Epileptic syndrome in Neonates and Infants

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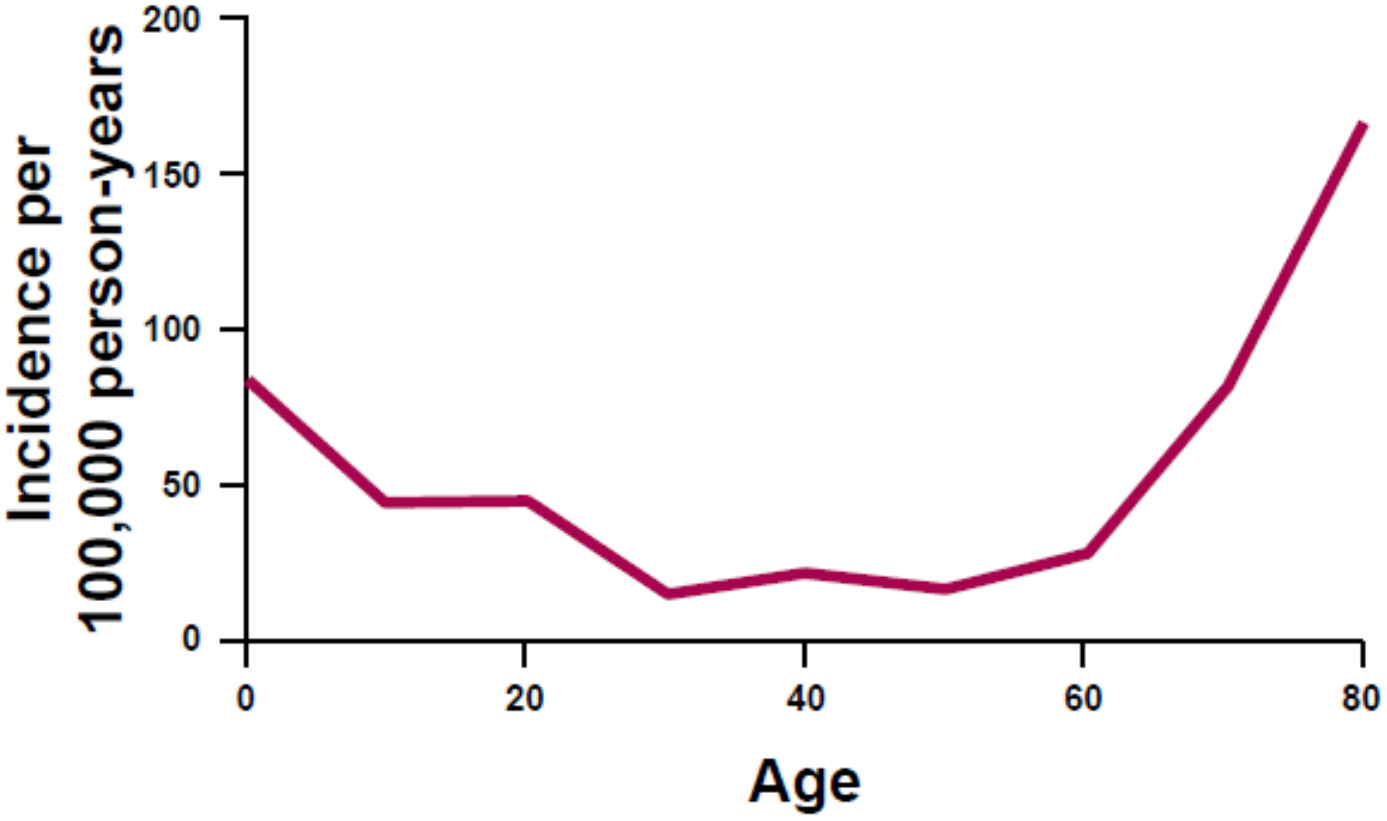
AGE SPECIFIC INCIDENCE OF EPILEPSY



Hauser WA, et al. Epilepsia. 1993;34:453-468

NEONATAL SEIZURES

- Seizures occurring in the first 4 weeks of life
- Most (80%) neonatal seizures occur in the first 1–2 days to the first week of life
- Incidence: 1.5 – 3.5 /1000 live births
- Very high incidence in preterm infants ((57–132 per 1000 live births)

COMMON CAUSES OF NEONATAL SEIZURES

- Hypoxic-Ischemic Encephalopathy (most common cause)
- Intracranial hemorrhage, cerebral infarction
- CNS infections (acute or congenital)
- Metabolic (Hypoglycemia, Hypocalcemia, hypomagnesemia, Hypo/hypernatremia)
- Inborn errors of metabolism (NKH, organic acidurias etc.)
- Maternal drug withdrawal
- Neonatal epileptic syndromes
  - Benign Familial Convulsions
  - Benign Neonatal Convulsions (fifth day fits)
  - EIEE (Ohtahara syndrome)

Classification of Neonatal Seizures

1. Subtle 50%

   (tonic, horizontal deviation of the eyes, eyelid blinking or fluttering, sucking, smacking or other oral–buccal–lingual movements, swimming or pedalling movements and, occasionally, apnoeic spells)

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

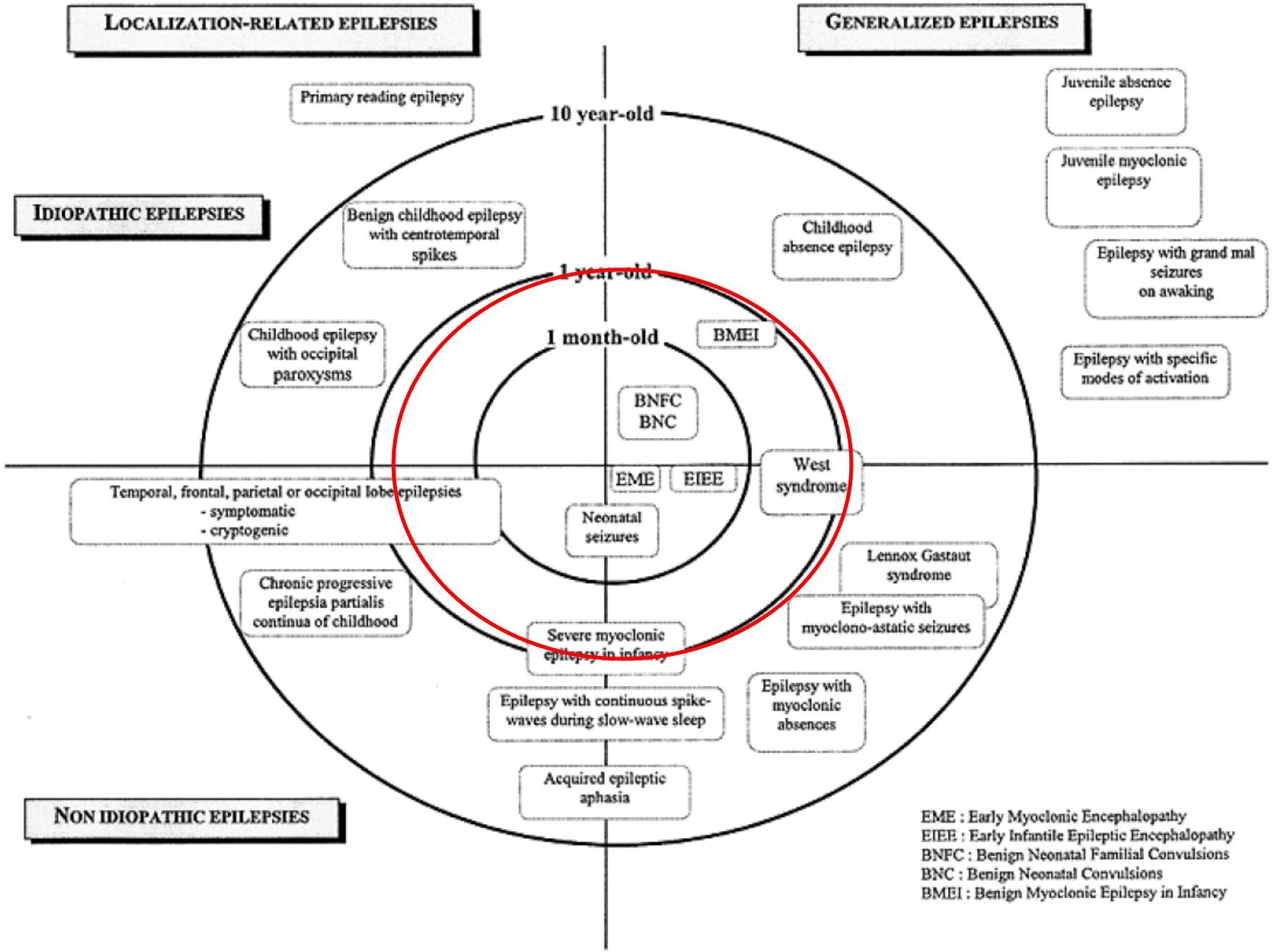
J. Volpe, Neurology of the Newborn 2008, p.203-237

CHALLENGES IN EVALUATING INFANTS WITH EPILEPSY

- Electro-clinical dissociation and some electro-graphic seizures do not produce clinical symptoms
- No recognisable post-ictal state
- Interictal and ictal EEG may show multifocal or generalized abnormalities even in those with focal epilepsy
- MRI difficult to interpret due to lack of myelination and higher water content of brain
- Decreased cortical activity on PET scans

Epileptic Syndrome

- Defined as " an epileptic state with specific signs and symptoms"
- Categorized by
  - Seizure type (s)
  - Age at the onset
  - EEG
  - Neurologic status
  - Precipitating factors
  - Response to AEDs
  - Natural history
  - Genetic
  - Neuroimaging studies


LOCALIZATION-RELATED EPILEPSIES
GENERALIZED EPILEPSIES
Primary reading epilepsy
Juvenile absence epilepsy
Juvenile myoclonic epilepsy
10 year-old
IDIOPATHIC EPILEPSIES
Benign childhood epilepsy with centrotemporal spikes
Childhood absence epilepsy
Epilepsy with grand mal seizures on awaking
1 year-old
Childhood epilepsy with occipital paroxysms
1 month-old
BMEI
Epilepsy with specific modes of activation
BNFC
BNC
West syndrome
EME
EIEE
Temporal, frontal, parietal or occipital lobe epilepsies
- symptomatic
- cryptogenic
Neonatal seizures
Lennox Gastaut syndrome
Chronic progressive epilepsia partialis continua of childhood
Epilepsy with myoclono-astatic seizures
Severe myoclonic epilepsy in infancy
Epilepsy with continuous spike-waves during slow-wave sleep
Epilepsy with myoclonic absences
Acquired epileptic aphasia
NON IDIOPATHIC EPILEPSIES
EME : Early Myoclonic Encephalopathy
EIEE : Early Infantile Epileptic Encephalopathy
BNFC : Benign Neonatal Familial Convulsions
BNC : Benign Neonatal Convulsions
BMEI : Benign Myoclonic Epilepsy in Infancy

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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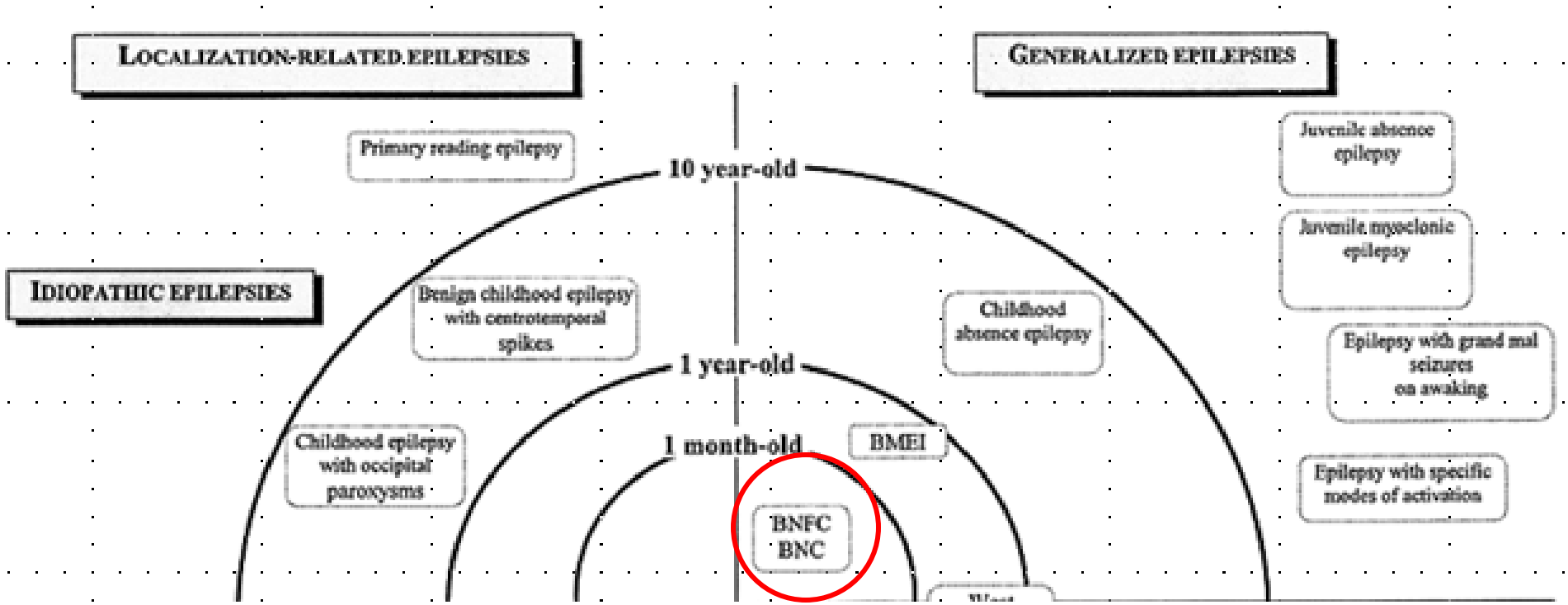
Electroclinical syndromes arranged by age at onset[a]

- 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 neonates



BNFC: Benign neonatal familial convulsion

BNC: Benign neonatal convulsion

BENIGN NEONATAL FAMILIAL CONVULSION (BNFC)

- Rare, Autosomal Dominant
- **Age of onset**: Seizures occur in well newborns on 2-3 day of life and remit by 6 weeks
- **Seizure type**: Tonic seizure or apnea
- sometimes with focal components (sliding eyes, motor automatisms) and clonic seizures (asymmetrical/ unilateral)
- Favorable outcome
- Seizures may recur in later life in 10%
- Mutation in the potassium channel genes (KCNQ2, KCNQ3) causing alteration of slowly inactivating and non-inactivating M-channel currents

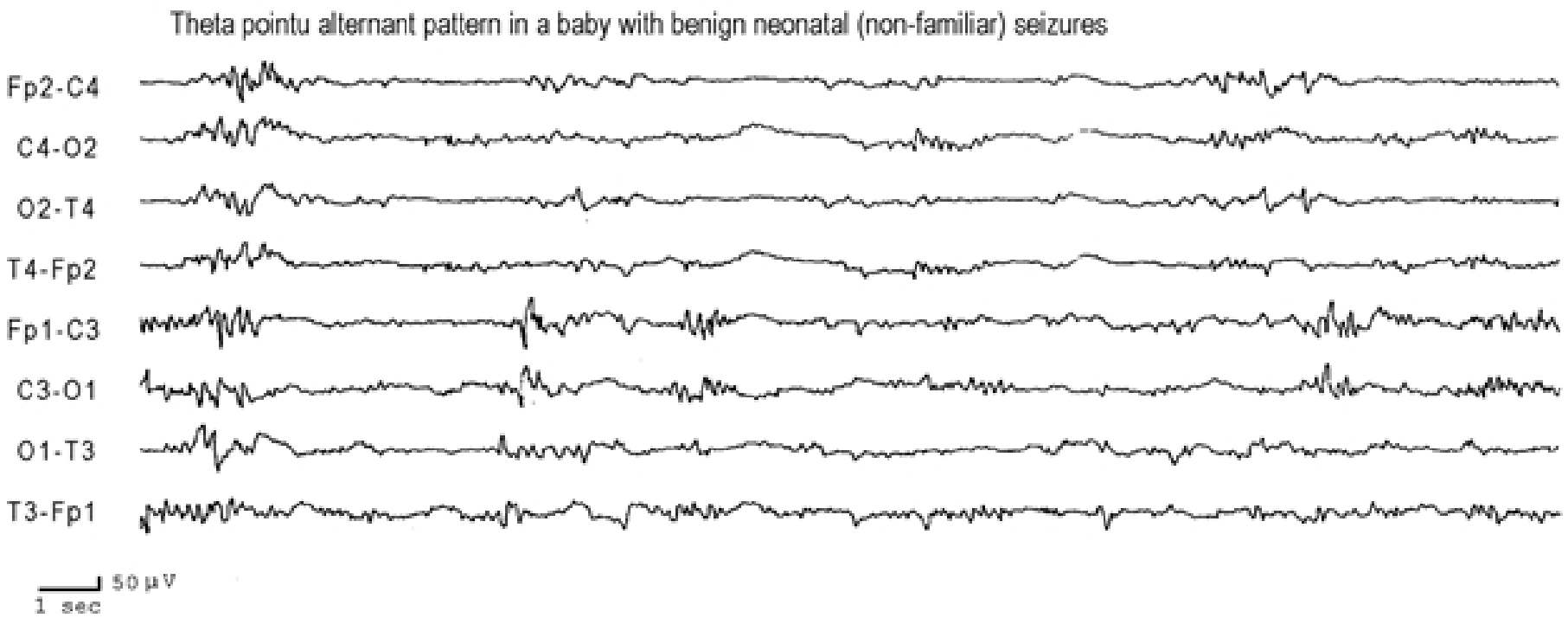
Nordli DR. Epilepsia 2005;46(Suppl 9):48-56

Benign Neonatal Convulsions (fifth day fits)

- **Age of onset:** occur around the fifth day of life
- **Seizure types:** clonic (unilateral) which may be accompanied by apnea

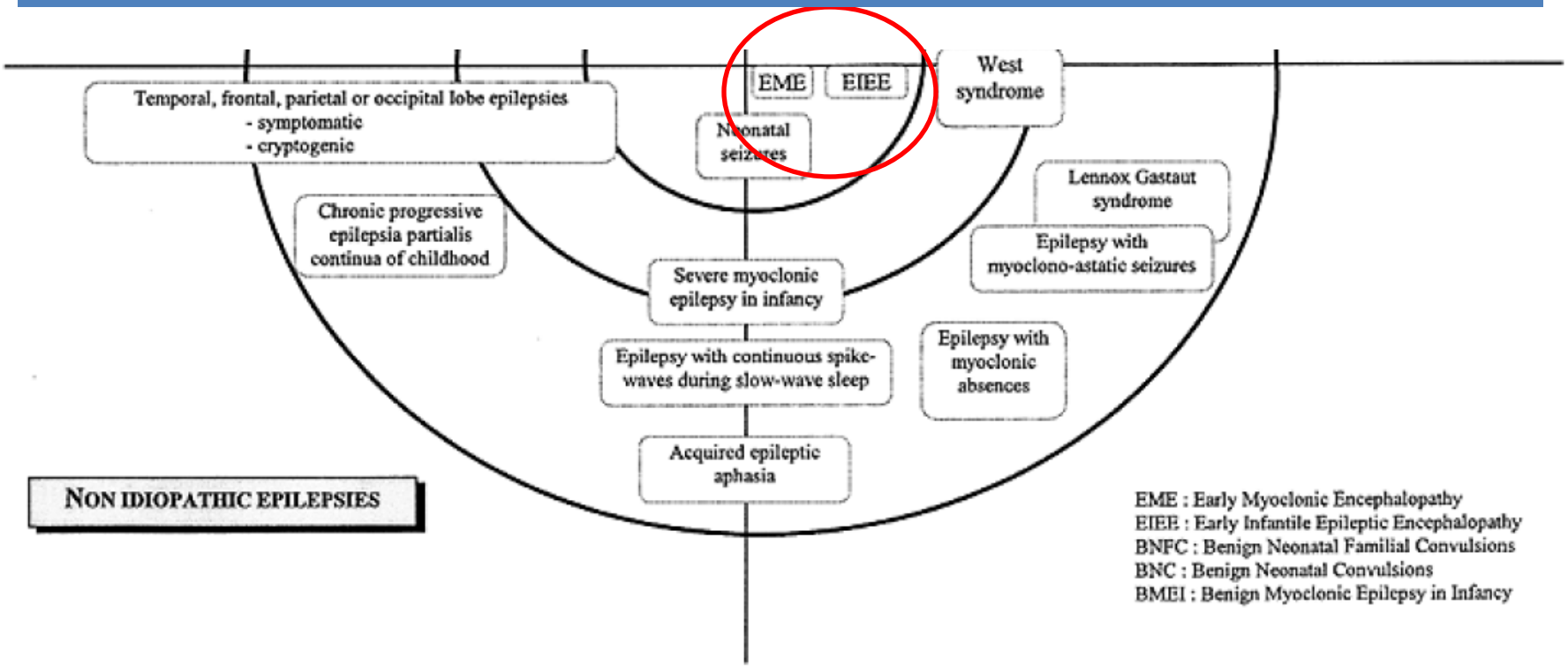
  : Status epilepticus (2 hours-2 days)
- **EEG patterns**:
  - Interictal : theta wave activity 4-7 Hz which changes sides
  - Ictal : rhythmic spike-slow waves predominantly in the centrotemporal region
- Healthy, full term infant
- Negative evaluations for etiology
- Good prognosis, seizures regress spontaneously

Benign Neonatal Convulsions (fifth day fits)



	BINC (fifth day fits)	BNFC
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	Familial (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

Epileptic syndrome in neonates



EIEE : Early Infantile Epileptic Encephalopathy (Ohtahara syndrome)

EME: Early Myoclonic Encephalopathy

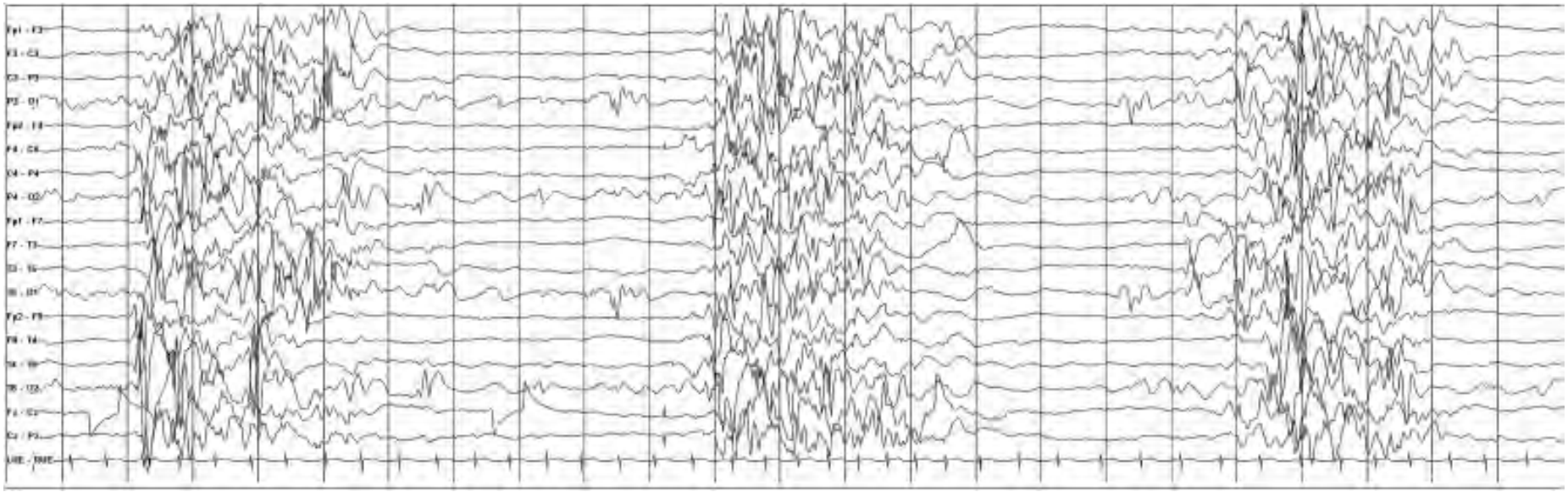
EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY (Ohtahara Syndrome)

- Seizure onset within few weeks after birth (< 3 months):
  - Tonic seizures which may occur in clusters
  - Focal motor seizures
  - Hemiconvulsions
  - Generalized tonic-clonic
- EEG: suppression-burst pattern both in sleep and wake states
- Etiology: Major brain malformations, non-ketotic hyperglycinemia, mitochondrial cytopathy, pyridoxine dependency, CPT deficiency, genetic (ARX, STXB1, SLC2A22)
- 75% progress to West syndrome, 12% to LGS

Beal JC et al. Pediatric Neurology 2012;47:317-23

Ohtahara S, Yamatogu Y. J Clin Neurophysiol 2003;30:398-407

EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY (Ohtahara Syndrome)



Beal JC et al. Pediatric Neurology, 2012;47:317 - 323

EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY (Ohtahara Syndrome)

- Poor prognosis for seizures, development
- Some overlap with Early Myoclonic Encephalopathy
- Limited response to conventional AEDs; some benefit with ACTH, Ketogenic Diet
- Treatment of Pyridoxine dependency or Biotinidase deficiency, NKH
- Cortical resection, hemispherectomy in selected cases

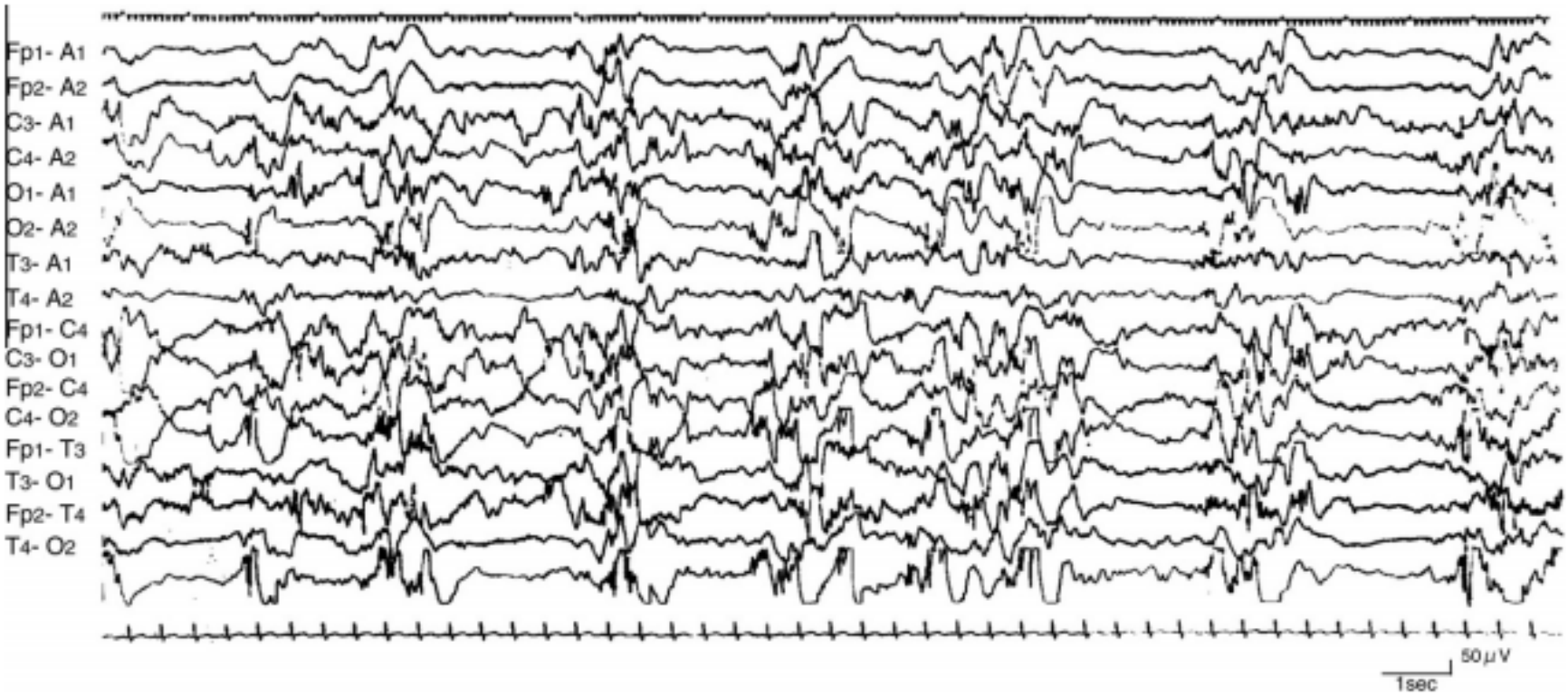
Beal JC et al. Pediatric Neurology 2012;47:317-23

Ohtahara S, Yamatogu Y. J Clin Neurophysiol 2003;30:398-407

Early Myoclonic Encephalopathy (EME)

- Age of onset: during 1 months of life
- Seizure patterns: myoclonic seizures
- Partial seizures (frequent)
- Tonic spasms (occasional)
- EEG: Burst-suppression pattern mainly during sleep
- Intractable to AEDs
- Poor developmental prognosis

Early Myoclonic Encephalopathy (EME)



EEG demonstrates suppression-burst pattern mainly noted during sleep
the burst phase is shorter with irregular longer periods of suppression phase than EIEE

H. Yamamoto et al. Brain & Development 2011

Early myoclonic encephalopathy (EME) VS. early infantile epileptic encephalopathy (EIEE)

	EIEE	EME
Age of onset	Within first three months	Neonatal period
Characteristic seizure type	Tonic spasm	Erratic or fragmentary myoclonus
Additional seizure types	Focal motor seizures Hemiconvulsions Generalized seizures	Massive myoclonus Simple partial seizures Infantile spasms (tonic)
Background EEG (Suppression-burst pattern)	Bursts- Longer Interburst- Regular, shorter (Sleep and awake)	Bursts-Shorter Interburst- Irregular, longer (accentuated by sleep)
Etiology	Malformation of cortical development	Genetic and metabolic
Long-term seizure evolution	West syndrome Lennox-Gastaut	Persistent regression

Epileptic syndrome in infants

- 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

WEST SYNDROME

- Described by West in 1841
- Triad:
  - Seizure: infantile spasm (symmetric, salaam-like contractions of trunk + extension and elevation of arms + tonic extension of legs)
  - Developmental delay (85-90%)
  - Typical EEG: hypsarrhythmia and variants
- Ictal EEG: generalized electrodecremental pattern often preceded by a generalized sharp/slow wave
- Age at onset: early infancy, peak 4-7 mo
- Etiology: various causes (FCD, Tuberous sclerosis, etc.)
- Very difficult to treat seizure

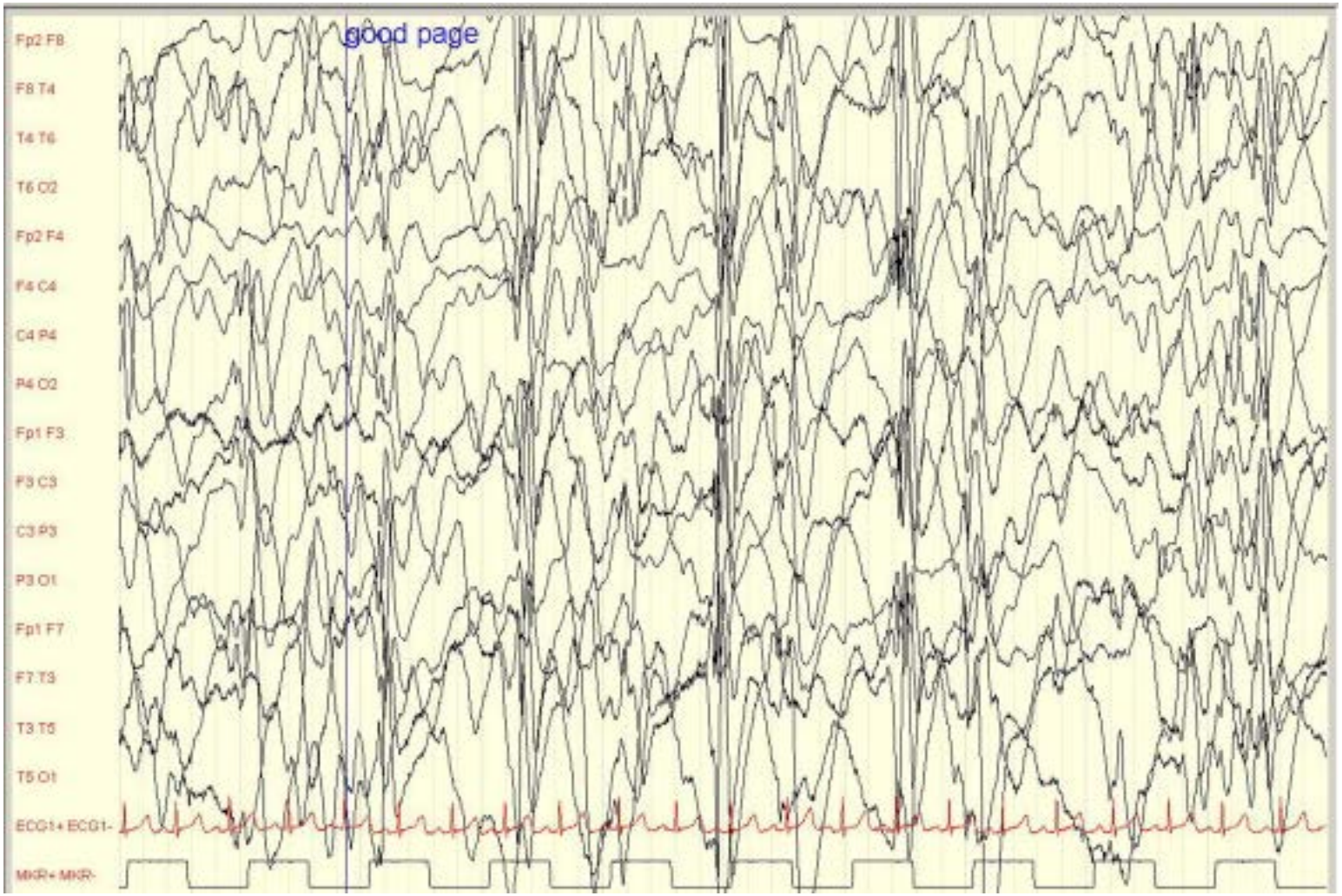
West syndrome
Common Etiologies

- Tuberous Sclerosis (10-30%)
- Perinatal (15-25%)
  - Fetal infections
  - HIE/perinatal brain injury
  - Hypoglycemia
- Brain malformations
- Metabolic abnormalities
- Pyridoxine deficiency

Chromosomal Abnormalities:

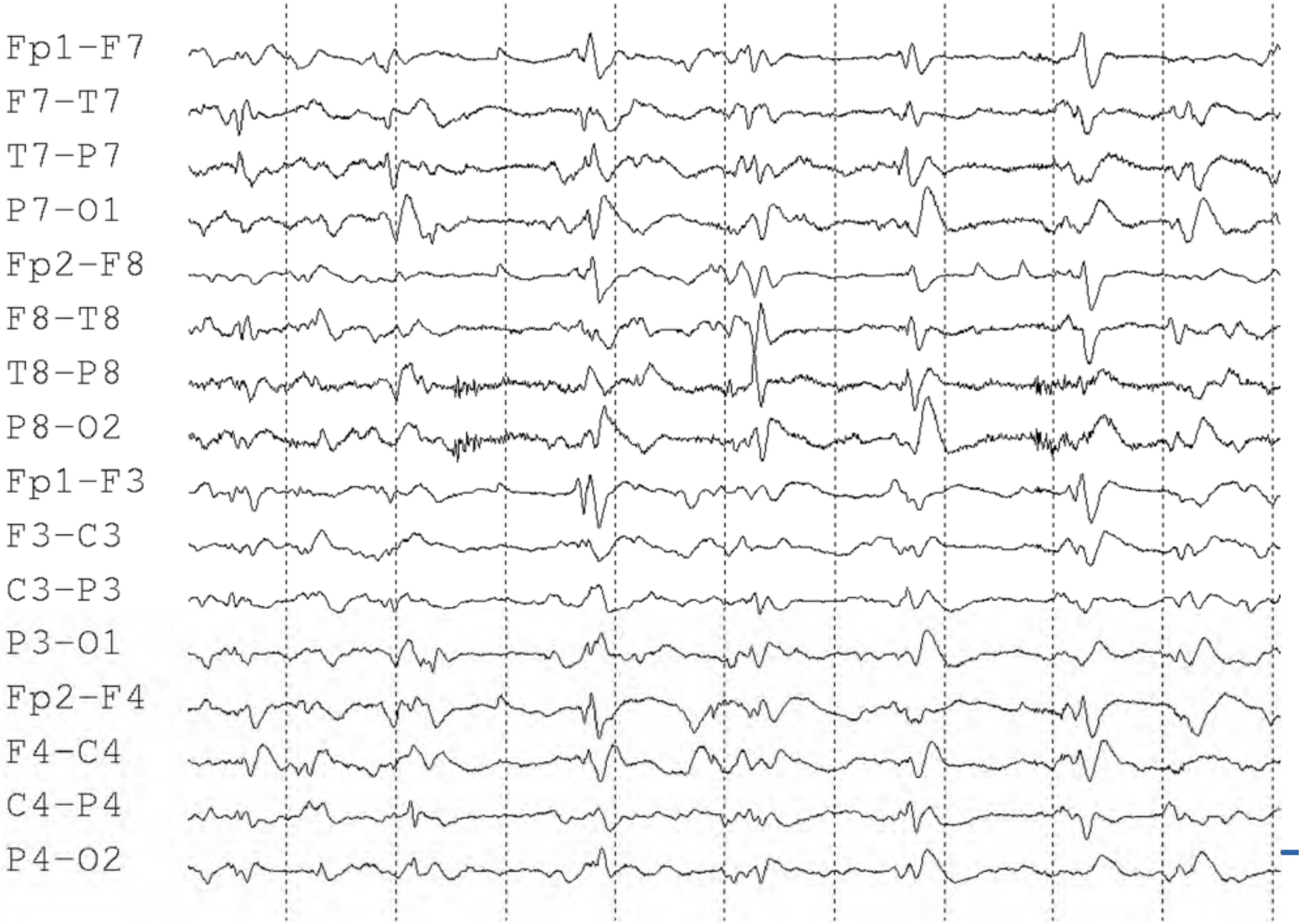
- Trisomy 21
- ARX
- TSC1
- TSC2
- RDXP2
- ALDH7A1
- POLG
- CDKL5
- STXBP1
- SCN2A
- FOXG1
- PCDH19
- SLC2A1
- MeCP2

Hypsarrhythmia pattern during wakefulness



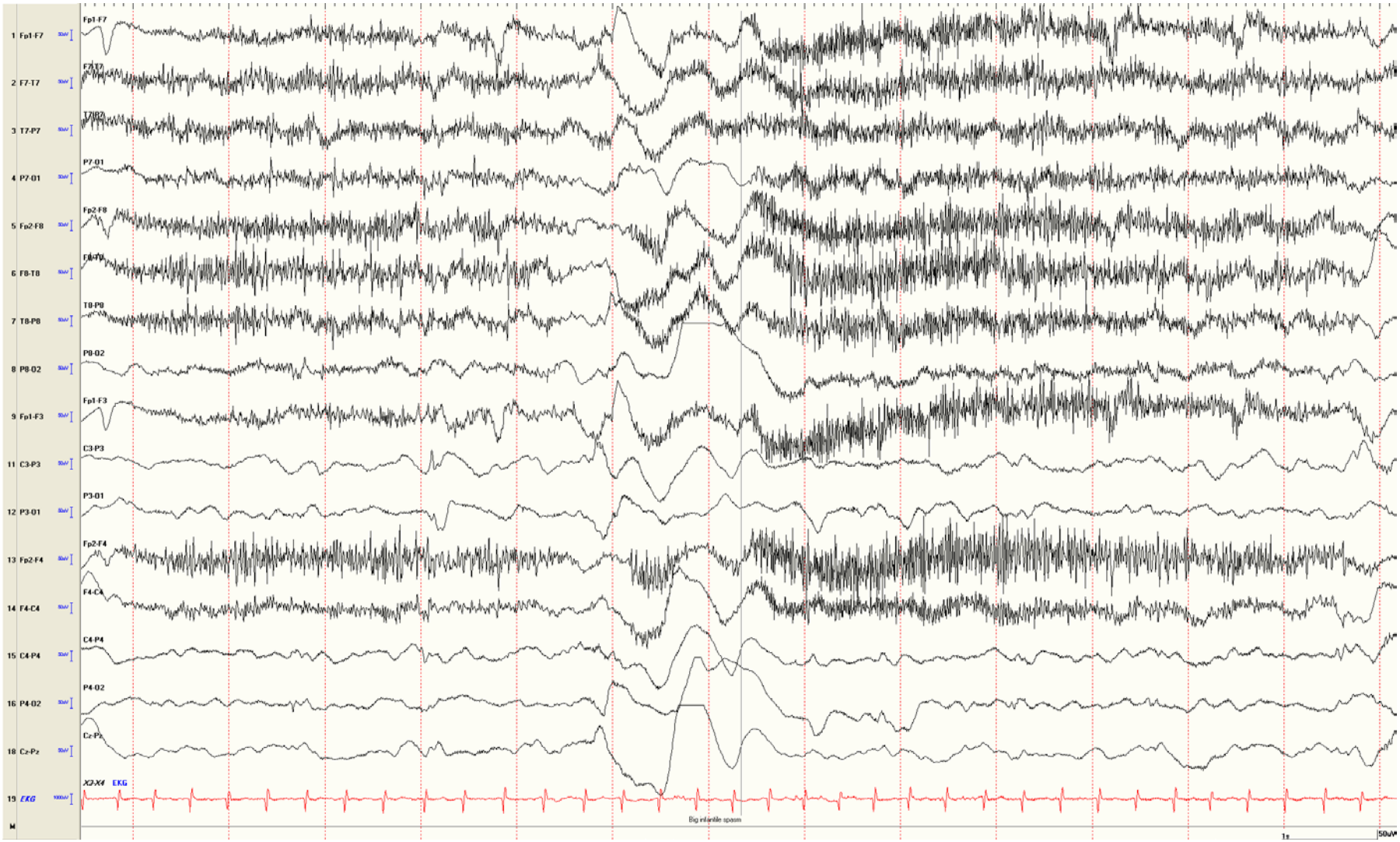
Chaotic mixture of asynchronous, high amplitude of slow wave intermixed with multifocal spikes

HYPSARRHYTHMIA PATTERN ALTERED BY NREM SLEEP



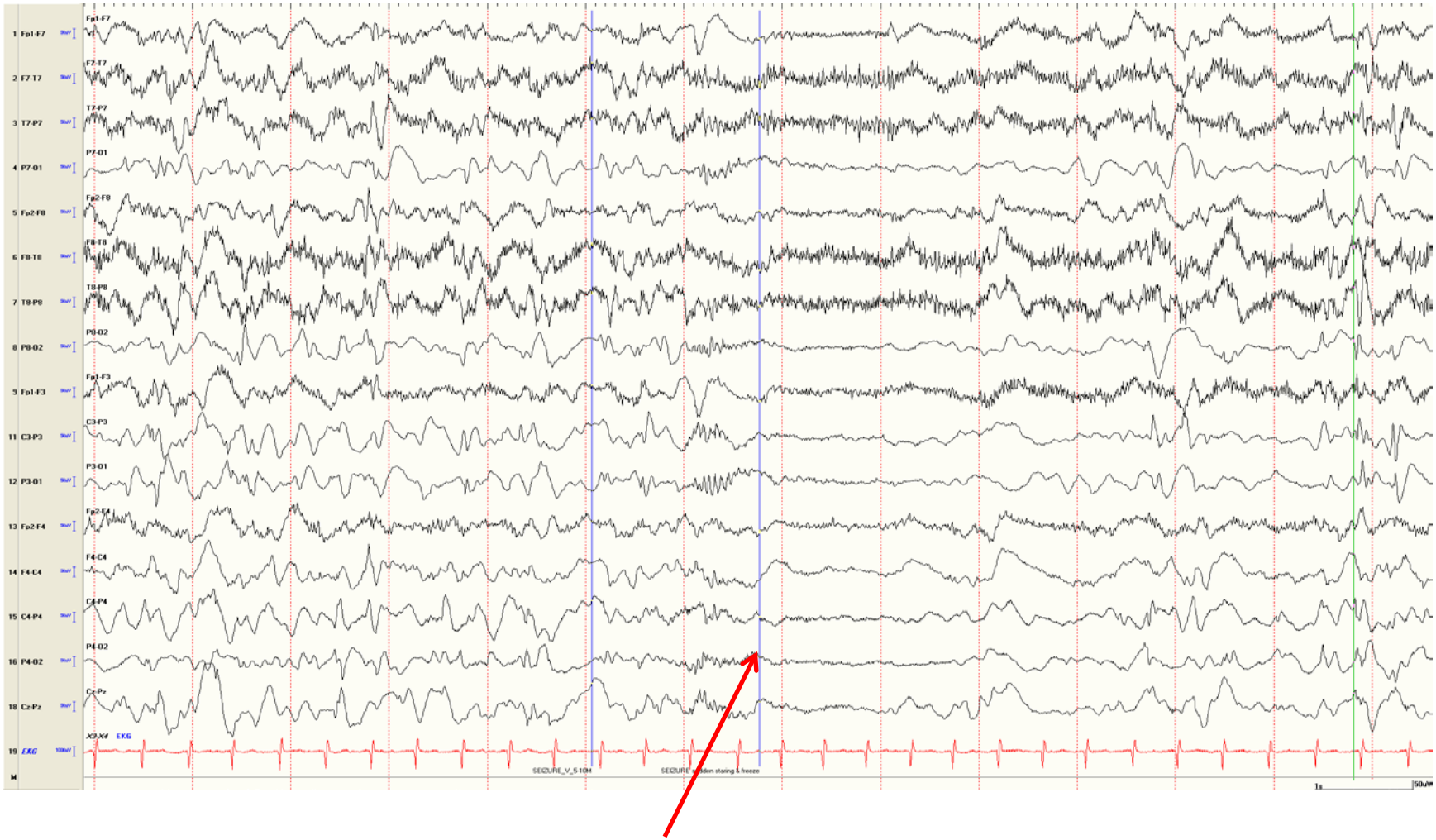
Video infantile spasm

Ictal EEG



Medium- to high-voltage,positive slow waves maximal at vertex regions with superimposed low-voltage fast activity (ictal), followed by electrodecremental event

Ictal EEG – electrodecremental pattern



TREATMENT OF INFANTILE SPASMS

- Pyridoxine worth trying – stop if no benefit in 3 days
- Benzodiazepine such as Clonazepam. If spasms are not promptly controlled proceed with:-
- ACTH / Vigabatrin which are the only drugs shown to be effective in clinical trials. Should be started within 3-4 weeks of seizure onset
- Topiramate, Zonisamide have some efficacy
- Valproic acid
- Ketogenic Diet
- Epilepsy Surgery when seizures are uncontrolled and there is a focal/unilateral lesion

BENIGN MYOCLONUS OF EARLY INFANCY

- Age of onset: 4-12 mo
- Myoclonic jerks involving neck and extremities
- May occur singly or in clusters
- Elicited by excitement, fear, anger, frustation
- Resemble Infantile Spasms
- EEG is normal both interictally and during jerks
- Video-EEG useful in excluding West Syndrome which requires prompt diagnosis and treatment
- Development progresses normally
- Myoclonic jerks diminish over time, disappear during second year of life

Lombroso CT, Fejerman N. Ann Neurol 1977;1(2):138-43.

Myoclonic Epilepsy in Infancy

- Rare idiopathic epilepsy – myoclonic seizures in previously healthy children
- Onset: 6 months- 2 years
- Family history of epilepsy in 1/3 of the patients
- Preceding febrile seizures in 20%
- EEG: Spike, multiple spike-wave complexes
- AEDs: VPA
- Mild cognitive impairment (20-40%)

SEVERE MYOCLONIC EPILEPSY OF INFANCY (SMEI) DRAVET SYNDROME

- Onset between 6-15 months, often triggered by fever, illness or immunizations
- Seizures:
  - Generalized or hemiclonic convulsions (including status)
  - Myoclonic
  - Atonic, drop attacks
  - Focal dyscognitive/CPS
  - Non-convulsive status epilepticus
- EEG may be normal initially or show focal spikes -> multifocal or generalized spikes, spike-wave complexes
- Developmental initially normal, then slows
- Imaging normal / shows nonspecific atrophy

Scheffer IE. Diagnosis and long-term course of Dravet syndrome. Eur J Ped Neurol 2012;16:S5-S8.

SEVERE MYOCLONIC EPILEPSY OF INFANCY (SMEI) DRAVET SYNDROME

- Unfavorable outcome due to ongoing seizures, MR
- Course appears to stabilize after age 5 years
- Genetic etiology
  - 70% - 80% have mutations of voltage gated sodium channel gene SCN1A (usually de novo)
  - Girls who are SCN1A negative may have mutations involving PCDH-19 (Protocadherin-19) gene
- Avoid drugs which act via the sodium channel:-
  - CBZ, OXC, PHT and LTG

Scheffer IE. Diagnosis and long-term course of Dravet syndrome. Eur J Ped Neurol 2012;16:S5-S8.

Main characteristics of epileptic syndrome in infancy

Table 1. Main characteristics of the epileptic syndromes that present in infancy

Syndrome	Main Characteristics
Early infantile epileptic encephalopathy	First months; tonic seizures, spasms; suppression-burst; severe outcome
Early myoclonic epilepsy	First months; myoclonias, spasms; suppression-burst (sleep); severe outcome
Infantile spasms	First year; spasms; hypsarrhythmia; developmental delay
Dravet syndrome	First year; partial and generalized seizures, myoclonias; normal EEG at onset; later: generalized spike-waves and multifocal spikes; severe outcome
Myoclonic astatic epilepsy	First year; generalized myoclonic and astatic seizures; interictal parietal theta activity and bilateral spike-waves; variable outcome
Malignant migrating partial seizures of infancy	First year; continuous electrographic seizures, multiple areas of onset; severe outcome
Generalized epilepsy with febrile seizures (+)	Variable seizure and developmental phenotype in addition to febrile seizures and afebrile generalized convulsions
Hemiconvulsion-hemiplegia-epilepsy	Prolonged unilateral febrile seizures; subsequent hemiparesis and partial epilepsy
Benign myoclonic epilepsy	First 3 years; myoclonic seizures; normal interictal EEG; normal development
Benign familial/nonfamilial seizures	First year; partial seizures; normal development

Korff CM, Nordli Jr DR. Epilepsy syndromes in infancy. Pediatr Neurol 2006

Thank you for your attention