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Neonatal Seizures: Advances in Mechanisms and Management

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Synopsis

Seizures occur in approximately 1–5 per 1,000 live births, and are among the most common neurologic conditions managed by a neonatal neurocritical care service. There are several, age-specific factors that are particular to the developing brain, which influence excitability and seizure generation, response to medications, and impact of seizures on brain structure and function. Neonatal seizures are often associated with serious underlying brain injury such as hypoxia-ischemia, stroke or hemorrhage. Conventional, prolonged, continuous video-electroencephalogram (cEEG) is the gold standard for detecting seizures, whereas amplitude-integrated EEG (aEEG) is a convenient and useful bedside tool. Evaluation of neonatal seizures involves a thorough search for the etiology of the seizures, and includes detailed clinical history, routine chemistries, neuroimaging (and preferably magnetic resonance imaging, MRI), and specialized testing such as screening for inborn errors of metabolism if no structural cause is identified and seizures persist after correction of transient metabolic deficits. Expert opinion supports rapid medical treatment to abolish electrographic seizures, however the relative risk *versus* benefit for aggressive medical treatment of neonatal seizures is not known. While there is increasing evidence to support a harmful effect of seizures on the developing brain, there is also evidence that commonly used medications are potentially neurotoxic in animal models. Newer agents appear less harmful, but data are lacking regarding optimal dosing and efficacy.

Keywords

Brain Injury; Developmental disability; Infant; newborn; Electroencephalography; Epilepsy; Magnetic Resonance Imaging; Neurocritical Care; Seizures

Introduction

Neonates are at especially high risk for seizures as compared to other age groups [1]. The high risk for seizures - and especially acute symptomatic seizures - is likely multifactorial, and due to both the relative excitability of the developing neonatal brain, as well as the high

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risk for brain injury due to global hypoxia-ischemia, stroke and intracranial hemorrhage [2]. The estimated rate of seizures in term newborns is said to be approximately 1–5 per 1,000 live births [3–5]. However, population-based studies do not take into account the low diagnostic accuracy of diagnosis by clinical observation alone [6, 7], and gold standard continuous, prolonged video-electroencephalogram (cEEG) monitoring is not widely available enough to make population-based predictions, therefore the true incidence remains unknown.

The differential diagnosis for neonatal seizures is broad, and includes both structural-metabolic, and genetic causes (Box 1). Seizures that arise from an acute symptomatic cause such as hypoxic-ischemic encephalopathy, transient metabolic disturbance, infection, stroke, or intracranial hemorrhage, are much more common than neonatal onset epilepsies, which may be due to malformation, prior injury or genetic causes. Rare conditions such as inborn errors of metabolism, vitamin-responsive epilepsies and neonatal epilepsy syndromes must be considered in the setting of refractory seizures [8, 9].

Box 1

Etiology of neonatal seizures

Differential Diagnosis of Acute Symptomatic Seizures
Global hypoxia-ischemia (hypoxic-ischemic encephalopathy, HIE)
Focal hypoxia-ischemia
Arterial stroke
Venous stroke
Intracranial hemorrhage
Intraventricular
Parenchymal
Subarachnoid
Subdural
Transient metabolic deficit
Hypoglycemia
Hypocalcemia and hypomagnesemia
Hyponatremia
Acute infection
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)

Neonatal seizures carry a high risk for early death. Among survivors, motor and cognitive disabilities, as well as epilepsy are common [10]. The outcome depends largely on the underlying disease process and severity of underlying brain injury. The impact of the seizures themselves is not known, though studies in animal models suggest that seizures can

alter brain development, leading to deficits in learning, memory and behavior (reviewed in [11]).

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 (see [12] for an excellent review).

Enhanced excitability of the neonatal brain

There are numerous mechanisms that render the immature brain hyperexcitable as compared to the adult brain [12, 13]. First, the neonatal period is a time of physiologic, use-dependent synaptogenesis, and both synapse and dendritic spine density are at their peak [14, 15]. Second, glutamatergic neurons - the primary excitatory mechanism of both the developing and adult brain - are over-abundant, and their receptors are configured with subunits that allow relative hyper-excitability [16, 17]. Third, gamma-amino-butyric acid (GABA) – the primary inhibitory mechanism of the adult brain – can exert a paradoxical excitatory action in the developing brain due to the preponderance of the NKCC1, and delayed expression of the KCC2 chloride co-transporters, which leads to a high intracellular chloride concentration, and *depolarization* in response to GABAergic agents [18–20].

Anticonvulsants and the developing brain

Immature development of the excitatory and inhibitory neurotransmitter systems leads to a lack of good targets for conventional anti-seizure medications, which makes neonatal seizures particularly difficult to treat. The immature brain may be resistant to medications that act as GABA agonists, not only as a result of the paradoxical chloride gradient as discussed above, but also due to overall lower receptor expression, and an immature subunit composition that is less sensitive to benzodiazepines than the adult brain [12, 13].

Seizures and early brain development

While early work with animal models demonstrated that the developing brain is more resistant than the adult brain to seizure induced necrosis, more recent work has shown that early life seizures can affect the developing brain nonetheless by altering neuronal circuitry, which can result in impaired learning and memory, and enhanced susceptibility to epilepsy later in life (reviewed in [11]). Animal models of early life seizures display developmental alterations that can include reduced density of dendritic spines in hippocampal pyramidal neurons, decreased neurogenesis, delayed neuronal loss, and changes in hippocampal plasticity such as decreased capacity for long-term potentiation, reduced susceptibility to kindling and enhanced paired-pulse inhibition [21–24]. 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 [25, 26].

Management Goals

The overall management goal for neonatal seizures is to quickly and accurately identify, and abolish electrographic seizures, while determining the most likely underlying etiology. Neonatal seizures are often the first sign of neurologic dysfunction, and are frequently an indication of serious underlying brain injury [27, 28]. Therefore, a suspicion of seizures in a newborn should be treated as a neurological emergency, and prompt rapid and thorough evaluation to identify the cause, as well as emergent medical management to abolish seizures while preventing secondary injury by maintaining physiologic temperature, glucose, oxygenation, ventilation, and blood pressure.

Seizure Detection and Monitoring

Common methods for identifying neonatal seizures are outlined in Table 1. Clinical evaluation of seizures is approximately 50% accurate for events detected at the bedside. Furthermore, clinical detection requires constant observation by the bedside staff, and even so will fail to detect seizures with no or very subtle clinical correlate (for example eye deviation or subtle clonic movements that are covered by the infant's blanket). Subclinical seizures account for the majority of all seizures in neonates, especially in the setting of severe brain injury, and in children who have received seizure medications [7, 29–31].

Recent guidelines from the American Clinical Neurophysiology Society set the standard for neurophysiology monitoring in neonates [32]. Continuous video-electroencephalograpy (cEEG), with electrodes placed according to the international 10–20 system, modified for neonates, is the gold standard for monitoring [33–35]. Barriers to implementing this technology include the need for specialized training for the application and interpretation of the recording, as well as variable access to equipment, and high cost. Once initiated, cEEG should be maintained until electrographic seizures have resolved for at least 24 hours, or 3–4 clinical events have been captured and determined not to be seizures [32].

Amplitude-integrated electroencephalography (aEEG, a simplified bedside neurophysiology tool that can be applied and interpreted by neonatologists, nurses, or other Intensive Care Nursery bedside staff) is used to supplement or even replace cEEG in a growing number of centers. Since aEEG uses a limited number of channels to record EEG signal that is heavily processed (filtered, rectified, and displayed on a semi-logarithmic amplitude and time-compressed scale), there are several limitations to this technology that must be taken into account when it is used for management of neonatal seizures (Table 1). Machines that allow for concurrent monitoring and display of aEEG (at the bedside) and cEEG (in the neurophysiology lab or remotely) using the same hardware have been suggested as a way to optimize use of both technologies, such that the both the bedside team *and* neurologist can be readily involved in the rapid, real-time management of electrographic seizures (Figure 1) [36].

Automated seizure detection - with an alarm to alert the bedside practitioner in the case of suspected seizures - is an attractive option that may offer the most practical solution for wide-scale implementation of seizure detection and management. However, there have been several challenges that limit the development of automated detection algorithms, including: highly variable nature of neonatal seizure patterns, high frequency of potential artifacts in the intensive care nursery, and uncertainty regarding the gold standard against which algorithms are tested given the limited information regarding inter-rater reliability among human expert readers (reviewed in [42]). Newer algorithms that use machine learning, as well as temporal and spatial weighting hold promise [43–46].

Diagnostic Evaluation

Initial evaluation of a neonate with suspected seizures should also focus on rapid identification of the etiology. Emergent evaluation of serum glucose and risk factors for infection is an important first step, since hypoglycemia and bacterial meningitis can lead to permanent injury if left untreated [8]. Additional bedside evaluations must include measurement and treatment of electrolyte disturbance. Comprehensive history and physical examination are important tools to assess for risk factors and signs of both common and rare causes of neonatal seizures. Further evaluation, including genetic testing, serum amino acids, ammonia, lactate, and very long chain fatty acids, urine organic acids and sulfites, and cerebrospinal fluid studies for glucose, glycine, lactate and neurotransmitters, as well as additional testing for inborn errors of metabolism may be warranted on a case-by-case basis,

especially in the setting of medically refractory seizures of unknown etiology, or a burst-suppression pattern on EEG in a neonate without brain injury.

Detailed neuroimaging using magnetic resonance (MR) is essential to identify underlying injury or developmental abnormalities, and to help clinicians and the family to better understand the prognosis [47]. Cranial ultrasound, which is readily available at the bedside in most units, is important for rapid initial assessment of a sick neonate to identify large space occupying lesions, such as hemorrhage, arteriovenous malformations or hydrocephalus, but is insensitive for global and focal hypoxic-ischemic injury, especially in the days after the ictus. Computed tomography (CT) exposes the infant to ionizing radiation and provides inferior resolution to MRI in most settings, and so should be avoided.

Pharmacologic Strategies

There are no evidence-based guidelines for the pharmacological management of neonatal seizures [48, 49]. Expert opinion supports use of pharmacological treatments with a goal of abolishing electrographic seizures, even those without clinical correlate [42]. However, evidence is lacking regarding the relative benefit *versus* potential harm of anticonvulsants used to treat seizures in neonates, many of which can lead to neuronal apoptosis in animal models [50].

Since seizures are refractory to initial doses of medication in approximately 50% of cases [51], frequent re-evaluation of cEEG and bedside monitoring is essential to accurately identify and treat ongoing seizures in real time. Though data are lacking regarding optimal treatment paradigms for neonatal seizures, experts advocate *rapid* administration of an adequate loading dose of medication since acute symptomatic seizure burden is highest at the onset [52], and patients with fewer seizures are easier to treat [51]. Similarly, experts advocate treatment of both clinical *and* subclinical seizures given similar pathophysiology, and that the only difference between the two may be slight anatomical differences in their cortical distribution [42]. Use of algorithms or guidelines to direct the treatment of neonatal seizures has gained favor given evidence that treatment guidelines can improve outcomes in other settings [53]. As discussed below, the optimal medication for seizure therapy in neonates is not known, and so guidelines should focus on an institution-specific, consensus-based protocol with input and acceptance by both neonatology and neurology services to help prevent unnecessary delays in treatment that may result from discussions over medication choice in the setting of an actively seizing neonate.

The optimal duration of pharmacologic therapy for acute symptomatic seizures is not known. Treatment practices are variable in spite of good evidence that there is no harmful effect of early discontinuation of seizure therapy, and no difference in seizure recurrence risk among neonates who are maintained on therapy *versus* those whose medication is maintained until several months of age [54–56] (Box 2).

Box 2

Principles for acute symptomatic neonatal seizure management

Rapid and accurate electrographic seizure identification

Rapid titration of medication(s) to abolish electrographic seizures

Early discontinuation of medication once seizures have resolved

International survey data support the use of phenobarbital as the first-line medication based on expert consensus [57–59] (Table 2). A single randomized, controlled trial found that

phenobarbital and phenytoin were equally efficacious as first-line agents for seizure cessation among term infants with seizures [51]. However, seizure control (defined by the study parameters as an 80% reduction in the severity of seizures), was achieved in fewer than half of the infants [51]. This result is supported by newer studies, which demonstrate that up to 50% of neonatal seizures are refractory to first line medications, and an additional 30% fail second line therapy [60].

Levetiracetam is gaining increasing support, in spite of limited efficacy data [61, 62]. This is likely due to the ready availability of an intravenous formulation in the United States, as well as a favorable safety and tolerability profile among children and adults [63]. In contrast to older agents such as phenobarbital and phenytoin, levetiracetam does not appear to enhance neuronal apoptosis in animal models [64, 65], and may in fact have neuroprotective and antiepileptogenic effects [66, 67]. The optimal neonatal dosage of levetiracetam is not yet known: reported doses range from 5 to 60mg/kg day (reviewed in [68]). However, the high volume of distribution and rapid clearance in neonates may necessitate a higher loading dose and more frequent dosing to maintain serum concentrations in the range used for adults and children [69, 70]. Published studies of the clinical efficacy of levetiracetam that report seizure reduction or resolution in 35–80% are limited by lack of standardized dosing, limited EEG monitoring, no placebo comparison, and/or variable timing and definition for determining the outcome [71–73].

Common agents for refractory seizures include midazolam infusion, which may be effective for neonatal status epilepticus, and lidocaine, which is widely used for refractory neonatal seizures in Europe [74–81]. Topiramate is an antiseizure medication that has multiple mechanisms of anticonvulsant action, and is an interesting option for acute symptomatic neonatal seizures because it appears to have neuroprotective effects in animal models of seizures and brain injury [82, 83]. A recently developed intravenous preparation of topiramate that is well tolerated in adult volunteers and has equivalent bioavailability to the oral formulation holds promise for use in neonates [84, 85].

Bumetanide is a loop diuretic that has been proposed as an adjunct to GABA-ergic drugs like phenobarbital to help overcome the depolarizing action of immature neurons to GABA agonists. The mechanism of action is presumed to be through reduction in intracellular chloride concentrations, thus rendering the normally excitatory response of immature cells with high NKCC1 expression to an inhibitory response [86]. Preclinical studies demonstrate mixed effects, with reduction in seizure frequency and duration, as well as enhanced neuroprotective efficacy when combined with phenobarbital [87–89]. A single clinical study showed reduction in seizure frequency and duration following bumetanide treatment [90]. Though promising as an add-on agent for neonatal seizures, the potential for adverse effects such as ototoxicity, and partial central nervous system bioavailability may ultimately limit the utility of bumetanide [91].

Information about agents other than phenobarbital and phenytoin is largely derived from case series rather than randomized, blinded, clinical trials, and so the true efficacy of these medications is not known. Seizures due to acute symptomatic causes such as hypoxic-ischemic brain injury and stroke rarely persist beyond a few days of life, making any add-on agent appear more effective than the initial therapy [52]. Furthermore, older studies do not include prolonged, video-EEG monitoring, and so non-convulsive seizures, which are very common following administration of phenobarbital, may go undetected.

If the underlying etiology of medically refractory seizures is unknown after initial screening laboratory and imaging studies, a trial of pyridoxine, pyridoxal 5′-phosphate and folinic acid should be considered, and a screening metabolic evaluation should be performed [9].

Summary/Discussion

Neonatal seizures are common and frequently reflect serious underlying brain injury. Prolonged cEEG is the gold standard for seizure monitoring, however availability remains limited at many centers. Phenobarbital, the preferred first choice medication internationally, is effective in only 50% of cases and may be harmful, especially when used in high doses or for prolonged periods. However, there is abundant evidence from animal models to show that seizures themselves disrupt the developing brain, and so there is urgent need for research to develop safe, accurate and widely available methods for identifying and treating electrographic seizures.

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Key Points

1. Seizures occur in 1–5 per 1000 live births, and are among the most common neurologic conditions managed by a neonatal neurocritical care service.
2. The high rate of seizures in the neonatal period reflects age-specific developmental mechanisms that lead to relative excitability.
3. Neonatal seizures are often caused by serious underlying brain injury such as hypoxia-ischemia, stroke or hemorrhage.
4. Clinical detection is unreliable; continuous, video-electroencephalogram is the gold standard in monitoring for presence and burden of neonatal seizures.
5. Seizures are refractory to first line medications in ~50%; expert opinion supports rapid treatment to abolish acute symptomatic seizures, and early discontinuation of medication(s).

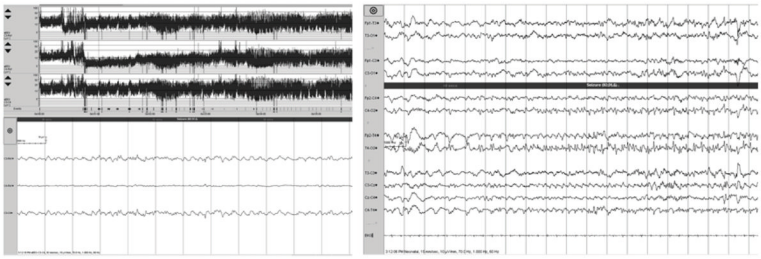

Figure 1.

Amplitude-integrated EEG (left) and EEG (right) from a term male with multiple intracranial hemorrhages and seizures that were refractory to phenobarbital 40mg/kg and fosphenytoin 30mg/kg, and abated after 60mg/kg levetiracetam. aEEG and EEG are recorded from a single machine at the bedside. Data are displayed differently for different users: the bedside team sees the aEEG display at left, which shows long term trends and allows a quick review of suspicious segments of EEG. The neurophysiologist can confirm the seizures through the review of conventional, neonatal montage EEG.

Table 1

Diagnosis of neonatal seizures.

Conventional video-EEG (cEEG)	• Gold standard for seizure detection • Recommended by the American Clinical Neurophysiology Society for monitoring neonates with paroxysmal events and/or at high risk for seizures [32]
Amplitude-integrated EEG (aEEG)	• Lower sensitivity and specificity than cEEG (reviewed in [36]) • 100% sensitivity for status epilepticus [37] • Lowest sensitivity for seizures that are brief, focal, distal from recording electrodes [38, 39] • Raw EEG tracing helps to distinguish artifact from seizure [40] • Experienced readers perform better than non- experts [41]
Clinical evaluation	• Accuracy ~50% [6] • Will not identify the majority of seizures (i.e., subclinical or non-convulsive seizures) [7, 29–31]

Table 2

Pharmacologic treatment for acute symptomatic neonatal seizures

Medication	Dosage	Side Effects	Notes
Levetiracetam	*Optimal dosing not known* Loading dose: 40–60 mg/kg intravenously Daily dosing: 30 mg/kg/day (target levels not known) [92]	Mild sedation/ drowsiness, and irritability	Limited information regarding dosing and side effects for neonatal population.
Lidocaine	Loading dose: 2 mg/kg over a period of 10 min, followed by a continuous infusion of 6 mg/kg per hour during the first 12 h; 4 mg/kg per hour for the next 12 h, and 2 mg/kg per hour for the last 12 h*	Arrhythmia	Should only be given in the intensive care setting with continuous cardiac monitoring. In case of cardiac arrhythmia, the infusion should be discontinued immediately. Lidocaine should not be given to patients with a congenital heart disease, or to neonates who have been treated with pro-arrhythmic drugs like phenytoin.
Lorazepam	0.05–0.1 mg/kg intravenously	Respiratory depression, depressed level of consciousness, and hypotension.	May cause myoclonus in very-low-birth-weight infants.
Midazolam	Loading dose: 0.2 mg/kg intravenously, followed by continuous infusion (1 mcg/kg/minute) increasing by 0.5–1 mcg/kg/minute every 2 minutes to 2–5 mcg/kg/minute	Respiratory depression, depressed level of consciousness, and hypotension.	
Phenobarbital	Loading dose: 20 mg/kg intravenously, repeated once as needed Daily dosing: 5 mg/kg/day (target level 40–60 mcg/mL)	Respiratory depression, depressed level of consciousness, hypotension, and hypotonia. Idiosyncratic skin rash, hepatotoxicity, and blood dyscrasia	Prolonged half-life in first week of life (43–217 hours) limits need for weaning phenobarbital in the case of short-term therapy.
Phenytoin and fosphenytoin	Loading dose: 20 mg/kg intravenously Daily dosing: 5 mg/kg/day (target level 10–20 mcg/ mL)	Infusion site reaction and arrhythmia with intravenous phenytoin. Idiosyncratic skin rash, hepatotoxicity, and blood dyscrasia	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.

*NB Lower doses recommended for neonates undergoing therapeutic hypothermia [79].