Neonatal Epileptic Encephalopathies

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Neonatal Seizures - Epidemiology

- The incidence of neonatal seizures 1.5–5.5 per 1.000 live births among term infants
- Higher in preterm or very low birth weight infants at 6 to 48%
- Most are acute, symptomatic, and provoked by severe brain insults such as hypoxic-ischemic encephalopathy (HIE) or intracranial haemorrhages (ICHs)
- Some may involve neonatal-onset epilepsy related to structural, metabolic, or genetic disorders.
- Age related pathophysiologic mechanisms with regard to seizure

Why are Neonatal Seizures Different

- Increased risk of seizures due to
  - Enhanced excitatory neurotransmitters (NT) – mature early
  - Paucity of inhibitory mechanisms (maturational changes in glutamate and GABA receptors) – mature late
  - Developmental alterations or modulation of neuronal ion channels and neuropeptides
  - Age dependent early microglial activation in early CNS development
  - Incomplete arborization of axons and dendritic processes and decreased myelination
- Fragmented seizures (focal and short) vs generalized tonic-clonic – (rare)
- More immature the brain the more brief and short the seizures and a higher proportion of subclinical seizures
- More advanced limbic system, midbrain and brainstem development -
  - higher frequency of mouthing, eye deviation and apnoea, electroclinical dissociation

Main Types of Neonatal Seizures

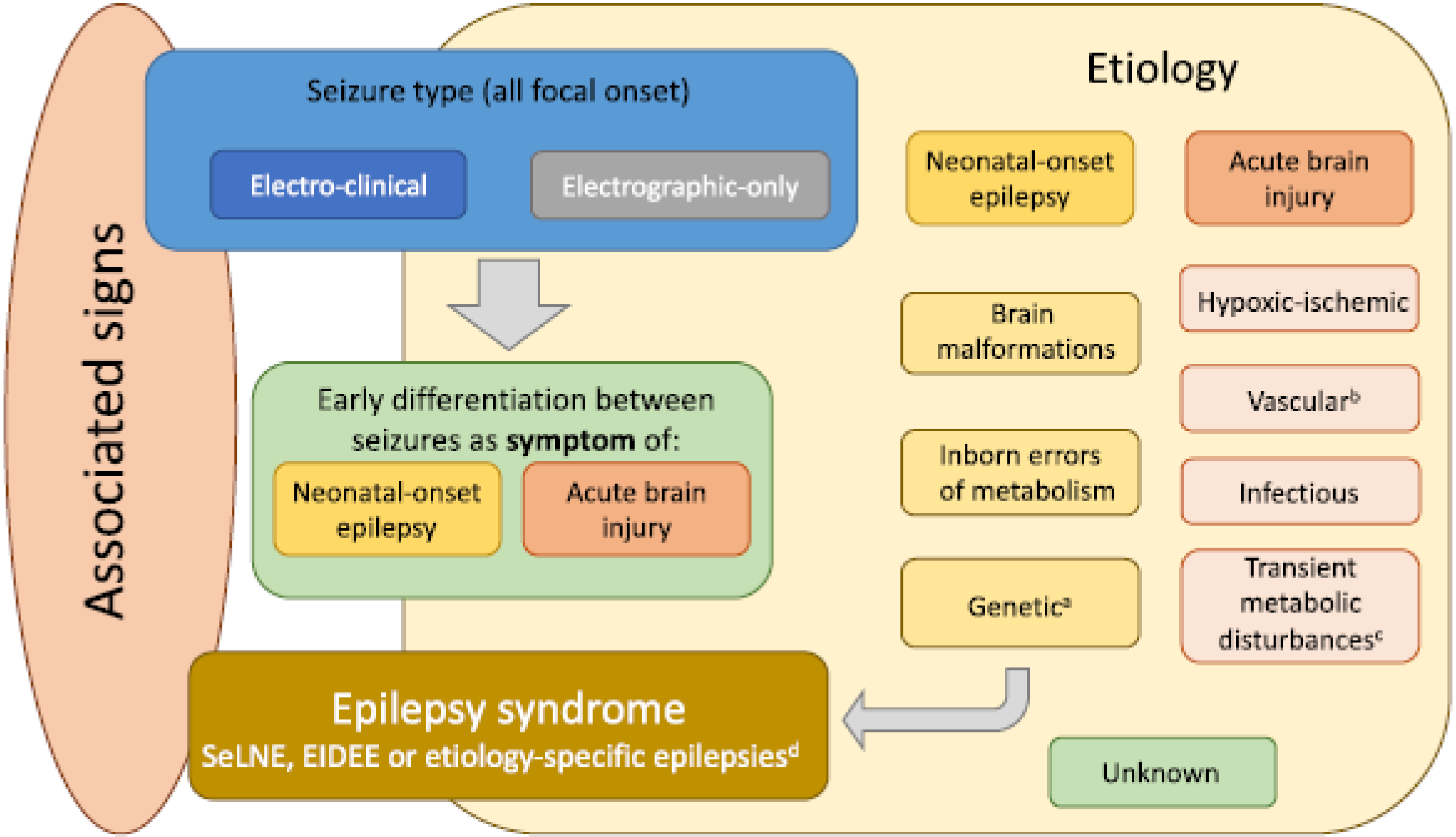
Seizure classification	Typical presentation	Other characteristics
Focal clonic seizures	Slow, rhythmic jerking	Occurs while awake; not suppressible; common manifestation in term neonates
Focal tonic seizures	Slow, sustained limb or trunk posturing	Not suppressible; common manifestation in term neonates
Myoclonic seizures	Rapid, single jerks, may be repetitive but generally not rhythmic	Occurs while awake; may be provoked by stimulation
Subtle motor seizures	Blinking, sucking, chewing, tongue protrusions	May be provoked or intensified by stimulation
Subtle autonomic seizures	Tachycardia, apnea, hypertension	Occurs more frequently in preterm infants
Epileptic spasms	Brief flexion, extension, or mixed flexor/extension	May occur in clusters; not suppressible; rare
Generalized tonic seizures	Slow, sustained posturing of limbs and trunk	May be provoked by stimulation; suppressible

Martin M et al Pediatr Ann 2020

Causes of Neonatal Seizures

Cause	Description
Hypoxic Ischaemic encephalopathy (50-60%)	Usually within 12 – 24 hours
Vascular Lesions (10-20%) Haemorrhage Stroke Congenital Vascular Anomaly	Includes sinus venous thrombosis, arterio-venous malformation, venous malformations
Congenital Brain Malformations (5-10%) Focal Diffuse	Focal – Agenesis of the corpus callosum, Dandy-Walker malformation Diffuse: schizencephaly, holoprosencephaly, polymicrogyria, lissencephaly
Infection (5-10%)	Early (<72hrs), late (>7 days), Seizures can be prolonged or difficult to treat
Metabolic (~1%) electrolyte abnormalities as well as inborn errors	Reversible causes – electrolyte abnormalities Other metabolic vitamin and co-factor deficiencies
Drug intoxication or withdrawal (~1%)	Narcotics, benzodiazepines, barbiturates, cocaine, alcohol, tricyclic anti-depressants
Neonatal Epilepsy Syndromes (~1%)	Very rare – family history or may be *de novo* mutations

ILAE Classification 2022



International League Against Epilepsy

Zuberi et al Epilepsia 2022

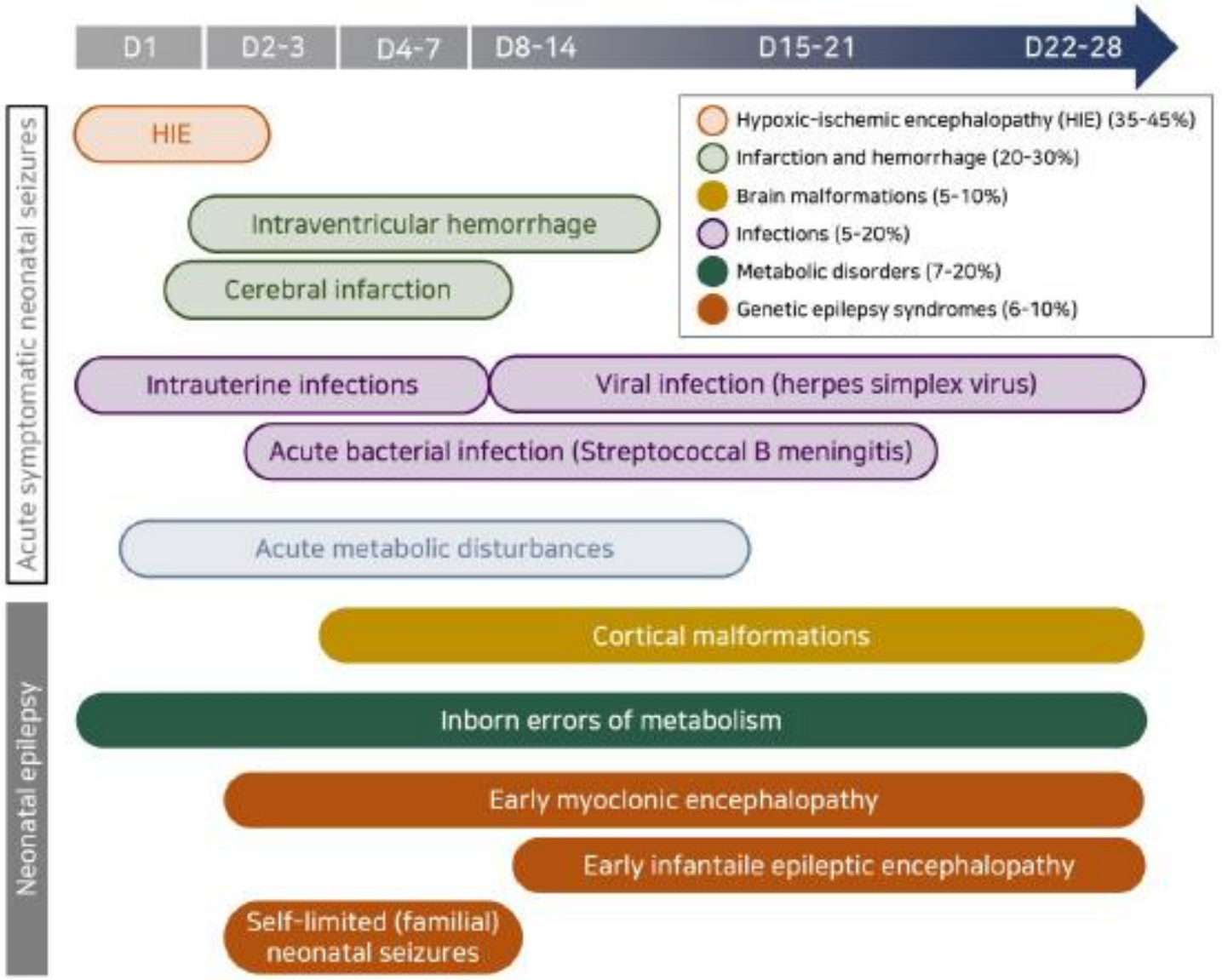
Acute Symptomatic Seizures

- Most common cause of seizures in neonates
- Aetiology –
  - Hypoxic Ischaemic Encephalopathy (HIE),
  - Stroke,
  - haemorrhage,
  - infection,
  - hypoglycaemia and electrolyte imbalances
- Most common cause is HIE – 35 -45%
- 2nd commonest – cerebrovascular events – infection or haemorrhage
- For electrolyte abnormalities – correct the electrolyte and may treat with anti-seizure medications (ASM)

Epilepsy Syndromes

- 13% of all neonatal seizures
- Aetiology –
  - Brain malformations,
  - Genetic variants,
  - Inborn error of metabolism (IEM)
- Divided into self limited epilepsy syndromes and developmental epileptic encephalopathies (DEE)
- Self limited epilepsy syndromes – usually go into remission and is associated with normal cognition
- DEE – severe early-onset epilepsy, neurodevelopmental comorbidity which may be attributable to the underlying cause and /or the uncontrolled epilepsy

Acute Symptomatic vs Neonatal Epilepsy



Kim EH et al Clin Exp Pediatr Vol. 65, No. 8, 387–397, 2022

Semiology Based Approach

I

Continuous video-EEG monitoring
in critically ill* neonates or in neonates with clinical suspicion of seizures
Seizure recording → Delineation of seizure type

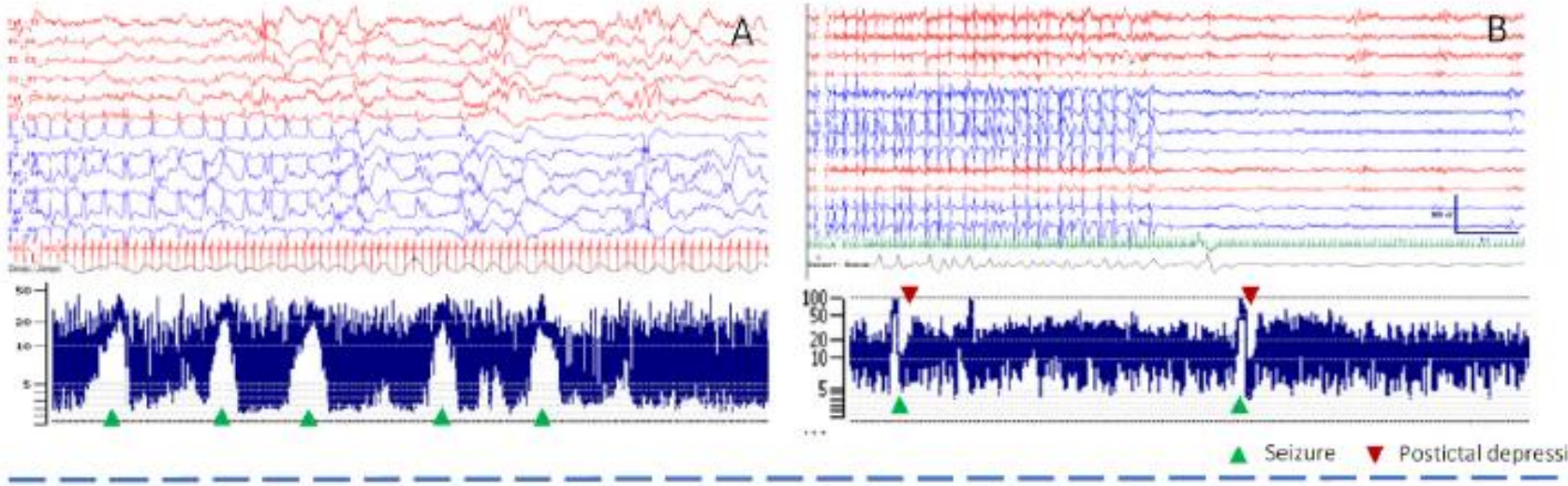
Pressler et al., 2021; Shellhaas et al., 2011

II.B

Distinction between

Acute provoked seizures

Neonatal-onset epilepsies



II.A

Semiology based approach

Acute provoked seizures

Semiology	Etiology
Unilateral clonic	Stroke
Multifocal clonic	Infections
Electrographic-only	HIE Cardio-pulmonary disease°

Neonatal-onset epilepsies

Semiology	Etiology
Tonic - Sequential	Channelopathies (e.g. *KCNQ2/3, SCN2A*)
Asymmetric tonic spasms	Brain malformations (e.g.large cortical dysplasia or hemimegalencephaly)
Myoclonic/spasms	Metabolic/Vitamin-dependent disorders

Cornet et al., 2021; Santarone et al. 2020; Massey et al., 2021

Carapancea E et al. Eur J. Pediatric Neurology 2023

Organization of Epilepsy Syndromes

Self-limited epilepsies

- Self-limited neonatal epilepsy (SeLNE)
- Self-limited familial neonatal-infantile epilepsy (SeLFNIE)
- Self-limited infantile epilepsy (SeLIE)
- Genetic epilepsy with febrile seizures plus (GEFS+)
- Myoclonic epilepsy in infancy (MEI)

Developmental and epileptic encephalopathies (DEE)

- Ealy infantile developmental and epileptic encephalopathy (EIDEE)
- Epilepsy in infancy with migrating focal seizures (EIMFS)
- Infantile epileptic spasms syndrome (IESS)
- Dravet syndrome (DS)

Etiology-specific syndromes

- *KCNQ2*-DEE
- Pyridoxine-dependent (*ALDH7A1*)-DEE (PD-DEE)
- Pyridox(am)ine 5'-Phosphate Deficiency (PNPO)-DEE (P5PD-DEE)
- *CDKL5*-DEE
- *PCDH19* clustering epilepsy
- Glucose Transporter 1 Deficiency Syndrome (GLUT1DS)
- Sturge Weber syndrome (SWS)
- Gelastic seizures with hypothalamic hamartoma (GS-HH)

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Epilepsy Syndromes in Neonates

Table 1
Comparison of the 2 groups of epilepsy syndromes with onset in the neonatal period: self-limited epilepsy syndromes and early infantile developmental epileptic encephalopathies

	Self-Limited Epilepsy Syndromes	Early Infantile Developmental Epileptic Encephalopathies
Age at onset	Typically 2–7 d of life	Within first 3 mo of life
Pregnancy and birth history	Normal	Typically normal
Family history of neonatal seizures	Yes, in the case of self-limited neonatal familial epilepsy	Not typically
Neurologic examination	Normal	Very abnormal—common findings include axial hypotonia, movement disorder, and poor visual tracking
EEG background	Normal or mildly abnormal	Severely abnormal
Developmental trajectory	Normal at onset and children typically continue to achieve developmental milestones appropriately	Often abnormal at onset though may not be initially recognized; moderate to severe developmental disability with feeding issues start early in life
Natural history	Seizures cease by 6 mo of age, often by 6 wk of age. Minority may develop seizures later in childhood.	Severe drug-resistant epilepsy that may be life-long; patients have shortened life-expectancy
Etiology	Mutation in the KCNQ2 gene is most common. KCNQ3 and SCN2A genes also implicated	Genetic etiologies include KCNQ2, SCN2A, STXBP1 pathogenic variants, among others. Genetic, metabolic, or structural etiology found in 80%.
Inheritance pattern	Autosomal dominant (in the case of self-limited neonatal familial epilepsy) or *de novo*	Dependent on underlying etiology

Mehta N, Pediatr Clinics N Am 2025

Neonatal Epilepsy Syndromes

Neonatal Epilepsy Syndrome	Onset	Seizure Semiology	Clinical Appearance	EEG	Treatment	Prognosis
Self-limited neonatal seizures	DOL 4-6	Unifocal clonic with apnea, bilateral, migratory clonic	Interictally healthy appearing	Theta pointu alternant		Seizures resolve within 2 wk
Self-limited familial neonatal seizures	Few days to one week of life	Multifocal clonic or tonic	Interictally healthy appearing	Nonspecific	OXC Carbamazepine	Resolve by age 2-3 mo
EIEE (Otahara syndrome)	In utero or postnatal	Tonic spasms, focal motor or hemiconvulsiv seizures		Burst- suppression pattern during sleep and wakefulness	Long term treatment with steroids, VPA ZNS, or vitamin B	Poor
EMEE	First few hours of life to later in neonatal period	Myoclonic and/or focal seizures; generalized myoclonus		Burst- suppression only during sleep	Trial of vitamins	Poor; resolve by 3-4 mo but then may progress to tonic spasms
KCNQ2 encephalopathy	First week of life	Tonic seizures, but not spasms	Encephalopathic with hypotonia and visual inattentiveness	Abundant multifocal negative sharp waves; can meet burst- suppression criteria		Seizures resolve by age 3; severe global delays
DEND syndrome	Neonate to infancy		Severe epilepsy in setting of neonatal diabetes		Oral sulfonylureas	Seizure control depends on judicious management of hyperglycemia; developmental delays
Epilepsy of infancy with migrating focal seizures	DOL 3 to late infancy	Migrating focal and/or tonic seizures with possible autonomic associations		Migratory epileptic discharges	LEV, BZD, STP, PHT; for apneas consider acetazolamide	Poor, death within a few years

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Severe Neonatal Epilepsy Syndromes

- Suspected when a trigger for acute symptomatic seizures not found
- Especially if have a burst-suppression interictal EEG pattern
- Refractory seizures and severe developmental delays
- Poor prognosis

Early Infantile Epileptic Encephalopathy

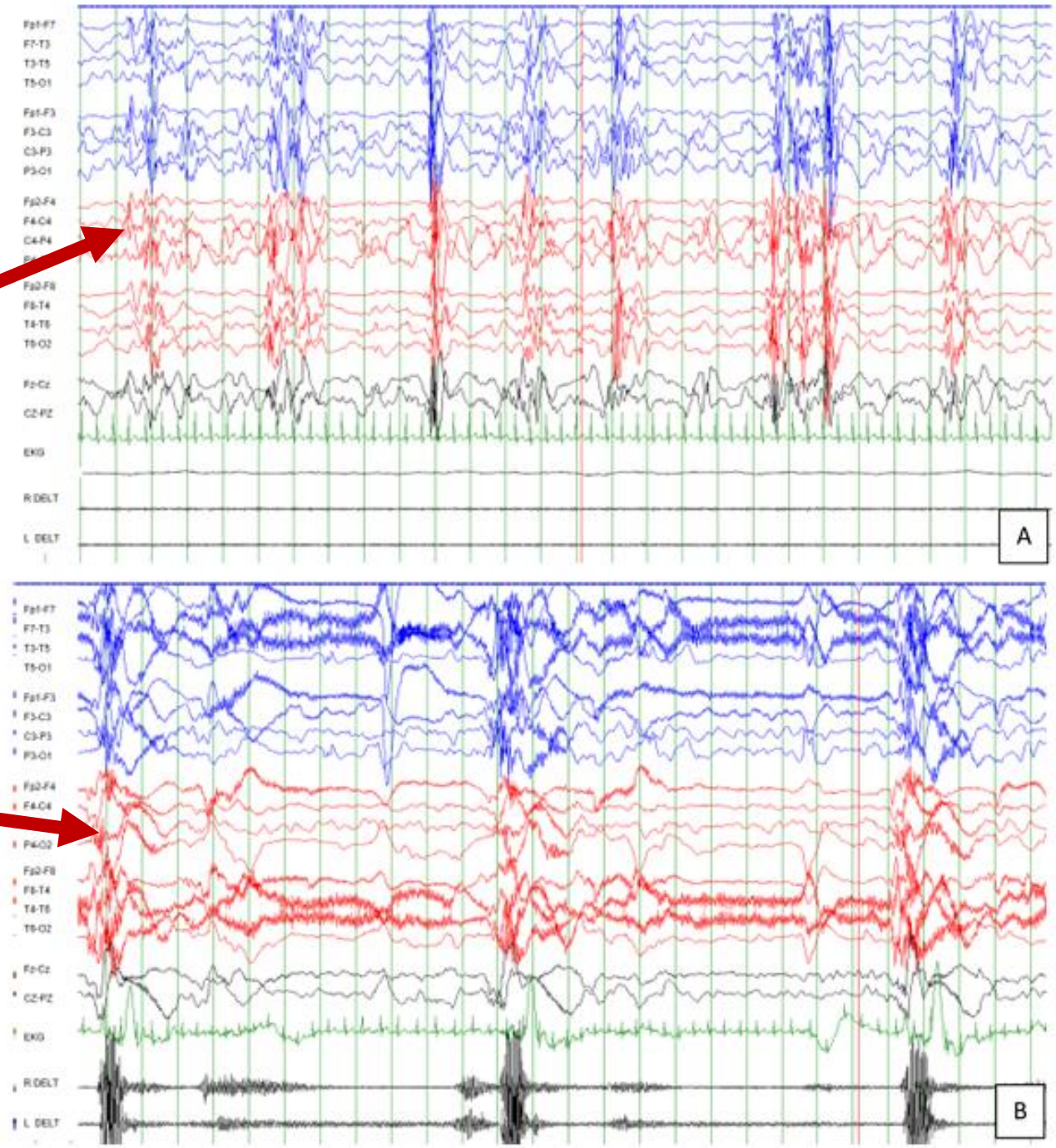
- Also known as Ohtahara Syndrome (OS)
- Rare – 10/100 000 live births
- Can have in utero or postnatal seizures
- Associated with tonic spasms and burst suppression
- Associated with numerous structural cerebral defects including:
  - Aicardi syndrome,
  - Hemi-megalencephaly,
  - Dentate-olivary dysplasia,
  - Porencephaly,
  - Migrational defects, and cerebral dysgenesis.
- Numerous genetic mutations are associated with EIEE – test with an epilepsy gene panel or whole exome sequencing is recommended

Early Infantile Epileptic Encephalopathy

- Genes associated with EIEE include CDKL5, ARX, PLCB1, PNKP, SCN3A, and STXBP1,
- Inborn errors of metabolism are a rare cause, except for nonketotic hyperglycinemia
- Tonic spasms are the predominant seizure type –
  - May be symmetric or asymmetric,
  - Occurs in isolation or in clusters
- Focal motor seizures and hemi- convulsive seizures may also occur.
- The EEG background shows burst-suppression with prolonged bursts (two to six seconds) of high-voltage (150 to 350uV) activity and shorter periods of suppression (3 to 5 seconds).
- This pattern is sustained across all stages of sleep and wakefulness.

Othahara syndrome

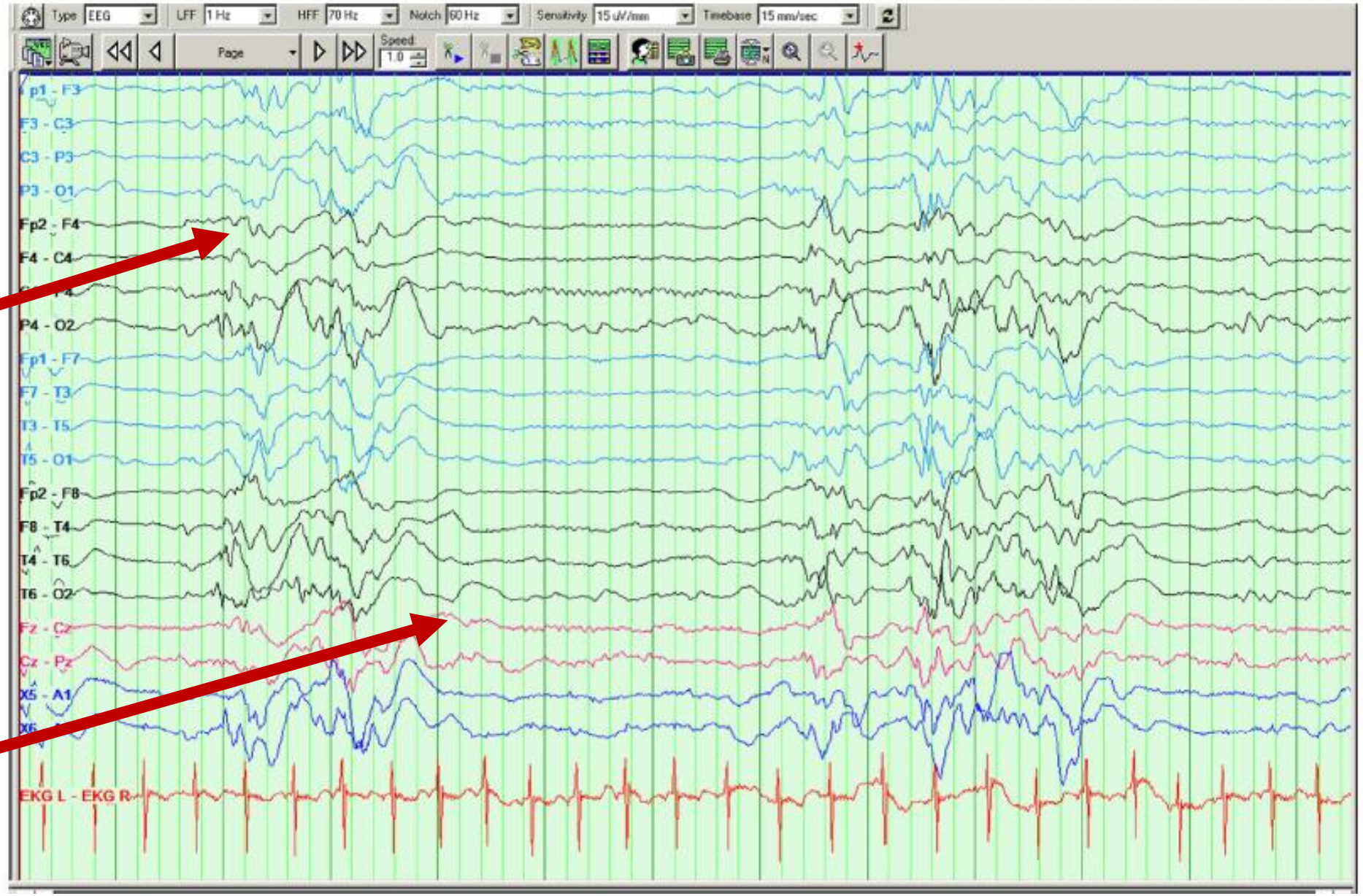
- Burst suppressions
- Tonic spasms



EIEE (OS)

Bursts

Suppression



Treatment

- Acute treatment same as other neonatal seizures.
- Genetic aetiology-guided therapy has shown promise
  - Levetiracetam can be considered for therapy of STXBP1 encephalopathy.
- Encouraging response has also been reported with zonisamide.
- Treatment with corticosteroids and valproate
- Surgical interventions including hemispherectomy and resection of cortical dysplasias has also been reported.
- Even with treatment, the outcome is poor with 50% of patients dying in infancy
- Survivors - severe neurodevelopmental deficits
- EIEE is on the earliest spectrum of a continuum of diseases that often progress to West syndrome and Lennox-Gastaut syndrome (LGS)
- The triad of syndromes share features of a specific age of onset, severe intellectual disability, and abundant epileptiform abnormality (hypsarrythmia)

Early Myoclonic Epileptic Encephalopathy (EMEE)

- A rare disorder
- Similar to Ohtahara syndrome.
- Predominant seizure type is myoclonic, rather than tonic.
- Encephalopathic neonate with erratic myoclonus and a burst-suppression pattern on EEG during sleep – consider EMEE
- There is no gender predominance
- Often associated with inborn errors of metabolism, less with congenital brain malformations
- Known causes of EMEE include
  - Sulfite oxidase deficiency,
  - Zellwegger syndrome,
  - Menkes disease,
  - Nonketotic acidaemia, and pyridoxine dependent seizures.

Early Myoclonic Epileptic Encephalopathy (EMEE)

- First few hours of life, erratic, fragmentary, or segmental myoclonic seizures begin, most often involving the distal limbs.
- Seizures evolve over time
  - Focal clonic seizures may develop a short while later, with eventual generalized myoclonus.
  - Seizures resolve by three to four months of age, can have repetitive tonic spasms occurring.
  - The diagnosis is aided by characteristic EEG patterns that demonstrate burst suppression in sleep,
  - 1 – 3 second bursts alternate with long periods of suppression lasting 2 –10sec.
- EEG correlate is seen with focal-clonic and tonic seizures but inconsistently with myoclonus.
- Evolution to hypsarrhythmia or multifocal spikes and sharp waves occurs with disease progression into early infancy – West syndrome or LGS

Treatment of EMEE

- Standard neonatal treatment of seizures is recommended.
- Recommend a trial of vitamin treatment.
- Vigabatrin may aggravate the myoclonic seizures
- Ketogenic diet can lessen the seizure burden caused by nonketotic hyperglycinemia.
- Fragmentary myoclonus resolves over weeks to months, but focal motor seizures tend to be refractory to treatment.
- Prognosis is poor
  - Delayed developmental outcomes and
  - 50% mortality within the two years of life

KCNQ2 Encephalopathy

- Severe epileptic syndrome,
- Presents in the the first week of life with
  - refractory seizures, hypotonia, encephalopathy, and lack of visual responsiveness
- These features are reminiscent of Ohtahara syndrome.
- Seizure semiology often consists of tonic movements which are not tonic spasms.
- EEG - multifocal sharp waves, which at times can meet criteria for burst suppression.
- MRI - Subtle thalami and basal ganglia hyperintensities (resolve)
- Seizure resolution by age three years, severe global developmental delays affect most children.
- Treatment - drugs that act on the sodium channels, (phenytoin,carbamazepine, and oxcarbazepine)

DEND Syndrome

- DEND Syndrome (developmental delay, epilepsy, neonatal diabetes)
- Rare and severe neonatal epilepsy syndrome
- Caused by a mutation in the KCNJ11 gene, which codes for the subunit of the potassium ion channel
- Control of hyperglycemia with oral sulfonylurea, instead of insulin, assists with improved seizure control and psychomotor development

Epilepsy of Infancy With Migrating Focal Seizures

- Epilepsy of infancy with migrating focal seizures may be observed in the neonatal period, mainly seen later in infancy.
- Seizure semiology is focal and tonic, occurring alone, or in combination with possible autonomic associations.
  - The seizure can migrate from one part of the body to another, as can the epileptic discharges on the EEG
- The KCNT1 potassium ion channel is the suspected genetic etiology
- Treatment is challenging
  - Stepwise therapeutic approach utilizing levetiracetam, then a benzodiazepine such as clonazepam, and then stiripentol
  - Other groups report seizure control with phenytoin, levetiracetam, and acetazolamide
- Poor prognosis - with refractory seizures, neuro-devastation
- Death within a few years

Genetic associations with DEE

Disease	Age of Onset	EEG Features	Clinical Features	Some Common Associated Genes
Early infantile DEEs	First 3 months of life	Suppression burst, multifocal epileptiform discharges, possible hypsarrhythmia	Tonic (independent of sleep), myoclonic, epileptic spasms; sequential seizures, neurodevelopmental deficits	*STXBP1* (~30%), *KCNQ2* (~20%), *SCN2A* (~10%), *AARS*, *ARX*, *BRAT1*, *CACNA2D2*, *GNAO1*, *KCNT1*, *NECAP1*, *PIGA*, *PIGQ*, *SCN8A*, *SIK1*, *SLC25A22*, *ERBB4*, *SETBP1*
EIMFS	First year of life	Migrating ictal patterns between hemispheres, multifocal discharges	Focal motor tonic or clonic seizures that migrate from one hemisphere to the other, neurodevelopmental delay	*KCNT1* (~50%), *SCN2A* (~25%), *PLCB1*, *QARS*, *SCN1A*, *SCN8A*, *SLC25A22*, *TBC1D24*, *SLC12A5*, *FARS2*
IESS	3-12 months (1-24 months)	Interictal: hypsarrhythmia/BASED score 4 or 5; ictal: electrodecremental response or high-amplitude midline slow wave with admixed fast activity	Epileptic spasms, neurodevelopmental disorders (preseizure development can be normal or abnormal; most plateau or regression occurs with spasm onset), may evolve into LGS	*CDKL5* (~10%), *STXBP1* (~2%), *ARX*, *ALG13*, *DOCK7*, *DNM1*, *FOXG1* (duplications), *GABRB1*, *GABRB3*, *GNAO1*, *GRIN1*, *GRIN2A*, *GRIN2B*, *MAGI2*, *MEF2C*, *NEDDL4*, *NDP*, *NRXN1*, *PIGA*, *PLCB1*, *PTEN*, *SCA2*, *SCN1A*, *SETBP1*, *SIK1*, *SLC25A22*, *SLC35A2*, *SPTAN1*, *ST3Gal3*, *TSC1*, *TSC2*, *TBC1D24*, *TCF4*, *WWOX*
Dravet syndrome	3-9 months (1-20 months)	Focal or multifocal epileptiform abnormalities, photoparoxysmal responses.	Developmental delays, prolonged hemiclonic seizures with fever, myoclonic and focal impaired awareness seizures	*SCN1A* (~90%) (mutations in >85%, copy number variants in <5%; >90% *de novo*, 5%-10% inherited [mostly missense mutations])
EMAtS	2-6 years	2- to 6-Hz spike and polyspike-slow wave, generalized paroxysmal fast discharges	Myoclonic-atonic seizures, atonic, absence, and generalized tonic-clonic seizures	*SCN1A*, *SCN1B*, *SCN2A*, *STX1B*, *SLC6A1*, *CHD2*, *SYNGAP1*, *NEXMIF*, *KIAA2022*, *SLC2A1*
LGS	18 months-8 years	Slow spike-wave (<2.5 Hz), generalized paroxysmal fast, focal, or multifocal epileptiform discharges	Tonic seizures in sleep, atypical absences, tonic-clonic, myoclonic, atonic seizures, neurodevelopmental delay	*ALG13*, *CACNA1A*, *CDKL5*, *CHD2*, *DNM1*, *FLNA*, *GABRB3*, *GRIN2B*, *HNPRNU*, *HNRNPH1*, *IQSEC1*, *IQSEC2*, *KCNQ3*, *MTOR*, *SCN1A*, *SCN2A*, *SCN8A*, *STXBP1*
DEE-SWAS	2-12 years	Slow (1.5-2 Hz) spike-wave abnormalities in non-REM sleep, abnormalities markedly activated in sleep	Cognitive, behavioral, or motor regression or plateauing temporally related to SWAS on EEG	*GRIN2A*, *ZEB2*, *CNSKR2*, *KCNQ2*, *KCNA2*, *KCNB2*, *SLC9A6*

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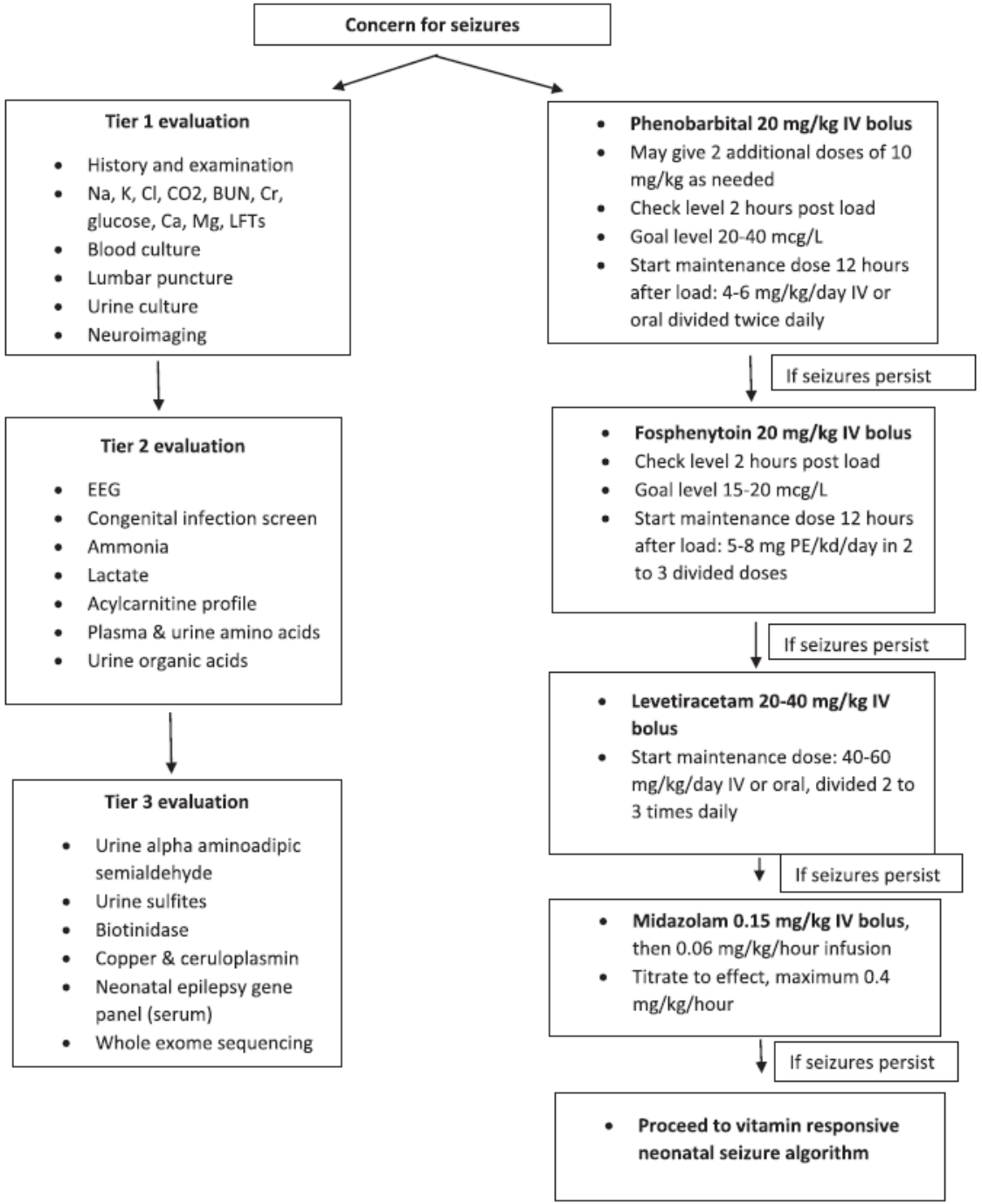
Management of Neonatal Seizures



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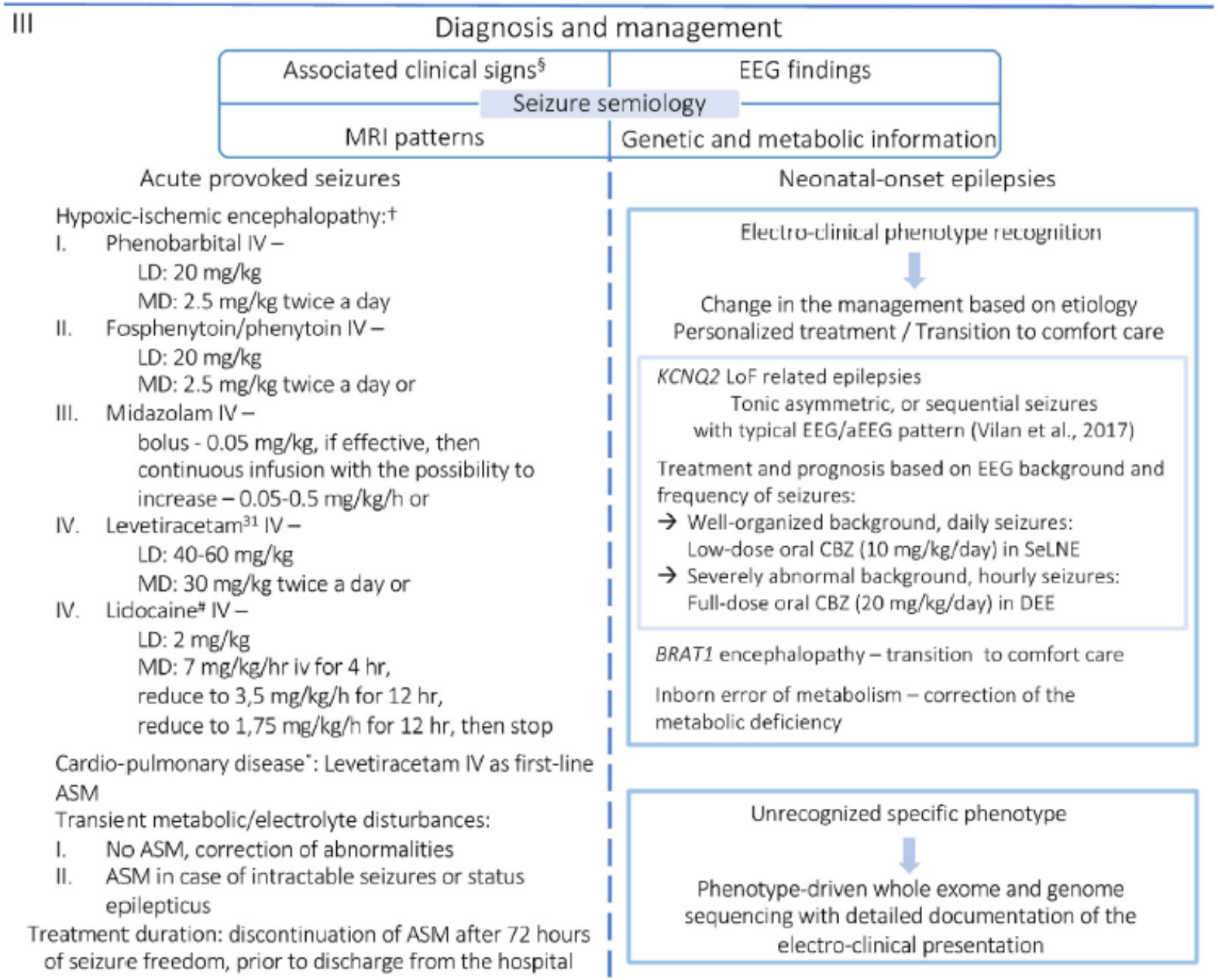
Management of Seizures



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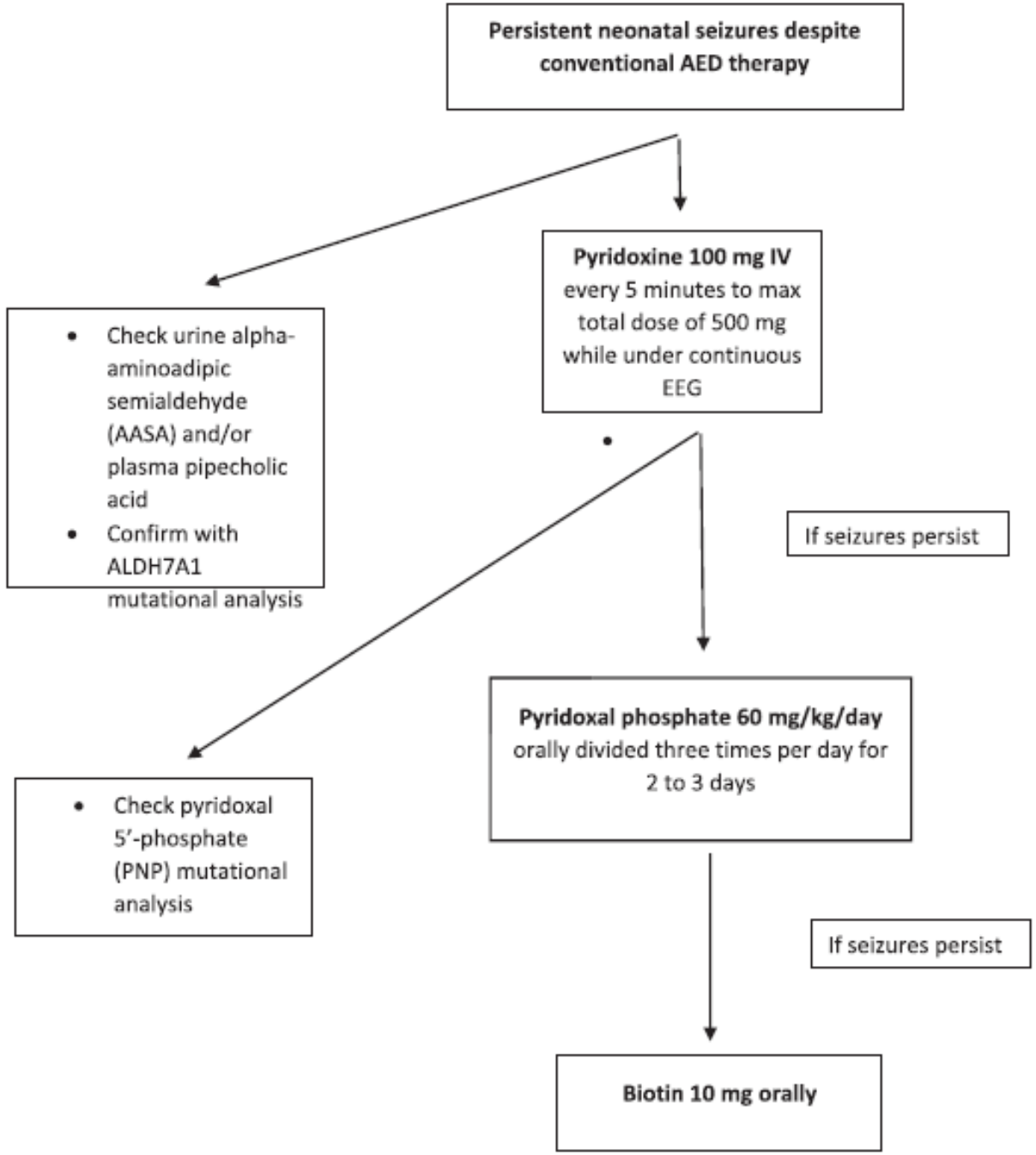
Management of Refractory Seizures



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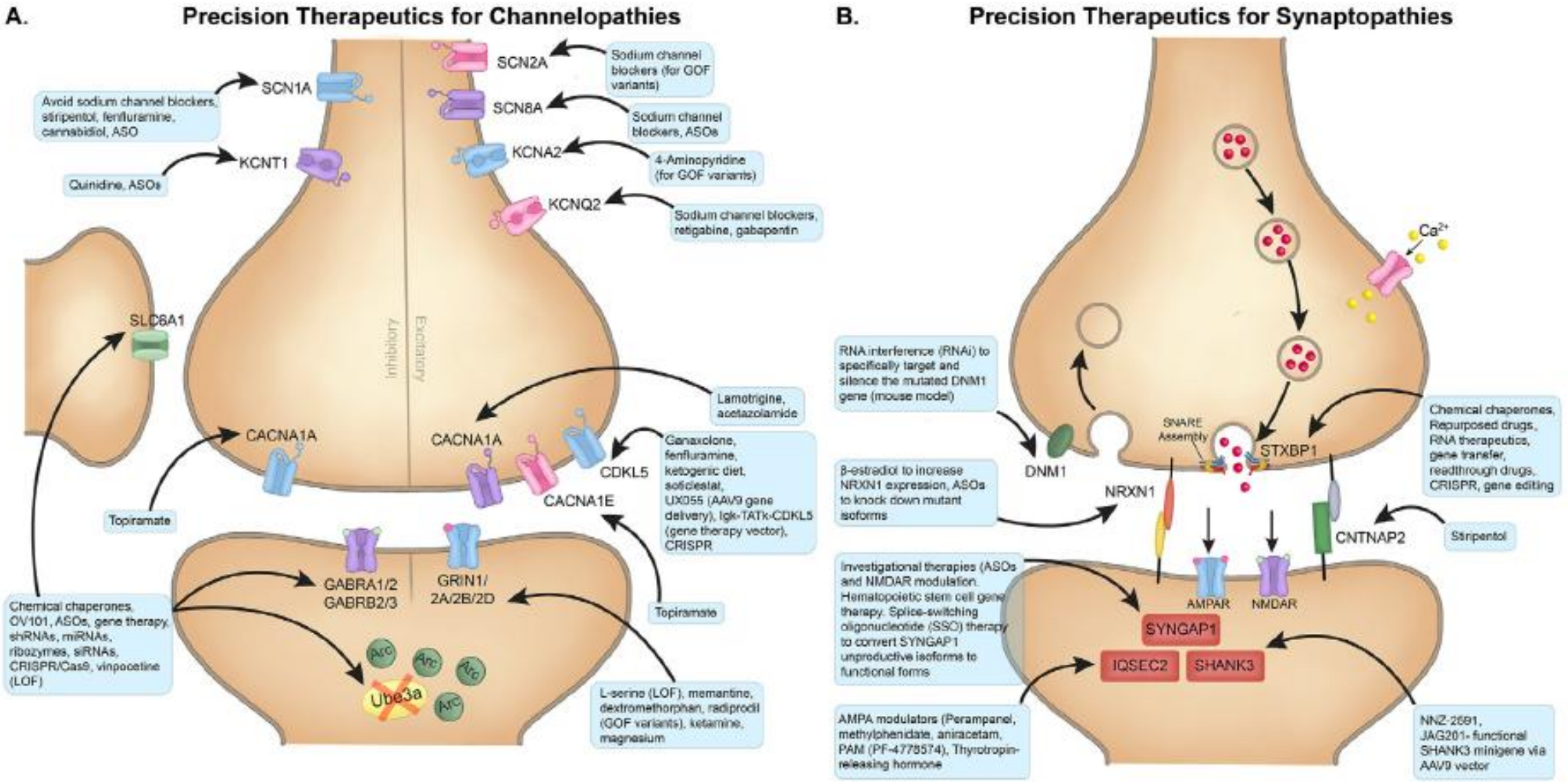
Precision Therapy for Neonatal Epilepsy



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Epilepsy of infancy with migrating focal seizures	DOL 3 to late infancy	Migrating focal and/or tonic seizures with possible autonomic associations		Migratory epileptic discharges	LEV, BZD, STP, PHT; for apneas consider acetazolamide	Poor, death within a few years

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Diagnostic criteria for Early Infantile Developmental Epileptic Encephalopathies

- **Age at onset** – birth to 3 months
- **Seizures** – tonic and/or myoclonic
- **Incidence** – 10/100000 live births
- **EEG** – burst suppression or multifocal discharges
- **Development and neurology** may be normal at onset but difficult to assess development in smaller neonates
- **Comorbidities** – developmental impairment
- **Course of illness** – abnormal development and intellectual disability

- Includes Ohtahara Syndrome (OS) and Early Myoclonic Encephalopathy (EME)

Take home Message

- Most neonatal seizures are acute symptomatic
- Seizures associated with IEM or brain abnormalities – may be refractory
- Semiology of the seizures may be a clue
- May only identify developmental delay later in life – not in the Neonatal period – liaise with the Neurology consultant
- Genetic epilepsies – gaining momentum for precision treatment

Thank you – any questions?