Epileptic Syndromes in Neonates and Infants

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"Age" does matter in young babies

Neonatal period:

the first 28 days of life of a full-term infant (FT)

For preterm infant (PT):

"conceptional age"

Conceptional age = Gestational age + Chronological age

GA: duration of pregnancy

Chronological age: age from the time of birth

Neonatal seizures

- Most vulnerable period of life for developing sz
- Greatest occurrence in the first week
- Incidence 3: 1,000 live births
- Very high incidence in PT 57-132: 1,000
- May be short lived event
- Acute symptomatic >> epilepsy
- Often signify serious malfunction/damage to the immature brain

Etiology of Neonatal Seizures

- Hypoxic-ischemic encephalopathy (FT,PT)
- Cerebral artery/vein infarction
- Hemorrhage
  - Subarachnoid, subdural (FT),
  - Germinal matrix-intraventricular (PT>FT)
- Metabolic:
  - hypoglycemia, ↓ Na, ↓Ca, ↓Mg, inborn errors of metabolism
- Infections: TORCH, meningitis, encephalitis
- Major malformations:
  - lissencephaly, pachygyria, polymicrogyria
- Drug withdrawal and toxic

Clinical Manifestations of Neonatal Seizures

- Paroxysmal, repetitive, stereotype

- Usually clinical subtle, inconspicuous and difficult to recognise from the normal behaviors or physiologic phenomena
- No recognisable post-ictal state.
- Frequently be overlooked

??

Classification of Neonatal Seizures

1. Subtle 50%
2. Clonic (focal, multifocal) 25%
3. Tonic (focal, generalized) 5%
4. Myoclonic (focal, multifocal, generalized) 20%
5. Non-paroxysmal repetitive behaviors

J. Volpe, Neurology of the Newborn 2008, p.203-237

Subtle Seizures In Neonates

- **Ocular phenomena**
  - Tonic deviation of eyes with/without jerking
  - Sustained eye opening with ocular fixation
- **Oral-buccal-lingual movements**
  - Chewing, sucking, smacking, tongue protrusion
- **Other manifestations**
  - Limb movements: swimming, pedaling, trashing, rowing
  - Autonomic: paroxysmal change in HR, respiration, BP
  - Apnea, hiccough

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Motor Seizures In Neonates

- Clonic (focal, multifocal) 25%
  - Face, limbs, axial muscle
  - Hemiconvulsion
- Tonic (focal, multifocal, generalized) 5%
  - Generalized (tonic extension)- no EEG correlate
- Myoclonic (focal, multifocal, generalized) 20%
  - PT>FT
  - Associated with the most severe brain damage
  - **Focal motor seizures → high correlation with focal brain lesion

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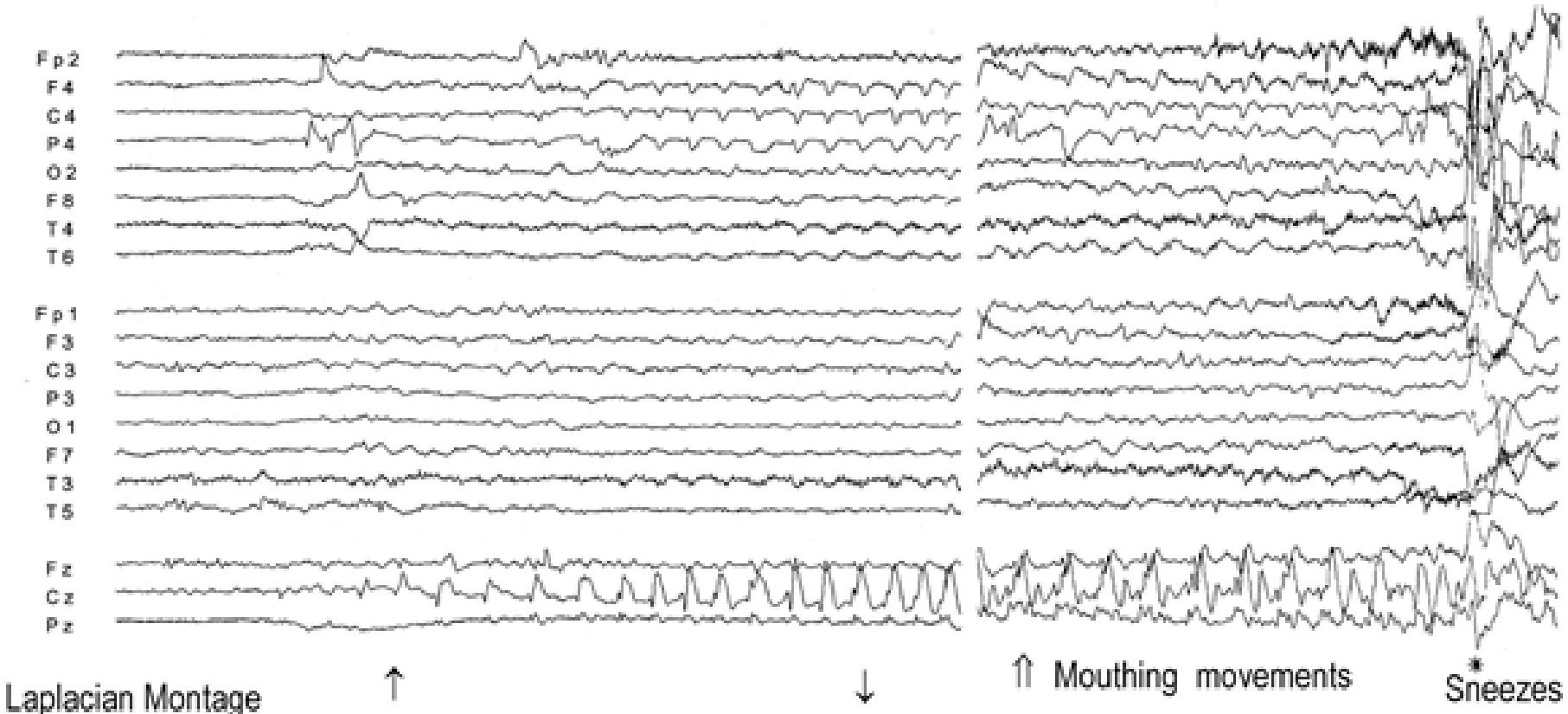
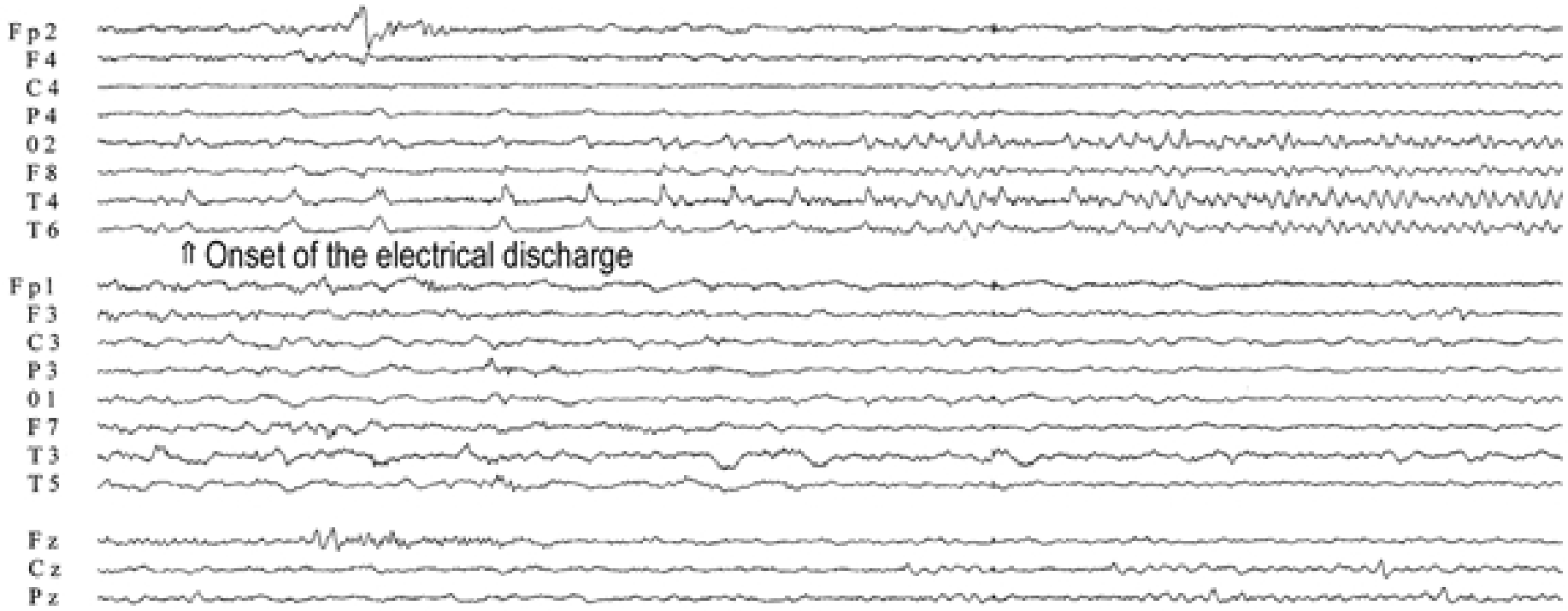
EEG in Neonatal Seizures

- Inter-ictal EEG:
  - sharp/spikes are not reliable marker
  - Suppression-burst pattern: syndrome diagnosis, severe HIE, Preterm, drugs
- Ictal pattern:
  - Highly variable, rhythmic activity
  - Localized to relatively small area
  - Usually focal
  - Multi-focal: independent discharges, differing morphology & frequency


Fp2
F4
C4
P4
O2
F8
T4
T6
Fp1
F3
C3
P3
O1
F7
T3
T5
Fz
Cz
Pz
Laplacian Montage
Jerking of left foot
No other apparent clinical manifestations
Mouthing movements
Sneezes



He looks undisturbed and there are no apparent clinical manifestations

Diagnosis of Neonatal Seizures

- Differentiate between non-epileptic vs epileptic:
  - Suppressed by restrain or repositioning?
  - Elicited by tactile stimulation?
- Detailed Hx of risk/etiology:
  - Pregnancy -> birth –> afterbirth, Family Hx
- Physical exam
  - Altered mental status, AF, focal neuro signs
  - Dysmorphic features, neurocutaneous stigmata
  - Peculiar odours

Diagnosis of Neonatal Seizures

- Screen for common and treatable etiology:
  - Infection: CBC, LP
  - Metabolic: electrolytes, Ca, Mg, lactate, NH3, UA (ketone)
- Consider possible structural brain lesion:
  - Otherwise healthy FT with focal seizure → stroke
  - Inv: USG for bleeding, CT for focal structural lesion eg stroke
- EEG (60 min) may be helpful in Dx of subtle sz, epileptic syndrome and Rx of SE

Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009

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Electroclinical syndromes arranged by age at onset[a]

- Neonatal period
  - Benign familial neonatal epilepsy (BFNE)
  - Early myoclonic encephalopathy (EME)
  - Ohtahara syndrome
- Infancy
  - Epilepsy of infancy with migrating focal seizures
  - West syndrome
  - Myoclonic epilepsy in infancy (MEI)
  - Benign infantile epilepsy
  - Benign familial infantile epilepsy
  - Dravet syndrome
  - Myoclonic encephalopathy in nonprogressive disorders

Epileptic Syndrome in Neonate

- Benign familial neonatal epilepsy (BFNC)
- Early Myoclonic Encephaopathy (EME)
- Ohtahara syndrome (Early Infantile Epileptic Encephalopathy, EIEE)

Epileptic Syndrome in Infancy

- Epilepsy in infancy with migrating focal seizures
- West Syndrome
- Myoclonic Epilepsy of Infancy
- Benign Infantile Epilepsy
- Benign Familial Infantile Epilepsy
- Dravet Syndrome (Severe myoclonic epilepsy of infancy, SMEI)
- Myoclonic encephalopathy in nonprogressive disorder

Benign Neonatal Convulsions

Benign Familial Neonatal Seizures (BFNC)

Benign Idiopathic (non-familial) Neonatal Seizures (BINC)

Clinical Case

- A previously healthy male neonate having frequent seizures at age 3 days.
- He had 4-8 sz/day, tonic motor activity, apnea 5-10 sec, vocalization, chewing and occasional focal clonic seizures. He was normal between his fits.
- Normal PE. All tests and interictal EEG were normal.
- Recommended treatment with AED was vigorously rejected by grandmom, who herself, her father and 2 of her 4 children had similar neonatal seizures without any consequences in their successful lives.

Benign Familial Neonatal Convusions (BFNC)

- Autosomal dominant, 85% penetrance
- Incidence 4.4: 100,000 live births, F=M
- Voltage-gated potassium channel: KCNQ2, KCNQ3
- Seizures in the 2^{nd}-3^{rd} day of life
  - Brief (1-2 min), frequent (20-30/day) seizures
  - Apnea, tonic, generalized clonic
  - Disappear by age 2-6 months
- Favorable outcome, subsequent epilepsy 14%

Benign (non-familial) neonatal seizures vs Benign familial neonatal seizure

	BINC	BFNC
Main seizures	Mostly clonic	Tonic-clonic
Onset	Fifth day of life	2nd or 3rd day of life
Duration of seizures	Status epilepticus	Repetitive isolated seizures
Main causes	Unknown, probable environmental	Autosomal dominant
Subsequent seizures	0.5%	11%
Psychomotor deficits	Minor	Nil
Ictal EEG	Localized spikes	Generalised flattening
Interictal EEG	Theta pointu alternant	Normal or focal abnormalities

BINC (Fifth-day fits)

- Occur around the fifth day of life (day 1- 7)
- Males > females
- Seizures: clonic (partial) and/or apneic,
- Status epilepticus: 2 hr–3days (median 20 hr)
- Variable inter-ictal EEG
- Ictal recordings: unilateral or generalized spikes or slow waves
- Diagnosis by exclusion
- Good outcome but increased risk of minor neurological impairment

Early Infantile Epileptic Encephalopathies with Suppression-Burst

Early Infantile Epileptic Encephalopathy

(EIEE: Ohtahara syndrome)

Early Myoclonic Encephalopathy (EME)

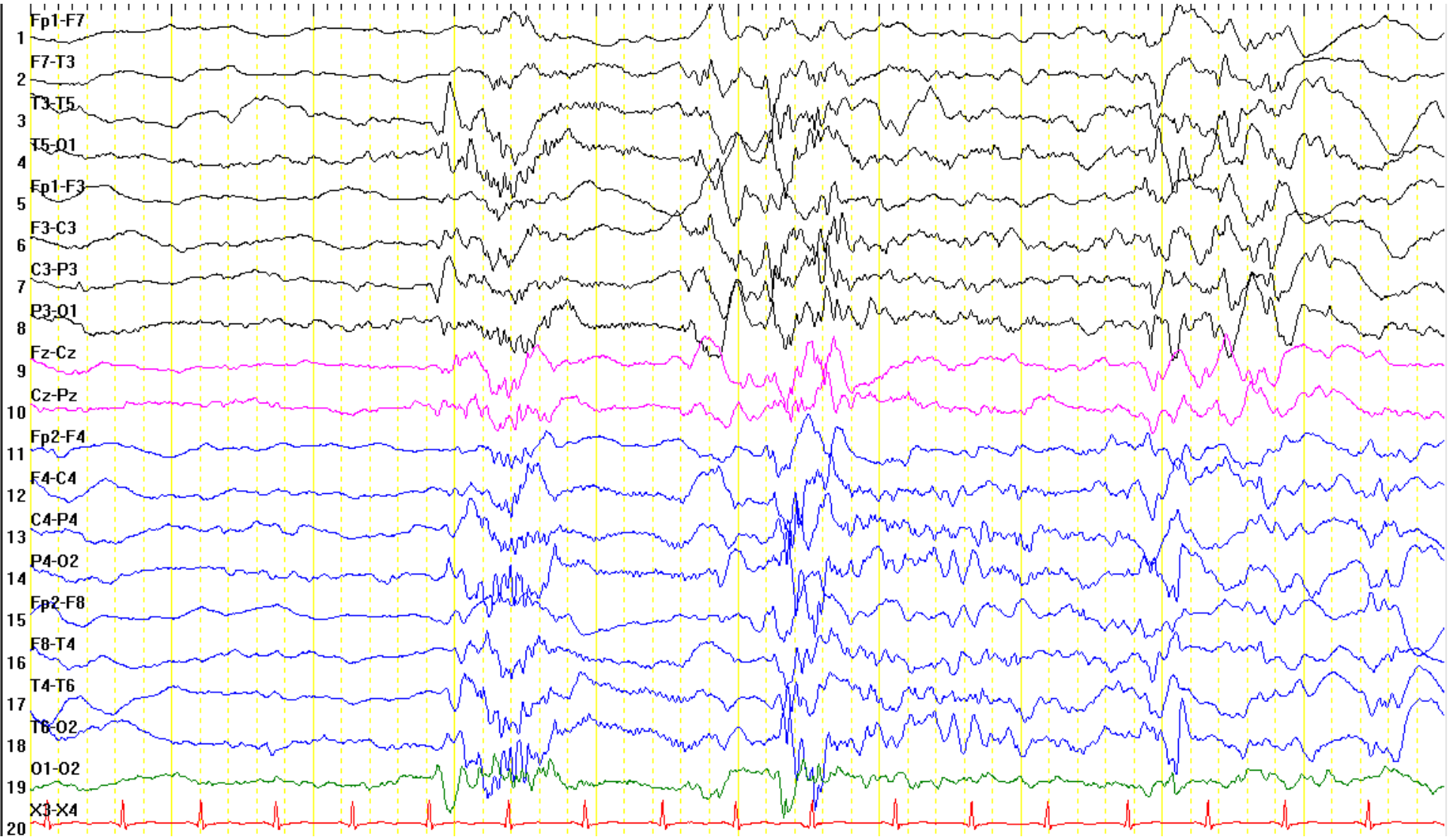
EIEE (Ohtahara Syndrome)

- Newborn or first 3 months of life
- Tonic spasms (isolated or clusters)
- Partial seizures (30-50%)
- Myoclonic seizures (rare)
- EEG: BS pattern (awake/sleep)
- Abnormal neuroimaging
- Resistant to AEDs
- Poor neurodevelopmental outcome

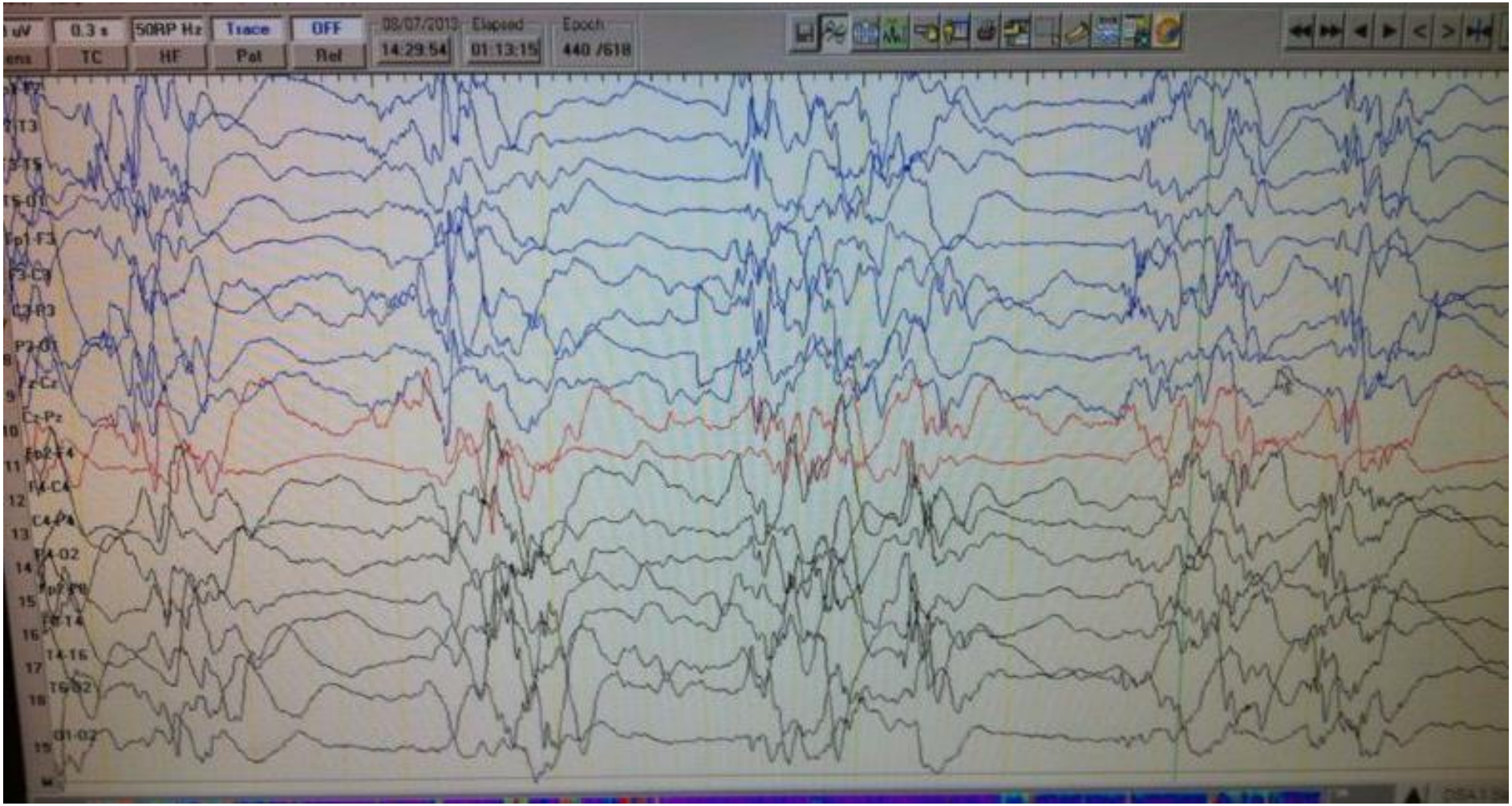
EIEE vs EME

	EIEE	EME
Etiology	Brain malformation	Genetic and Metabolic
Clinical sz	Tonic spasms Focal sz	Erratic myoclonic, focal sz
EEG: BS - Interburst - Circadian cycle - Evolution	Regular, shorter Sleep⇔Awake Hypsarrhythmia	Irregular, longer Predom. sleep Persist after 1 Y
Sz evolution	To West synd, LGS	Persistent regression

Burst-Suppression



Burst-Suppression



Early Myoclonic Encephalopathy (EME)

- Mostly within 1 month of birth
- Fragmentary myoclonic seizures
- Partial seizures (frequent)
- Tonic spasms (occasional/transient)
- EEG: BS pattern (enhanced by sleep)
- Inborn error of metabolism
- Intractable to AEDs
- Very poor outcome & high mortality rate

Epileptic Spasms

- Sustained contraction of axial muscles
- Flexion of neck & trunk with abduction and elevation of both arms
- **"Salaam position"**
- Initial movement relatively fast (myoclonic-like)
- Remain in the Salaam position for few seconds before relaxation
- Duration of each spasm: milliseconds to 5-10 seconds
- In **CLUSTER**
- Ictal EEG: Diffuse high-voltage slow followed by background attenuation

West Syndrome

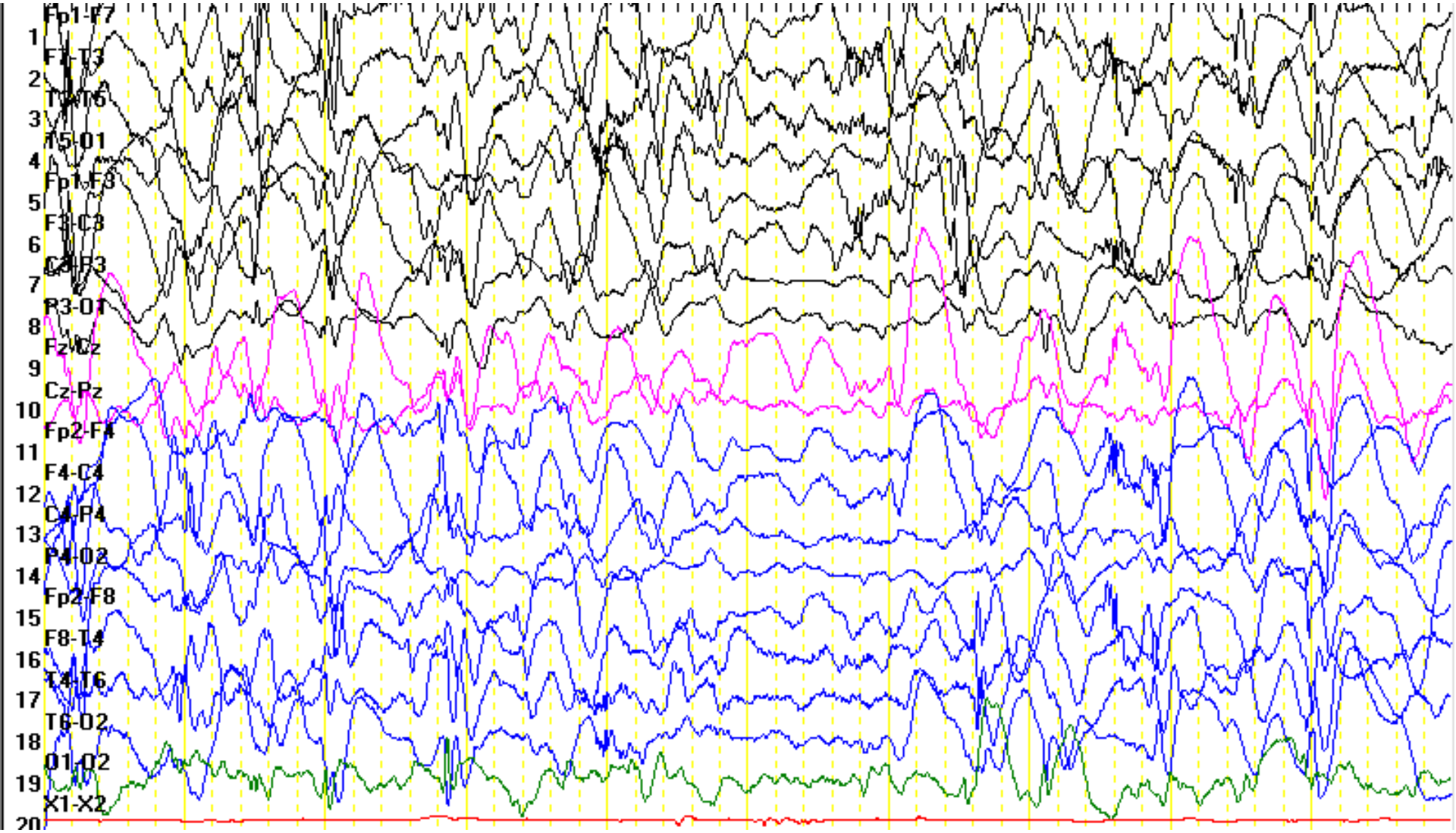
- Epileptic(infantile) spasms
- Delayed development
- EEG- Hypsarrhythmia

West Syndrome

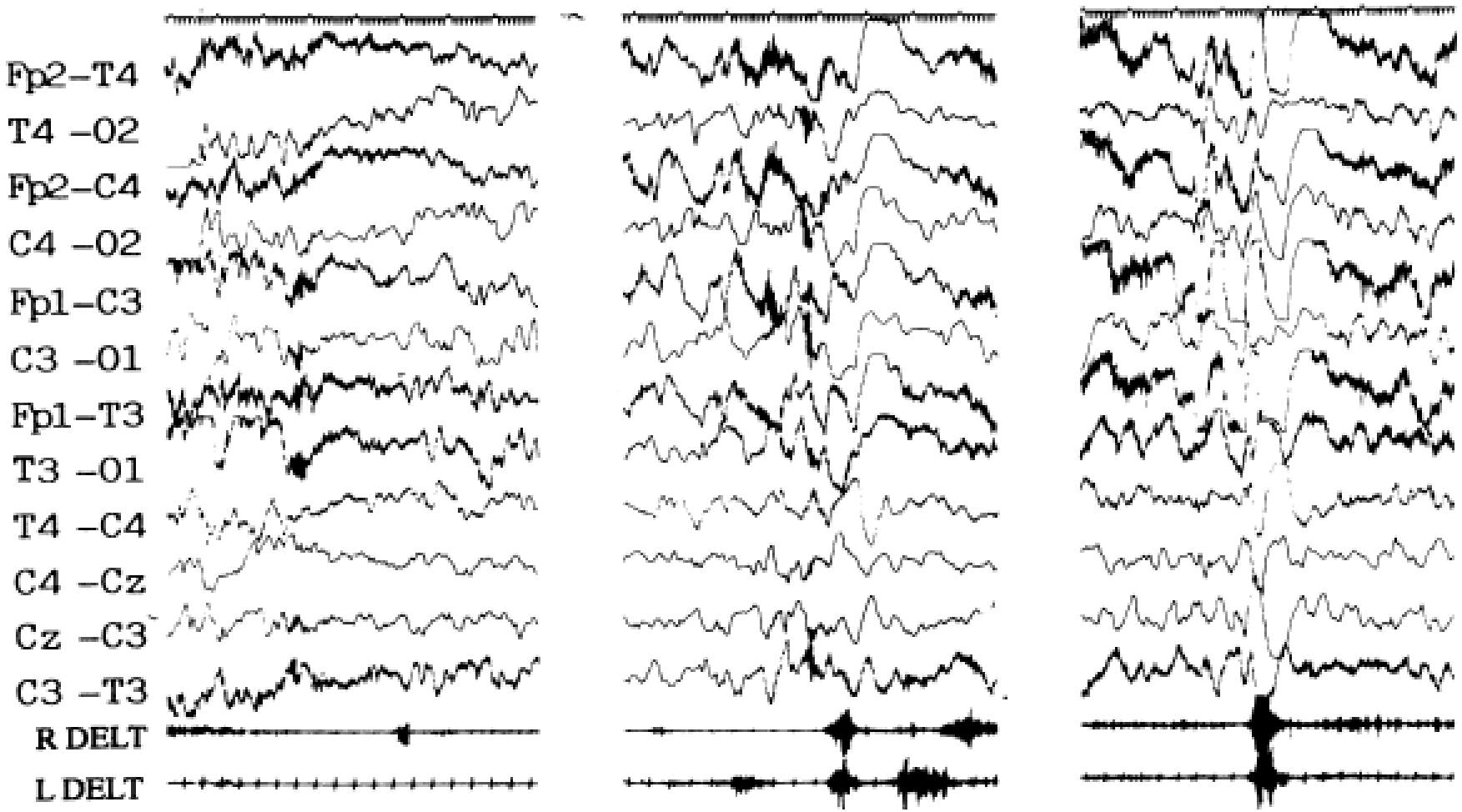
- Onset 3-7 months of age
- 1.6-4.3: 10,000 live births
- Spasms- flexor, extensor or mixed
- In clusters, frequently during drowsiness/arousal
- EEG: Hypsarrhythmia

(chaotic, irregular, diffuse asymmetric, high-voltage, interspersed with sharp waves and spikes)

Hypsarrhythmia



Ictal EEG and EMG during Spasms



Federico Vigevano, Brain & Development 23 (2001) 467–472

Etiologies of West Syndrome

Causes	%
Brain malformation/ Tuberous sclerosis	35
Perinatal insults	9
Undetermined pre/perinatal factors	19
Infections	2
Hypoglycemia	8
Metabolic causes	9
Idiopathic	18

Benign non-epileptic myoclonus of infancy (Benign non-epileptic infantile spasms)

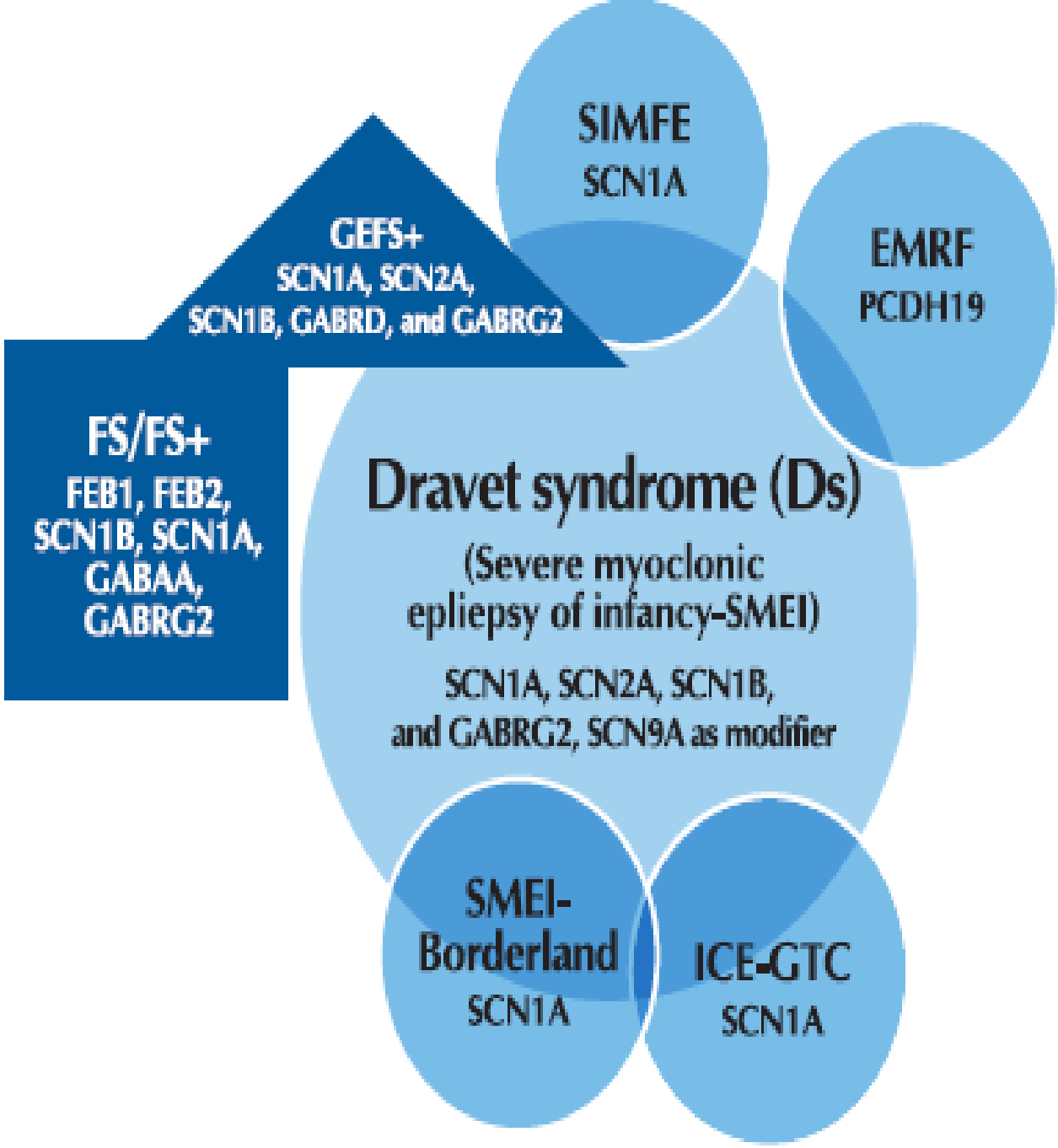
- Onset 4-12 mo, F=M
- Clusters of spasms during awake and sleep, elicited by excitement, fear, anger, frustation, need to void
- Normal development, normal EEG
- Exaggeration of physiologic myoclonus, same category with shuddering attacks

Myoclonic Epilepsy in Infancy

- 2% of children<3 years with epilepsy
- Neurologically normal
- Onset: 6 months- 2 years
- Family history of epilepsy in 20-25%
- Preceding febrile seizures in 20%
- EEG: gen. SAW or polyspike-waves (drowsiness/early sleep stages) w/photosensitivity
- AEDs: VPA
- Educational difficulties (20-40%)

Severe Myoclonic Epilepsy of Infancy(SMEI)

- Dravet syndrome
- 1:20,000-1:40,000 infants
- Boys>girls
- Neurodevelopment intact prior to onset
- 1st year: gen/unilateral clonic or GTC asso. with fever
- 2nd year: myoclonic seizures
- Progressive regression, hyperactivity


SIMFE
SCN1A
EMRF
PCDH19
GEFS+
SCN1A, SCN2A,
SCN1B, GABRD, and GABRG2
FS/FS+
FEB1, FEB2,
SCN1B, SCN1A,
GABAA,
GABRG2
Dravet syndrome (Ds)
(Severe myoclonic
epliepsy of infancy-SMEI)
SCN1A, SCN2A, SCN1B,
and GABRG2, SCN9A as modifier
SMEI-
Borderland
SCN1A
ICE-GTC
SCN1A

Severe Myoclonic Epilepsy of Infancy(SMEI)

- Highly intractable to AEDs
  - Useful AEDs: VPA, Benzodiazepines(CNZ, Clobazam, Lorazepam), Stiripentol
  - Alternative: ZNS, VGB, Ketogenic diet
  - Avoid: LTG?, PHT, CBZ
- Prognosis is very poor

Thank You
for Your Attention