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Neonatal Seizures: New Evidence, Classification, and Guidelines

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Abstract

Neonates are susceptible to seizures due to their unique physiology and combination of risks associated with gestation, delivery, and the immediate postnatal period. Advances in neonatal care have improved outcomes for some of our most fragile patients, but there are persistent challenges for epileptologists in identifying neonatal seizures, diagnosing etiologies, and providing the most appropriate care, with an ultimate goal to maximize patient outcomes. In just the last few years, there have been critical advances in the state of the science, as well as new evidence-based guidelines for diagnosis, classification, and treatment of neonatal seizures. This review will provide updated knowledge about the pathophysiology of neonatal seizures, classification of the provoked seizures and neonatal epilepsies, state of the art guidance on EEG monitoring in the neonatal ICU, current treatment guidelines for neonatal seizures, and potential for future advancement in treatment.

Keywords

neonatal seizures, guidelines, neuromonitoring, EEG, phenobarbital, hypoxic-ischemic encephalopathy, neonatal neurology

Introduction

Several unique physiologic features underlie the rapid neurodevelopmental processes of early infancy, but also leave the immature brain uniquely susceptible to seizures. Immature neurons have a reversed chloride gradient due to developmentally mediated expression of chloride transporters, NKCC1 and KCC2.[1,2] When GABA binds to the postsynaptic receptor, the result is an efflux of chloride and

depolarization of the neuron as the negatively charged chloride ions leave the cell. As neurons mature, KCC2 expression increases, with resulting increased export of chloride from the cell; this leads to the mature hyperpolarization response upon $GABA_A$ receptor activation.[1-3] In addition, maturationally regulated expression of NMDA and AMPA receptor subunits also promotes hyperexcitability and renders glutamate a more excitable neurotransmitter in the neonatal brain than the adult brain.[4-6] Developmental regulation of ion channels and neuropeptide systems may also promote hyperexcitability in the neonatal period, in addition to the developmental overabundance of synaptic connections and microglial responses.[4,6-8]

As a result of this developmental neurophysiology, neonatal seizures (seizures within the first 28 days of birth) are relatively common, with an incidence of 1 to 4 per 1000 live births, and as many as 130 per 1000 preterm infants.[9] Neonatal seizures are usually symptoms of acute brain injury, with hypoxic-ischemic encephalopathy (HIE) making up 35% to 45% of cases.[9] Neonatal physiology and a paucity of myelin also means that neonatal seizures have different clinical manifestations than seizures in older children and adults. Clinical seizure semiologies are difficult to discern in neonates and the seizures may have more subtle electrographic signatures than older children or adults.[10,11] Additionally, the impact of seizures in newborns may be especially significant since potentiation of early brain injury may result in a lifetime of developmental consequences. Recent research has yielded updated classifications, guidelines, and best practices for diagnosis and treatment for neonates with seizures. These exciting advances are now opening doors for future opportunities to maximize outcomes for this unique population.

Which Newborns Should Be Monitored With EEG?

Neonatal seizures are of high concern to families and clinicians, but an accurate diagnosis is often challenging. Neonates, and particularly critically ill neonates, can exhibit a variety of abnormal, paroxysmal movements and abrupt fluctuations in vital signs—most of these events are not seizures. Conversely, most neonatal seizures are not recognizable at the bedside because even as the brain is seizing, there may be no outward clinical signs (particularly if the motor cortex is not involved). For these reasons, continuous EEG (cEEG) monitoring is recognized as the gold standard for neonatal seizure detection.[12] Increasingly, cEEG is used in neonatal intensive care units (NICUs) for seizure diagnosis and, more broadly, for brain monitoring. However, cEEG is highly resource intensive—it requires expensive equipment, trained technologists, infrastructure for timely remote review, and clinical neurophysiologists with specific expertise for interpretation. There is variability in how and when cEEG is used in neonates.

The American Clinical Neurophysiology Society (ACNS) published a first guideline in 2011, as an "expression of idealized goals" for cEEG use, based on expert consensus.[13] More recently, the ACNS updated that work to create an evidence-based clinical practice guideline on "Indications for Continuous Electroencephalography Monitoring in Neonates" (to be published at https://www.acns.org/practice/guidelines).[14] This guideline addresses a set of priority questions regarding the use of cEEG for specific purposes in neonates. The process included a systematic review of the literature and applied a modification of Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology[15] to evaluate the quality of evidence and draft recommendations. For each priority question, a recommendation was made regarding whether cEEG was suggested. Each recommendation was either "strong," meaning it should be applied across almost all settings, or "conditional," meaning the recommendation may not apply in some circumstances.

The systematic review identified >200 published studies relevant to the priority questions. Overall, the evidence available was often of low or very low quality; most studies were retrospective or did not directly compare cEEG to another modality. Even so, for many topics there was a consistent direction of evidence to support recommendations. The guideline suggests cEEG be used to improve accuracy of seizure diagnosis in neonates with clinically suspected seizures, as compared with clinical observation alone, amplitude-integrated EEG (aEEG) alone, or spot/routine EEG. Likewise, it suggests cEEG be used to confirm diagnosis of aEEG events suspected to be seizures.

Beyond confirming diagnosis, cEEG monitoring is recommended as a seizure screening tool for certain high risk neonates (ie, prior to any clinically suspected seizures).[16] There was moderate quality evidence to support screening cEEG for neonates undergoing extracorporeal membrane oxygenation (ECMO), with congenital heart disease (CHD) following surgical repair, and with hyperammonemia. The available low or very low quality evidence supported screening cEEG monitoring for neonates with HIE, intracranial hemorrhage, acute ischemic stroke, extreme prematurity, intracranial infection, encephalopathy, and inborn errors of metabolism. There was insufficient evidence to make a recommendation regarding cEEG monitoring for seizures among neonates with sinovenous thrombosis, intraventricular hemorrhage, sepsis, neonatal systemic inflammatory syndrome, congenital brain malformation, therapeutic paralysis, or transient metabolic disturbance.

After seizures are confirmed, cEEG is recommended to assess for response to treatment and to confirm resolution of seizures. However, there was insufficient evidence to make a recommendation for or against cEEG monitoring after weaning or discontinuing anti-seizure medications (ASMs). Given the lack of high-quality evidence, and in recognition of the high-resource requirement for cEEG, all of the above recommendations were conditional. The complete guideline, including recommendations regarding cEEG for non-seizure indications will be available at https://www.acns.org/practice/guidelines.[14]

EEG Monitoring in Complex Congenital Heart Disease

While neonates with CHD are often primarily hospitalized for cardiac indications, they are also at high risk for neurologic injury related to empiric and acquired exposures. Empiric risks associated with underlying genetic syndromes, prenatal environmental factors, and the impacts of the cardiac pathology can result in structural signs of brain immaturity and white matter injury.[17,18] Acquired risks to the brain arise from the underlying cardiac pathology and life-sustaining technologies which can result in cerebral emboli, hemorrhage, and/or hypoperfusion. These risks for acute brain injury are the impetus for neuromonitoring in neonates with CHD.

New surgical techniques spurred neuromonitoring practice in the care of neonatal CHD. Specifically, cardiopulmonary bypass (CPB) with deep hypothermic circulatory arrest was guided by cEEG monitoring—an isoelectric EEG was used to denote when optimal cooling was achieved for circulatory arrest. Since that time, there has been rapid expansion of cEEG monitoring for interictal background assessment and seizure detection. In the pre- and post-operative period, most neonates have abnormal EEG background patterns and particular abnormalities may be associated with brain injury. Delayed recovery of normal EEG patterns (particularly sleep-wake cycling) is associated with mortality and poor neurodevelopment.[19-25] The incidence of seizures in the post-operative period following surgical repair with CPB in complex CHD is 1% to 20%, and affected neonates have high rates of status epilepticus and electrographic-only seizures, especially in the initial 24 hours following surgical repair.[13,26-31] Thus, the 2011 ACNS guideline on neonatal EEG monitoring in neonates recommended consideration of at least 24 hours of cEEG monitoring for neonates with CHD who require early surgery with CPB.[13]

Neurodevelopmental and neurobehavioral outcomes are abnormal for many survivors of complex CHD. Contributing factors are multifactorial and span the prenatal, birth, postnatal, and surgical repair periods—genetics, the maternal-placental environment, changes to systemic blood flow that impact cerebral perfusion, exposure to ECMO and other surgical techniques, and the impactful role of socioeconomic factors.[32] Seizures in neonates with CHD can exacerbate the risk of poor outcomes throughout the pediatric lifespan.[26-29,31] Rapid, effective seizure management may minimize the long-term impacts of seizures.

There are many potential future directions for research in neonates with complex CHD, including (1) exploring the role of multimodal neuromonitoring, (2) investigating novel seizure treatment strategies specific to cardiac pathology or genetic etiologies, (3) development and validation of seizure prediction models to tailor neuromonitoring practices,[30,33] and (4) evaluation of cEEG background data to predict nonseizure events, such as cardiac arrest.[34]

Quantitative EEG and Automated Seizure Detection in the NICU

Quantitative EEG (qEEG) broadly describes the process of breaking down the digital EEG waveform into its component parts, such as the amplitude or frequency of the waveform, transforming the raw EEG into powerful visualization and analytic tools. Quantitative EEG can help bedside clinicians visualize seizures in real-time, and amassing techniques now harness qEEG analytics to create accurate automated neonatal seizure detection.

The most utilized qEEG tool in the NICU is the aEEG, which has been used for decades in clinical care for interictal background categorization and neonatal seizure detection. The aEEG signal is a purely amplitude-based trend and displays amplitude variations over time and part of its signal generation begins with passing the signal through a 2-30 Hz bandpass filter, which limits detection of very slow (<2 Hz) patterns. Being purely amplitude-derived inherently renders this tool inadequate for detecting low-amplitude seizures, the time condensed display makes very brief seizures difficult to detect, and detection of very focal seizures depends on whether ictal electrodes are included in the aEEG montage. Neonatal seizures are frequently low-amplitude, of brief duration, and very focal without significant spread. Therefore, despite extensive experience with this tool in the NICU, it does not perform well enough to be a reliable method for acute neonatal seizure detection. Yet, in resource constrained settings, with appropriate training and realistic appreciation of the pros and cons of the tool, aEEG can be helpful to monitor background trends and detect some seizures.

Modern neonatal seizure detection algorithms take advantage of not only amplitude-based qEEG trends such as aEEG but also rely on a number of other EEG signal components to increase accuracy of seizure detection, including frequency, rhythmicity, entropy, variance, and skewness, among others.[35,36] Using a variety of signal features and machine learning to identify variable importance, researchers have designed automated seizure detection models with sensitivity of neonatal seizure detection up to 88%.[35] Another step toward improved automated seizure detection in the NICU is the design of algorithms that can identify and remove common artifacts (eg, pulse and patting artifacts) which may mimic rhythmic seizures in newborns.[37,38]

While automated neonatal seizure detection continues to improve in accuracy, it is arguably just as important to understand how qEEG can be utilized to anticipate neurodevelopmental outcomes. While aEEG is frequently utilized to assess neonatal EEG background abnormalities—and has prognostic accuracy in some settings[39-41]—interpretation of the raw EEG background by a neurophysiologist remains more accurately predictive of outcome after neonatal brain injury.[42] Parallel to the improvements in neonatal seizure detection, advanced processing of the EEG signal beyond amplitude characteristics is proving to be far more predictive of outcomes; in some cases, outperforming highly detailed neuroimaging such as magnetic

resonance imaging.[36] Although it does not replace the gold standard of an electroencephalographer's EEG interpretation, qEEG can be a powerful tool for real-time screening for seizures, optimizing time to seizure recognition, and informing discussions of prognosis.

Neonatal Epilepsy Classification

While most neonatal seizures are caused by acute brain injury (eg, acute provoked seizures), 10% to 15% of neonatal seizures are caused by epilepsy.[43] The ILAE Task Force on Nosology and Definitions position statement defining epilepsy syndromes with onset in the neonatal period[44] facilitates diagnostic and prognostic determinations. The ILAE categorization is divided into: (1) self-limited epilepsy syndromes, and (2) developmental and epileptic encephalopathies (DEEs). Self-limited syndromes are characterized by spontaneous seizure resolution and normal interictal background EEG patterns. The DEEs are associated with intractable seizures and accompanied by developmental impairment or regression (often due to an underlying cause or to superimposed epileptiform activity). The EEG background is markedly abnormal and often is characterized by hypsarrhythmia, burst suppression, or persistent focal slowing. The neonatal epilepsy syndromes may be conceptualized as due to a pathogenic genetic variant or to another specific etiology (eg, structural, metabolic, immune, or infectious).

Self-Limited Neonatal Epilepsy (SeLNE) typically begins between 2 and 7 days following birth and remits within 6 months. The neonatal seizure semiology is typically focal tonic, but focal clonic, myoclonic, or sequential semiologies also can occur. A positive family history is an important predictor of SeLNE since it is inherited in an autosomal dominant pattern. When there is a loss-of-function due to pathogenic variants in *KCNQ2* or *KCNQ3*, sodium-channel blockers may be effective to treat the seizures.

Early Infantile Developmental and Epileptic Encephalopathy (EIDEE) is a newly characterized entity manifested by medication-resistant seizures presenting in the first 3 months of life. EIDEE is associated with severe developmental impairment, abnormal findings on neurological examination, and burst suppression on EEG. As the seizures are nearly always resistant to treatment, early epilepsy surgery can be an option if a structural lesion is identified.

The ILAE task force further described several etiology-specific DEEs—electroclinical phenotypes associated with specific genetic etiologies. This number of etiology specific DEE syndromes will continue to expand as more genetic etiologies are identified.[44]

Genetic Diagnosis and Precision Therapy in Neonatal DEEs

Advancements in DNA sequencing and bioinformatics over the last decade have decreased costs of genetic testing and enabled widespread use in the pediatric epilepsies. Genetic testing has proven invaluable in the diagnostic workup of neonates with DEE in particular, with "pathogenic" or "likely pathogenic" variants identified in 83% of patients.[43] Genetic testing should be considered early in the disease course of these infants, guided in part by risk factors such as seizure semiology.[45] For example, tonic seizures are rarely seen in acute provoked neonatal seizures yet are the predominant seizure type in newborns with channelopathies (ie, SCN2A-DEE).[46,47] Similarly, myoclonic seizures and epileptic spasms are a clinical biomarker for synaptopathies (ie, STXBP1-DEE), inborn errors of metabolism or vitamin-related disorders.[47] EEG background, medication responsiveness, and family history also guide which newborns are most likely to benefit from early genetic testing.

Commonly ordered genetic tests for epilepsy include targeted multigene panels (MGP), chromosomal microarrays (CMA), whole exome sequencing (WES), and whole genome sequencing (WGS). Multigene panels analyze a specific set of 200+ genes known to be associated with epilepsy. These panels provide the highest cost to yield ratio in neonatal-onset DEEs, with a diagnostic yield of 35% to 57%.[48-50] Lower yield, yet informative, tests include (1) CMA, evaluating copy number variants, with a diagnostic yield of 3% to 5%;[51,52] and WES, which evaluates all exons within the genome, has a diagnostic yield of <4% after a negative targeted gene panel.[53] Whole genome sequencing, which evaluates coding AND intronic/noncoding DNA, will undoubtedly help resolve the diagnostic odyssey for children in whom a genetic epilepsy is suspected but MGP, CMA, and/or WES is negative. However, our understanding of noncoding rare variants and their functional impact on epilepsy-related gene expression is nascent. As in the earlier days of WES, a negative WGS may reflect our evolving knowledge of variant pathogenicity. Systematic reanalysis every 2 years may enhance yield.[54]

Genetic testing significantly impacts the management of neonatal-onset DEE and allows for accurate estimates of prognosis.[55] Moreover, parents desire answers and welcome conversations about genetic testing in the NICU.[56] While precision therapies can resolve seizures in neonatal-onset DEEs (ie, sodium-channel blockers in KCNQ2-DEE),[57] their impact on long-term neurodevelopment remains limited. In this regard, *disease-modifying therapies* hold great promise. Targeted oligonucleotides, delivered intrathecally or intraventricularly, are being trialed in SCN1A-epilepsies (ie, NCT04740476), and other targeted oligonucleotides and virally delivered gene therapies are in the development pipeline. Early genetic testing in neonates with DEE will be necessary to quickly identify infants for whom emerging therapies can be trialed and offering hope for improved outcomes.

Treatment Guidelines for Neonatal Seizures

Despite the relatively common occurrence of neonatal seizures, treatment remains challenging with limited options.[58] Until recently, most recommendations were based on scant evidence and relied on expert consensus and historical practice with substantial management variability.[12] However, the neonatal

Table 1. Summary Recommendations of the ILAE Clinical Practice Guideline on treatment of neonatal seizures.[a]

	Recommendation	Based on
1a	In neonates with seizures requiring ASM, phenobarbital should be the first-line ASM.	Evidence-based with moderate strength
1b	Phenobarbital should be the first-line ASM regardless of etiology (including hypoxic-ischemic encephalopathy, stroke, and hemorrhage).	Expert consensus with high level of agreement
1c	If channelopathy is the likely cause for seizures due to family history, then phenytoin or carbamazepine (sodium channel blocker) should be the first-line ASM.[b]	Expert consensus with moderate level of agreement
2a	In neonates with seizures not responding to first-line ASM, phenytoin or levetiracetam may be used as a second-line ASM for most etiologies (hypoxic-ischemic encephalopathy, stroke, or hemorrhage). Other possible options include midazolam or lidocaine.	Expert consensus with moderate level of agreement
2b	If channelopathy as an etiology for the seizures is suspected because of clinical or EEG features, then a sodium channel blocker should be used as a second-line ASM.[b]	Expert consensus with high level of agreement
2c	In neonates with cardiac disorder(s), levetiracetam may be preferred as a second-line ASM.	Expert consensus with moderate level of agreement
3	Following cessation of acute provoked seizures (electroclinical or electrographic), without evidence for neonatal onset epilepsy, antiseizure medications should be discontinued before discharge home, regardless of MRI or EEG findings.	Expert consensus with high level of agreement
4	Therapeutic hypothermia may reduce seizure burden in term neonates with hypoxic-ischemic encephalopathy. *However, the impact of therapeutic hypothermia as a specific seizure therapy was not assessed.*	Evidence-based with weak strength and expert consensus with high level of agreement
5	Treating neonatal seizures (including electrographic-only seizures) to achieve a lower seizure burden may be associated with improved outcome (neurodevelopment, reduction of subsequent epilepsy).	Expert consensus with moderate level of agreement
6	A trial of pyridoxine (add-on to ASM) should be attempted in neonates presenting with clinical features or EEG characteristics suggestive of vitamin B6-dependent epilepsy and neonates with seizures unresponsive to second-line ASM without an identified etiology.	Expert consensus with high level of agreement

Abbreviations: ASM, anti-seizure medication; MRI, magnetic resonance imaging.

[a]Recommendations are based on a systematic review and expert-based consensus via Delphi if insufficient evidence was available.

[b]May be phenytoin or carbamazepine depending on the clinical state of the neonate (critically ill or otherwise well baby) and the regional availability of ASM and monitoring of drug levels.

task force of the ILAE has now developed recommendations about the use of ASMs in neonates based on a systematic review and expert consensus where evidence was lacking, in accordance with ILAE standards.[59] Six priority questions were formulated, a systematic literature review and evaluation of evidence via GRADE performed, and results reported following the PRISMA 2020 standards.[15] Bias was evaluated using the Cochrane tool and ROBINS-I. The strength of recommendations was defined according to the ILAE Clinical Practice Guidelines development tool. If GRADE could not be applied but the Delphi process yielded an agreement of >66%, then a recommendation was made based on the Delphi process. Agreement was labeled "high" (>75% agreement) or "moderate" (66%-75% agreement). The 6 main recommendations are summarized in Table 1.[60]

Additional considerations include a standardized pathway for the management of neonatal seizures in each neonatal unit and informing parents/guardians about the diagnosis of seizures and initial treatment options. While these guidelines are based on better evidence than earlier publications,[12] several key limitations remain. These include lack of sufficiently powered randomized controlled trials, lack of EEG-based outcome evaluations, lack of ASM safety studies, and lack of long-term outcome evaluation. There is an urgent need to develop and evaluate safe and effective ASMs for neonates.

Conclusions

Neonatal seizures present multiple diagnostic and therapeutic challenges. The recent evidence summarized here aim to aid clinicians to provide evidence-based, standardized, high-quality care for neonates with seizures. Continuous EEG monitoring of high-risk infants and the growing integration of qEEG aim to identify seizures and evolving brain injury efficiently and accurately. Treatment guidelines aim to facilitate efficient and effective treatment while seizure and epilepsy classification can further guide testing and tailored therapies for neonatal epilepsies. Though these guidelines provide an exceptional contemporary framework to optimize care, additional work is necessary to further refine diagnostic and therapeutic interventions and maximize outcomes for neonates with seizures.

Partnerships between researchers and patient-family organizations must guide study designs. Families impacted

by neonatal seizures experience significant anxiety and distress during their neonatal course, as well as into childhood, even when the seizures stop or are well-controlled.[61] Patient-family communities highlight key unmet needs and unanswered questions, as well as insights into study design, results interpretation, and dissemination. Topics such as ASM use and duration, school-age outcomes, seizure recurrence, genetic influences in neonatal seizures, and others have already been coproduced in this patient and family-centered approach to research.[61-66] These studies support a strong call to action for increased, consistent mental health screening of parents—both while infants are admitted and throughout childhood—the development and implementation of effective interventions, and education and prognostic assessment about risk factors for neurodevelopmental delays, specific types of post-neonatal epilepsy syndromes like infantile epileptic spasms, and additional concerns. Consistent implementation of the evidence-based guidelines in the diagnosis, classification, and treatment of neonatal seizures is the contemporary standard of care. Continued multidisciplinary research will support refined future guidelines and maximized neurodevelopmental outcomes in this vulnerable population.

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