EST 30th ANNIVERSARY ANNUAL MEETING

Neonatal Epilepsies :

Early Intervention and Long-Term Outcomes

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Scope

- Summary of current diagnostic pathways for neonatal epilepsy.
- Key clinical features differentiating acute provoked seizures from neonatal-onset genetic epilepsies.
- Review of precision treatment and etiology-specific management.

Neonatal Epilepsies

- Epilepsy accounts for approximately 15 % of seizures in neonates
- Neonatal Epilepsy
  - Neonatal Onset Epilepsies
    - Genetic Epilepsies
    - Channelopathies & Synaptopathies
    - Cortical malformations
    - Inborn errors of metabolism
  - Acute provoked – later epilepsy 20%–30% of survivors of neonatal seizures.
    - Risk factors for post-neonatal epilepsy include severely abnormal neonatal EEG background patterns, ≥3 days of EEG-confirmed seizures, and abnormal neurological examination at hospital discharge.

Davis K, et al. Contemp Nurse 1999.

Epilepsy Syndromes with onset in Neonates and Infants

- Spontaneous remission
- Normal development/ neurological exams
- Interictal EEG: normal background
- Normal lab and imaging
- Drug-responsive

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)

- Developmental impairment related to both the underlying etiology independent of epileptiform activity and the epileptic encephalopathy
- Frequent/drug-resistant seizures
- Abnormal neurological exams
- Background slow/frequent discharges on EEG

Higher chance to identify epilepsy syndrome and etiology in infants

(severe epilepsy onset before 18 months, 2/3 are DEEs)

ILAE classification, Epilepsia 2022.

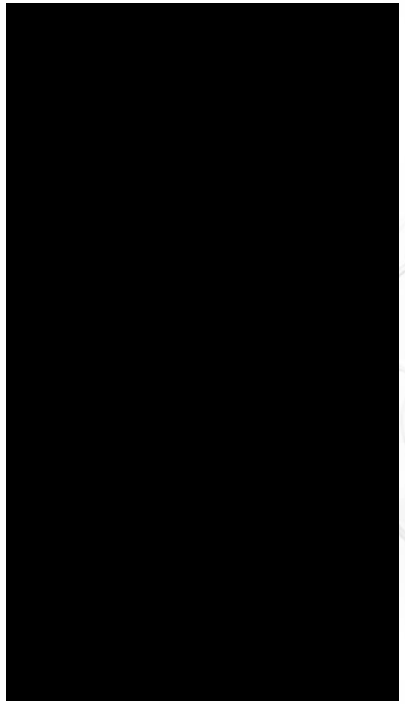
Early diagnosis : Seizure Confirmation

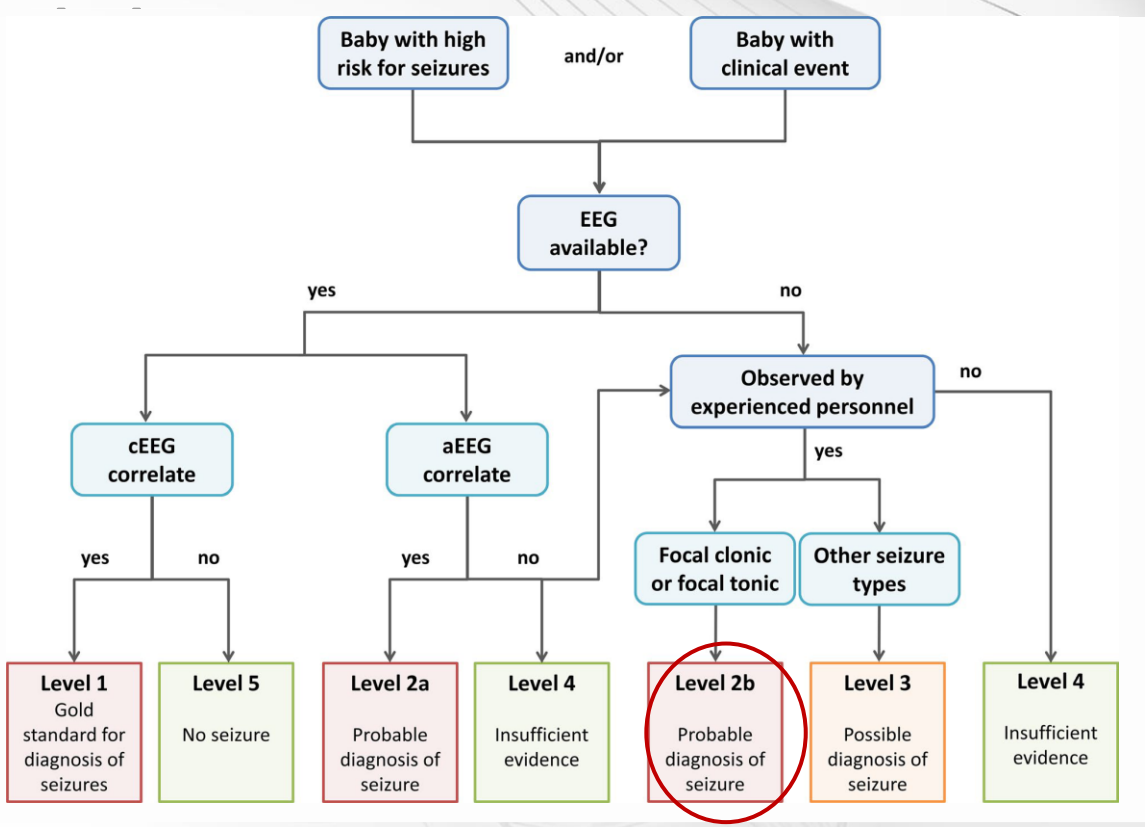
- Infants with clinical events or at high risk for seizures
  - Early Seizure Detection and Accurate diagnosis of seizures
  - High-risk neonates: Paroxysmal events, Acute brain injury, Encephalopathy, ECMO, Congenital brain malformations, hyperammonemia
    - Guidelines by the ACNS: High-risk newborns should ideally be monitored with at least 24 hours of video-EEG, since nearly all neonates with seizures will be identified within 24 hours of monitoring. If seizures are identified, monitor with EEG until seizure-free for at least 24 hours.
    - Neonates with acute symptomatic seizures, mainly due to HIE and stroke, treated within one hour of seizure onset experienced significantly better seizure control and shorter seizure burden than those with delayed treatment

Pavel AM, et al. Pediatr. 2022.
Shellhaas RA, et al. J Clin Neurophysiol. 2011.

Confirm Diagnosis : EEG Monitoring

- The only seizure types that can be diagnosed with certainty on purely clinical grounds are **focal clonic and focal tonic**





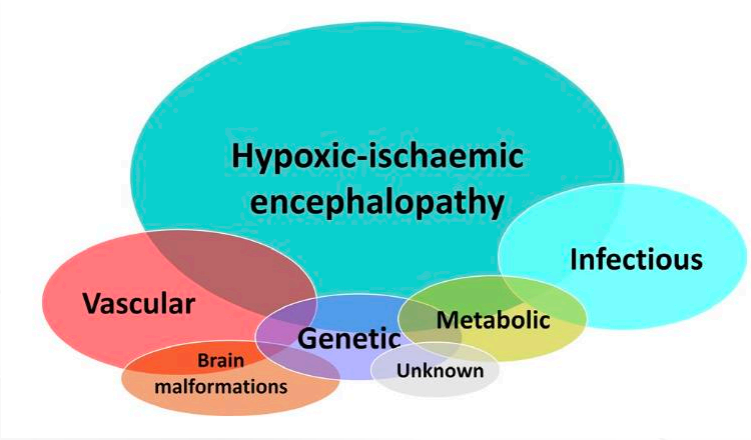
Clinical observation is unreliable for neonatal seizure detection
EEG is the gold standard for neonatal seizure diagnosis.

Massey SL, et al. Epilepsia. 2025.
Ronen. Neurology 2007.Pressler RM, et al., ILAE classification 2021.

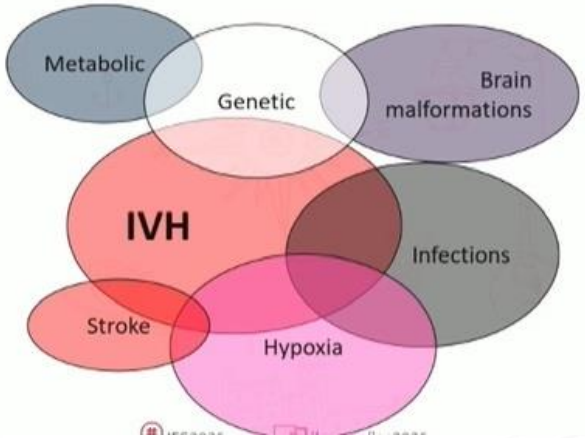
Identify etiologies

Differentiating between acute provoked seizures and neonatal onset genetic epilepsy & Identified treatable causes

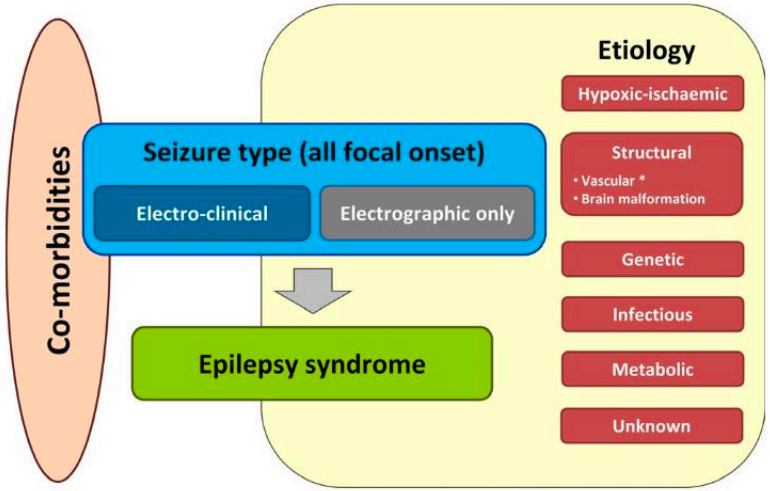
- **Prevalence of Etiology in Term vs Preterm**
- Age at seizure onset
- Seizure Semiology



Term



Preterm



Pressler RM, et al., ILAE classification 2021.
Maria C, et alCurr Treat Options Neurol. 2022.

Identify etiologies

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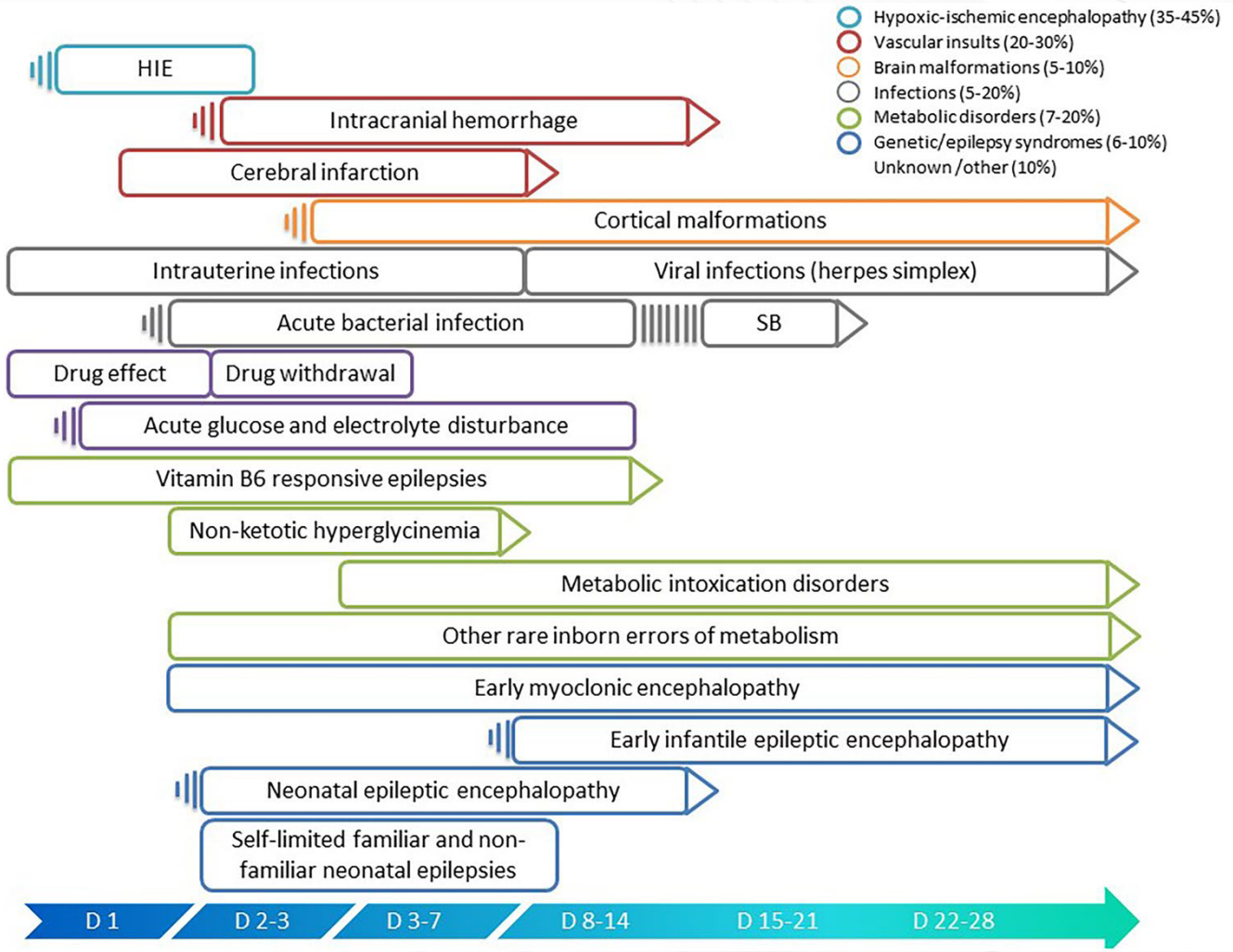
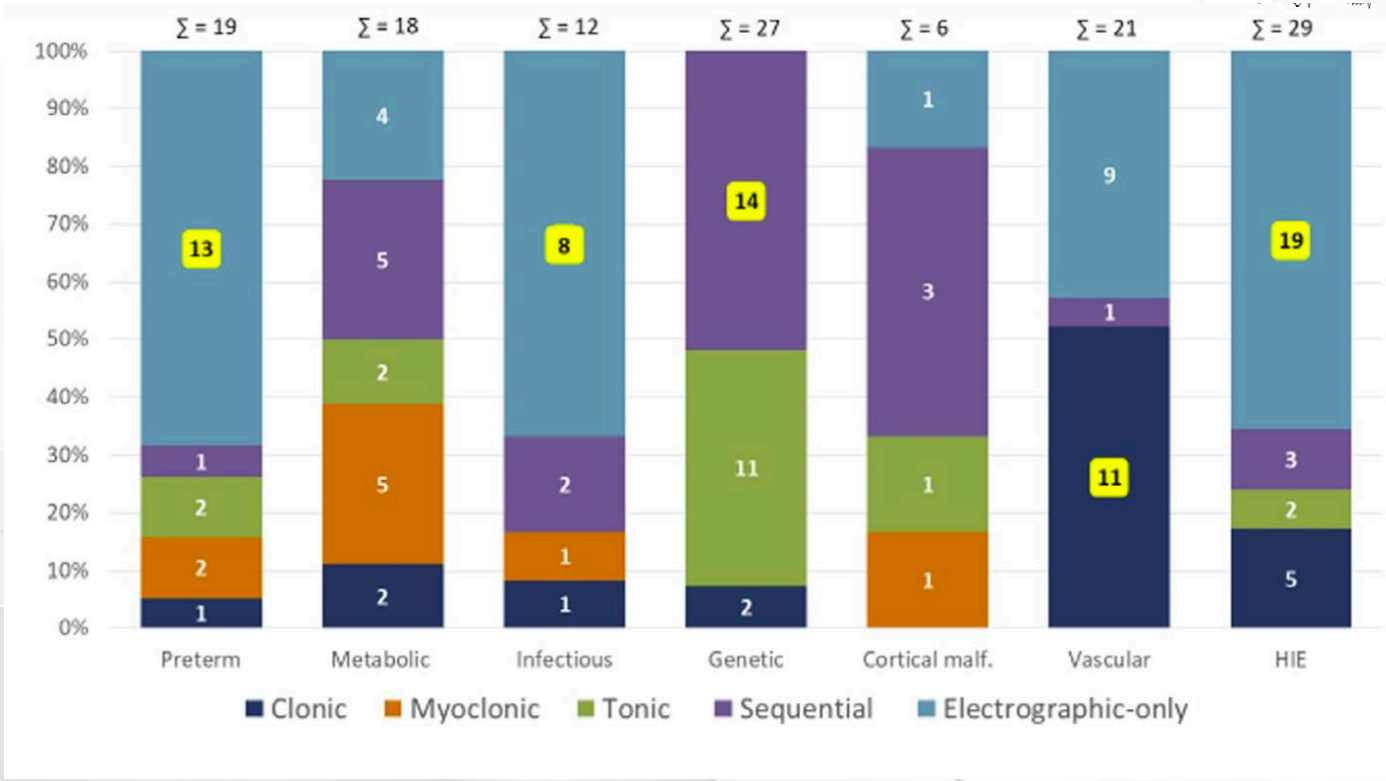


Pressler RM, et al., ILAE classification 2021.
Maria C, et alCurr Treat Options Neurol. 2022.

Seizure semiology & Etiology

ILAE neonatal seizure framework to aide in determining etiology

Elissa G. Yozawitz[1] | Maria Roberta Cilio[2] | Eli M. Mizrahi[3] | Jee-Young Moon[4] | Solomon L. Moshé[5] | Magda L. Nunes[6] | Perrine Plouin[7] | Sameer Zuberi[8] | Ronit M. Pressler[9]



- **Clonic sz** - vascular etiology.
- **Tonic and sequential sz** -genetic etiology.
- **Myoclonic sz** -metabolic etiology.
- **Electrographic sz**- HIE or vascular etiologies.

Yozawitz EG, et al. Epileptic Disorders. 2025.

Seizure semiology & Etiology

Type	Special Consideration	Clinical Context
Automatism	Typically, oral in neonates. Behavior in term and preterm infants may mimic ictal automatisms, thus EEG/ aEEG mandatory.	**HIE** and preterm infants.
Clonic	Seizure type, which is more reliably diagnosed clinically.	**Neonatal stroke or cerebral hemorrhage.** /HIE or infection.
Tonic	Focal, unilateral or bilateral asymmetric. Generalized tonic posturing not of epileptic origin.	**Genetic** /metabolic disorders, channelopathies, vascular, cortical malformation
Myoclonic	Difficult to differentiate from non- epileptic myoclonus, requires EEG	**IEM/**preterm infants, genetic
Behavioral arrest	EEG/ aEEG mandator	Rare as an isolated seizure type
Sequential seizure	No predominant feature can be determined	**Genetic** epilepsies such as KCNQ2 encephalopathy. Metabolic,Vascular,HIE,cortical malformation
Epileptic spasms		**Genetic**/Metabolic

- Semiology of neonatal seizure can aid in etiology diagnosis and lead to management

Pressler RM, et al., ILAE classification 2021.

Genes know to cause epilepsy in neonates

Gene	Inheritance[74]	Neonatal Epilepsy Syndrome(s)[14]	Precision Medicine Considerations
Single Gene Epilepsies[1]			
KCNQ2/KCNQ3	AD	SeLFNIE, *KCNQ2*-DEE	Sodium-channel blockers
SCN2A	AD	SeLFNIE, *SCN2A*-DEE	Sodium-channel blockers for gain of function variants
STXBP1	AD	*STXBP1*-DEE	NA
CDKL5	XLD	*CDKL5*-DEE	Ganaxolone
SCN8A	AD	*SCN8A*-DEE	Sodium-channel blockers
KCNT1	AD	*KCNT1*-DEE	Quinidine with mixed response (Variant dependent)
SCN1A	AD	*SCN1A*-related disorders[75]	Avoid sodium channel blockers.
PRRT2	AD	SeLFNIE	NA
Inborn Errors of Metabolism			
ALDH7A1	AR	Pyridoxine-dependent epilepsy	Pyridoxine with lysine-restricted diet
PNPO	AR	Pyridoxal phosphate-responsive epilepsy	Pyridoxal-5′-phosphate (PLP)
SLC2A1	AD	Glucose transporter type 1 deficiency syndrome (GLUT1DS)	Ketogenic diet
Brain Malformations			
TSC1/TSC2	AD	TSC-associated epilepsy	Vigabatrin
LIS1 (PAFAH1B1)	AD	Lissencephaly spectrum	NA
TUBAA1A	AD	Lissencephaly/polymicrogyria spectrum	NA
DCX	XL	Sex-dependent[2]	NA

- Targeted use of existing ASMs in specific genetic epilepsies

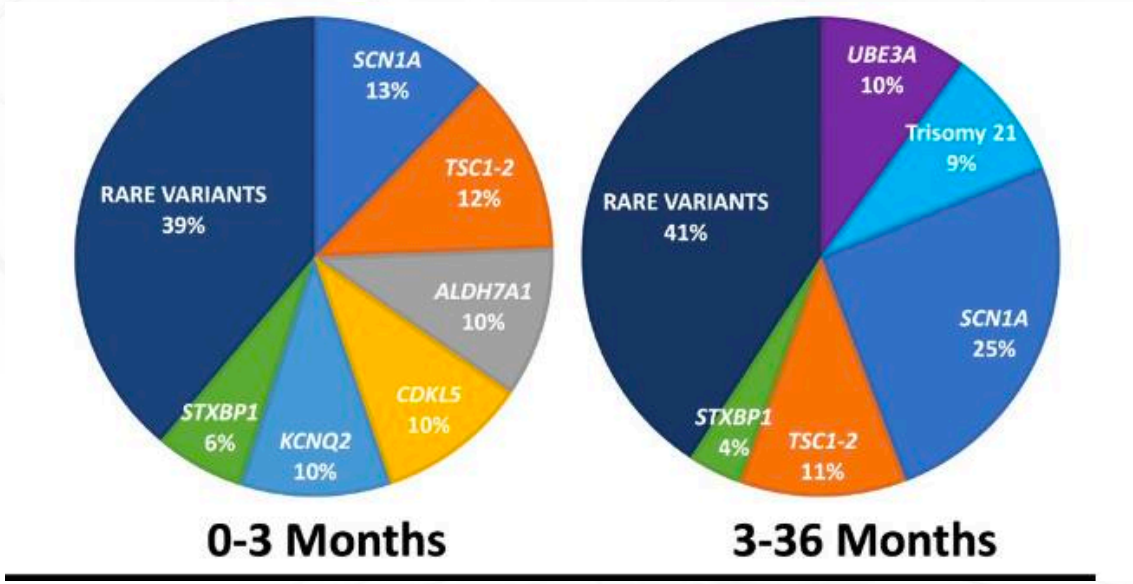
Genetic Advances in Epilepsy Etiology

Neonatal/infantile-onset genetic epilepsies: The utility of genetic testing for molecular etiology-specific diagnosis concerning therapeutic implications

Muhittin Ozcan[1] | Seda Kanmaz[2] | Erdem Simsek[2] | Dilara Ece Toprak[2] | Cemile Büsra Olculu[2] | Tugce Ince[2] | Ozlem Yılmaz[2] | Yavuz Atas[2] | Gursel Sen[2] | Ayca Aykut[3] | Asude Durmaz[3] | Hüseyin Onay[3] | Sanem Yılmaz[2] | Hasan Tekgul[2]

Genetic testing	The utility of genetic testing, *n* (%)	Diagnostic rate, *n* (%)
NGS-based testing		
SGA	65 (50.7)	30 (44.6)
EP	51 (39.8)	35 (68)
WES	38 (29.6)	34 (89.4)
WGS	1 (.7)	1 (100)
Chromosome-based testing		
Karyotyping	28 (21.8)	7 (25)
CMA	25 (19.5)	3 (12)
FISH	17 (13.2)	6 (35.2)

- N = 128, aged 0-36 mo, single center
- The molecular-genetic diagnostic provided a potential treatment yield of 61.7% (79/128) for targeted therapy with ASM/precision therapy.



Ozcan M,et al. Epileptic disorder.2024.

Channelopathies & Synaptopathies

- Most frequent genetic epilepsies presenting in the neonatal period
  - KCNQ2; 35%
  - SCN2A, STXBP1; 15–20%
  - CDKL5, KCNQ3, and SCN8A; 2-5%
  - KCNT1, PRRT2, SCN1A – infantile onset

KCNQ2-DEE

- **Seizure:** Onset first few days of life
  - Focal tonic (most frequent)/myoclonic and/or focal seizures, sequential
  - Exclusively tonic seizures associated with a burst suppression or a multifocal EEG
  - Family history**
- **Inter-ictal EEG**: Burst suppression pattern (60% of cases).
- **Imaging**: Abnormal signal in MRI at BG or thalamus during neonatal period
- **Progression**: Epilepsy frequently remits, but the developmental outcome is typically moderately to severely impaired.
- **Treatment:** Seizure responds partially or completely to sodium channel blockers, carbamazepine and phenytoin should be considered early in this clinical context
- Potassium channel activators; ezogabine/retigabine/novel K channel activator

Pisano T, et al., Epilepsia 2015.
Weckhusen S, et al. Ann Neurol 2012.
Falsaperla R, et al. Neuropediatrics 2023.

Inborn errors of metabolism

- Rare – 1/160,000-several has specific treatment
  - Treat early lead to seizure resolution and higher likelihood of favorable neurodevelopmental outcome
- Always be considered in the setting of a neonate with intractable seizures and no apparent cause.
  - Vitamin deficient epilepsies
  - Glucose Transporter Type 1 Deficiency Syndrome (GLUT1 DS)
  - Other IEMs provoked seizure along with brain injury (sulfite oxidase deficiency, urea cycle defects,amino acidopathies, and non-ketotic hyperglycinemia, (e.g., molybdenum cofactor deficiency)

Jamali A, et al., Epilepsy Research 2023.

Pyridoxine-dependent (ALDH7A1)-DEE (PD-DEE) and Pyridox(AM)INE 5'-phosphate deficiency (PNPO)-DEE (P5PD-DEE)

- **Seizure onset**: Shortly after birth (or antenatal) and resistant to ASMs (25% seizure onset outside newborn, within 3 years of life), various seizure type

A hyperkinetic, seemingly distressed, and agitated infant with multifocal myoclonus and spasms should alert the clinician

- **Inter-ictal EEG**: Burst-suppression or with multifocal sharp or spike complexes
- **Imaging**: Normal
- **Metabolic**: α-aminoadipic semialdehyde (α- AASA) and pipecolic acid are elevated in urine, plasma, and CSF.
- **Genetics**: ALDH7A1 (most cases)

Preventing Epilepsy

- Conditions with a high risk of epilepsy, such as tuberous sclerosis complex (TSC), **preventive Vigabatrin** started at the appearance of epileptic discharges on EEG, has been shown to lower the incidence of infantile spasms and improve developmental outcomes

Bebin RM, et al. Annals of Neurology 2024.
Kolttuska K, et al. Annals of Neurology 2020.

Etiology Targeted Approach

SPECIAL REPORT

Epilepsia™

Treatment of seizures in the neonate: Guidelines and consensus-based recommendations—Special report from the ILAE Task Force on Neonatal Seizures

4.1 | Recommendation 1: First-line ASM

Evidence-based recommendation

In neonates with seizures requiring ASM, phenobarbital should be the first-line ASM.

Strength of recommendation: **Moderate.**

Consensus-based recommendations:

Phenobarbital should be the first-line ASM regardless of etiology (including HIE, stroke, and hemorrhage).

Level of agreement: **High.**

If channelopathy is the likely cause for seizures due to family history, then phenytoin or carbamazepine (sodium channel blocker) may be the first-line ASM.

Level of agreement: **High.**

4.2 | Recommendation 2: Second-line ASM

Consensus-based recommendations

In neonates with seizures not responding to first-line ASM, phenytoin or levetiracetam may be used as a second-line ASM for most etiologies (HIE, stroke, or hemorrhage). Other possible options include midazolam or lidocaine.

Level of agreement: **Moderate.**

If channelopathy as an etiology for the seizures is suspected because of clinical or EEG features, then a sodium channel blocker may be used as a second-line ASM. This can be phenytoin or carbamazepine, depending on the clinical state of the neonate (critically ill or otherwise well baby) and the regional availability of ASM and monitoring of drug levels.

Level of agreement: **High.**

In neonates with cardiac disorder(s), levetiracetam may be preferred as a second-line ASM.

Level of agreement: **Moderate.**

Pressler R,et al. Epilepsia..2023

Etiology targeted approach

Epilepsia™

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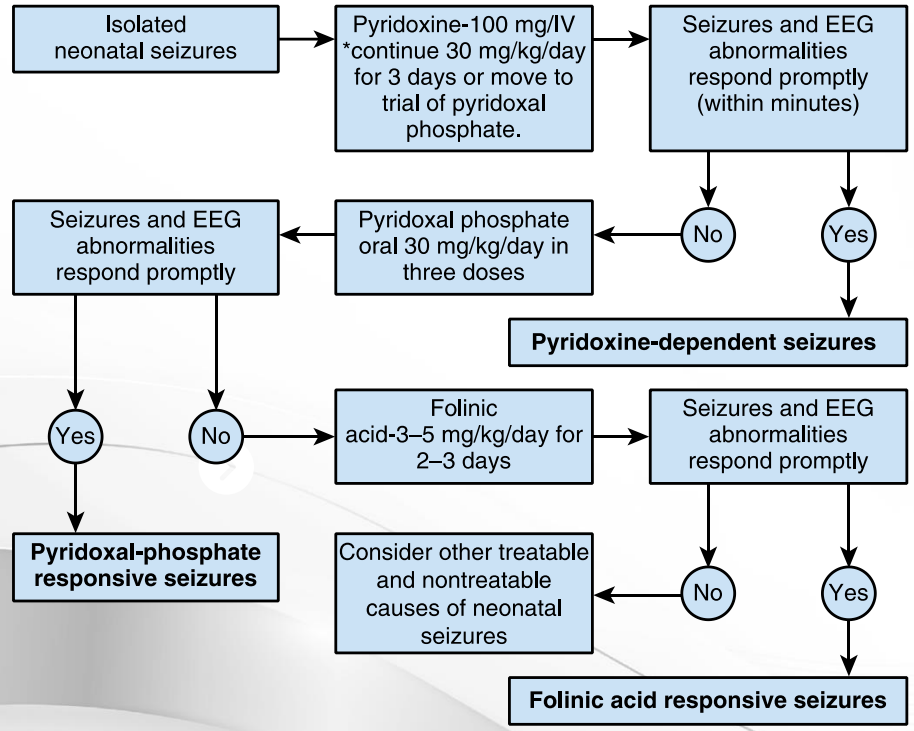

4.6 | Recommendation 6: Treatment with pyridoxine and pyridoxal 5′-phosphate

Consensus-based recommendations

A trial of pyridoxine (add-on to ASM) may be attempted in neonates presenting with clinical features or EEG characteristics suggestive of vitamin B6-dependent epilepsy and neonates with seizures unresponsive to second-line ASM without an identified etiology.

Level of agreement: **High**.

Pressler R,et al. Epilepsia..2023

Conclusion: New Standard of Care

- Rapid Etiology Identification: Next-generation sequencing (NGS) enables high-yield, etiology-specific diagnoses and should be utilized for unexplained neonatal epilepsies.
- Etiology-Specific Intervention: Early, personalized care—incorporating innovations like sodium channel blockers, mTOR inhibitors, and gene therapies—is crucial to reduce seizures and optimize neurodevelopment.