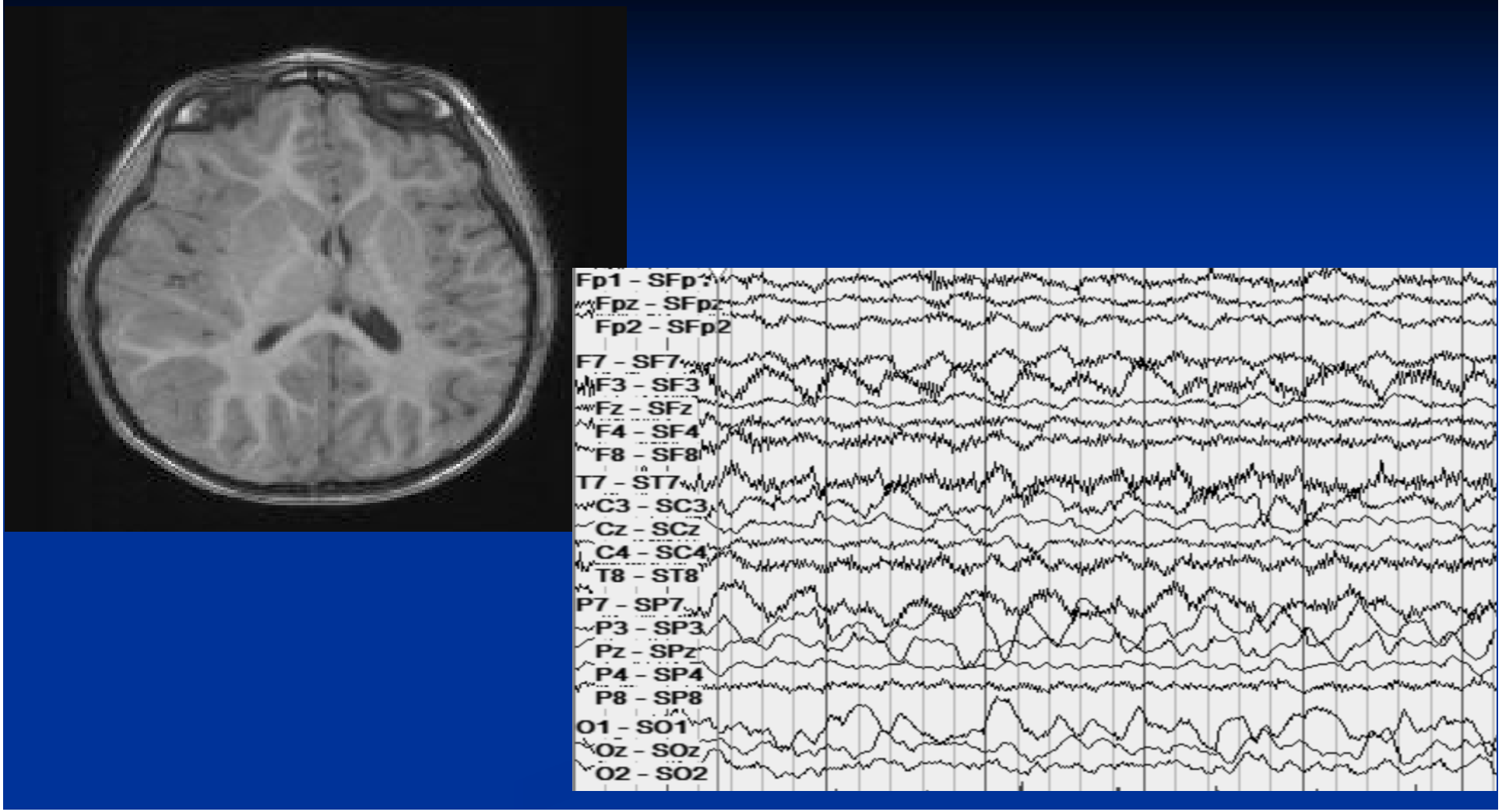
Lagae et al. Lancet 2019, Devinsky et al. NEJM 2017, Chiron et al. Lancet 2000

Dravet: Prognosis

- Seizures are pharmacoresistent
- By early adolescence/adulthood: brief, nocturnal GTCS continue but other seizures have resolved
- ID in all but severity varies – worse outcome if longer use of CIM *(de Lange et al. 2018)*
- High risk of SUDEP
- Parkinsonian features as adults

Hemiconvulsions, Hemiplegia, and Epilepsy Syndrome (HHE)

- Rare, onset <4 yrs with prolonged unilateral SE with febrile illness followed by immediate hemiplegia
- Months-years later - intractable focal epilepsy
- EEG – slowing and EDs over affected hemisphere
- MRI – edema of affected hemisphere at time of initial SE, then progressive atrophy
- Hemispherotomy often required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T7 – ST7
C3 – SC3
Cz – SCz
C4 – SC4
T8 – ST8
P7 – SP7
P3 – SP3
Pz – SPz
P4 – SP4
P8 – SP8
O1 – SO1
Oz – SOz
O2 – SO2

Conclusions: Early-life Epilepsies

- High rates of intractability (1/3) and significant neurological disability
- Identifying etiology and syndrome assists with prognosis and informs best therapy
- Genetic testing is high yield
- Consider surgical evaluation if medically intractable and possible focal structural lesion
  - TIME is BRAIN