Neonatal seizures: Management: New and old

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Neonatal seizures

1) 1 to 5 per 1000 live births: the most common neurologic emergency in NB

2) The high rate of seizures in the neonatal period reflects age-specific developmental mechanisms that lead to relative excitability.
Cause of neonatal seizures

- Global hypoxia-ischemia (hypoxic-ischemic encephalopathy)
- **Focal hypoxia-ischemia**
  - Arterial stroke
  - Venous stroke
- **Intracranial hemorrhage**
  - Intraventricular
  - Parenchymal
  - Subarachnoid
  - Subdural
- **Transient metabolic deficit**

Metabolic
- Hypoglycemia
- Hypocalcemia and hypomagnesemia
- Hyponatremia

- Acute infection: Meningitis

Differential Diagnosis of Neonatal Onset Epilepsy
- Brain malformation
- Intrauterine injury or congenital infection
- Inborn error of metabolism and vitamin-responsive epilepsies
Neonatal Onset Epilepsy Syndromes

• Benign familial neonatal seizures (eg., KCNQ2, KCNQ3)
• Neonatal epileptic encephalopathies
  Early myoclonic epilepsy
  Early infantile epileptic encephalopathy (Ohtahara syndrome)
PATHOPHYSIOLOGY

- There are several, age-specific factors that are particular to the neonatal brain that lead to enhanced excitability and seizure generation, poor response to conventional medications, and adverse impact on brain development.

- Human studies in children with hypoxic-ischemic injury show an independent association between seizures and impaired brain metabolism, as well as poor long-term neurodevelopmental outcome.
Principles for acute symptomatic neonatal seizure management

1. Rapid and accurate electrographic seizure identification

2. Determining the most likely underlying cause

2. Rapid titration of medication to abolish electrographic seizures

3. Treatment of both clinical and subclinical seizures given similar pathophysiology, and the only difference between the 2 may be slight anatomic differences in their cortical distribution.

4. Early discontinuation of medication once seizures have resolved
Is this- This is time for us to move from clinical to electrographic monitoring of seizures/at risk babies
Detection/ Diagnosis of neonatal seizures

• **Conventional cEEG/ 24 Hr video EEG: Gold** standard for seizure detection
• for monitoring neonates with paroxysmal events and/or at high risk for seizures
• **aEEG**: **Lower** sensitivity and specificity than cEEG
  - **Hundred** percent sensitivity for status epilepticus
  - **Lowest** sensitivity for seizures that are brief, focal, and distal
  - **Experienced** perform better than non-experts
Diagnostic Evaluation

A) Comprehensive history and physical examination are important tools to assess for risk factors and signs of both common and rare causes of neonatal seizures.

B) Emergent evaluation of serum glucose and infection is an important first step, because hypoglycemia and bacterial meningitis can lead to permanent injury if left untreated.

C) ABG, Ca Na K for electrolyte disturbance.

D) CSF studies
Advanced testing: may be warranted on a case-by-case basis

- genetic testing,
- serum amino acids, ammonia, lactate,
- for inborn errors of metabolism: very-long-chain fatty acids, urine organic acids and sulfites
- especially in the setting of medically refractory seizures of unknown cause or a burst-suppression pattern on EEG in a neonate without brain injury.
Neuroimaging

• MRI brain: to identify underlying injury or developmental abnormalities and to help clinicians and the family to better understand the prognosis: IOC

• Bedside Cranial USG: identify large SOL, such as ICH, AVM or hydrocephalus (insensitive for HIE)

• Computed tomography exposes the infant to ionizing radiation and provides inferior resolution to MRI in most settings, and so should be avoided.

• DEFINITELY NO REPEATED CT HEADS
Genetic diagnosis of neonatal-onset seizures

In recent years, with the development of next-generation sequencing (NGS), a large number of genes involved in early-onset epilepsy have been discovered.

These have been shown to lead to cortical dysplasia, metabolic abnormalities, ion channel dysfunctions and so on.

In a recent report, 83% of newborns with early-onset epilepsy had genetic aetiologies.

The study by Yang et al also confirmed that about 28% seizures had pathogenic genes, and some of them had co-morbidities such as developmental delay.
Antiepileptic Drug Therapy

• Antiepileptic drug (AED) therapy should be given if seizures occur after correction of hypoglycemia or hypocalcemia.

• AED should be considered in the presence of even a single clinical seizure since clinical observations tend to grossly underestimate electrical seizures (diagnosed by EEG) and facilities for continuous EEG monitoring are not universally available.
Clinical versus Electrical Seizures

• As per World Health Organization (WHO) recommendations, all clinically apparent seizures lasting for more than 3 minutes or brief serial seizures are to be treated.

• If continuous EEG monitoring is available, all electrical seizures should be treated even in absence of clinically apparent seizures, especially if babies are paralyzed.
WHO guidelines on neonatal seizures

- emphasize the lack of evidence for the management of NNSz

- Only a few of the recommendations in this guidance document are strong and nearly all are based on very low quality of evidence

- In particular the choice of first and second line AEDs in the neonatal period is highly empiric.

- Phenobarbitone is the drug of choice in neonatal seizures

- Phenytoin closely follows in use: WHICH DRUG IS SUPERIOR?
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and Administration</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>20 mg/kg intravenously, repeated once or twice as needed Daily dosing: 5 mg/kg/d (target level 40–60 mcg/mL)</td>
<td>Respiratory depression, depressed level of consciousness, hypotension, and hypotonia Idiosyncratic skin rash, hepatotoxicity, and blood dyscrasia</td>
<td>Prolonged half-life in first week of life (43–217 hours) limits need for weaning phenobarbital in the case of short-term therapy</td>
</tr>
<tr>
<td>Phenytoin and fosphenytoin</td>
<td>20 mg/kg intravenously Daily dosing: 5-8 mg/kg/d (target level 10–20 mcg/mL)</td>
<td>Infusion site reaction and arrhythmia with intravenous phenytoin Idiosyncratic skin rash, hepatotoxicity, and blood dyscrasia</td>
<td>Fosphenytoin has fewer cardiovascular, central nervous system, and local cutaneous side effects than phenytoin. Significant variability and changes in pharmacokinetics over the first weeks of life may lead to inconsistent drug levels</td>
</tr>
</tbody>
</table>
Phenobarbitone versus phenytoin (20mg/kg) for treatment of neonatal seizures: RCT on 110 FT/NT

- Neonates whose seizures were not controlled by the assigned drug were then crossed over to be treated with other drug in same dose.
- Seizures control: 8 of the 55 (14.5%) phenytoin, and 39 of 54 (72.2%) with phenobarbitone (P <0.001).
- Not responders: (after cross-over) seizure control in 44/55 (80%) with phenytoin and 49/54 (91%) with phenobarbitone first (P=0.014).
- After maximum dose of phenobarbitone seizures were controlled in 49/55 (89%) in phenytoin group and 52/54 (96%) in phenobarbitone group (P<0.05).
- **Phenobarbitone superior to phenytoin**

Comparison of phenobarbitone and levetiracetam as first line

Clinically apparent seizures were controlled in only 23.3% neonates assigned to receive levetiracetam as compared to 86.7% neonates assigned to receive phenobarbitone (p<0.05)

LVR cannot be used as a first line drug

Clinical seizure only
NO EEG corelates

Amit Upadhyay et al
Levetiracetam versus Phenobarbitone in Neonatal Seizures - RCT on 100 FT/NT

• Randomized to IV Levetiracetam (20 mg/kg) or Phenobarbitone (20 mg/kg)
• Cessation of CLINICAL seizures with one or two doses of the first drug, and remaining seizure-free for the next 24 hours.
• Seizures stopped in 43 (86%) and 31 (62%) neonates in Levetiracetam and Phenobarbitone group, respectively (RR 0.37; 95%CI 0.17, 0.80, P<0.01).
• Levetiracetam achieves better control than Phenobarbitone for neonatal seizures when used as first-line antiepileptic drug, and is not associated with adverse drug reactions

Clinical seizure only
NO EEG correlates

• Indian Pediatr. 2019 Aug 15;56(8):643-646.
• Gowda VK¹
Role of levetiracetam

• needs to be aggressively evaluated, considering its wide therapeutic index.

• Details of drug later
End point of treatment

• Expert opinion supports use of pharmacologic treatments with a goal of abolishing electrographic seizures, even those without clinical correlate. Not an impossible goal, usually!! (None of Indian studies have done so)

• If facility for continuous EEG monitoring is not available, abolition of all clinical seizures should be the target till three drugs are used.

• Weight benefits of controlling all electrical or clinical seizures against risks with multiple AED

• After use of three AEDs, not all twitch/movement should be treated. Further AED only if seizures with abnormality in HR or BP.
Maintenance Dose of Antiepileptic Drugs

- Traditionally, loading dose of AED has been followed by maintenance dose of AED to maintain the desired serum level and prevent recurrence of seizures for the duration.
- After the pathophysiology which caused seizures has been corrected or reverted, the AED can be gradually tapered and stopped.
- Duration of maintenance dose therapy has been significantly curtailed from months to weeks and now to a few days only.
Maintenance therapy and follow-up

• Seizures controlled for 72 h: Make attempt to stop all AEDs except phenobarbitone in maintenance dose of 3-5 mg/kg/day

• If neurological examination normal: Stop all AEDs at discharge, phenobarb in end.

• If neurological examination abnormal at discharge
  • Continue AED till 1 month
  • If at 1 month normal examination and seizure free: Taper phenobarbitone over 2 weeks
  • If neurological assessment is not normal: Get EEG
    • EEG not sowing paroxysmal electrical activity: Taper AED
    • If EEG is overtly abnormal: Reassess in the same manner at 3 months and then 3 monthly till 1 year of age
Effect of Withholding Phenobarbitone Maintenance in Neonatal Seizures: A RCT

• 152 term and near term neonates (34 weeks), weight ≥2 kg with clinically apparent seizures (IV) 20 mg/kg of phenobarbitone.

• those who respond to loading dose of phenobarbitone after a single seizure episode, withholding of phenobarbitone maintenance may not significantly increase the risk of breakthrough seizures.

• Upadhyay A et al

Clinical seizure only
NO EEG correlates
**Second line drugs:** seizures not responding to phenobarbitone 20 mg/kg

- Repeat Phenobarb 10 and then 10mg/kg

- Other drugs: midazolam, phenytoin and lidocaine being used as second and third-line drugs.

- Off-label AEDs are quite widely used despite a lack of information about safety or efficacy in newborn babies.: LEVETERACETAM
Neonate with seizures

- Identify and characterize the seizure
- Secure airway and optimize breathing, circulation and temperature
- Start oxygen, if seizures are continuous
- Secure IV access
- If hypoglycemic (blood sugar <40 mg/dL); administer 2 mL/kg of 10% dextrose
- If blood sugar is in normal range, investigate serum calcium, if abnormal 2 mL/kg of calcium gluconate should be given

Administer phenobarbitone 20 mg/kg IV stat over 20 min

Seizures persist

Repeat phenobarbitone in 10 mg/kg/dose aliquots until 30–40 mg/kg dose is reached*

Seizures persist

Administer Fosphenytoin or phenytoin 20 mg/kg IV slowly over 20 min (max) under cardiac monitoring

Levetiracetam if not earlier; lorazepam/midazolam bolus and infusion if needed; consider ventilation in all such babies

Consider pyridoxine/exchange transfusion in cases of metabolic disorders; consider ventilation
LEVETIRACETAM

- It has been used for over a decade in adults and older children with good efficacy, an excellent safety profile, and near-ideal pharmacokinetic characteristics.

- Levetiracetam has a broad spectrum of antiepileptic activity;

- Adults: as initial monotherapy and as add-on therapy in partial onset seizures as well as in patients with idiopathic generalized epilepsy for myoclonic and generalized tonic clonic seizures.
Levetiracetam

• does not cause neuronal apoptosis in the immature brain or disrupt synaptic development and may even have neuroprotective properties.

• levetiracetam may be an effective antiepileptic and antiapoptotic drug for hypoxia induced seizures.
Levetiracetam has a favourable safety profile in adults and older children.

In children and adults, the most common side-effects are somnolence and behavioural side-effects.

No adverse events related to levetiracetam were observed in any of these studies.

Serum drug level measurement not required.
BUMETANIDE

• It is a loop diuretic with a rapid onset and short duration of action. It has been used routinely as a diuretic in many NICU in USA for last 30 years.

• Augments phenobarbital bioactivity in neonatal rodents (esp with hypothermia)

• Combination of phenobarbital and bumetanide may provide a clinically feasible antiepileptic therapy for neonatal seizures with the possible additional benefit of augmenting the neuroprotective efficacy of therapeutic hypothermia in asphyxiated neonates.
Bumetanide for seizures in newborn with HIE (NEMO): an open-label, dose finding, and feasibility phase 1/2 trial. Lancet Neurol. 2015 May
(dose allocation: 0·05 mg/kg, n=4; 0·1 mg/kg, n=3; 0·2 mg/kg, n=6; 0·3 mg/kg, N – 10)

Results suggested that bumetanide as an add-on to phenobarbital does not improve seizure control in newborn infants who have HIE and might increase the risk of hearing loss.

The primary efficacy endpoint was a reduction in electrographic seizure burden of more than 80% without the need for rescue antiepileptic drugs in more than 50% of infants
3/11 of the survivors had significant hearing loss on follow up

This trial highlights the risks associated with the off-label use of drugs in newborn infants before safety assessment in controlled trials.
TOPIRAMATE

• Effective in children for focal refractory epilepsy and infantile spasms.

• 25 mg/kg/day may not be an efficacious add-on agent for infants aged 1 month to 2 years with refractory epilepsy.

• It has received FDA approval as initial monotherapy and as adjunctive therapy in adults and children (ages 2-16 years) with partial-onset seizures with or without secondarily generalized seizures as well as for primary GTCS and for seizures associated with Lennox-Gastaut syndrome.
Topiramate

- Neuroprotective properties in animal models of neonatal brain injury.
- Animal models it reduced the severity of cerebral damage either alone or with hypothermia.
- Currently only available as an oral formulation limiting the utility in critically ill infants.
- Stable intravenous formulation has been developed and is tolerated.
- The safety and tolerability of topiramate have been well described in older children and adults.
- Topiramate has more ADR
SEIZURE TREATMENT

Neonate with seizures

- Identify and characterize the seizure
- Secure airway and optimize breathing, circulation and temperature
- Start oxygen, if seizures are continuous
- Secure IV access
- If hypoglycemic (blood sugar <40 mg/dL); administer 2 mL/kg of 10% dextrose
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Seizures persist

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Consider pyridoxine/exchange transfusion in cases of metabolic disorders; consider ventilation
Old

- Treat clinical seizures only
- EEG after few days (5-7 or at discharge)
- Phenobarb is the DOC 20/10/10 mg/kg
- Then Phenytoin/ Midazolam
- Maintenance for 5-7 days

Useless
Treating each twitch in refractory seizures sec to dysgenesis/ HIE

New

- Clinical seizures unriable
- EEG must in all: All electric and clinical seizures should be treated until all electrical seizures abolished
- Pheno 20/kg; max 10 more dose
- Leveteracetam can potentially become 1st 2nd line AED and even first line in near future
- Maintenance therapy may not be required in single seizure babies
- Bumetanide: new drug is coming up
Implication of the talk

• seizures themselves disrupt the developing brain, and so urgent need for safe, accurate, and widely available methods for identifying and treating electrographic seizures.

THANKS
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Genetic diagnosis of neonatal-onset seizures

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In a recent report, 83% of newborns with early-onset epilepsy had genetic aetiologies. The study by Yang et al also confirmed that about 28% seizures had pathogenic genes, and some of them had comorbidities such as developmental delay.
• In term infants, the most common type of gene-induced seizures are sequential seizures, followed closely by tonic seizures,
• preterm infants, electrographic seizures only are commonly observed.
• metabolic diseases often manifest as myoclonic seizures
<table>
<thead>
<tr>
<th>Num</th>
<th>Related gene</th>
<th>Mutant site&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Onset age(d)</th>
<th>Seizure type</th>
<th>Seizure control</th>
<th>Development delay&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Etiology diagnosis for seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KCNQ2</td>
<td>chr20,c.998G &gt; A (exon7)</td>
<td>1</td>
<td>generalized</td>
<td>well</td>
<td>without</td>
<td>epilepsy; BFNE</td>
</tr>
<tr>
<td>2</td>
<td>KCNQ2</td>
<td>chr20,c.1678C &gt; T (exon15)</td>
<td>16</td>
<td>asymmetric</td>
<td>badly</td>
<td>with</td>
<td>epilepsy; Ohtahara syndrome</td>
</tr>
<tr>
<td>3</td>
<td>SCN9A</td>
<td>chr2,c.2132T &gt; C (exon14)</td>
<td>1</td>
<td>generalized</td>
<td>badly</td>
<td>–</td>
<td>epilepsy; EOEES</td>
</tr>
<tr>
<td>4</td>
<td>SCN8A</td>
<td>chr12,c.5257T &gt; G (exon27)</td>
<td>2</td>
<td>generalized</td>
<td>badly</td>
<td>–</td>
<td>epilepsy; EOEES</td>
</tr>
<tr>
<td>5</td>
<td>KCNQ2</td>
<td>chr20,c.916G &gt; C (exon6)</td>
<td>2</td>
<td>generalized</td>
<td>well</td>
<td>without</td>
<td>epilepsy; BFNE</td>
</tr>
<tr>
<td>6</td>
<td>TSC2</td>
<td>chr16,c.169C &gt; T (exon3)</td>
<td>1</td>
<td>generalized</td>
<td>well</td>
<td>with</td>
<td>symptomatic seizure</td>
</tr>
<tr>
<td>7</td>
<td>TSC1</td>
<td>chr9,c.3266G &gt; C (exon23)</td>
<td>7</td>
<td>generalized</td>
<td>badly</td>
<td>with</td>
<td>epilepsy; EOEES</td>
</tr>
<tr>
<td>8</td>
<td>ALFM1</td>
<td>chrX,c.1030C &gt; T (exon10)</td>
<td>1</td>
<td>focal</td>
<td>well</td>
<td>with</td>
<td>epilepsy</td>
</tr>
<tr>
<td>9</td>
<td>IFIHI1</td>
<td>chr2,c.2020_c.2023(exon10)</td>
<td>1</td>
<td>focal</td>
<td>well</td>
<td>with</td>
<td>epilepsy; EOEES</td>
</tr>
<tr>
<td>10</td>
<td>GABRQ2</td>
<td>chr5,c.406C &gt; T (exon4)</td>
<td>14</td>
<td>focal</td>
<td>well</td>
<td>without</td>
<td>epilepsy</td>
</tr>
<tr>
<td>11</td>
<td>RPGRIP1L</td>
<td>chr16,c.910G &gt; A (exon8)</td>
<td>15</td>
<td>generalized</td>
<td>well</td>
<td>with</td>
<td>epilepsy</td>
</tr>
<tr>
<td>12</td>
<td>PCCA</td>
<td>chr13,c.524G &gt; A (exon7)</td>
<td>7</td>
<td>focal</td>
<td>badly</td>
<td>–</td>
<td>epilepsy; EOEES</td>
</tr>
<tr>
<td>13</td>
<td>–</td>
<td>–</td>
<td>7</td>
<td>generalized</td>
<td>well</td>
<td>without</td>
<td>low calcium convulsions</td>
</tr>
<tr>
<td>14</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>generalized</td>
<td>well</td>
<td>without</td>
<td>epilepsy</td>
</tr>
<tr>
<td>15</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>generalized</td>
<td>badly</td>
<td>without</td>
<td>epilepsy; cortical dysplasia</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mutant site: point mutation such as chr20,c.998G > A (exon7) means that the gene is located on chromosome 20, and the base G of the coding sequence at position 998 is mutated to A, and the mutation is located in the 7th exon; while deletion mutation such as chr2,c.2020_c.2023(exon10)delAGAT means the bases AGAT are deleted, whose location is from the position of coding sequence 2020 to 2023 (at the 10th exon).

<sup>b</sup> Development delay: children with SCN9A, SCN8A, TSC1 and PCCA gene mutations died 21 days, 40 days, 3 months, and 10 days after birth respectively, so follow-up for developmental delay is unachievable.
<table>
<thead>
<tr>
<th>Variable</th>
<th>group 1 (N₁ = 12)</th>
<th>group 2 (N₂ = 3)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial clinical manifestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset age &lt;3d</td>
<td>7 (58.3)</td>
<td>2 (66.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Seizure type: focal</td>
<td>5 (41.7)</td>
<td>0 (0.0)</td>
<td>0.505</td>
</tr>
<tr>
<td>Single seizure duration &gt; 1min</td>
<td>4 (66.7)</td>
<td>3 (100.0)</td>
<td>0.500</td>
</tr>
<tr>
<td>Seizure frequency &gt; twice a day</td>
<td>10 (83.3)</td>
<td>2 (66.7)</td>
<td>0.516</td>
</tr>
<tr>
<td>Quiescent stage abnormal</td>
<td>7 (58.3)</td>
<td>2 (66.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Stereotype</td>
<td>7 (58.3)</td>
<td>2 (66.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Poor response to stimulus</td>
<td>11 (91.7)</td>
<td>0 (0.0)</td>
<td>0.009</td>
</tr>
<tr>
<td>Hypermyotonia</td>
<td>3 (25.0)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>NBNA score</td>
<td>33.170 ± 1.722</td>
<td>34.330 ± 1.528</td>
<td>0.356</td>
</tr>
<tr>
<td>Initial laboratory test and image results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic abnormal</td>
<td>4 (33.3)</td>
<td>1 (33.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Electrolyte abnormal</td>
<td>3 (25.0)</td>
<td>1 (33.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Initial EEG* abnormal</td>
<td>9 (81.8)</td>
<td>0 (0.0)</td>
<td>0.027</td>
</tr>
<tr>
<td>Initial MRI abnormal</td>
<td>7 (63.6)</td>
<td>1 (33.3)</td>
<td>0.538</td>
</tr>
<tr>
<td>Follow-up after discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>4 (36.4)</td>
<td>0 (0.0)</td>
<td>0.505</td>
</tr>
<tr>
<td>Poor seizure control</td>
<td>6 (50.0)</td>
<td>1 (33.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Initial long-term AEDS</td>
<td>5 (41.7)</td>
<td>2 (66.7)</td>
<td>0.569</td>
</tr>
<tr>
<td>Multiple AEDs now</td>
<td>3 (37.5)</td>
<td>0 (0.0)</td>
<td>0.491</td>
</tr>
<tr>
<td>Development delay</td>
<td>5 (62.5)</td>
<td>0 (0.0)</td>
<td>0.182</td>
</tr>
<tr>
<td>Diagnosed as epilepsy</td>
<td>11 (91.7)</td>
<td>2 (66.7)</td>
<td>0.371</td>
</tr>
</tbody>
</table>

* Initial EEG: if video-EG was done in the neonatal period, the video-EEG results were preferred. If not, other kinds of EEG results including common EEG and amplitude integrated encephalogram (aEEG) would be considered.
Conclusion

Despite the recent progress in genetic technology, molecular diagnosis for neonatal-onset epilepsy can pose numerous challenges due to genetic and phenotypic heterogeneities.

However, some genotypes are known to be associated with specific clinical manifestations and EEG activities.

Early genetic diagnosis is helpful in providing optimal management and potentially improving outcomes of children with early-onset epilepsy.
Thank you