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Advances in Management of Neonatal Seizures

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Abstract

Seizures are more common in the neonatal period than any other time in the human lifespan. A high index of suspicion for seizures should be maintained for infants who present with encephalopathy soon after birth, have had a stroke, central nervous system (CNS) infection or intracranial hemorrhage or have a genetic or metabolic condition associated with CNS malformations. Complicating the matter, most neonatal seizures lack a clinical correlate with only subtle autonomic changes and often no clinical indication at all.

Over the last three decades, several tools have been developed to enhance the detection and treatment of neonatal seizures. The use of electroencephalography (EEG) and the later development of amplitude-integrated EEG (aEEG), allows for Neurologists and non-Neurologists alike, to significantly increase the sensitivity of seizure detection. When applied to the appropriate clinical setting, time to diagnosis and start of therapy is greatly reduced. Phenobarbital maintains the status of first-line therapy in worldwide use. However, newer anti-epileptic agents such as, levetiracetam, bumetanide, and topiramate are increasingly being applied to the neonatal population, offering the potential for seizure treatment with a significantly better side-effect profile.

Seizures in premature infants continue to confound clinicians and researchers alike. Though the apparent seizure burden is significant and there is an association between seizures and adverse outcomes, the two are not cleanly correlated. Compounding the issue, GABA-ergic anti-epileptic drugs are not only less effective in this age group due to reversed neuronal ion gradients but may also cause harm. Selecting an appropriate treatment group remains a challenge.

Keywords

seizures; aEEG; infants; HIE

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Contribution

Both the authors are responsible for writing and editing the review article. Dr. Amit M. Mathur will act as guarantor for this paper.

Conflict of Interest

None

Introduction

Seizures during the neonatal period are common, occurring in 0.1–0.5% of all newborn infants, indeed more so than any other period in the human lifespan [1,2]. The potential causes of seizures during this period are myriad owing to the unique coincidental timing of risk factors including hypoxia, metabolic derangement, infection and genetic disorders along with developmental evolution of glutamate and GABA receptors. Evolving technological achievements for the detection of seizures and new agents for treatment have steadily changed the field.

In this article we discuss the current trends in both the detection and treatment of seizures in term and preterm infants.

Seizures in the Term Infant

The 2011 *American Clinical Neurophysiology Society Guidelines on Continuous EEG Monitoring* lists six conditions in which carry a high risk for seizures; encephalopathy after hypoxia (including perinatal asphyxia and in the setting of cardiac or pulmonary risks for hypoxia), CNS infection, intracranial hemorrhage, inborn errors of metabolism, perinatal stroke and genetic disease predisposing the infant to CNS malformations [3]. Regardless of etiology, seizure activity is associated with adverse neurologic and cognitive outcomes, highlighting the need for rapid diagnosis and the opportunity to improve outcomes with definitive management [4].

The detection of seizures can be challenging, even for an experienced clinician. Seizures in the immediate newborn period do not typically manifest as the classical generalized tonic-clonic activity of older children and adults, largely due to incomplete myelination of the corticospinal tract and a higher threshold for secondary generalization [1]. Indeed, Hellström-Westas et al. found more than 50% of infants with sustained ictal discharges had no clinical manifestations [5].

Seizures in the neonatal period can be classified into one of three categories, described by Glass et al. as “clinical-only,” “electrographic only” and both [6]. “Clinical-only” seizures may be explained by non-epileptic phenomena such as sleep myoclonus, jitteriness from hypocalcemia or hypoglycemia, neonatal abstinence syndrome and breathing-holding spells [2]. So called “subtle-seizures” may be epileptic phenomena arising from the brainstem or other deep cortical structures which are difficult to detect with electroencephalography (EEG) but may be expressed by autonomic changes. Scher states, “Any subtle paroxysmal event which interrupts the expected behavioral repertoire of the newborn infant, and appears stereotypical or repetitive should alert the clinician to the possibility of seizures” [7].

With the aid of EEG technology, it quickly became clear that “electrographic-only” seizures in neonates are common. Clancy reviewed 394 electrographic seizures and found that only 84/394 (21%) had simultaneous clinical correlate [8].

The conventional 21-lead EEG has significant limitations, namely the need for specialized neurophysiologists and staff trained in complex lead placement on the small neonatal scalp.

With some of these limitations in mind, Maynard and Prior developed limited-channel cerebral function monitoring (CFM) in the 1960s [9]. This technology was subsequently applied to neonates in the form of amplitude-integrated EEG (aEEG) by Hellström-Westas and others in the 1980s [5]. aEEG recordings from modern devices provide a time-compressed overview of the frequency distribution of cerebral activity. Seizure activity causes a sudden and characteristic elevation of the baseline, enabling rapid detection (Fig 1).

Recognition of seizures by the use of the clinical exam or an electrographic recording has long been plagued by inherent subjectivity. Detection of seizures using purely clinical evaluation is even more challenging. Murray et al. found a 9% rate of detection using the observations of experienced clinicians. Worse yet, 73% of episodes identified as clinical seizures had no electrographic correlate [10]. Even with the aid of monitoring technology, seizure detection is imperfect; serial evaluations of Neonatologists revealed the ability to detect between 22–57% of seizures using a time-compressed aEEG recording [11,12]. Simultaneous examination of the raw EEG trace in conjunction with the time-compressed trace improves the seizure detection rate to 76% [12]. Quantitative EEG technology has demonstrated superior, and more importantly, reproducible, seizure detection. Automated seizure detection algorithms, which use wave-based analysis, have a sensitivity upwards of 80% [13,14].

Having a high index of suspicion in the appropriate clinical setting, initiation of monitoring as soon as possible and the use of a multi-modal analysis model will allow the clinician to make a timely diagnosis and initiate the appropriate treatment. Indeed, the findings of Shellhaas et al. demonstrated that early use of aEEG monitoring reduced the time to diagnosis and limited the number of infants with a diagnosis of seizures without electrographic confirmation [15]. A summary of the suggested evaluation for a new onset seizure in a neonate is provided in Table 1.

Trends in Seizure Treatment

Phenobarbital

Phenobarbital has been the gold standard for the management of neonatal seizures for over 90 y [16]. Gilman et al. demonstrated that a loading dose of 20 mg/kg followed by smaller 5 mg/kg to 10 mg/kg bolus doses up to a maximum of 40 mg/kg will achieve control in 70% of clinical seizures and 40% of electrographic seizures [17]. Mechanistically, targeting the GABAA receptors should provide a strong inhibitory response in the brain by hyperpolarization of the cell membrane *via* active transportation of the chloride ion. Immature neurons, however, over-express the sodium/potassium/chloride co-transporter isoform 1 (NKCC1) and under-express the potassium/chloride co-transporter (KCC2) leading to a reversal of the chloride gradient. GABA-ergic stimulation therefore causes chloride efflux and subsequent depolarization rather than the expected hyper-polarization [18]. Though a switch in predominant ion transporter subtype is thought to occur around the time of birth, the exact timing is unclear. Indeed, term-equivalent animal and human studies have demonstrated an excitation response from GABA stimulation produced by cortical neurons rather inhibitory, leading to the previously noted incomplete phenobarbital response and potentially even worsening seizures [2]. In addition, further studies have demonstrated

neurotoxicity and apoptosis associated even with low dose phenobarbital [16]. However, given the low cost, relative ubiquity and well-understood safety profile, phenobarbital continues to be the first-line agent recommended by the WHO for use in both the developing and industrialized world [19].

Phenytoin

Phenytoin is recommended as a second line agent by the WHO [19] and has shown to achieve an 80% reduction in electrographic seizures in 80% of infants when used in conjunction with phenobarbital [20]. Given in a bolus dose of 20mg/kg, phenytoin has a substantial higher side effect profile than phenobarbital, specifically arrhythmia and the risk of soft tissue injury in the case of accidental extravasation due to the highly basic pH. The pro-drug Fosphenytoin is substantially safer to use in infants, with a more physiologic pH and substantially low risk of arrhythmia, yet still provides the same degree of efficacy after conversion to phenytoin by plasma phosphatases [2].

Levetiracetam

Levetiracetam is a novel antiepileptic agent in clinical use since 2000. It is believed to bind to synaptic vesicle glycoprotein SV2A, inhibiting presynaptic calcium channels thereby reducing the rate of neurotransmitter release [18,21]. Though originally licensed as add-on therapy, it has been used as monotherapy for neonates in case reports and pharmacokinetic studies. In contrast to many other antiepileptic agents, levetiracetam has a good safety profile and may even confer neuroprotective properties [22]. Several US-based randomized control trials are ongoing.

Hypothermia

Since the publication of the results of the Cool Cap and Whole Body Hypothermia Trial in 2005, the use of therapeutic hypothermia has revolutionized the treatment of infants with hypoxic-ischemic encephalopathy. As the original trials were powered to detect a change in radiographic brain injury, the antiepileptic properties of hypothermia were not initially known. However, more recently a measurable seizure reduction has been described in infants with mild to moderate encephalopathy [23,24]. These findings offer hope for the future use of adjunctive non-pharmacologic anti-epileptic treatment methods and deserve further evaluation.

Lidocaine

Several small studies have reported the successful use of lidocaine as a second or third line treatment for refractory seizures. The response rate varies from 70–92% [25–27]. Lidocaine passes the blood brain barrier effectively. Adverse cardiac effects such as ventricular tachycardia should be closely monitored for and lidocaine should not be used in conjunction with phenytoin due to potential for cumulative cardiac toxicity. Lidocaine dosing should be reduced during hypothermia because of decreased clearance [28].

Bumetanide

Bumetanide, a commonly used loop diuretic that acts by directly inhibiting NKCC1, has been proposed as a novel antiepileptic drug. It acts upon the reversed chloride gradient of immature neurons by preventing the influx of chloride, thus maintaining a depolarized state and preventing the activation of these presumably excitatory GABA-ergic neurons, likely enhancing the efficacy of phenobarbital [29]. Limited human data exist for the treatment of neonatal seizures with bumetanide and concern about side effects, particularly hearing loss and electrolyte disturbance remain. Indeed, the EU-based bumetanide trial was halted prior to recruitment goals due to concern about hearing loss, although a US-based trial is ongoing [18].

Topiramate

Topiramate is an antiepileptic agent in widespread use for the treatment of seizures in older children. Topiramate exerts an antiepileptic effect *via* four mechanisms: (1) blockade of voltage-dependent sodium channels, (2) GABAA agonist, (3) AMPA/kainate glutamate receptor subtype antagonist and (4) inhibition of carbonic anhydrase isoenzymes type I and IV. Although topiramate is well-studied in adults and older children, limited data exist for the application to neonates. US and European trials to explore both kinetics and therapeutic value are ongoing.

Limited pharmacokinetic data show that topiramate is generally well tolerated and has a linear dose-serum concentration response; however clearance was prolonged in infants who were undergoing therapeutic hypothermia and in those who were also receiving other antiepileptic agents [18]. The promulgation of topiramate in neonates has been met with two significant challenges: First, to date no intravenous formulation is commercially available, precluding use in patients who are unable to tolerate oral medications. Promising pilot data has demonstrated safety of an experimental intravenous form in adults [30], however neonatal data is lacking. Second, there is significant concern that topiramate adversely affects language development, even in healthy volunteers. There are a number of reports which show a decrement in word finding ability and a decreased overall verbal IQ [31]. The effect on the developing newborn brain is currently unknown.

Table 2 provides dosing for the most commonly used anti-epileptic drugs.

Seizures in the Preterm Infant

The reported incidence of seizures in premature infants, particularly those born before 28 wk, varies widely between 4% and nearly 50% [32,33]. The immature brain does not generally produce the same clinically evident epileptic event as occurs in many term infants and older children largely due to incomplete myelination of the descending corticospinal tracts. The seizures of preterm infants have been described in the literature as generally brief, lasting less than 2 min, and without obvious clinical correlate [32].

Nevertheless, seizures in a preterm infant have repeatedly been shown to have an association with adverse outcomes including intraventricular hemorrhage, white matter injury, death and

moderate to severe impairment on subsequent developmental testing [5,8,32–35]. Furthermore, the incidence of seizures has an inverse relationship with gestational age [36].

Seizure detection in premature infants requires a prospective electrographic approach. Hellström-Westas et al. describe a series of series of 31 premature infants who were prospectively monitored for epileptiform activity. Twenty seven of the thirty one infants had electrographic seizures, however, clinical correlates were only seen in approximately half of the study population, an enormous gap [33]. Even the detection of electrographic seizures can be challenging as the epileptiform activity of preterm infants is brief and often below the frequency filter threshold (<2 Hz). The use of an automated seizure detection algorithm and inspection of the raw tracing are important adjuncts to improve sensitivity [36].

The same monitoring techniques developed for term infants can be applied to preterm infants, with some degree of modification [37]. Conventional EEG monitoring is technically challenging due to (1) the elevated temperature and humidity in the isolette causing non-adherence of leads and (2) limited scalp surface area. A modified version of the 10–20 International System using eight electrodes (AF3-C3, C3-O1, AF4-C4, C4-O2, AF3-T3, T3-O1, AF4-T4, T4-O2) has been used in order to accomplish EEG studies on preterm infants [38]. Limited channel aEEG monitoring using hydrogel electrodes on well-prepared skin or needle electrodes has fewer technical hurdles to overcome and is increasingly being used in centers around the world [36].

Treatment

Though most respondents in a recent international survey reported that they would choose phenobarbital as a first line agent for seizures in preterm infants, there is significant concern that a GABA-ergic medication would, in fact, lead to paradoxical excitation of cortical neurons due to the previously described over-expression of NKCC1 [36]. Furthermore, recent work soon to be published by authors' lab, demonstrates that, though the prevalence of seizures in the population is relatively high, only those infants with the highest seizure burden have an association with radiographic injury and adverse language development, raising the possibility that seizure treatment could perhaps be targeted to a specific sub-population. Nevertheless, until a more complete understanding of seizures in the preterm population is made, treatment remains fraught with many potential risks and a lack of obvious clear benefit.

Emerging Topics in Neonatal Seizure Management

Although there have been many proposals to use drugs other than phenobarbital as a first-line therapy, there is limited pharmacokinetic data to support the use of other drugs such as levetiracetam and topiramate. This gap in knowledge persists despite concerns about phenobarbital's limited effectiveness, given the biology of the newborn brain, and even the tendency to cause neuroapoptosis. The practice persists due to widespread comfort on the part of clinicians and easy availability [36]. Several international trials are ongoing to fill in this gap including the NEMO trial examining the use of bumetanide, the NEOLEV2 trial examining levetiracetam and NeoNATI examining topiramate.

Similarly, there are efforts underway to examine the modification of seizure management during hypothermia. One factor of significant interest is the effect of hypothermia on the clearance and efficacy of anti-epileptic drugs. A recent examination of phenobarbital demonstrated no significant effect of hypothermia on pharmacokinetics but did seem decrease the time needed for normalization of EEG background, perhaps suggesting a neuroprotective effect [39]. Further study of second- and third-line antiepileptics during hypothermia treatment is needed to assess for alteration in pharmacokinetics and therapeutic effect.

Striking a balance between treating all observed seizures, whether clinical or electrographic-only, and limiting the exposure to drugs with potential short- and long-term side effects, remains a challenge for clinicians even in this era of modern medicine. While there is no evidence to suggest that suppressing all epileptiform discharges will improve neurodevelopmental outcomes, Miller et al. suggest that an increased seizure burden is associated with adverse changes in brain injury on MRI [40]. The previously mentioned NeoNATI trial, in addition to quantifying the kinetics of the drug during hypothermia, aims to determine the role of a prophylactic antiepileptic in improving neurodevelopmental outcomes.

In 2007 the WHO and the International League Against Epilepsy (ILAE) published a proposal to improve the diagnosis and management of neonatal seizures in resource limited settings [41]. These guidelines provide comprehensive tables that allow the clinician to determine the likelihood that a given constellation of symptoms, physical exam findings and clinical history is caused by an epileptogenic cause. These tools can be used to quickly determine which patients need a more advanced diagnostic evaluation and which are likely to benefit from treatment.

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Figure 1.

Screenshot of aEEG trace demonstrating seizures. The upper raw trace (10 s) demonstrates signal from the left (C3-P3-upper) and right (C4-P4- lower) channels. The lower compressed trace (3.5 h) demonstrates aEEG signal from the left and right channels. Seizures are depicted as sudden rise in the upper and lower margin of the aEEG trace. The red cursor on the aEEG shows the raw EEG trace at that moment. The orange bar on the raw trace is the activated seizure detection algorithm that is also seen on the aEEG.

Table 1

Diagnostic approach to neonatal seizures

Diagnostic approach	Evaluation
History	<ul style="list-style-type: none"> • Time of seizure onset after birth • Birth and labor history • Fetal distress • Apgar scores and resuscitation • Cord gases, if available • Lethargic • Feeding history after birth • Maternal herpes simplex virus (HSV) infection or gastroenteritis • Maternal drug exposure [opiates, selective serotonin reuptake inhibitors (SSRIs)] • Family history of seizures • Response to anticonvulsants
Clinical examination	<ul style="list-style-type: none"> • Vital signs (heart rate, respiratory rate, pulse oximetry, blood pressure) • Encephalopathy stage • Clinical seizure vs. jitteriness • Dysmorphic features (suggest syndrome) • Neurological exam
Laboratory evaluations	<ul style="list-style-type: none"> • * Glucose, sodium, potassium, calcium, magnesium, total and fractionated bilirubin, liver enzymes, ammonia, urea, creatinine, arterial blood gas, lactate • * Complete blood count with differential and C-reactive protein • * Blood culture and catheterized urine culture • * CSF studies for cell counts, glucose (with simultaneous blood glucose) and protein; culture and HSV and enterovirus PCR • Serum amino acids and urine organic acids • Surface swabs and blood PCR for HSV • Urine CMV, blood toxoplasma titers
Monitoring	<ul style="list-style-type: none"> • Either amplitude integrated EEG (aEEG) or full montage video-EEG monitoring continuously for 24 h
Imaging	<ul style="list-style-type: none"> • MRI with spectroscopy and magnetic resonance venography (MRV) or if not available, then a cranial ultrasound

* Essential initial workup

Table 2

Recommended dosing for the most commonly used anti-epileptics

Anti-seizure drug	Recommended dosage
Phenobarbital	<ul style="list-style-type: none"> • Loading: 20 mg/kg IV followed by 10–20 mg/kg IVH • Maintenance (if required): 3–5 mg/kg/d IV or PO • Goal drug level: 40 mg/L
Fosphenytoin	<ul style="list-style-type: none"> • Loading dose: 20 mg/kg IV
Midazolam	<ul style="list-style-type: none"> • Loading dose: 0.05–0.1 mg/kg over 10 min
Lidocaine (do not use with Fosphenytoin)	<ul style="list-style-type: none"> • Loading dose 2 mg/kg • 7 mg/kg/h for 3.5 h • 3.5 mg/kg/h for 12h • 1.75 mg/kg/h for 12 h and then stop
Levetiracetam	<ul style="list-style-type: none"> • Loading dose: 50 mg/kg IV • Maintenance dose: 5 mg/kg every 8–12 h