2023 GW Epilepsy Board Review & Best Practices

ELECTROCLINICAL EPILEPSY SYNDROMES

GWU Board Review Course
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What constitutes an electroclinical syndrome?

- Specific clinical and EEG features, etiologic findings, and prognostic/treatment implications
- Age-dependent presentations
- Range of co-morbidities (development, IQ, psychiatric)

Classification based on age

- Neonatal and infantile onset
- Childhood Onset
- Variable age at onset

Etiology-specific epilepsy syndromes

- Etiology specific epilepsies with distinct phenotype
  - Genetic: CDKL5-DEE, KCNQ2-DEE
  - Immune-mediated: Rasmussen's, FIRES
  - Structural- Mesial temporal lobe epilepsy with hippocampal sclerosis, gelastic seizures with hypothalamic hamartoma

Neonatal and Infantile Onset

- **Self-limited epilepsies**
  - Self-limited neonatal epilepsy
  - Self-limited familial neonatal-infantile epilepsy
  - Self-limited infantile epilepsy
  - Genetic epilepsy with febrile seizures plus
  - Myoclonic epilepsy in infancy
- **Developmental and epileptic encephalopathies (DEE)**
  - Early infantile developmental and epileptic encephalopathy
  - Epilepsy in infancy with migrating focal seizures
  - Infantile spasms
  - Dravet syndrome
- **Etiology specific syndromes**
  - KCNQ2-DEE, Pyridoxine-dependent-DEE, Pyridoxamine 5-phosphate-DEE, CDKL5-DEE, Glucose transporter 1 deficiency syndrome, Sturge Weber, Gelastic seizures with hypothalamic hamartomas

Childhood Onset

- **Self-limited focal epilepsies**
  - BECTS→ Self-limited epilepsy with centrotemporal spikes (SeLECTS)
  - Panayiotopoulos→ Self-limited epilepsy with autonomic seizures (SeLEAS)
  - Benign occipital epilepsy→ Childhood occipital visual epilepsy (COVE)
  - Photosensitive occipital lobe epilepsy (POLE)
- **Genetic generalized epilepsies**
  - Childhood absence epilepsy (CAE)
  - Jeavons→ Epilepsy with eyelid myoclonia (EEM)
  - Epilepsy with myoclonic-absence (EMA)
- **DEEs**
  - Doose→ Epilepsy with myoclonic-atonic seizures (EMAtS)
  - Lennox-gastaut syndrome
  - CSWS→Epileptic encephalopathy with spike and wave activation in sleep (EE-SWAS), Landau-Kleffner
  - Developmental epileptic encephalopathy with spike and wave activation in sleep (DEE-SWAS)

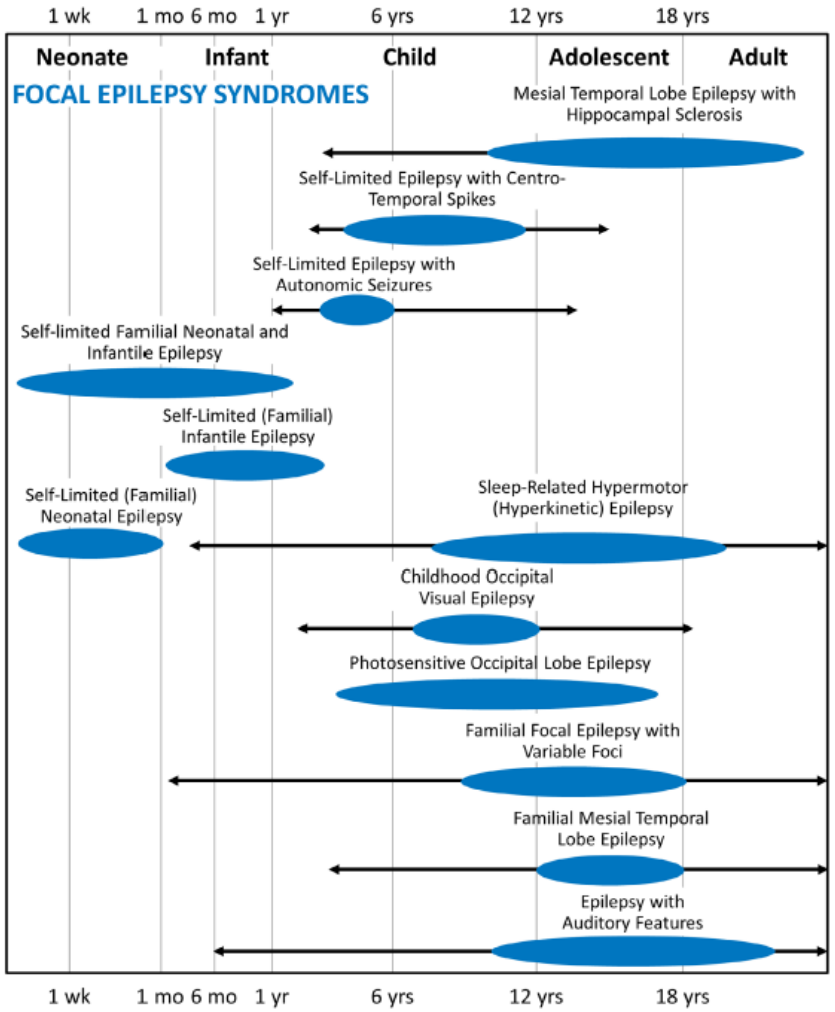
Adolescent onset

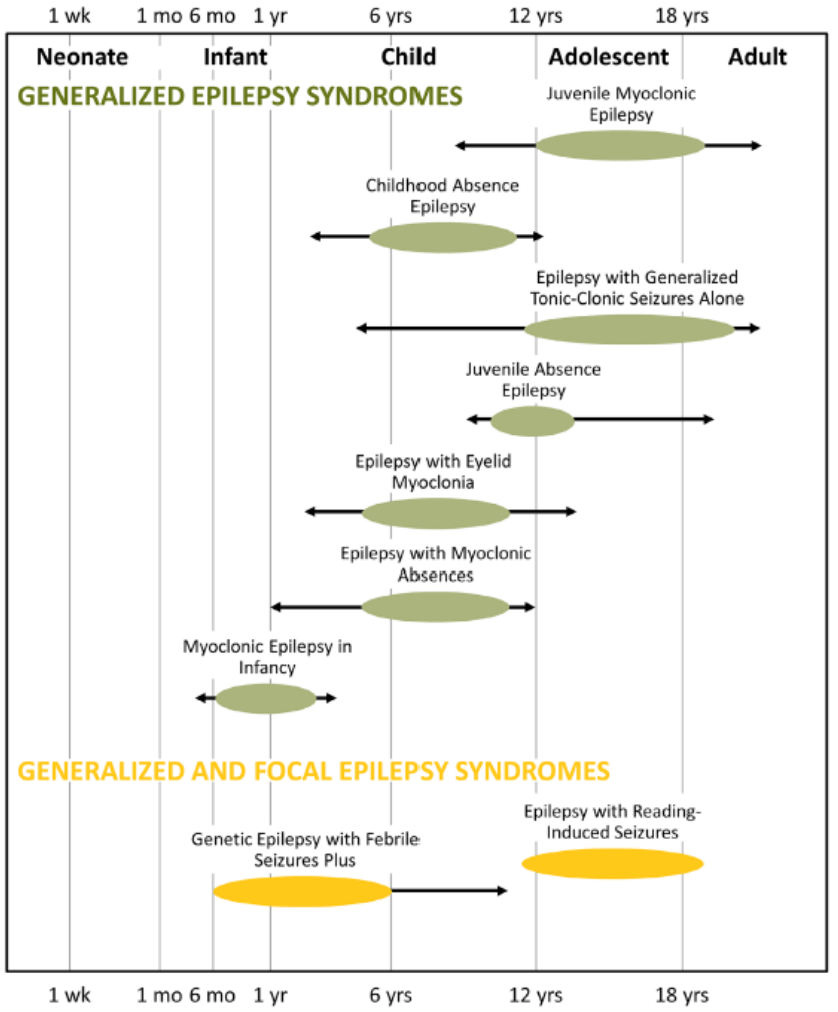
- **Genetic generalized epilepsies**
  - Juvenile absence epilepsy
  - Juvenile myoclonic epilepsy

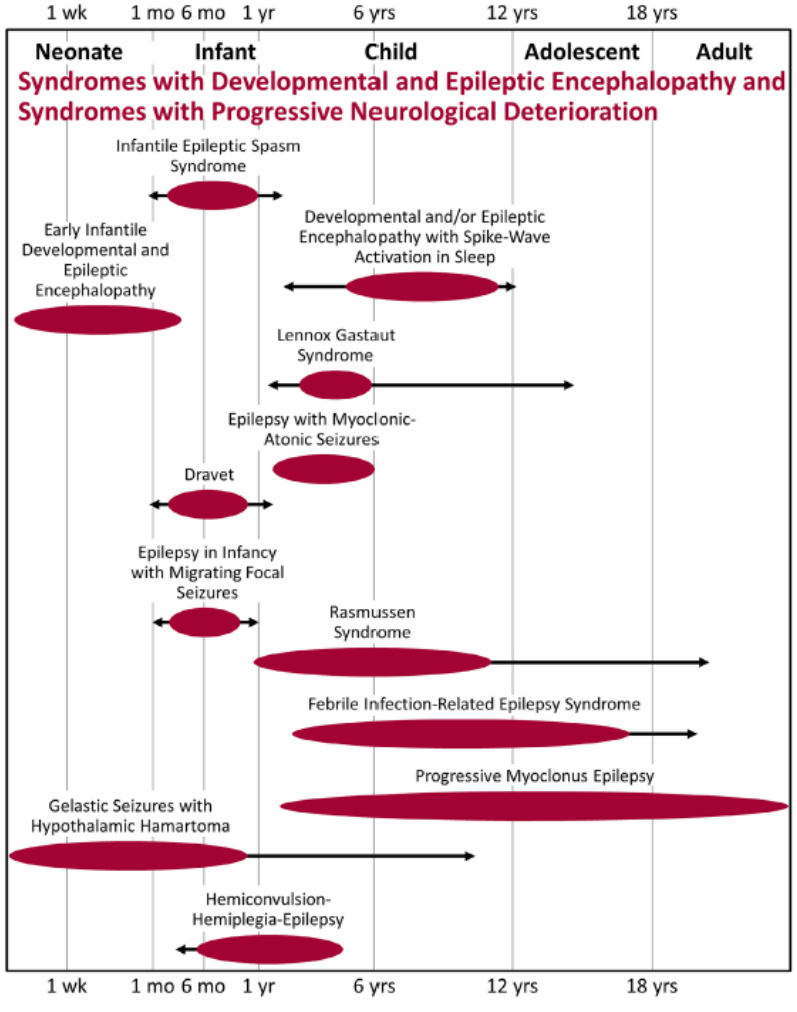
Variable age at onset (childhood, adolescent or adult)

- Genetic generalized epilepsy
  - Epilepsy with generalized tonic-clonic seizures (GTCA)
- Focal epilepsy syndromes
  - Familial mesial temporal lobe epilepsy (FMTLE)
  - Epilepsy with auditory features (EAF)
  - MTLE with hippocampal sclerosis (MTLE-HS)
  - Sleep related hypermotor epilepsy (SHE)
  - Familial focal epilepsy with variable foci
- Generalized + focal epilepsy
  - Epilepsy with reading induced seizures (EwRIS)
- Epilepsy with DEE or progressive neurologic decline
  - Febrile-infection related epilepsy syndrome (FIRES)
  - Rasmussen syndrome
  - Progressive myoclonic epilepsies (PME)

Subgroup classification based on syndrome type







ILAE 2022 Task Force

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Neonatal onset epilepsies

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Epilepsy	Age onset (mean)	Gene	Sz control	Outcome
Self-limited familial neonatal-infantile epilepsy	DOL 2- 30 (1st week)	**KCNQ2**, KCNQ3	Resolve 6-12mo, respond best to oxcarbazepine	Good
Self-limited neonatal epilepsy	DOL 1- 7	?		
Self-limited infantile epilepsy	DOL2- 6 mos (3mos)	SCN2a		
KCNQ2 DEE	First week of life	KCNQ2	Poor until 3 years old	Intellectual disability, CP
Early Infantile Epileptic Encephalopathy (EIEE/Ohtahara)	First week -3 mos	STXBP1, ARX, dysgenesis	Poor	Dev arrest
Early Myoclonic Encephalopathy (EME)	First week -3 mos	Inborn error	Poor	Dev arrest
Epilepsy in infancy with migrating focal seizures	First 6 mos (1 day to 7 mos)	SCN1a, KCNT1	Poor until 1-5 years old	Intellectual disability, CP
Focal dysgenesis, hemimegalencephy	Days to first year of life	Multiple	Variable	Variable
Global dysgenesis	First year of life	Multiple	Usually fair	Intellectual disability
Tuberous sclerosis	First year of life	TSC 1	Variable	Variable

Slide courtesy of Dr. Tammy Tsuchida; Deprez, Neurology 2009; Ottman, Epilepsia 2010; Yamamoto, Brain Dev 2011; Hildebrand, J Med Gen 2013

Self-limited (familial) neonatal-infantile epilepsies

- Seizure onset first week of life in >80%
- Seizure appearance variable- generalized or focal tonic with autonomic (apnea,cyanosis), oral automatisms, body or limb clonic
- Respond best to Na channel ASM: CBZ or OXC
- EEG in between seizures often normal-mild abnormalities
- Causes: KCNQ2, KCNQ3, SCN2A (infantile onset)
  - Autosomal dominant, 85% penetrance
- Seizures often stop by 4-18 months BUT
  - Febrile seizures in 5%
  - Epilepsy in 11-25%
- Normal neurodevelopmental outcome

Singh Brain 2003; Borgatti Neurology 2004; Grinton Epilepsia 2015; Sands Epilepsia 2016; Shellhaas Neurology 2017

KCNQ2-DEE

- Presents in first week of life with seizures similar to BFNS.
- EEG:
  - Neonatal- suppression burst or discontinuous or multifocal epileptiform discharges.
  - Infancy- hypsarrhythmia or multifocal epileptiform discharges
- Epilepsy can be difficult to control initially
  - Those with refractory epilepsy- seizure frequency decreases over the first years of life.
  - Some seizure free from 3-8 years.
  - Can respond well to CBZ, PHT
- Neurodevelopmental outcome- mild to profound intellectual disability, cerebral palsy (Better if early seizure control)

Weckhuysen Ann Neurol 2012, Neurol 2013; Saitsu Ann Neurol 2012; Kato Epilepsia 2013; Pisano Epilepsia 2015

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Early infantile developmental and epileptic encephalopathy

Early myoclonic epilepsy (EME) vs. Early infantile epileptic encephalopathy (EIEE)

	EME	EIEE
Etiology	Inborn errors of metabolism Genetic Unknown	Cerebral dysgenesis Genetic Unknown
Seizure onset	Neonatal	Within 3 weeks of life
Neurologic status at presentation	Abnormal from birth or increasingly abnormal after seizure onset	Abnormal prior to seizure onset
Hallmark seizure semiology	Erratic myoclonus	Tonic spasms
Interictal neonatal EEG	Burst suppression, especially during sleep	Burst suppression, during wakefulness and sleep
Natural history	Progressive neurologic impairment High risk of infantile spasms High risk of death in infancy	Static neurologic impairment High risk of infantile spasms and, later, Lennox–Gastaut syndrome High risk of death in infancy or childhood

De Vries and Glass, Handbook of Clinical Neurology: Neonatal Neurology 2019

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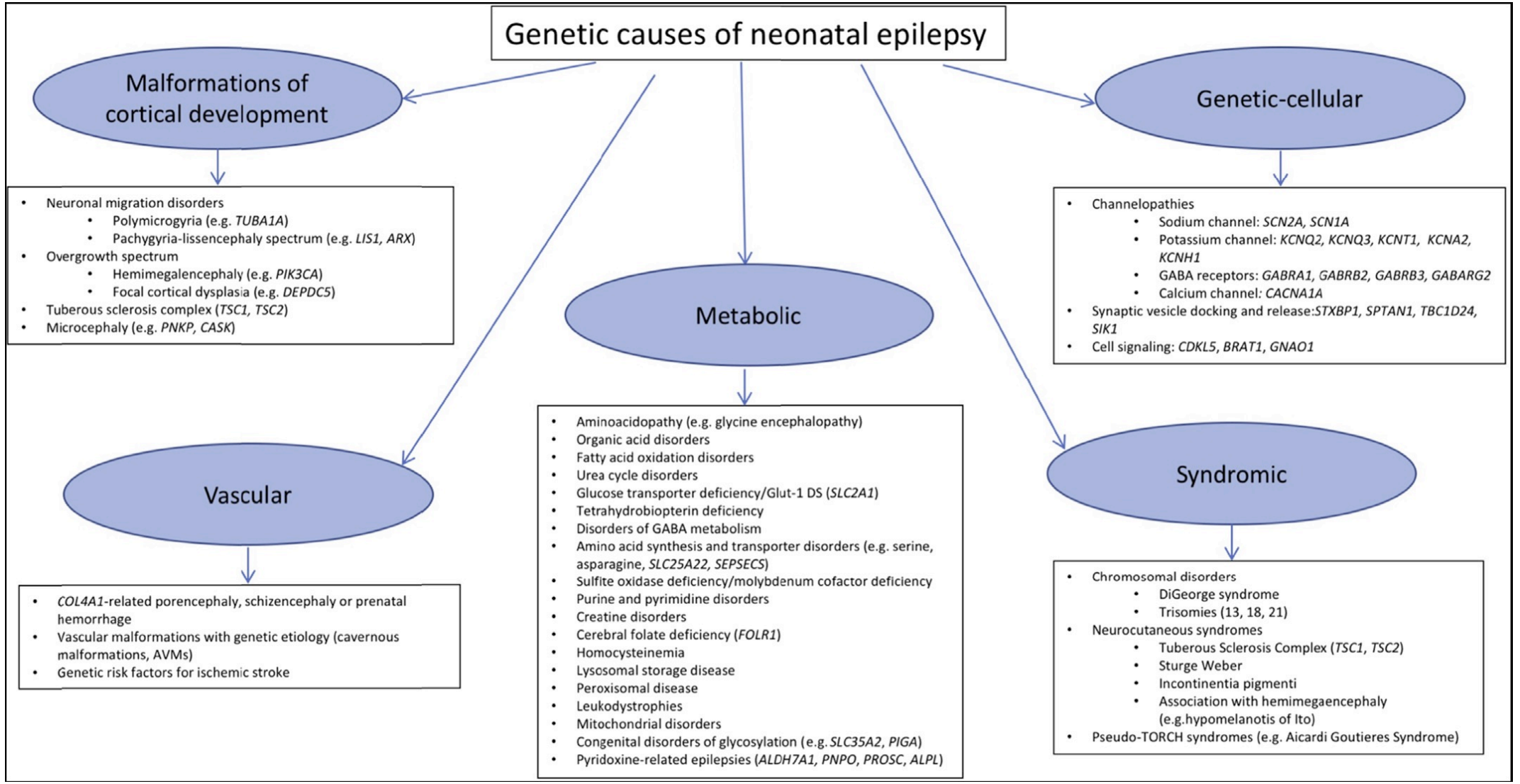
Epilepsy in infancy with migrating focal seizures (EIMFS)

- Normal development prior to sz
- Seizures
  - Onset 40 days-3mos (1day-6 months) and initially up to 30/day or status epilepticus refractory to therapy then infrequent seizures after 1-5 years of age
  - Appearance-initial migrating focal motor seizures, prominent autonomic (apnea, flushing,cyanosis) and later multifocal sz or infantile spasms
- Interictal EEG
  - Initial- normal or slow with few or multifocal epileptiform discharges
  - Later- periods of attenuation, (modified) hypsarrhythmia
- Cause:KCNT1 gain of function (39% cases)
- Treatment
  - rufinamide, levetiracetam, valproic acid, stiripentol, potassium bromide, ketogenic diet, vigabatrin, ethosuximide, quinidine* (if KCNT1; monitor for long QT, torsades, other arrhythmia)
- Outcomes
  - Profound psychomotor delay and death in those with refractory seizures

Coppola, Epilepsia 2009; Carranza, Neur 2011; Frelich, Arch Neur 2011; Barcia, Nat Gen 2012, McTague, Brain 2013



Axeen and Olson, Sem Fetal Neonat Med 2018

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Treatable vitamin-dependent epilepsies

Disease	Diagnosis	Treatment
Pyridoxine dependency	Serum pipecolic acid, α-aminoadipic semialdehyde, csf chromatogram for folinic acid/pyridoxine dependent sz peak, ALDH7A1 mutation analysis	On EEG with code cart- pyridoxine 100mg, repeat up to 500 mg IV Chronic 15-30 mg/kg/day (max 500 mg/day)
Pyridoxal phosphate (PLP) dependency	Csf aa, pyridoxal phosphate, NT metabolites (L-DOPA, HVA, 5-HIAA, 3-OMD), urine vanillacetic acid, PNPO mutation	Pyridoxal phosphate 30-50 mg/kg/day (divided TID or QID)
Folinic acid responsive	csf chromatogram for folinic acid/pyridoxine dependent sz peak	Folinic acid (leucovorin) 3-5 mg/kg/day, pyridoxine
Congenital folate malabsorption	Serum and csf 5-methyltetrahydrofolate	Folinic acid 0.5-5 mg/kg/day, methionine, vitamin B12
Biotinidase deficiency	Biotinidase, Lactate/pyruvate, plasma amino acids, urine organic acids	Biotin 10-20 mg/day
Holocarboxylase synthetase deficiency	Lactate/pyruvate, plasma amino acids, urine organic acids	Biotin 10-20 mg/day
Glucose transporter deficiency (Glut-1)	CSF glucose < 40 mg/dl (csf/blood <0.65), lactate < 1.3 mM SLC2A1 genetic mutations	Ketogenic diet Avoid inhibitors of glucose transporter: phenobarbital, valproate, benzodiazepines

Slide courtesy of Dr. Tammy Tsuchida, Inherited Metabolic Epilepsies, Pearl, 2012

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Infantile epilepsy panel

Gene	Inheritance	Condition
ADSL (22q13.1)	AR	Adenylosuccinate lyase deficiency
ALDH7A1 (5q23.2)	AR	Pyridoxine-responsive epilepsy
ARX (Xp21.3)	XL	Development and Epileptic Encephalopathy 1 (DEE)
ATP6AP2 (Xp11.4)	XL	Congenital disorder of glysolation
CDKL5 (Xp22.13)	XL	Atypical Rett's/DEE2
CHRNA7 (15q13.3)	AR	Microdeletion syndrome
CLN3 (16p12.1)	AR	Neuronal Ceroid Lipofuscinosis (NCL)
CLN5 (13q22.3)	AR	NCL
CLN6 (15q23)	AR	NCL
CLN8 (8p23.3)	AR	NCL
CNTNAP2 (7q35-36.1)	AR	Pitt-Hopkins Syndrome
CTSD (11p15.5)	AR	NCL
FOLR1 (11q13.4)	AR	Cerebral folate transport deficiency
FOXG1 (14q12)	AD	Rett syndrome
GABRA1 (5q34)	AD	DEE19
GABRG2 (5q34)	AD	DEE74
GAMT (19p13.3)	AR	Guanidinoacetate methyltransferase deficiency
GRIN2A (16p13.2)	AD	Focal epilepsy with speech disorders with or without mental retardation
GRIN2B (12p13.1)	AD	DEE27
KANSL1 (17q21.31)	AD	Koolen-de Vries syndrome
KCNJ10 (1q23.2)	AR	EAST syndrome
KCNQ2 (20q13.33)	AD	Benign familial neonatal epilepsy (BFNE), DEE7
KCNQ3 (8q24.22)	AD	BFNE
KCTD7 (7q11.21)	AR	Progressive myoclonic epilepsy
LIAS (4p14)	AR	Pyruvate dehydrogenase lipoic acid synthetase deficiency
MAGI2 (7q21.11)	AR	Infantile spasms
MBD5 (2q23.1)	AD	MBD5 Haploinsufficiency
MECP2 (Xq28)	XL	Rett syndrome, severe neonatal-onset encephalopathy with microcephaly
MEF2C (5q14.3)	AD	Rett-like syndrome: Neurodevelopmental disorder with hypotonia, stereotypic hand movements and impaired language (NEDHSIL)
MFSD8 (4q28.2)	AR	NCL
NRXN1 (2p16.3)	AR	Pitt-Hopkins-like syndrome
PCDH19 (Xq22.1)	XL	DEE9
PNKP (19q13.33)	AR	DEE10
PNPO (17q21.32)	AR	Pyridoxal phosphate-responsive seizures
POLG (15q26.1)	AR	Progressive mitochondrial disorder
PPT1 (1p34.2)	AR	NCL
PRRT2 (16p11.2)	AR	Benign familial infantile epilepsy
SCN1A (2q24.3)	AD	DEE6
SCN1B (19q13.11)	AD	DEE52
SCN2A (2q24.3)	AD	DEE11
SCN8A (12q13.13)	AD	DEE13
SLC25A22 (11p15.5)	AR	DEE3
SLC2A1 (1p34.2)	AD	GLUT1 deficiency
SLC9A6 (Xq26.3)	XL	Christianson syndrome
SPTAN1 (9q34.11)	AD	DEE5
STXBP1 (9q34.11)	AD	DEE4
TBC1D24 (16p13.3)	AR	DEE16, Familial myoclonic epilepsy
TCF4 (18q21.2)	AD	Pitt-Hopkins syndrome
TPP1 (11p15.4)	AR	NCL
TSC1 (9q34.13)	AD	Tuberous sclerosis
TSC2 (16p13.3)	AD	Tuberous sclerosis
UBE3A (15q11.2)	AD	Angelman syndrome
ZEB2 (2q22.3	AD	Mowat-Wilson syndrome

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Infantile onset epilepsies

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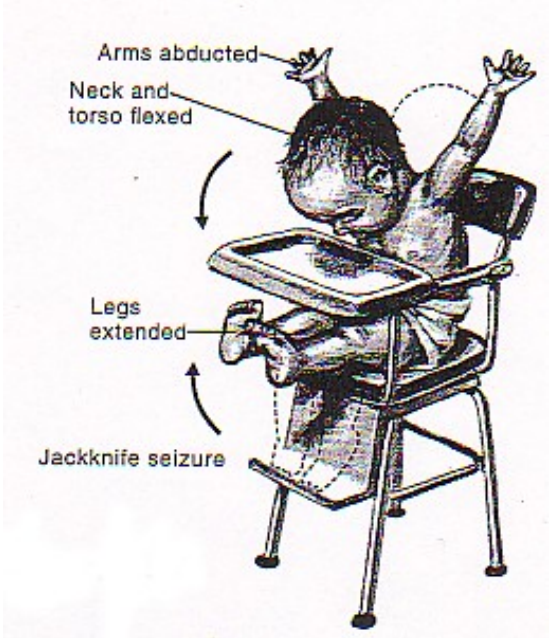
Infantile Spasms

- Onset 3-12mo (range 1-24months)
- Associated developmental regression or stagnation
- Clinical spasms (1-2 secs)
  - a subtle momentary flexion or extension of the body
  - occur in clusters when drowsy (waking or falling asleep)
- Factors associated with best prognosis:
  - Short time btn spasms and tx
  - Cryptogenic etiology
  - Normal neurodev prior
  - Age of onset <4mo
  - Absence of atypical spams or focal sz
  - Absence of asymmetries on EEG
  - Quick and sustained response to tx
- Refractory cases often evolve to Lennox-Gastaut



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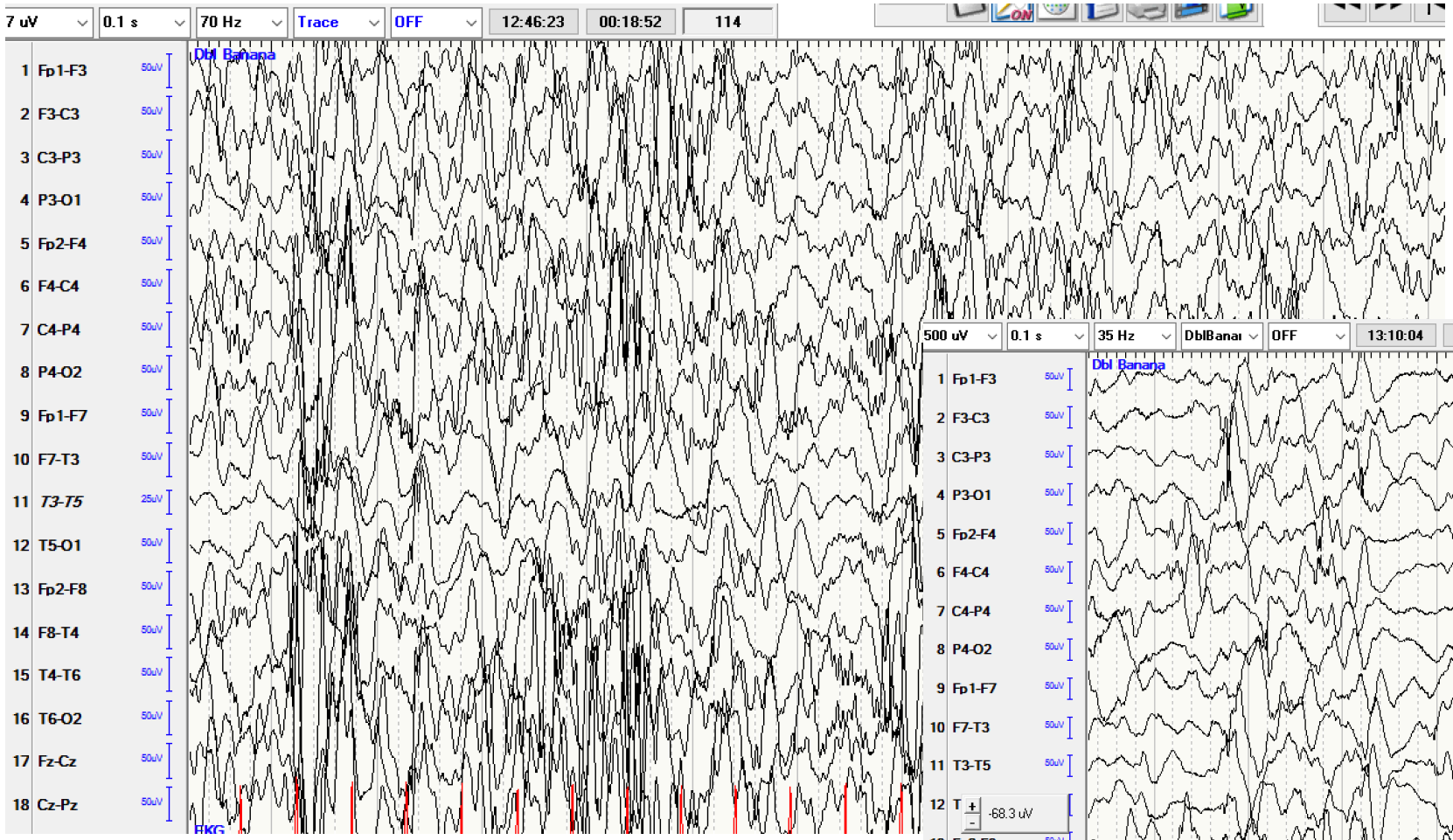
IS Etiology

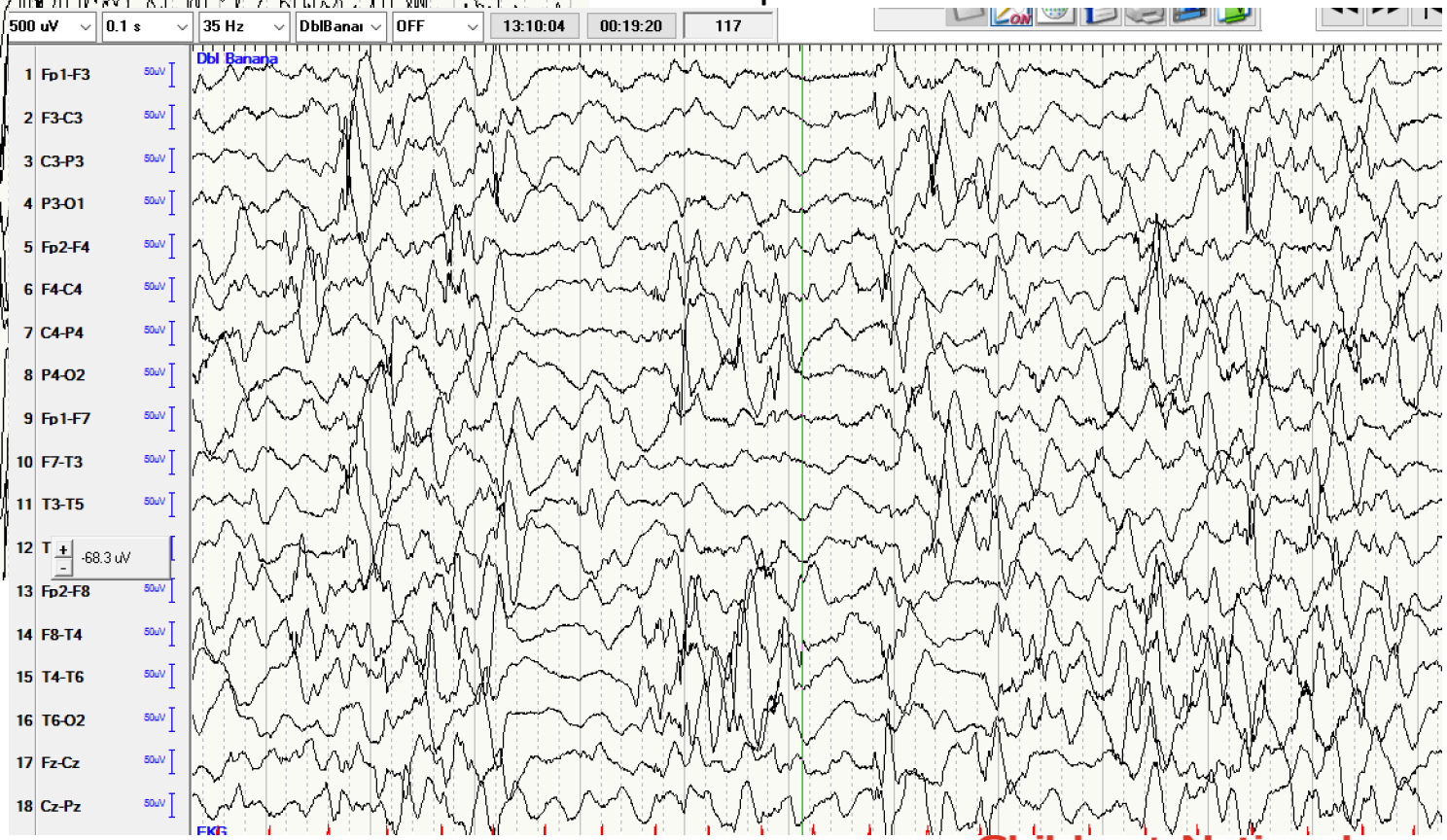
Symptomatic	
Structural	Hypoxic-ischemic encephalopathy at birth, meningoencephalitis, brain malformations, tuberous sclerosis (up to 50% will develop IS)
Genetic/Metabolic	Trisomy 21, *ARX*, *CDKL5*, *STXBP1*, *IQSEC2*, *TSC1*, *TSC2 etc*
Idiopathic or Cryptogenic	

- Workup
  - MRI high resolution (repeat if ongoing concern for FCD)
  - Genetic testing: epilepsy panel, whole exome, PSP

IS- EEG



- Disorganized
- High amplitude slow waves >200
- Abundant multifocal high amplitude spike waves



A reliable interictal EEG grading scale for children with infantile spasms – The 2021 BASED score- Mytinger et al, Epilepsy Res July 2021

BASED score	Description
0	Normal
1	Any definite nonepileptiform abnormality
2	<3 spike foci **AND** no channel with abnormal high amplitude
3	≥3 spike foci <50% of one second bins **AND** no channel with abnormal high amplitude, **OR** <3 spike foci but ≥1 channel with abnormal high amplitude
4 (Probable EE)	≥3 spike foci <50% of one second bins **AND** ≥1 channel with abnormal high amplitude, **OR** Not meeting criteria for 5 but includes GMFS or paroxysmal voltage attenuations
5 (Definite EE)	≥3 spike foci that are ≥50% of one second bins

BASED: Burden of AmplitudeS and Epileptiform Discharges, GMFS: grouped multifocal spikes, EE: epileptic encephalopathy.

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IS treatment

- ACTH:
  - First line for most cases except TS
  - Thought to reduce CRH, an endogenous neuropeptide that provokes seizures in immature brains
  - No difference in initiating high vs low dose: usually do course of 2 weeks then taper
  - Cons: costly, IM administration
- Prednisone/Prednisolone
  - Oral
  - Cheaper but more side effects than ACTH
- Vigabatrin
  - Main SE: retinal toxicity
  - Continue for 3mo-1year

IF above fails, trial next agent. If relapse then repeat course of steroids with slow taper (4-6 weeks)
If remains refractory: Topiramate/Zonisamide, Clobazam, Ketogenic Diet

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Dravet Syndrome

- Severe myoclonic epilepsy in children, 1-20months
- Initial hx of febrile seizures then develop frequent febrile and afebrile seizures
  - Seizures initially unilateral hemiclonic seizures that may evolve into GTCs, frequent episodes of status epilepticus in setting of fever/immunizations
  - Additional seizure types can develop: myoclonic, atypical absence, atonic
- Developmental delay starts later ~2-4 yo: cognitive delay, hypotonia
- EEG: may initially be normal then can progress to slowing and interictal discharges that can be focal, multifocal or generalized
- Mutation in SCN1A – Na voltage channel
  - >80% cases, loss of function mutation, most de novo
  - Other genes rarely associated- *GABRG2*, *GABRA1*, *STXBP1*, SCN1b,
- Higher risk of SUDEP
- Treatment: Very drug resistant
  - Avoid Na channel drugs: OXC/CBM, LMT, PHT
  - Class A evidence for stiripentol, Class C for TPM, VPA, ZNM, bromide, Ketogenic diet
  - Other meds: CBD, fenfluramine, Clobazam, VNS

Myoclonic epilepsy in infancy

- Onset 6mo-2y, males>females
- 1/3 with hx of febrile seizures
- EEG:
  - Interictal: usually normal
  - Ictal: myoclonic seizures associated with GSW, some with +IPS
- Normal development at onset, can develop cognitive/motor/behavioral issues if seizures are not controlled
- Self-limiting, seizures remit 6mo-5 years after onset

Childhood onset epilepsies

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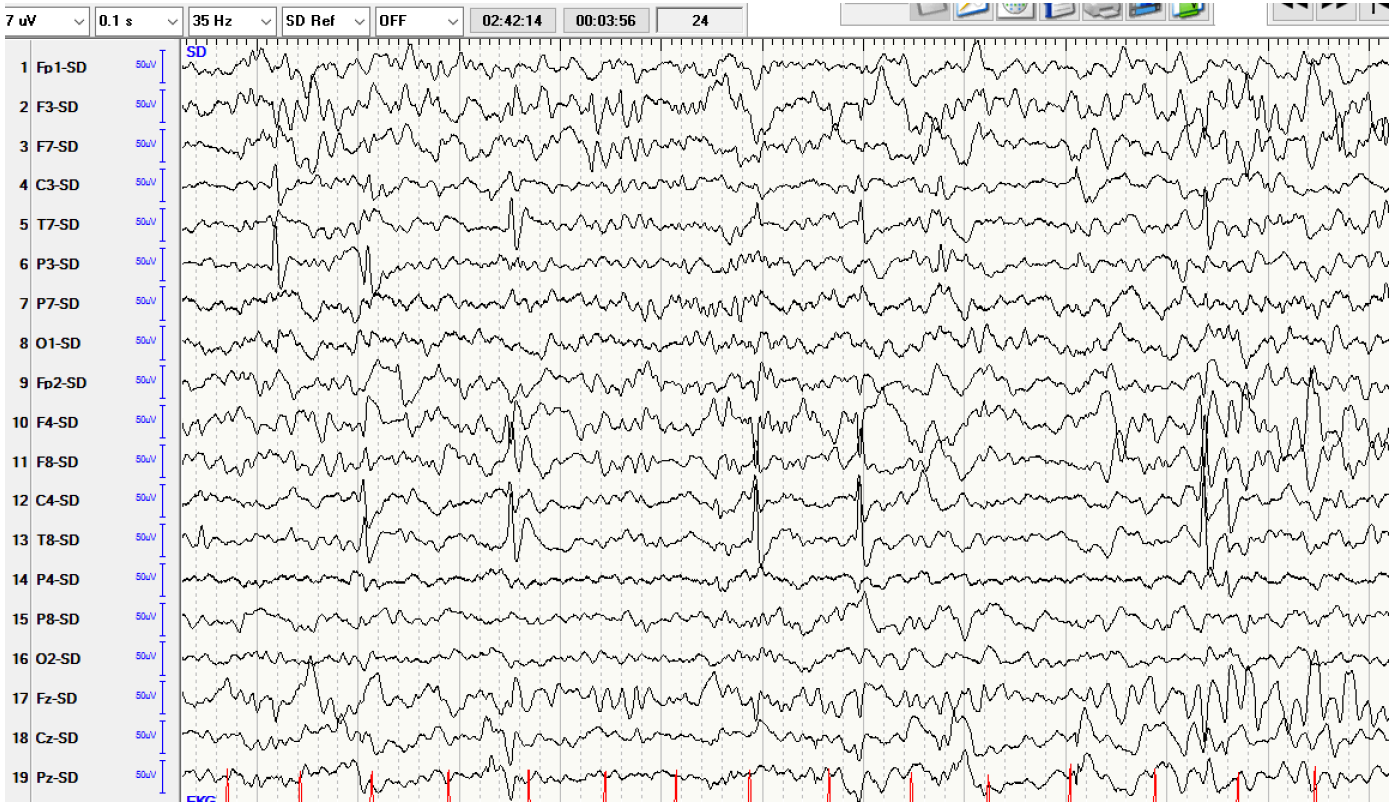
Self-limited epilepsies of childhood

Self-limited epilepsy with centrotemporal spikes (SeLECTS)

- Onset 3-13 years old (peak 4-10y), boys > girls
- Normal IQ, normal exam, normal MRI
- High Remission rate (>80%) by age 18
- Seizure description:
  - When awake:
    - twitching and/or tingling on one side of body
    - speech arrest, speech difficulty, may drool or gag
    - no loss of consciousness, usually < 2 minutes
  - When asleep (nocturnal):
    - "grand mal" with focal features



Sleep potentiated centrotemporal spikes associated with frontal horizontal dipole

- Can defer tx if infrequent, focal seizures
- Those with language deficits should be tested for GRIN2A
- Rarely, SeLECTS can evolve to EE-SWAS
- Treatment: focal meds- OXC

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Other self-limited epilepsies

- Self-limited epilepsy with autonomic seizures (SeLEAS)
  - Early onset benign childhood occipital epilepsy (range 1-14y, peak 3-6y)
  - Infrequent focal autonomic seizures usually out of sleep
    - vomiting, pallor, flushing, abdominal pain, pupillary changes
    - can progress to focal motor or GTC seizures
  - EEG: background normal, interictal sleep potentiated occipital spikes
  - High remission rate, usually within 3 years after diagnosis
- Childhood occipital visual epilepsy (COVE)
  - Late onset benign childhood occipital epilepsy (range 1-19y, peak >8-10y)
  - High remission rate usually by puberty
  - Frequent focal sensory visual seizures
    - Elementary visual phenomenon like small multicolored circles in peripheral vision that can grow and move horizontally, and can progress to eye/head deviation
    - Ictal blindness, complex visual hallucinations or illusions, repeated eye closure
    - Ictal or postictal headache
  - EEG: normal background, sleep potentiated occipital spikes
- Photosensitive occipital lobe epilepsy (POLE)
  - Rare syndrome, onset usually 4-17y, females>males
  - Photic-induced focal seizures
  - Focal aware seizures: visual aura with head version that may progress to ictal headache, autonomic symptoms, secondary GTC
  - EEG: normal background, occipital spikes induced by eye closure and photic stimulation (more generalized/polyspikes)

Treatment: focal meds- OXC

Genetic generalized epilepsies of childhood

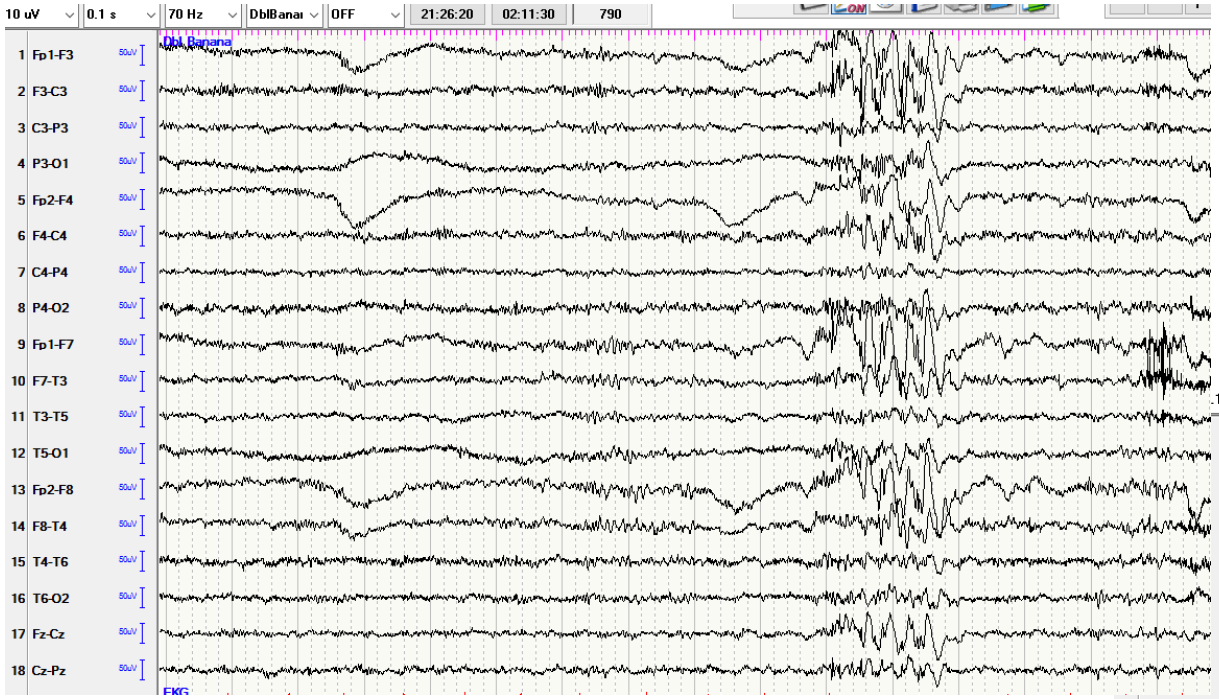
Childhood Absence Epilepsy (CAE)

- Onset 4-10y
- Development typically normal (mild learning, ADHD)
- EEG: 3Hz GSW, triggered by HV and IPS; OIRDA
- HV induced absence seizures
  - sudden onset complete loss of awareness +/- eye blinking/fluttering that can progress to oral/hand automatisms and UI, with immediate return to normal activity after
  - Last 3-20second
  - Occur multiple times daily
- Typical CAE does not require more workup (e.g. MRI)
- Treatment: ETX, VPA, LMT
- Up to 60% remission by adolescence, small subset may evolve into JME
- Caution:
  - Benzos may worsen seizures
  - Onset <4yo may require more workup (MRI, genetic testing esp for SLC2A1)

Epilepsy with eyelid myoclonia (EEM)

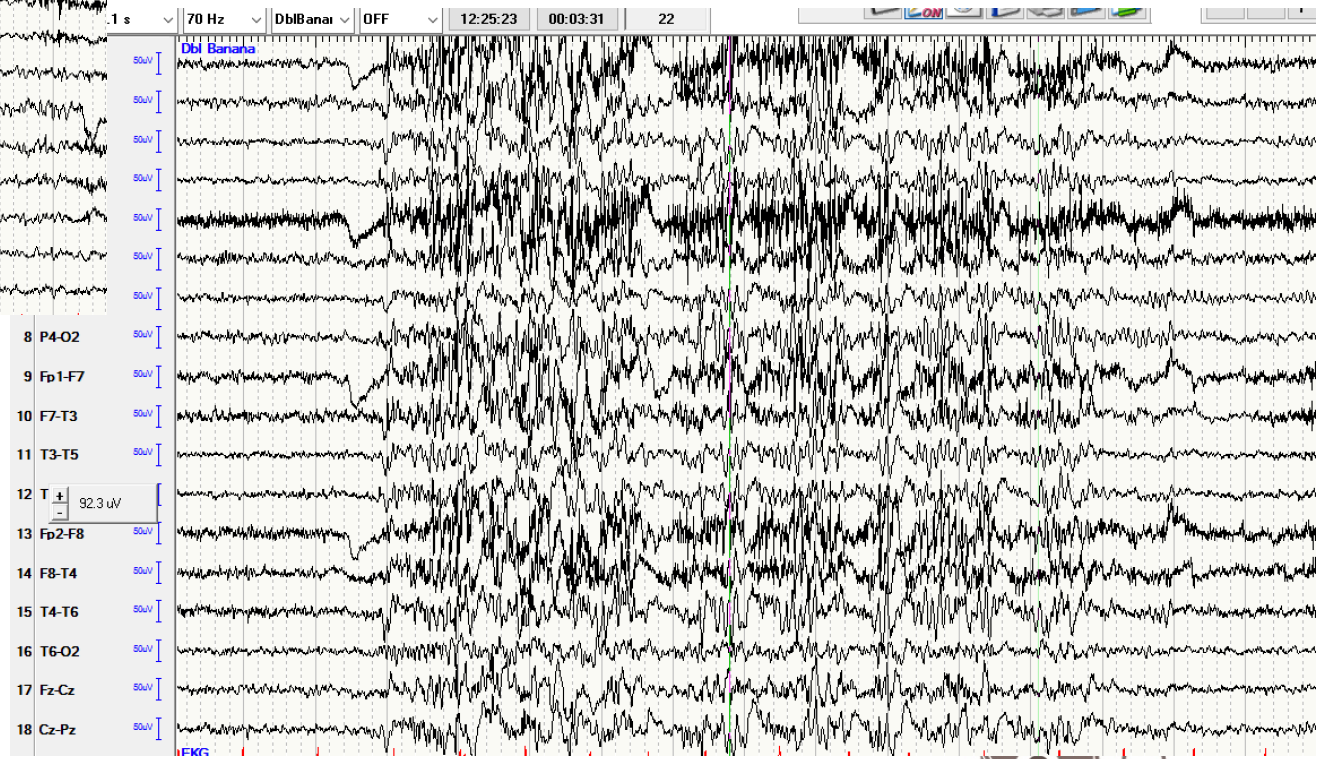
- Triad of
  - Eyelid myoclonia +/- absence = jerking of eyelids and upward deviation with extension of head lasting <1 to 6s
  - Eye closure induced paroxysms/myoclonia
  - Photosensitivity →subgroup with prominent photic induced eyelid myoclonia, absence and/or myoclonic seizures
- Onset 2-14y (peak 4-6y), females>males
- Normal development or mild ID, ADHD
- Can have multiple other generalized seizure types- GTC, myoclonic, absence
- EEG:
- Eyelid myoclonia very refractory, and can be lifelong
- Treatment VPA, LVT but often refractory; environmental measures like sunglasses

EEM- EEG



Interictal: normal background, bursts of 3-6Hz irregular GSW/polyspikes, fixation-off sensitivity

Photoparoxsymal response, can elicit eyelid myoclonia



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Epilepsy with myoclonic-absence (EMA)

- Onset ~7y, males>females
- Developmental delay, ID in ~50% cases
- Seizures: absence seizures associated with myoclonic jerks of the arms with tonic abduction/slight raise lasting 10-60s and occur multiple times daily
- EEG:
  - Interictal: normal background, GSW complexes increased during HV, drowsiness, sleep
  - Ictal:
- Poorer prognosis if develop multiple seizure types, can progress to LGS
- Treatment: VPA, ETX

Focal epilepsies of childhood

Hemiconvulsion-hemiplegia epilepsy syndrome

- Onset <4y
- Normal development at onset
- Acute stage: Initial presentation is focal motor status epilepticus, often in setting of febrile illness, with associated hemiparesis
  - MRI- affected hemispheric with edema and restricted diffuse and T2 changes in subcortical white matter
- Chronic stage: drug-resistant focal epilepsy, permanent hemiparesis
  - MRI: evolving hemispheric volume loss +/- MTS
- EEG
  - Interictal: Focal spikes and fast activity in affected hemisphere, bilateral synchronous spikes, generalized slowing
  - Ictal: 2-3Hz rhythmic continuous spikes in affected hemisphere
- Etiology unclear
- May benefit from hemispherectomy

Sleep-related hypermotor epilepsy

- Onset first 2 decades
- Seizures: nocturnal focal motor that can cluster
  - Hyperkinetic movements, asymmetric tonic/dystonic +/- autonomic signs
  - May be preceded by focal sensory or cognitive aura
  - Usually no loss of awareness or postictal state
- EEG:
  - Interictal: usually normal or anterior predominant epileptiform discharges
  - Ictal: movement artifact intermixed with diffuse rhythmic delta/theta or attenuation, occasionally more clear sharps/spikes at onset
- Etiology:
  - Structural: FCD
  - Genetic: CHRNA4/2/B2, KCNT1, DEPDC5
- Treatment: OXC with good response in 70%

Developmental and epileptic encephalopathies of childhood

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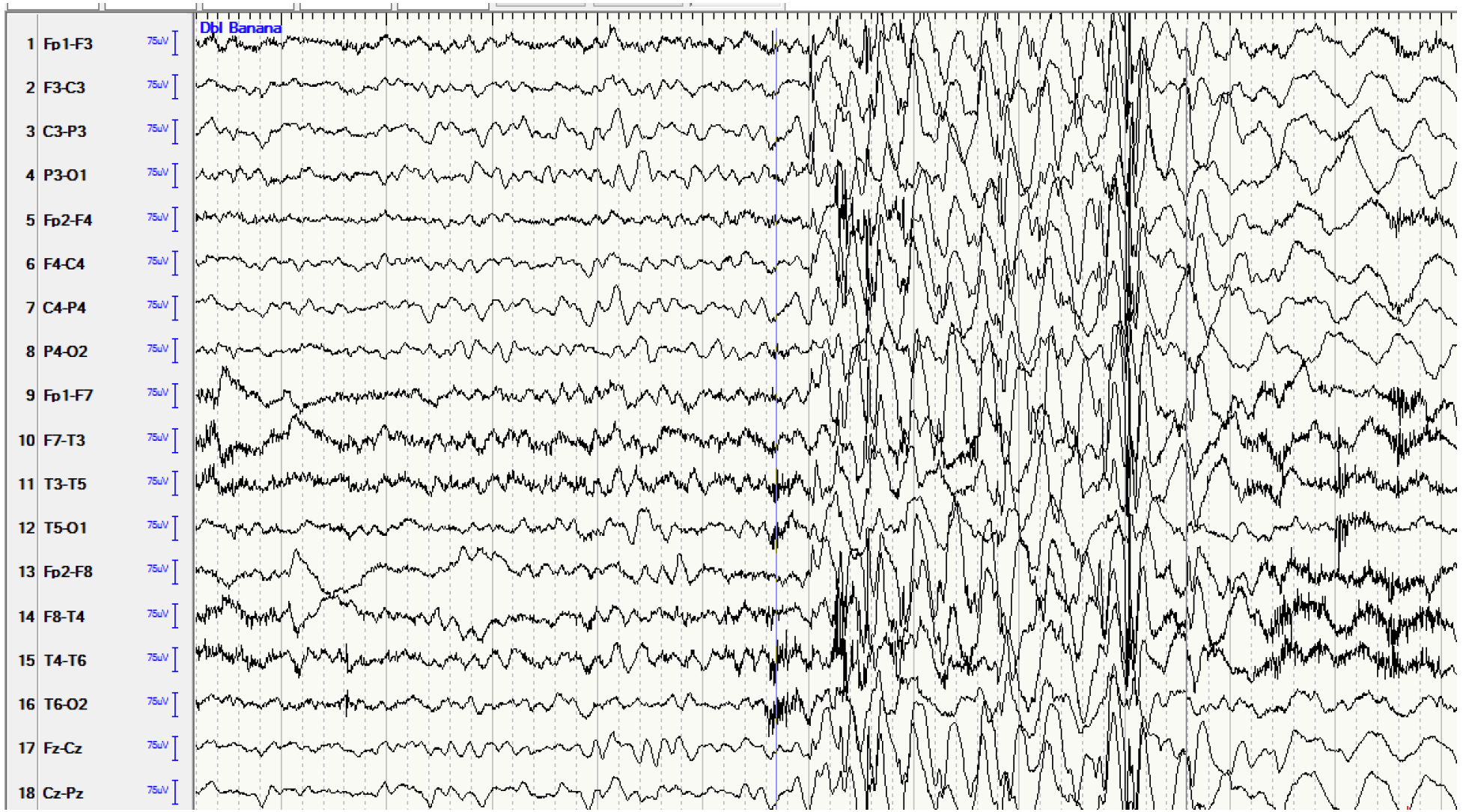
Epilepsy with myoclonic-atonic seizures (EMAtS)

- Onset 2-6y, male>female
- Strong FHx of febrile seizures (more favorable outcome), epilepsy
- Normal development at onset then stagnation or regression during active seizure phase, which improves with seizure control
- Seizures:
  - Myoclonic-atonic seizures
  - abrupt, explosive onset
  - Other seizure types: myoclonic, GTC, absence, tonic(poorer prognosis)
  - Can present with nonconvulsive status epilepticus
- EEG:
- Initially refractory but ~60% achieve remission within 3 years of onset
- Treatment: VPA, LVT, ZNM/TPM, LMT, LVT, Ketogenic diet
- Genetics: SCN1A, SCN1B, SCN2A, Glut1 and others

EMAtS- EEG



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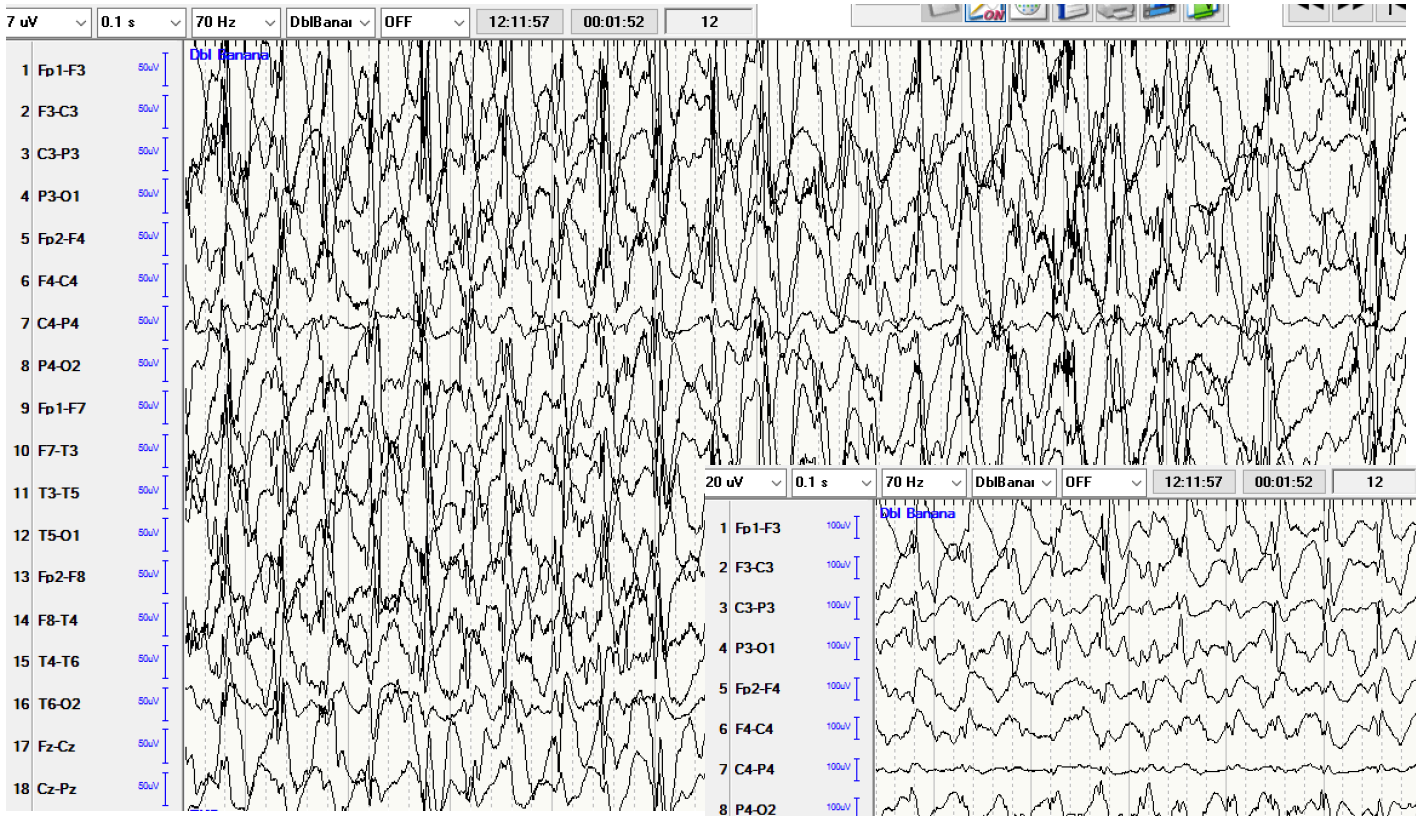
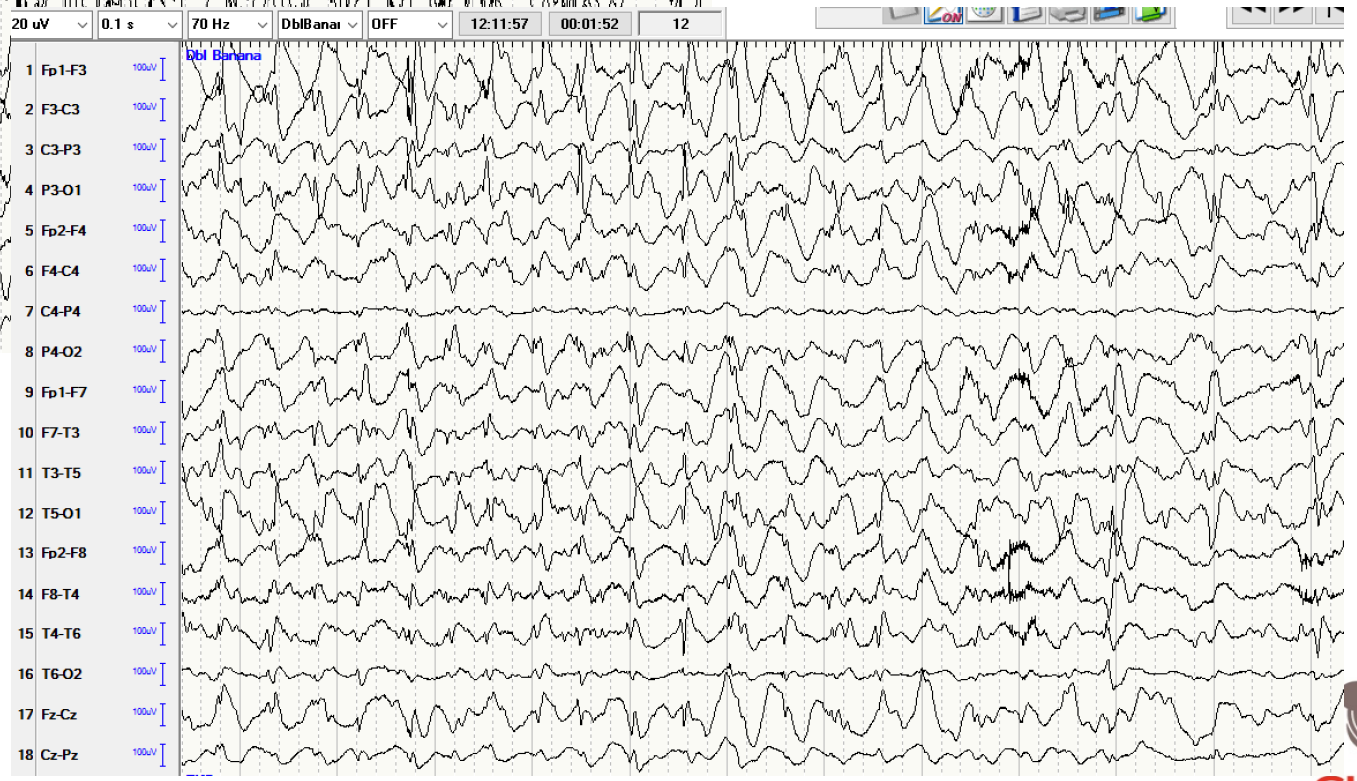
Lennox-gastaut syndrome

- Onset <8years (peak 3-5 years)
- Severe epileptic encephalopathy:
  - Multiple seizure types: **Tonic**, Atypical absence, GTCs, Atonic, Myoclonic, Focal, epileptic spasms
  - Developmental/Cognitive deterioration, behavioral disorders, ASD
  - Slow spike waves (1.5-2.5Hz) and generalized paroxysmal fast activity on EEG
- Often evolves from severe neonatal/infantile epilepsy syndrome
- Various etiologies
  - Structural: diffuse brain malformations, TS, severe HIE
  - Genetic: SCN1A/2A, CDKL5, GABARB3, STXBP1
- Treatment: VPA, CLB, ZNM, TPM, CBD, RFM, FLB, Fenfluramine, Ketogenic diet, VNS, DBS, Corpus callosotomy

LGS- EEG



Disorganized
High amplitude spike waves



Slow spike waves
Multifocal spikes

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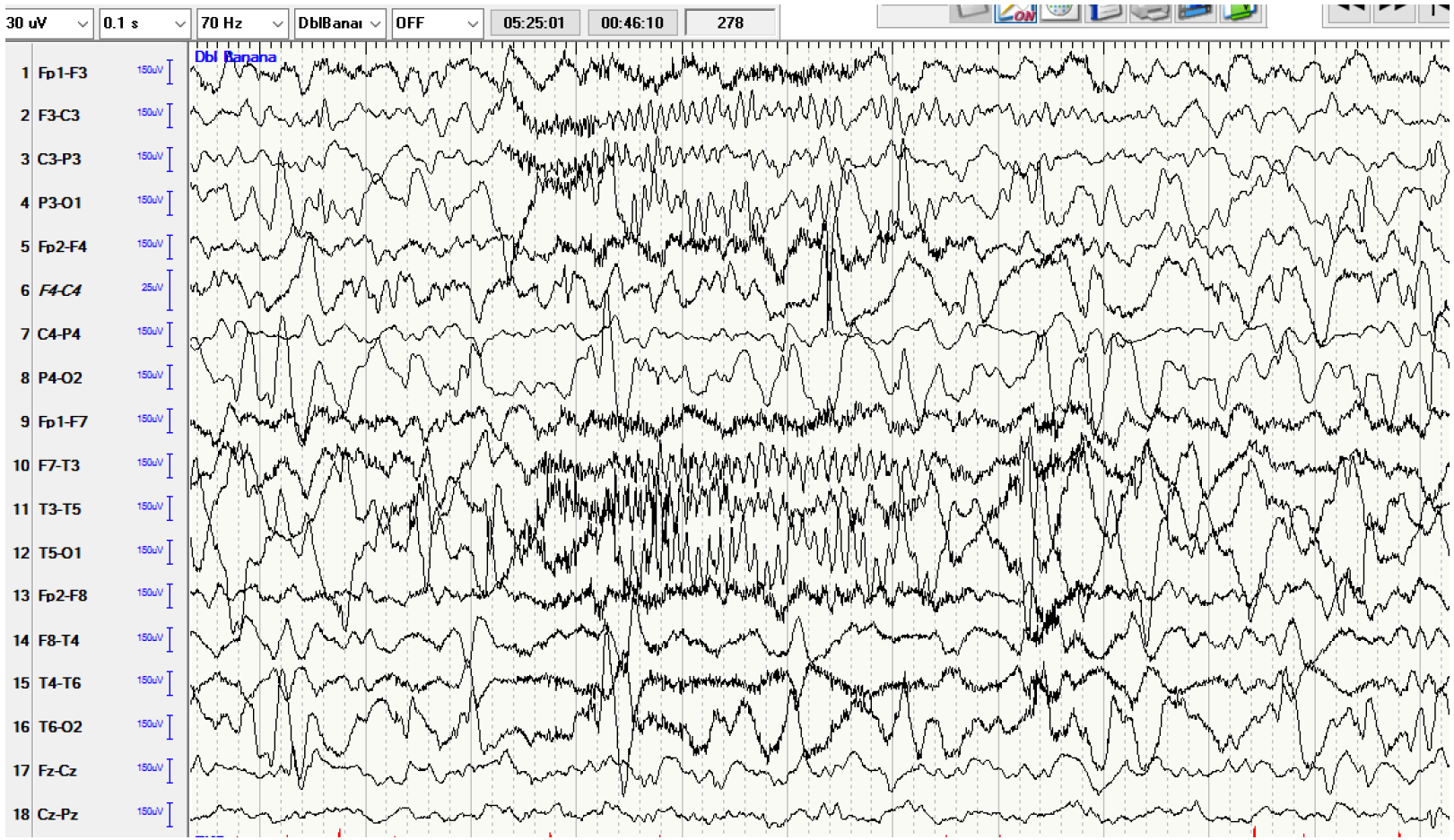
LGS- EEG



Generalized paroxysmal fast activity

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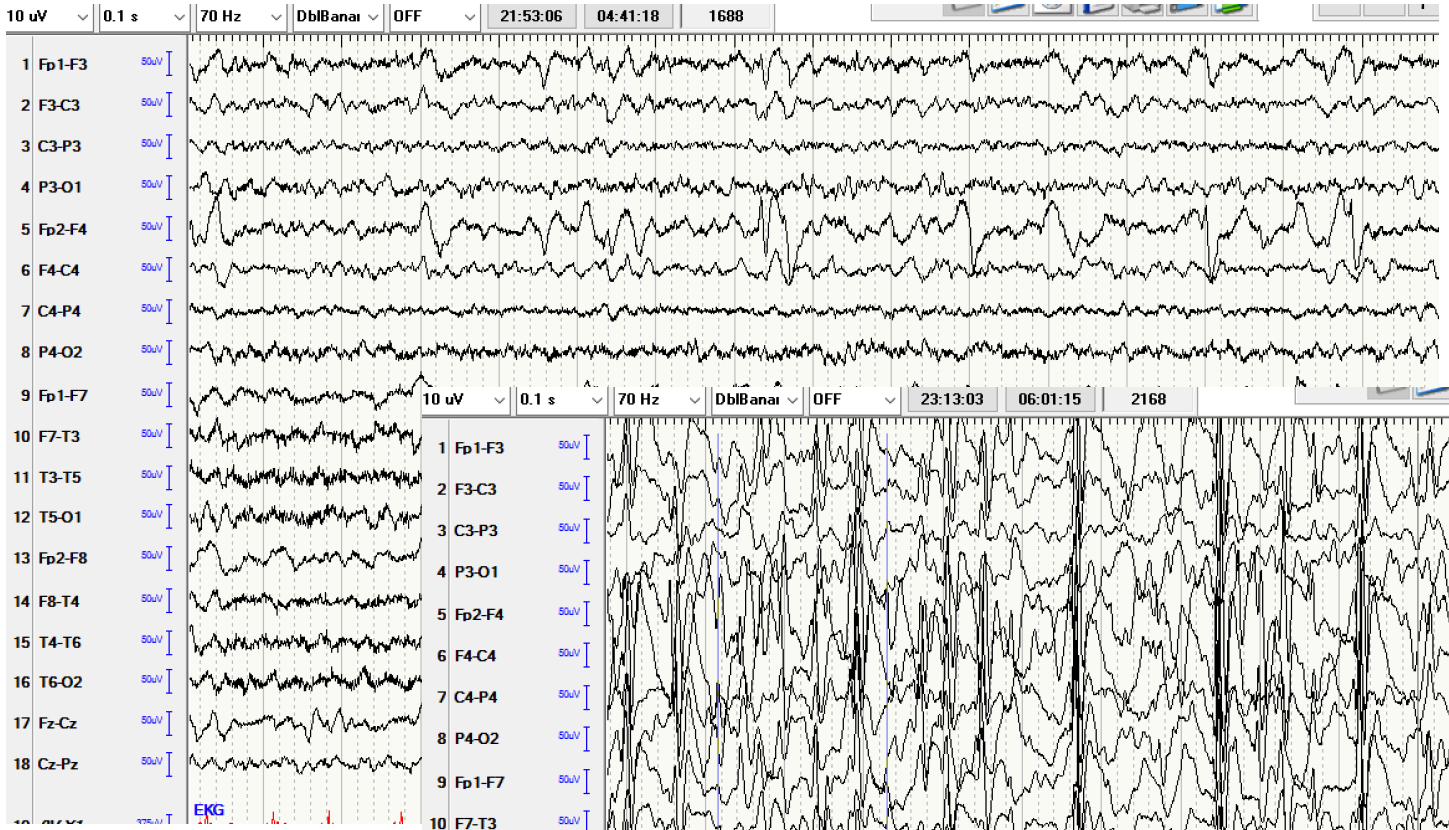
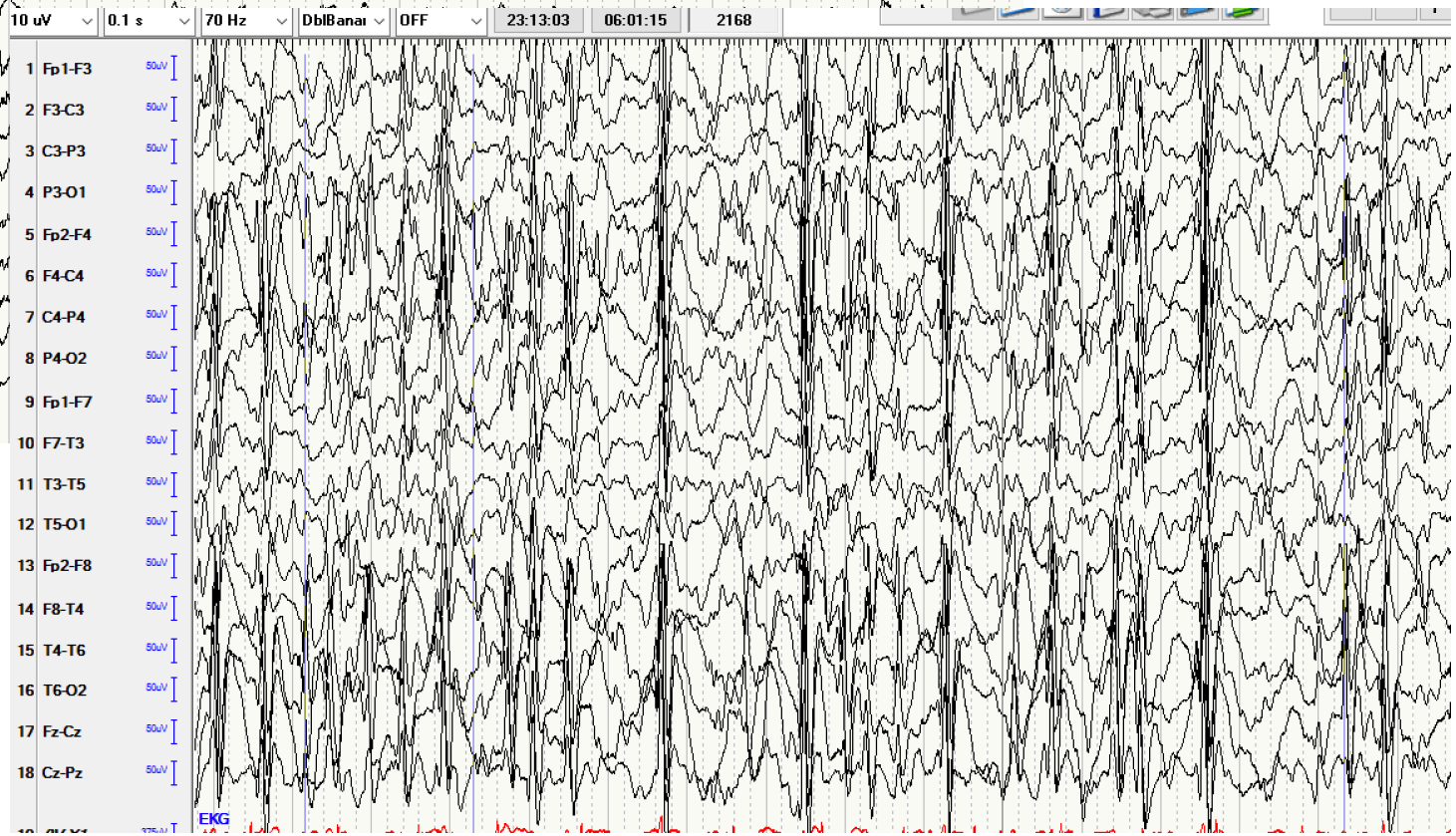
Epileptic encephalopathy with spike and wave activation in sleep (EE-SWAS)

- Onset 2-12y (peak 4-5y)
- Cognitive, language, behavioral, motor regression with marked spike-wave activation in sleep (SWAS)
  - EE-SWAS: pre-existing normal development
    - Landau-Kleffner: subtype of EE-SWAS mainly with language regression = auditory agnosia
    - Some focal epilepsy syndromes can evolve into EE-SWAS: SeLECTs, SeLEAS
  - DEE-SWAS: pre-existing neurodevelopmental disorder with worsening neurocognitive or behavioral function and SWAS
- Course:
  - Initially can present with seizures (multiple types)
  - High rates of remission by adolescence
- Etiology
  - Structural: Risk thalamic injury (stroke), bilateral perisylvian polymicrogyria
  - Genetic: major monogenic cause is GRIN2A
- Treatment: Steroids, ASMs, Surgery, Ketogenic diet, Amantadine, Acetazolamide

EE-SWAS EEG



Awake background: normal, slowing, epileptiform discharges that aren't continuous



Sleep: near continuous
slow spike waves 1.5-2Hz
in NREM and stage 2 sleep,
usually diffuse but can be focal
or multifocal
Loss of normal sleep architecture

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Genetic generalized epilepsies of adolescence

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Juvenile absence epilepsy

- Onset 9-13y
- Development typically normal (mild learning, ADHD)
- EEG: 3-6Hz GSW, triggered by HV and IPS
- HV induced absence seizures
  - staring/behavioral arrest but less complete loss of awareness
  - Last 5-30 seconds
  - Less than daily
- Higher risk for other generalized seizures: GTCs
- Treatment- broad spectrum ASMs
- Less likely to outgrow

Juvenile myoclonic epilepsy

- Onset 10-24y
- Development normal (co-morbid psych d/o)
- EEG 4-6Hz GSW/polyspikes
- Seizures:
  - Myoclonic often upon wakening
  - GTCs often preceded by series of myoclonic seizures
  - Absences in 1/3 cases
  - Provoked by: sleep deprivation or arousals from sleep, photic stimulation, alcohol intake
- High rates of relapse, may require lifelong treatment
- Treatment: broad spectrum ASMs (Na channel may worsen)

Other adolescent and adult-onset epilepsies

- Epilepsy with GTCs alone
  - Seizures: GTCs often before awakening
  - Usually infrequent seizures, good response to meds but may require lifelong treatment
  - EEG: 3.5-5Hz generalized spikes/polyspikes
  - MRI normal
- Familial mesial temporal lobe epilepsy

- Typical mesial temporal semiology: focal aware cognitive (déjà vu), sensory, autonomic (epigastric rising) that can progress to focal unaware or secondary b/L tonic clonic
- Normal development
- MRI: normal or hippocampal atrophy/MTS (poorer prognosis)
- EEG: normal or focal temporal slowing and/or temporal spikes
- Strong family history

- Epilepsy with auditory features
  - Focal aware seizures: auditory (humming, buzzing, ringing, alteration in volume, specific songs), receptive aphasia, vision alteration
  - Normal development
  - MRI: usually normal
  - EEG: normal,
  - LGI1 mutations in 50%

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- Hirsch E, French J, Scheffer IE, Bogacz A, Alsaadi T, Sperling MR, et al. ILAE definition of the Idiopathic Generalized Epilepsy Syndromes: Position statement by the ILAE Task Force on Nosology and Definitions. Epilepsia. 2022;63:1475–1499.
- Wyllie's Treatment of Epilepsy: Principles and Practice, 7th edition

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Questions

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A 2 week old baby girl presents to the emergency room with episodes of stiffening and apnea. Her mother reports she had also had seizures when she was a baby and outgrew them after a year. Which gene is the suspected cause of her symptoms?

A. SCN2A
B. TS1
C. CDKL5
D. KCNQ2
E. SCN1A

Which of the following is not a criteria used to diagnose infantile spasms?

A. Disorganized background
B. High amplitude slow waves >200
C. Abundant multifocal spike waves
D. Electroclinical spasms that occur in clusters
E. Loss of sleep architecture

A 10 month old developmentally appropriate baby boy with history of febrile seizures presents with an episode of focal status epilepticus marked by continuous jerking of his right arm and leg in the setting of a viral illness. Which medication for status should be used with caution in this patient?

A. Valproate
B. Phenobarbital
C. Phenytoin
D. Levetiracetam
E. Lorazepam

A 5yo girl presents to your office with daily episodes of staring, behavioral arrest and eye fluttering with immediate return to baseline. You perform 2 minutes of hyperventilation and elicit a typical episode. What is the best next step in the management of this patient?

A. Order continuous video EEG
B. Start Ethosuximide
C. Order MRI brain
D. Send genetic testing for Glut1 transporter deficiency
E. Start lamotrigine

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A 3yo developmentally appropriate boy with a history of febrile seizures presents with abrupt onset of body jerks followed by falling occurring multiple times per day. His routine EEG is normal, but no episodes are captured. The mother asks what is the likelihood he can outgrow these?

A. 20%
B. 80%
C. 50%
D. 60%
E. 0%

A 2yo boy with a history of severe hypoxic-ischemic encephalopathy and refractory infantile spasms presents with new episodes of full body stiffening accompanied by bilateral arm raise. Which of the following therapies is approved specifically for this syndrome?

A. Lacosamide
B. Rufinamide
C. Valproate
D. Felbamate
E. Ketogenic diet