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Review Article

Diagnosis and Recent Advances in the Treatment of Neonatal Seizures: A Comprehensive Review

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Abstract

Purpose: *Neonatal seizures, defined as paroxysmal events associated with abnormal electrical activity in the neonatal brain, are a clinical emergency that requires immediate attention. Around 50 million people globally suffer with epilepsy, making it the third most common chronic brain ailments. It is a neurological condition that affects people of all ages and is non-communicable. This systematic review offers an overview of the most important pharmacological and non-pharmacological recommended treatments for neonatal seizures, as well as a description of the most recent clinical diagnostic considerations along with pharmacogenomic considerations supporting recent advances and recommendations of therapy.*

Design/methodology/approach: *Online databases and pertinent scholarly papers about the diagnosis and management of newborn seizures are used in the thorough review-based study. Using keywords, academic publications were generally retrieved from the PubMed database, Google Scholar, MEDLINE, as well as Web of Science, among other research database sites. The review-based analysis was conducted using the outcome papers, which included systematic reviews, research papers, and clinical guidelines in addition to the available pharmacogenomic data. Data from the selected articles were compiled and presented in accordance with various therapeutic modalities.*

Findings/conclusion: *Neonatal seizures distinct from those in infants and children in terms of their etiologies and electroclinical symptoms. Maximizing neurodevelopmental outcomes requires early detection, accurate diagnosis, and timely treatment of neonatal seizures. Due to the frequent application of continuous EEG monitoring, a correct diagnosis will lead to less unnecessary medical care and improved outcomes through quicker treatment. Numerous ongoing clinical trials have not yet had their findings published.*

Keywords: *Neonatal seizures, therapies, non-communicable, causes, treatment*

1. INTRODUCTION:

Neonatal seizures are rather typical; in fact, this is the life stage at which they are most inclined to happen. They frequently appear as the very first symptom of severe brain dysfunction. Despite being frequently short-lived, they are nonetheless excellent warning signs of long-term developmental and cognitive dysfunction. [1,2]

Early recognition and treatment are crucial to prevent long-term neurological sequelae. Others have measured the incidence rate of neonatal seizure earlier, which ranges from 1.8 to 3.5 per 1000 births. Due to their immature brains and high risk of injury, newborns are most prone to developing seizures. The most prevalent neurological disorder, neonatal seizures, is linked to characterized by high mortality rates of up to 20%. [3] Depending on their etiologies and clinical results, neonatal seizures might result in long-term consequences like epilepsy, cerebral palsy, developmental abnormalities, and psychomotor impairments. [4,5] According to reports, term babies have a 1.5-5.5 per 1,000 live births incidence of newborn seizures, although preterm or extremely low birth weight babies likely to have greater incidences. [6] Children who have experienced newborn convulsions are at an 8–20% risk of experiencing another seizure, and those who experience seizures more frequently are more likely to experience post neonatal convulsions.[7] Almost half of term infants with seizures are at risk of developing cerebral palsy, cognitive deficits, and epilepsy. [8] Neonatal seizures can be classified clinically into clonic, myoclonic, tonic, and mild seizures. Muscles in the limbs, face, or trunk contract in a repeated, rhythmic (1-4/s) manner during clonic seizures. They may be either focal or multifocal. [9] Preterm neonates are more likely to experience neonatal seizures (22.2%) than full-term newborns (0.5%).[10]

2. OBJECTIVE:

This systematic review offers an overview of the most important pharmacological and non-pharmacological recommended treatments for neonatal seizures, as well as a description of the most recent clinical diagnostic considerations. It is anticipated that this study will aid researchers in detecting and comprehending new initiatives regarding the application of numerous existing and novel medicines, as well as pharmacogenomic considerations for accurate disease diagnosis and treatment, as well as serving as a medium of reference for ongoing research.

3. METHODOLOGY:

Online databases and pertinent scholarly papers about the diagnosis and management of newborn seizures are used in the thorough review-based study. Using keywords, academic publications were generally retrieved from the PubMed database, Google Scholar, MEDLINE, as well as Web of Science, among other research database sites. The review-based analysis was conducted using the outcome papers, which included systematic reviews, research papers, and clinical guidelines in addition to the available pharmacogenomic data. Data from the selected articles were compiled and presented in accordance with various therapeutic modalities.

4. DIAGNOSTIC CONSIDERATIONS:

According to clinical definitions, newborn seizures are abnormal, stereotyped, and paroxysmal central nervous system dysfunctions arising within 44 weeks of delivery. Due to their numerous clinical features and overlapping presentations, newborn seizures are difficult to diagnose. A thorough evaluation is necessary to accurately recognize and categorize the seizures in newborn seizures.

Clinical Presentation: Neonatal seizures can present with various clinical manifestations. Seizures may be focal or generalized and can involve various body regions. Common seizure types observed in neonates include tonic seizures (sustained muscle stiffening), clonic seizures (repetitive jerking movements), myoclonic seizures (brief muscle twitches), and subtle seizures (subtle changes in movement, behavior, or autonomic function). Some seizures may be present at birth or shortly thereafter. Seizures in neonates can be brief or prolonged, ranging from a few seconds to several minutes. Some seizures may occur in clusters or have a repetitive pattern. Neonates with epilepsy may exhibit additional symptoms or signs that can provide clues to the underlying cause. These may include abnormal eye movements, changes in heart rate or breathing patterns, abnormal movements or postures, altered consciousness, poor feeding, irritability, or lethargy. [11]

Electroencephalography (EEG): EEG is an essential tool for diagnosing and characterizing neonatal seizures. Continuous video-EEG monitoring is preferred as it allows for simultaneous observation of clinical events and EEG patterns. EEG findings may include focal or generalized electrographic seizures, burst suppression patterns, or interictal epileptiform discharges. In the NICU situation, noninvasive EEG-based

diagnostics offer an excellent temporary option with little risk of scalp irritability since they are simple to set up, portable, useful for bedside testing, and noninvasive. Routine EEG, continuous EEG monitoring (cEEG), video-EEG monitoring, and amplitude integrated EEG (aEEG) are some of the EEG approaches that can be used. Neonatal seizures have different EEG characteristics than seizures in older children and adults. Despite the possibility of electrical seizure activity in neonates before 34–35 weeks after conception (CA), premature infants are less likely to experience it than term babies. Within a single electrical seizure or from one infant to the next, frequency, voltage, and morphology can all vary significantly. Except for the generalized activity connected to some forms of myoclonic jerks or epileptic spasms, all electrical seizure activity in neonates starts out focally. In neonates, the central or temporal region of one hemisphere or the midline central region is where electrical seizure activity most frequently manifests. The occipital and frontal areas are less frequent locations of start. The motor manifestations of clinical seizures are based on the cortical region where the electrical seizure activity is present. Patients with vascular injury or electrolyte imbalance may experience focal discharges, those with vitamin-related illnesses may experience multifocal discharges, and those with severe epileptic encephalopathies may experience suppression-bursts, showing unique relationships between ictal EEG patterns and underlying etiologies. [12,13]

Neuroimaging: The detection of structural brain pathology, such as hemorrhage, infarction, or anomalies of cortical development, requires the use of neuroimaging. Brain MRI provides excellent anatomic resolution and is extremely sensitive for detecting cerebral anomalies, ICH, stroke, and ischemia alterations. When a vascular etiology is suspected, MR angiography and venography should be carried out. The diagnosis of inborn metabolic abnormalities can often be facilitated by magnetic resonance spectroscopy. Due to its lesser resolution than MRI and substantial ionizing radiation exposure, computed tomography is typically avoided in newborns. Due to its portability and ease of use at the bedside, cranial ultrasonography is the most often utilized neuroimaging technique in newborns. It produces images of the brain using high-frequency sound waves. The use of cranial ultrasound can be used to spot structural anomalies including hemorrhage, ischemic damage, or congenital deformities. MRI provides detailed images of the brain and is useful for assessing the structural and functional aspects of neonatal brains. It can detect various conditions related to neonatal seizures, including brain malformations, ischemic or hypoxic injury, and metabolic disorders. MRI is particularly helpful when cranial ultrasound findings are inconclusive or if a more detailed evaluation is needed. Cross-sectional images of the brain are produced by CT scans using X-rays. The neonate is exposed

to ionizing radiation during a CT scan, which can result in speedy findings but should be avoided in this population. When an MRI is not an option or when there is an urgent need, CT scans could be considered. Through the detection of variations in blood flow and oxygenation, fMRI analyses brain activity. It can assist in locating the seizure focal and identifying brain regions that become active during seizures. [14,15]

Metabolic and Genetic Investigations: In cases where there is suspicion of an underlying metabolic or genetic disorder, laboratory investigations may be conducted. Metabolic disorders such as inborn errors of metabolism can cause seizures in neonates. Initial laboratory examinations for neonatal convulsions ought to look for short-term metabolic changes such hypoglycemia, hypocalcemia, or electrolyte imbalance. Complete blood count, blood culture, CSF analysis, urine culture, toxicological testing, TORCH (toxoplasmosis, rubella, CMV, herpes simplex, and HIV) screening, metabolic testing, and ophthalmologic evaluation should all be part of such evaluation. Serum amino acid levels (glycine and serine), ammonia, lactate, pyruvate, very long chain fatty acids, urine organic acid, biotinidase, pipecolic acid, CSF lactate, CSF amino acids, CSF chromatogram for folinic acid/pyridoxine-dependent seizures, and CSF pyridoxal-5-phosphate (active form of vitamin B6) are possible additional laboratory tests. [16]

In neonates with epilepsy for whom an acute provoked seizure etiology is not detected on the initial history, examination, and neuroimaging, genetic testing should be highly explored. More than 75% of patients with newborn epilepsy may be able to determine the potential etiology of their epilepsy using genetic testing. The discovery of a genetic cause has ramifications for both the course of treatment as well as prognostications, genetic counselling, and the avoidance of further thorough etiologic testing. Because of the clinical overlap of several genetic epilepsies, full exome sequencing is recommended when genetic testing is carried out utilizing a gene panel for epileptic encephalopathies and brain abnormalities. [17,18]

Maternal and Obstetric History: A detailed maternal and obstetric history is important in identifying potential risk factors for neonatal seizures. Maternal factors such as infection, substance abuse, or medication use during pregnancy, as well as obstetric complications like maternal hypertension, placental insufficiency, or intrauterine growth restriction, may contribute to neonatal seizures.

Neonatal epilepsy risk can be increased by obstetric variables such birth trauma, such as protracted labour, the use of forceps or vacuum extraction, or delivery problems. Epileptic episodes may start soon after

delivery or in the early neonatal period as a result of birth trauma. A risk factor for newborn epilepsy can be maternal epilepsy itself. Pregnancy-related seizure activity may raise the newborn's risk of developing seizures. Additionally, the developing fetus may be at danger if the mother uses specific antiepileptic drugs while she is pregnant. Neonatal epilepsy risk can be increased by maternal infections during pregnancy, such as maternal herpes simplex virus (HSV) or cytomegalovirus (CMV) infection. These illnesses may cause swelling and damage to the growing fetus's brain. Neonatal epilepsy is more likely to occur if the mother abuses drugs, alcohol, or tobacco while she is pregnant. These drugs may be harmful to the developing brain, causing abnormalities and an increased risk of seizures. Neonatal epilepsy risk may be elevated in cases of maternal hypertension diseases like preeclampsia or eclampsia. These diseases can hinder fetal brain development and result in placental insufficiency, which may induce seizures. HIE (Hypoxic-ischemic encephalopathy) happens when the baby's brain receives insufficient oxygen and blood during delivery. Complications include placental abruption, issues with the umbilical cord, or maternal hypotension may cause this syndrome. HIE is a recognized risk factor for newborn epileptic episodes and may have long-term neurological effects. [17,18] Testing for transitory metabolic changes including hypoglycemia, hypocalcemia, or electrolyte imbalance should be part of the initial laboratory evaluation for neonatal convulsions.[19]

Neurological Examination: A thorough neurological examination helps in assessing the overall neurological status of the neonate, identifying any focal deficits, abnormal movements, or signs of encephalopathy. It aids in determining the severity of the seizures and potential underlying brain injury.

a) Jitteriness:

A common phenomenon with babies is jitteriness. It is characterized by rhythmic, involuntary tremors in the limbs towards the middle of the body, which stop when the affected limb is tightly gripped. [20] There are a few distinctions between clonus and myoclonus, while tremors can resemble them. In general, tremors have a higher rate and a smaller amplitude. A slower rebound and faster movements are hallmarks of seizures.[21] Tremors start after the first day of life in roughly 50% of cases and persist an average of 7.2 months, or even longer if they are more severe. There are no discernible distinctions between symptoms that appear later and those that appear from postnatal day 1 on.[20]

Three categories of jitteriness in newborns can be recognized: When the baby cries, the tremor is (1) light; when the baby wakes from sleep, (2) moderate; and (3) severe, when the tremor becomes evident even when the baby is sleeping soundly or awake.[22]

Metabolic conditions like hypoglycemia or hypocalcemia, systemic issues like an infection or thyroid disease, and nervous system damage like hypoxic-ischemic encephalopathy or intraventricular hemorrhage may all result in severe tremors. The use of anesthetics or other medicines, difficult labour, fetal distress, and placental insufficiency are a few factors that have been linked to tremor. Other factors include a history of maternal or perinatal illness such as maternal diabetes, thyrotoxicosis, sepsis, hemorrhage, or other conditions.[23]

The newborn could display hyperexcitability and tremors due to withdrawal if the mother uses medicines such serotonin reuptake inhibitors (fluoxetine, fluvoxamine, sertraline), haloperidol, benzodiazepines, opiates, cannabis, and cocaine, thus caution must be exercised. Likewise breastfeeding practices should be examined. Infant hyperexcitability may be linked to chocolate, caffeine, and mate tea. [24,25] Deficiencies in vitamin D, carminatives, heavy metals, and pesticides must all be taken into account.[26]

b) Neonatal sleep myoclonus:

Myoclonus is identified by bodily trembling as you sleep. Clinically, it is frequently seen on both sides throughout stages II to III of NREM sleep, and it totally vanishes after awakening. Arms and legs are usually affected by synchronous or asynchronous myoclonus. Rarely does it affect just one region of the body; it usually affects the entire body. The face, head, or abdomen are not frequently impacted.[27] Usually, sleep myoclonus starts before two weeks after delivery.[28] Nearly 95% of the time, myoclonus tends to grow over the first 3–4 weeks after birth before declining until age 6. A large number of myoclonus episodes take place during NREM (non-rapid eye movement) sleep and last for around an hour on average.[27]

c) Hyperekplexia:

A relatively rare kind of hypertonia called hyperekplexia results by waking up from hypotonia while sleeping or from external stressors. It can happen at birth or at some point in life, and in the mild case, it may be followed by startle. Apnea, cyanosis, and hypertonia in the extremities are all signs of severe cases, and they last for many seconds. A sudden visual or aural stimulus may cause it. By the age of three, hypertonia has

improved, although it can reappear in teenage years or later as a result of abrupt stimulus, cold, or pregnancy. Patients may respond to mild dosages of clonazepam, valproic acid, and levetiracetam if their intellectual faculties are intact. A brain disability or developmental delay may be present in some situations, necessitating watchful monitoring. [29]

d) Sleep apnea: It is characterized by breathing pauses of at least 10 to 15 seconds during sleep. In premature infants, it is usually noted within the first two months of life. It can result from a premature brain, gastric reflux, or medication use. Regular tracking may be necessary for several months until symptoms resolve since in severe circumstances, it can result in sudden newborn death. [30]

5. PHARMACOLOGICAL TREATMENT:

5. 1. FIRST LINE AED'S:

Gamma-aminobutyric acid (GABA) receptor-based first-line therapy, such as phenobarbital and benzodiazepines.

a) Phenobarbitone:

Phenobarbitone has the potential to decrease myocardial function and produce respiratory depression. Phenobarbitone, up to a maximum loading dose of 30 mg/kg in divided doses, should be used aggressively to treat prolonged newborn seizures (longer than one minute) or frequent seizures (more than two in one hour), followed by a single loading dose of phenytoin (20 mg/kg). [31] When provided to asphyxiated term newborn infants at danger of convulsions, phenobarbitone (40 mg/kg) dramatically decreased severe neurodevelopmental disability or death compared to those who received it after seizures became apparent. [32] Learning deficiencies are caused by lower brain capacity in infancy after prenatal exposure to phenobarbitone or phenytoin.[33] Phenobarbitone can also worsen anxiety-related behaviour and is linked to substantial motor and cognitive impairments.[34]

b) Benzodiazepine:

Sedation is a severe side effect of benzodiazepines, particularly midazolam, which may cause respiratory depression and intubation. Midazolam might be thought of as a second- or third-line therapeutic option,

particularly in newborns who have already been intubated. [35,36] Midazolam, loading dose of 0.05–0.2 mg/kg in 10 minutes, then increasing doses of 0.1–0.5 mg/kg/hour (maximum 1.0 mg/kg/hour).[37] A continuous infusion of midazolam, which is increasingly used to sedate infants and children receiving intensive care and seems to have good safety margins, may be the most effective way to manage ongoing seizures.[31]

Compared to diazepam or midazolam, lorazepam has a longer half-life, requiring less frequent administration and intermittent dosing (minimizing cumulative exposure to hazardous excipients). This may be the reason lorazepam is frequently chosen over other benzodiazepines. Because of its metabolic route, which leads to the formation of pharmacologically active metabolites, midazolam is short-acting and has a quicker onset of action. Loading dose of lorazepam, 0.05-0.15 mg/kg over 5 minutes, no maintenance doses (loading dose repeatable). [38]

Clonazepam has been successful in treating newborns who are resistant to phenobarbitone and phenytoin. In one trial, phenobarbital (more than 30 mg/kg) and phenytoin (15–20 mg/kg)-resistant individuals experienced seizure cessation within 120 minutes of receiving clonazepam.[39] Major adverse consequences include reduced awareness, hypotension, and multiorgan failure (particularly at high doses). Clonazepam, which is loaded with a 0.1 mg/kg bolus dosage and then given up to five times within a 24-hour period at 0.01 mg/kg doses.[40] When phenobarbitone and phenytoin-unresponsive babies are concerned, clonazepam has also proved successful. In one trial, clonazepam was administered to two patients who had failed phenobarbital (more than 30 mg/kg) and phenytoin (15–20 mg/kg), and after 120 minutes, the patients' seizures had stopped.[38]

5. 2. SECOND LINE AED'S:

a) Levetiracetam:

Due to its success in treating neonatal seizures, levetiracetam, an antiseizure drug of second generation, is receiving more and more attention. It is one of the few FDA-approved antiepileptics for children as young as one month old, does not require blood-level monitoring, and is simple to maintain as outpatient therapy.[41] Levetiracetam or phenytoin as a second-line treatment have not shown better outcomes. Levetiracetam has a neuroprotective effect that makes it appealing, however a recent study found that it had inferior seizure termination effectiveness when compared to phenobarbital. Use of levetiracetam (10–20

mg/kg load, followed by 10–80 mg/kg/day divided into two doses each day; average dose: 45 mg/kg/day) following phenobarbital and, in rare cases, phenytoin, as first-, second-, or third-line treatment in 23 neonates. Within 24 hours of starting levetiracetam, 35% of newborns experienced a reduction in seizures of more than 50%, and 88% of them stopped having seizures altogether. No significant negative effects were reported.[42]

Levetiracetam dosage for neonatal seizures can change depending on the infant's age, weight, renal function, and the intensity of the seizures, among other variables. It is crucial to remember that a healthcare provider with knowledge of managing neonatal seizures should always decide on the precise dosing. The following details give a comprehensive overview of levetiracetam dosage recommendations for newborns:

Dosing based on age and weight:

- Term Neonates (≥37 weeks gestational age) and Infants: The recommended starting dose is typically 20 mg/kg/day, divided into two equal doses given every 12 hours.

- Preterm Neonates (<37 weeks gestational age): Lower doses may be considered based on gestational age and individual patient factors. The starting dose can range from 10 to 20 mg/kg/day, divided into two equal doses given every 12 hours.

Titration methods:

- Levetiracetam dosage can be gradually increased based on clinical response and tolerability. The dose is typically raised once every two to three days until seizure control is attained or the maximum dosage is reached.

- The dose increments during titration can range from 10 to 20 mg/kg/day. The maximum recommended daily dose is generally 60 mg/kg/day.

- During titration, the dose increments might be between 10 and 20 mg/kg/day. The maximum dose that is often advised is 60 mg/kg/day.

Modification of Renal Function:

- Levetiracetam is mainly excreted by the kidneys, hence renal function should be taken into account when choosing a dosage.

- To prevent medication buildup in newborns with compromised renal function, dosage modifications may be required.

Individualized Dosing and monitoring:

- It is crucial to closely evaluate the infant's clinical response, seizure frequency, and any potential side effects in order to optimize the dosing schedule.

- Levetiracetam is not frequently monitored for serum drug levels. Therapeutic drug monitoring, however, may be taken into consideration in some situations where there are questions about efficacy or toxicity.

b) Phenytoin: Phenytoin was found to be as effective, but due to the possibility of adverse effects, the unpredictable nature of neonatal metabolism, and the requirement for frequent blood-level monitoring, we are unable to suggest it as a first-line treatment.[43] Second-line phenytoin (15–20 mg/kg) was administered after phenobarbital (40 mg/kg), and phenytoin caused seizure cessation to occur within 120 minutes of its addition. Phenytoin is known to cause cardiac arrhythmia and hypotension.[38] Phenytoin was introduced as a second-line therapy for seizures that were resistant to phenobarbital, and this improved seizure control in an extra 10-15% of patients.[44] Phenytoin (phosphenytoin) is typically not advised for long-term maintenance due to its distinct pharmacokinetics and is only advised for acute treatment.[45]

c) Lidocaine: Compared to benzodiazepines, lidocaine looks to be more effective; nonetheless, it has a limited therapeutic window, the potential to result in cardiac arrhythmias or hypotension, and, at high doses, can cause seizures.[46] Phosphenytoin/phenytoin should not be administered after lidocaine since it may have additional cardio-depressive effects. In a recent trial, lidocaine was found to be moderately effective as second-line therapy after benzodiazepines for refractory seizures.[47]

5.3. NEUROSTEROIDS:

Neurosteroids, such as allopregnanolone, have shown promise in preclinical studies for their anticonvulsant effects. These compounds enhance GABAergic neurotransmission and exert neuroprotective effects, making them potential candidates for the treatment of neonatal seizures. The creation of progesterone and other precursor hormones by the placenta, which are then quickly converted to pregnane steroids like allopregnanolone in the fetal brain till birth, is what causes the high levels of neurosteroids in the brain before birth.[48] Both brexanolone and allopregnanolone, often referred to as 5-pregnan-3-ol-20-one or 3-, 5-tetrahydroprogesterone (3-, 5-THP), positively regulate the GABAA receptor, which results in a general suppression of CNS activity. In order to find potential neuroprotective drugs, we carefully looked at the

neurosteroid synthesis route after hypoxia-ischemia.[49] In addition to promoting brain development and preventing hypoxic injury in fetuses, allopregnanolone also provides a tonic suppression of brain activity, as seen by EEG, as well as fetal mobility and breathing patterns.[50] After the placenta is removed, the neurosteroid-induced suppression of brain activity at birth quickly disappears, and neurosteroids like allopregnanolone, whose half-life is estimated to be 10 minutes, are quickly eliminated from the neonate's circulation.[51] The healthy term foetus "wakes up" once the tonic inhibition of in utero neurosteroids has been removed following delivery, which is the physiological sense of this rapid alteration of CNS neurochemistry. The lack of this physiological inhibition, however, exposes the post-hypoxic fetus's brain to oxidative stress and other neurochemical alterations that raise excitability, potentially leading to the beginning of seizures. The growth-promoting environment that neurosteroids provide in utero is lost for a protracted period of time for the prematurely born kid in addition to the immediate loss of protective inhibition. When it comes to administering steroids to infants, there appears to be a higher risk of cerebral palsy if it happens after birth as opposed to a reduced risk if it happens during the antenatal stage. [48,51]

6. PHARMACOGENOMICS:

Pharmacogenetics is the study of genetic variations in people that impact how they react to drugs. By examining the genetic sequence differences between individuals, it is now able to anticipate the disparities in treatment results in patients with diseases and treatments that appear to be the same. The absorption, transportation, metabolism, clearance, and site of action of drugs are all significantly impacted by these genetic sequence variations or polymorphisms.[52]

Numerous studies on genetic association have identified various genes, which are implicated in AED transport (Multidrug-resistant protein/adenosine triphosphate-binding tape protein, MDR1/ABCB1, MDR2/ABCB2), metabolizing enzymes (cytochrome P450, CYP2D6, CYP3A4, CYP2C9, CYP2C19, and CYP2E1; glucuronosyltransferase, UGT1A6 and UGT1A9), ion channels (SCN1A), and immune system (HLA-DR, HLA-DQ, and HLA-B).[53] Drug efflux transporter P-glycoprotein is connected to the MDR1/ABCB1 gene. It is known that the AEDs phenytoin and valproic acid suppress the expression of P-glycoprotein, making it a possible target for pharmaco-resistance.[54]

a) Interindividual diversity:

Neonatal responses to antiseizure medicines (ASMs) show significant interindividual diversity. Genetic

elements that affect therapeutic targets, drug transporters, and drug metabolism can be partly responsible for this variation.

b) Metabolism of drugs:

Most AEDs are metabolized by the liver enzymes Cytochrome P450. The metabolism and removal of AEDs from the body can be affected by genetic differences in these enzymes. For instance, people with poor metabolizer alleles of the CYP2C9 or CYP2C19 genes require fewer dosages of phenytoin to reach the ideal blood level than people with normal alleles. The detection of such genotypes can shield patients from needless phenytoin toxicity.[55]

c) Drug Targets:

Voltage-gated sodium channels (SCN1) are the means of action for many AEDs, namely phenytoin, carbamazepine, and lamotrigine. Genetic variations in drug targets can impact the effectiveness of ASMs. Identifying such genetic variants can help tailor treatment strategies based on the patient's genotype. Children with febrile seizures and Dravet syndrome have been recorded to have mutations in the sodium channel's alpha subunit (SCN1A).[56] Patients with the AA genotype in the SCN1A gene demanded larger dosages of phenytoin and carbamazepine to manage their seizures than those with the GG genotype, according to research.[57]

d) Adverse Drug Reactions/ Potential side-effects:

AEDs frequently trigger negative medication responses, such as cutaneous hypersensitivity reactions. The strongest relationship that exists between the HLA-B*1502 allele and AED-induced Steven-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) in Asian individuals serves as the greatest illustration of this. Similar links between HLA-A*3101 and carbamazepine-induced cutaneous responses have also been discovered, although the results of the follow-up investigations failed to hold up over time. Currently, the only clinically applicable test available for Asian patients having AED medication is testing for the HLA-B*1502 allele. [58,59]

e) Choice of treatment and Optimization:

To decrease mortality and limitations and to improve long-term outcomes, early treatment should be offered to neonates who have seizures (including electrical seizures), especially in very and extremely preterm

newborns. Pharmacogenomic information can assist in selecting the most appropriate ASM for an individual neonate. Genetic testing may provide insights into the expected response to specific medications, allowing for tailored treatment plans. For example, genetic variants associated with reduced drug efficacy or increased toxicity can guide medication selection and dosing adjustments to optimize seizure control. [52]

f) Future Perspectives:

The discovery of novel genetic markers linked to treatment reactivity in neonatal seizures is evolving along with the science of pharmacogenomics. Pharmacogenomic data integration into medical care has the potential to boost therapeutic outcomes, lessen side effects, and eliminate the need for drug trial-and-error methods. In a nutshell by identifying genetic variables that affect drug adaptability, pharmacogenomics shows potential for tailoring the treatment of newborn seizures. Clinical decision-making might profit from combining pharmacogenomic data in order to improve medication selection, dosage optimization, and treatment results in newborns with seizures.

7. DRUGS RARELY USED FOR NEONATAL SEIZURES:

- Vigabatrin's pharmacokinetics in newborns with uncontrolled seizures were described in a single study. One negative consequence is peripheral vision loss, which has been estimated to affect 15% of youngsters.[60]
- Lamotrigine is well tolerated in children but there is very little research showing that it is clinically useful or effective in newborns. In one case report that was published, a newborn's seizures were quickly and effectively controlled after receiving the medication at a single daily dose of 4.4 mg/kg as an add-on therapy.[61]
- By inhibiting frequency, usage, and voltage-dependent sodium channels, carbamazepine stops neurons in depolarized states from firing action potentials repeatedly.[62] For neonates, a loading dose of 5-20 mg/kg and maintenance doses of 5-8 mg/kg per dose, given every 8–12 hours, would be the "ideal" carbamazepine dosage. Due to a shortage of parenteral formulations and the low activity of the cytochrome P450 3A4 isoenzyme at birth, the use of carbamazepine in newborns is constrained.[63]

- By interacting with the N-methyl-D-aspartate receptor's strychnine-insensitive glycine recognition region, felbamate inhibits the N-methyl-D-aspartate receptor and potentiates GABAergic action.[64] Oral felbamate is likely inadequate for achieving enough neuroprotective levels in a timely manner in neonates with hypoxic-ischemic encephalopathy since it is only accessible as an oral preparation and has sluggish absorption.[65]
- Rarely is dexamethasone mentioned as an additional therapy for newborn seizures. The dosage ranges from 0.6 to 2.8 mg/kg intravenously and is typically administered in four daily doses over a period of three to ten days.[66]
- An AED with various modes of action, topiramate also inhibits glutamate receptors and blocks sodium. Despite having a neuroprotective impact, alternatives like topiramate are used less frequently due to the lack of an intravenous formulation which reduces brain damage in a dose-dependent manner and improves neurobehavioral symptoms. Topiramate administration was additionally associated with a reduced requirement for drug titration, a decreased fatality rate in babies with HIE, and a decreased prevalence of epilepsy when paired with hypothermia.[62]

8. COMBINATION THERAPY:

Lamotrigine and sodium valproate together have been shown to help treat partial-onset and generalized seizures in a number of animal models.[67] Other commonly advised combinations include lamotrigine and topiramate for treating a variety of seizures and valproate with ethosuximide for controlling absence seizures.[68] In the mouse model of tonic-clonic seizures, Lacosamide, Phenobarbitone, and Valproic Acid brought about additivity.[69]

9. NON-PHARMACOLOGICAL TREATMENT:

Adjunctive non-pharmacological approaches, including therapeutic hypothermia and ketogenic diet, have shown promise in the management of neonatal seizures. Many different forms of seizures appear to be easier to manage with a ketogenic diet. A ketogenic diet is recognized for controlling gene expression via the epigenetic process. It has been discovered that dietary methyl donor consumption, such as choline, can have a significant impact on the DNA methylation process. Children with refractory seizures are often treated with ketogenic diets that are high in fat and low in carbohydrates.[70] Vitamin B12 deficiency, for example,

suggests a potential role in the pathway and may therefore be advantageous in future therapeutic approaches.[71] The use of the vagus nerve stimulator in adults and adolescents with partial-onset seizures that are drug-resistant has been approved as an additional therapy.[72] The patient has a vagus nerve stimulator implanted in the upper chest that produces a pulse and sends electrical current to the neck's vagus nerve.[73] In animal models of epilepsy, a number of natural or herbal medications, including Cicuta virosa and Nux vomica, have been demonstrated to be beneficial in lowering seizure activity and other physiological parameters. Evidence that suggests that cooling the brain can help lower the risk of brain injury and improve long-term neurological outcomes in infants underlies the use of therapeutic hypothermia in neonatal convulsions. Insufficient oxygen and blood flow to the brain causes hypoxic-ischemic encephalopathy (HIE), which is a major underlying cause of newborn seizures. The goal of cooling therapy is to lessen the severity of brain damage brought on by HIE.[74]

10. RECURRENT SEIZURES:

Despite appropriate initial treatment, some neonatal seizures may remain refractory to standard therapies. This section explores the rescue therapies, such as continuous infusions of midazolam or pentobarbital, as well as newer interventions like ketogenic diet that can be considered in cases of refractory neonatal seizures. If phenytoin has not already been used, lidocaine is another option in refractory patients. A subclass of seizures known as the "group of vitamin-responsive seizures" is exclusive to the newborn stage. During EEG monitoring, 100 mg of pyridoxine or 500 mg if it is ineffective should be administered to treat status epilepticus or therapy-resistant neonatal seizures. Pyridoxine should thereafter be continued intravenously or orally with 30 mg/kg/day split into two or three single doses over three consecutive days.[75] An efficient AED for status epilepticus and recurrent seizures is valproic acid.[76] However, due to a relatively significant risk of catastrophic hepatotoxicity in neonates, especially with polytherapy and/or if an underlying inborn metabolic mistake is detected, it should be administered with extreme caution. There is currently a lack of pharmacokinetic information to help determine the proper intravenous dosages; initial loading doses studied have ranged from 20–25 mg/kg orally, 20–30 mg/kg topically, and 10–25 mg/kg intravenously, while maintenance dosages have ranged from 5–10 mg/kg per dose orally.[77] For patients with refractory epilepsy that can't be controlled with monotherapy, lacosamide, phenobarbitone, and valproic acid may be combined.[62]

11. RECENT ADVANCES AND RECOMMENDATIONS:

11.1. RECENT ADVANCES AND RECOMMENDATIONS FOR DIAGNOSIS:

Continous EEG Monitoring:

The gold standard for accurately detecting neonatal seizures, rapid treatment beginning, and monitoring is continuous video EEG (v-EEG). The ACNS advises 24-hour vEEG for newborns who are at high risk of seizures. Phenotypic variability hinders precise suggested changes, but a sound, consistent approach departing from previously published standards aids in accurately assessing these neonates in order to give greater attention, especially in light of the growing field of precision therapeutics. [78]

Closed circuit videotapes:

Motion-segmentation techniques built around optical flow computation were used to extract temporal motion-strength signals from video segments in order to quantify the mobility of the infants' body parts. By grouping the motion components gathered from fitting an affine model to the pixel velocities, the region of each frame encompassed by the infants' moving body parts was identified. Additionally, the mobility of the infants' body parts was measured using temporal motion-trajectory signals that were robust motion trackers derived from block-motion models retrieved from video recordings. The detection and separation of myoclonic and focal clonic neonatal seizures from random infant movements was accomplished by conventional direct brain networks, quantum neural connections, and cosine axial basis function neural networks. [79]

Genetic epilepsies:

Neonatal epilepsies can have genetic origins such as metabolic defects, cortical malformations, or changes in cortical function lacking a corresponding anatomical lesion. Neonatal onset epilepsy genes have been discovered to cluster, preferably into discrete pathways, then at least into categories with related functions, with no metabolic or structural mutations: ion channels (such as KCNQ2), forebrain development regulators (such as ARX), and synaptic function regulators (such as STXBP1) have been found to cluster, if not into distinct pathways, then at least into groups with related functions, as are the genes responsible for neonatal onset epilepsies despite metabolic or structural alteration. Examinations into the roles of these gene products and the impact of pathogenic modification in the ideal scenario could result in new therapies, as recently demonstrated for epilepsy of infancy with migrating focal seizures (EIMFS). When medically refractory

multifocal seizures shift from one focus to yet another, sometimes developing numerous independent seizures at once, EIMFS might manifest towards the end of the newborn period and cause developmental impairment. The fact that the same genes that cause benign epileptic seizures can also be linked to diseases marked with severe encephalopathy and convulsions is an emerging subject in the inherited epilepsies, notably the channelopathies. KCNQ2, which causes most instances of benign familial newborn epilepsy (BFNE), is the classic case. [80]

Positron emission tomography:

Noninvasive approaches make it possible to investigate several facets of the neuropathologic underpinnings of uncontrollable seizures as well as the link between functional abnormalities and both structural and focal abnormalities. The hippocampus is clearly visible in the anatomy of the brain due to new MRI techniques, which also provide details about the metabolism of various brain areas and high-resolution functional activity in the brain. The alterations that had previously been observed by methods requiring tissue destruction cerebral acidosis brought on by seizures and a decrease in the concentration of phosphocreatine were successfully identified in vivo by magnetic resonance spectroscopy. [81]

Cassette encephalopathy:

In neonates with ongoing clinical episodes, cassette EEG can improve seizure detection and classification, but it has minimal yield in all other situations. It enables researching aberrant sleep patterns by recording and assessing all-night sleep. [82]

Differential diagnosis:

Some clinical characteristics, such as stimulus sensitivity, adaptation (present in startle reflex but lacking in hyperekplexia), and connection with behavioural states (benign neonatal sleep myoclonus ceases with arousal), may help with differential diagnosis. Examples include different stimuli, primarily auditory, for startle reflex; weeping and stress for tremor and jitteriness; abrupt visual stimuli or shift for paroxysmal tonic up/downward gaze. Some paroxysmal non-epileptic symptoms can be distinguished from epileptic ones by grasping the affected limbs or moving the newborn: Light constraint prevents physiological tremors but has no effect on epileptic occurrences. For the purpose of identifying various clinical disorders, polygraphic v-EEG is a crucial tool. Finally, non-epileptic paroxysmal occurrences in the neonate should be investigated just as methodically and completely as epileptic seizures since they are frequently symptoms of an underlying disorder. The majority of rapid changes in neonatal vital signs, including blood pressure, heart rate, and

respirations, do not indicate epileptic seizures; instead, when these changes do indicate seizures, they are typically accompanied by motor phenomena or other clinical symptoms. When oxygen depletion or apnea took place especially in the context of aberrant eye movements or rapid tone shifts, these sudden changes in vital signs were more inclined corresponding to epileptic seizures [83]

11.2 RECENT ADVANCES AND RECOMMENDATIONS FOR TREATMENT:

Pyridoxine-dependent epilepsy:

- An uncommon autosomal recessive condition known as pyridoxine-dependent epilepsy (PDE) is regarded as the archetypal example of metabolic epilepsy. PDE responds to pharmacological quantities of pyridoxine and is characterized by repeated seizures in the prenatal, neonatal, and/or postnatal periods that are resistant to traditional anti-epileptic medications. However, there are currently no definite dose guidelines for long-term therapy. Even while pyridoxine supplementation is the first line of treatment and need to be started at a young age in all confirmed PDE patients, a number of additional treatment options are becoming available. A lysine-restricted diet and arginine fortification are two examples of this.
- In newborns with clinical signs of vitamin B6-dependent epilepsy and seizures resistant to second-line ASM, pyridoxine may be tested. In the decarboxylation and transamination of amino acids, vitamin B6 functions as a coenzyme. The cofactor for the enzyme glutamic decarboxylase and -aminobutyric acid transaminase, which are essential for the synthesis and metabolism of brain -aminobutyric acid, is pyridoxal phosphate. Infantile convulsions, eczema, anemia, and peripheral neuritis have all been linked to vitamin B6 deficiency. The administration of isonicotinic acid hydrazide may result in a neuropathy that responds to vitamin B6.
- Normal vitamin B6 levels do not prevent seizures brought on by vitamin B6 dependence. Paediatric and neurological texts claim that these seizures start just after birth and last for up to six months. [84]
- Short-term intractable seizures characterize pyridoxine dependence, a peculiar deficiency in an enzyme that assists in the generation of the regulatory neurotransmitter GABA. Although the EEG may display broad spurts of bilaterally concurrent high voltage 1-4 Hz activity with intermittent spikes, the diagnosis is made by watching the cessation of seizures shortly after receiving 50–100 mg of pyridoxine (although the EEG's return to normal may take longer). These symptoms are typically

caused by the mother abusing narcotic analgesics, barbiturates, cocaine, and alcohol. [85]

- Levetiracetam may be the recommended second-line anti-seizure medication in newborns with cardiac conditions.
- Initially regardless of the source of the seizures, phenobarbital should be the first-line ASM. However, if channelopathy is likely to be the cause of the seizures (for example, due to a family history), then phenytoin or carbamazepine should be used.
- Regardless of results from magnetic resonance imaging or electroencephalography, ASMs should be stopped before patients are sent home once acutely induced seizures have stopped and there is no sign of neonatal-onset epilepsy.
- Therapeutic hypothermia may lessen the burden of seizures in newborns with hypoxic-ischemic encephalopathy. Reducing infant seizure burden through treatment may lead to a better result.
- The care of neonatal seizures in each neonatal unit should follow a defined protocol, and parents and guardians should be informed of the diagnosis of seizures and available early therapies. [84]
- Chlormethiazole infusions have occasionally been used to manage uncontrollable seizures.[86]
- Aldehyde may serve as a helpful supplement. It is eliminated through the metabolism in the liver and pulmonary movement and remains unaffected by decreased renal function; its half-life is only 12 to 24 hours. Hepatic degeneration and pulmonary edema are two side effects that have been reported. To manage seizures, an initial dose of 200–400 mg/kg can be either orally or intravenously. This is followed by a continuous infusion of 15–150 mg/kg/hour (0.3–3 ml/kg/hour of a 5% solution, composed up of 5% dextrose). Every 12 hours, plastic syringes must be replaced, and the solution must be shielded from light. [87]
- Neonatal withdrawal seizures linked to methadone can happen at any moment up to 3 weeks of age.
- ASM should be stopped abruptly in newborns with acutely triggered seizures after 72 hours of seizure-free time and prior to discharge from the hospital. Neonates with epilepsy that began before birth should be kept on ASM and constantly monitored in specialized neuropediatric clinics.
- Misuse of cocaine may increase the risk of prenatal cerebral artery infarction, which may result in seizures.[85]

- The therapy of seizures in KCNQ2 encephalopathy has had the most results to date with sodium channel blockers, particularly carbamazepine. Indeed, carbamazepine is an old medicine with a new application in the treatment of early-onset genetic epilepsies, as evidenced by reports of some success in the management of early epilepsy associated with SCN2A and SCN8A. [88]

12. FUTURE PERSPECTIVES:

The field of neonatal seizure treatment is constantly evolving, with ongoing research focusing on novel therapeutic targets and strategies. This section highlights potential future directions, including the use of neuroprotective agents and precision medicine approaches tailored to the individual patient's genetic profile.

13. CONCLUSION:

Neonatal seizures must be identified early, correctly diagnosed, and promptly treated in order to maximize neurodevelopmental outcomes. The use of drugs with distinct mechanisms of action and the avoidance of neurotoxic substances should be preferred, with the potential to negatively affect the result of neurodevelopmental treatment, even though phenobarbital is still the drug of choice in the initial stages of treatment. Theoretically, utilizing bumetanide promises to be the most effective course of action considering its mechanism of action. An accurate diagnosis will result in less needless treatment and a better prognosis through earlier treatment owing to the active use of continuous EEG monitoring. This review highlights both well-established and recently developed treatment techniques, offering an in-depth examination of the current therapeutic strategies for newborn seizures. The therapy of newborn seizures must be further improved, and collaborative studies must be conducted to improve the long-term results for affected infants.

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